# General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee

Benefits and Risks of Breast Implants
March 25-26, 2019

## Opening Remarks

Binita Ashar, M.D., FACS
Division of Surgical Devices
Office of Device Evaluation
Center for Devices and Radiological Health
U.S. Food and Drug Administration

# General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee

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## Welcome from FDA's Office of Women's Health

Kaveeta Vasisht, M.D., Pharm.D.
Office of Women's Health
Office of the Commisioner
U.S. Food and Drug Administration

# Breast Augmentation and Reconstruction

## Clinical Overview

Steven Nagel, M.D., FACS
Division of Surgical Devices
Office of Device Evaluation
Center for Devices and Radiological Health
U.S. Food and Drug Administration

# Agenda

- Breast Augmentation and Reconstruction
- Surgical Mesh in Breast Reconstruction
- Local Complications
- Breast Implant Rupture
- BIA-ALCL
- Breast Implant Illness
- Risk Benefit

# Breast Augmentation

Increase the size of the breast, enhance shape

- ~300,000 cases per year US
  - Most common cosmetic surgery
- Fill: Silicone gel or saline
- All approved implants have silicone shell
  - can be textured or smooth

# Breast Reconstruction

~85,000 cases per year

- After surgical removal of the breast or for congenital or traumatic deformity
- Placed above or behind the pectoralis muscle
- Performed with a temporary tissue expander, or placed immediately
- With or without surgical mesh

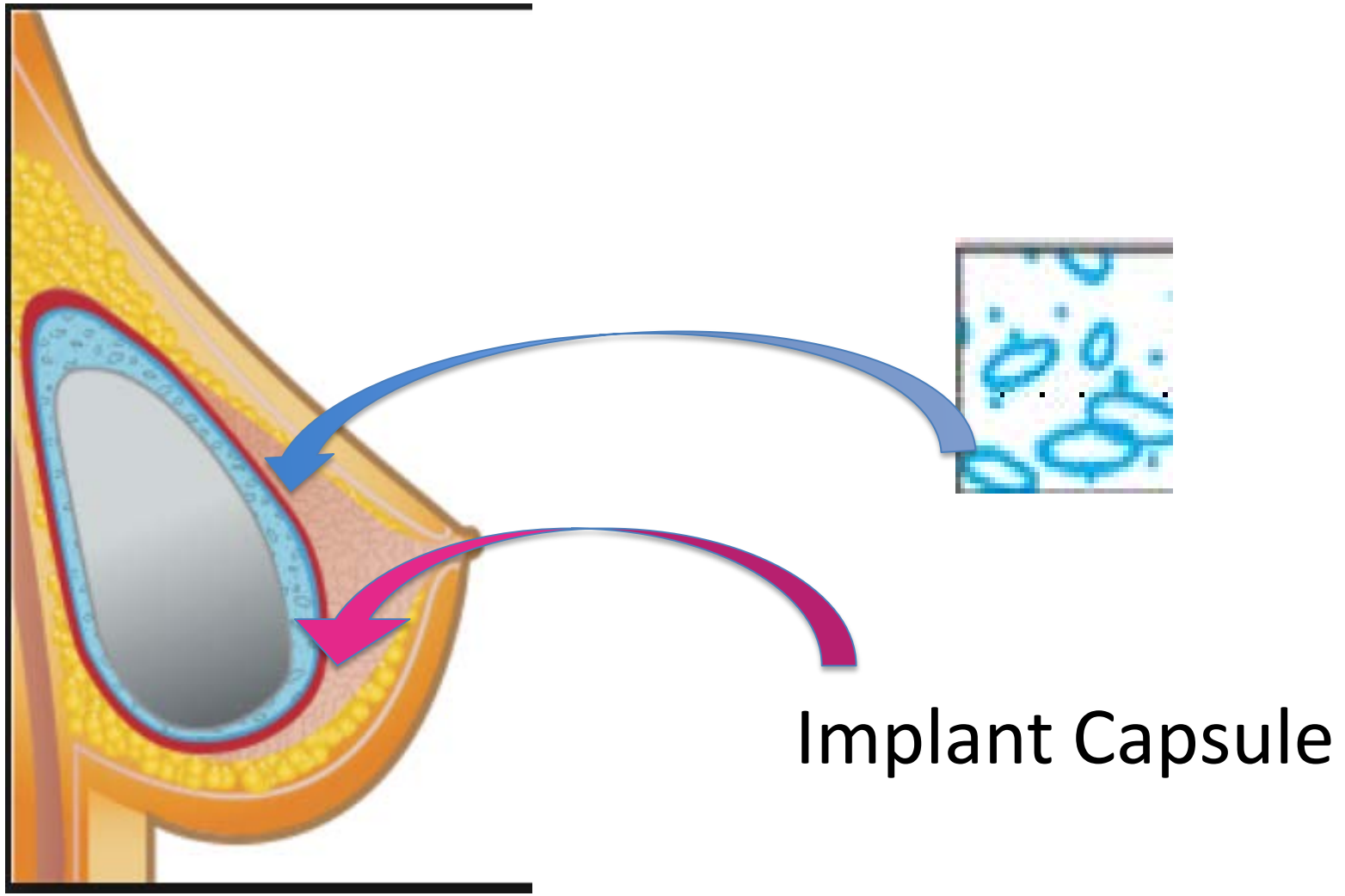
# Local Complications

- Capsular contracture
- Seroma
- Reoperation
- Rupture
- Silicone leakage
- Pain
- Wrinkling
- Asymmetry
- Scarring
- Infection
- BIA-ALCL

# Breast Implant Rupture

- Breast implant rupture is one of the most commonly reported events related to breast implants.
- For silicone implants rupture may be symptomatic or silent, intracapsular or extra-capsular.

# Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)



Implant Capsule

# Breast Implant Illness Symptoms

- Many symptoms have been reported including:
  - Memory Loss
  - Brain Fog
  - Fatigue
  - Joint Pain
  - Rash

# Long Term Benefits

- Patient Satisfaction
- Body Image
  - Body Esteem
- Self Concept
  - Self Esteem
- Quality of Life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# Overview of the FDA Mandated Post-Approval Studies

Nilsa Loyo-Berríos, M.Sc., Ph.D.
Division of Epidemiology
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
U.S. Food and Drug Administration

# 2011 Breast Implants Advisory Committee

- Discussed the postmarket experience of the 2006 approved silicone gel-filled breast implants
- Updated the Panel on status of ongoing PAS
  - Provided transparency and a public forum for discussion of interim data
  - Discussed limitations of the studies and strategies for current or potential future studies
- Provided an opportunity for all stakeholders input

# Recommendations 2011 Advisory Committee

- Redesign the Large Studies
  - Changes to questionnaire
  - Leverage safety data from other studies, and use smaller studies for more common endpoints
  - Aggregate data across manufacturers or devices using similar technologies
- Use well publicized registries for rare endpoints
- Collaborations with stakeholders
- National Registry  in the U.S.
- Update assessment of published evidence

# Since 2011 Advisory Committee

- Redesigned Large Studies
- New device post-approval studies
  - silicone gel (2012, 2013)
  - saline (2014)
- Established registries of national scope
  - PROFILE (2012), NBIR (2018)
- Tufts systematic assessment of published literature (2015)
  - Case-Control studies required for latest approvals were terminated based on this report

# FDA Post-Approval Study Activities

- Updates to Webpages
  - Post-Approval Studies Program
- Compliance actions for new enrollment combined cohort studies
  - Mentor due to low enrollment of Memory Shape
  - Sientra due to low follow-up rate


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# FDA Presentation on BII Symptoms and BIA-ALCL Medical Device Reporting (MDR)

Karen Nast, M.S.,RN
Division of Postmarket Surveillance
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
Food and Drug Administration

# FDA's BIA-ALCL Cumulative MDRs*

| | | As of 9/2017 (n = 414) | | As of 9/2018 (n = 660) | |
|---|---|---|---|---|---|
| | | n | % | n | % |
| Age at time of diagnosis | Median | 53 | - | 53 | - |
| | Range | 24 – 90 | - | 24 - 90 | - |
| | *Not Specified (# of Reports)* | 174 | 42 | 240 | 36 |
| Time from last implant to diagnosis (years) | Median | 8 | - | 8.5 | - |
| | Range | 0 – 44 | - | 0 - 44 | - |
| | *Not Specified (# of Reports)* | 173 | 42 | 231 | 35 |
| Implant Surface | Textured | 242 | 60 | 425 | 64 |
| | Smooth | 30 | 7 | 39 | 6 |
| | *Not Specified* | 142 | 34 | 196 | 30 |
| Implant Fill | Silicone | 234 | 56 | 399 | 60 |
| | Saline | 179 | 43 | 260 | 39 |
| | *Not Specified* | 1 | 0.2 | 1 | 0 |
| Reason for Implant | Reconstruction | 58 | 14 | 119 | 18 |
| | Augmentation | 88 | 21 | 125 | 19 |
| | *Not Specified* | 268 | 65 | 416 | 63 |
| Clinical Presentation (Breast) | Seroma | 203 | 49 | 350 | 53 |
| | Breast Swelling/Pain | 101 | 24 | 188 | 28 |
| | Capsular Contracture | 42 | 10 | 75 | 11 |
| | Peri-Implant Mass/Lump | 45 | 11 | 85 | 13 |
| | Others | 141 | 34 | 226 | 34 |
| | *Not Specified* | 141 | 34 | 187 | 28 |
| Anaplastic Lymphoma Kinase (ALK) | Positive | 0 | - | 0 | - |
| | Negative | 124 | 30 | 239 | 36 |
| | *Not Specified* | 290 | 70 | 421 | 64 |
| CD30 Status | Positive | 126 | 30 | 239 | 36 |
| | Negative | 0 | - | 0 | - |
| | *Not Specified* | 288 | 70 | 421 | 64 |

**Analysis based on initial MDRs and may include duplicates*

**Death Reports**

- In 2017: 9 reports representing 6 patients
- In 2018: 12 reports representing 9 patients

# FDA's BIA-ALCL Cumulative MDRs: Overall versus Filtered Reports*

| | | Overall (n=660) | | Filtered (n=457) | |
|---|---|---|---|---|---|
| | | n | % | n | % |
| Age at time of diagnosis | Median | 53 | - | 53 | - |
| | Range | 24 - 90 | - | 27 - 90 | - |
| | *Not Specified (# of Reports)* | 240 | 36 | 111 | 24 |
| Time from last implant to diagnosis (years) | Median | 8.5 | - | 9.0 | - |
| | Range | 0 - 44 | - | 0 - 34 | - |
| | *Not Specified (# of Reports)* | 231 | 35 | 110 | 24 |
| Implant Surface | Textured | 425 | 64 | 310 | 68 |
| | Smooth | 39 | 6 | 24 | 5 |
| | *Not Specified* | 196 | 30 | 123 | 27 |
| Implant Fill | Silicone | 399 | 60 | 274 | 60 |
| | Saline | 260 | 39 | 183 | 40 |
| | *Not Specified* | 1 | 0 | 0 | 0 |
| Reason for Implant | Reconstruction | 119 | 18 | 108 | 24 |
| | Augmentation | 125 | 19 | 104 | 23 |
| | *Not Specified* | 416 | 63 | 245 | 54 |
| Clinical Presentation (Breast) | Seroma | 350 | 53 | 266 | 58 |
| | Breast Swelling/Pain | 188 | 28 | 135 | 30 |
| | Capsular Contracture | 75 | 11 | 69 | 15 |
| | Peri-Implant Mass/Lump | 85 | 13 | 82 | 18 |
| | Rupture/Deflated | - | - | 54 | 12 |
| | Others | 226 | 34 | 43 | 9 |
| | *Not Specified* | 187 | 28 | 105 | 23 |
| Anaplastic Lymphoma Kinase (ALK) | Positive | 0 | 0 | 0 | 0 |
| | Negative | 239 | 36 | 229 | 50 |
| | *Not Specified* | 421 | 64 | 228 | 50 |
| CD30 Status | Positive | 239 | 36 | 215 | 47 |
| | Negative | 0 | 0 | 0 | 0 |
| | *Not Specified* | 421 | 64 | 242 | 53 |

**Filtered analysis removed duplicates and supplemental MDR reports reviewed*

**Death Reports**

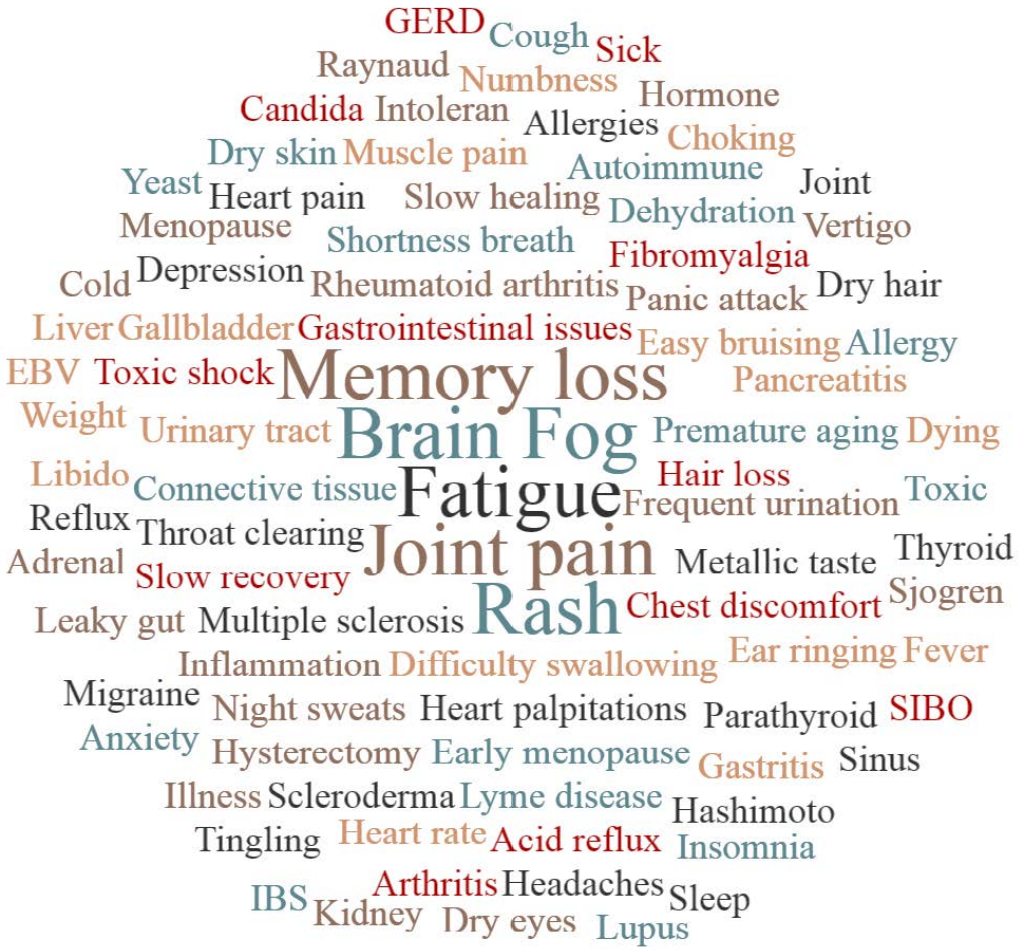
- 12 Death Reports representing 9 patients

# ALCL Associated With Devices Other Than Breast Implants

- FDA is not aware of any MDRs reporting ALCL in devices other than breast implants
- ALCL has been associated with devices other than Breast Implants in literature, including:
  - Metal implants
  - PTFE polymer Vascular Graft
  - Gluteal implants
  - Lap-Band

# BII Search Terms

FDA conducted a query of the MDR database for all reports entered between January 1, 2008 and October 31, 2018 referring to a saline- or silicone-filled breast implant with the following search terms taken from the website *Healing Breast Implant Illness*



# BII Search Results

- Reports entered between January 1, 2008 and October 31, 2018, for Saline and Silicone gel filled implants
- N = 1328, the majority were reported by Voluntary reporters (n=851, 62%)

| | |
|---|---|
| **Deaths** | 8 reports, 4 patients |
| **Injuries** | 1311 |
| **Patient Ages** | Range: 9 years to 76 years, Mean: 43 years. |
| **Time to explant-<br>(Implant and explant dates provided in 565 MDRs)** | Range: <1 month to 40 years, 10 months<br>Mean: 9 years, 7 months |
| **Time to Onset of Symptoms<br>(Implant and Event dates provided in 969 MDRs)** | Range: <1 month to 38 years, 9 months<br>Mean: 5 years, 2 months. |
| **Improvement in symptoms after explant** | N= 101 |
| **Top 5 reported symptoms** | Fatigue, Brain Fog, Rash, Joint Pain, Memory Loss |

# MDR Limitations

- While the MDR system is a valuable source of information, this passive surveillance system has limitations, including incomplete, inaccurate, untimely, unverified, or biased data in the reports.
- In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting, duplicate reporting of events, and the lack of information about the total number of devices.
- These data do not represent a complete understanding of Breast Implant Illness and do not demonstrate that breast implants are causing the symptoms of Breast Implant Illness.

# Panel Question

- The panel will be asked to make recommendations regarding next steps for the characterization of BIA-ALCL incidence and its risk factors
- The panel will be asked to discuss methods for assessing and addressing breast implant illness symptoms.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# FDA Presentation on Breast Implant Illness (BII) from Post Approval Studies (PAS)

Michael DeLong, M.D.
Division of Surgical Devices
Office of Device Evaluation
Center for Devices and Radiological Health
U.S. Food and Drug Administration

# Manufacturer Post Approval Studies

| | Study | Redesign |
|---|---|---|
| **Allergan** | Large Post Approval Study | Breast Implant Follow up Study (BIFS) |
| | Core Study Continuation | N/A |
| **Mentor** | Large Post Approval Study | GLOW Combined Cohort |
| | Core Study Continuation | N/A |
| **Sientra** | US-PAS | N/A |
| | Core Study Continuation | N/A |
| **IDEAL** | Core Study Continuation | N/A |

# Manufacturer Post Approval Studies

| | Study | Redesign |
|---|---|---|
| **Allergan** | Large Post Approval Study | Breast Implant Follow up Study (BIFS) |
| | Core Study Continuation | N/A |
| **Mentor** | Large Post Approval Study | GLOW Combined Cohort |
| | Core Study Continuation | N/A |
| **Sientra** | US-PAS | N/A |
| | Core Study Continuation | N/A |
| **IDEAL** | Core Study Continuation | N/A |

# PAS Reporting

- In November 2018, FDA requested that sponsors submit BII related systemic symptoms data from their PAS

- Each manufacturer submitted or referenced data from a different study

***Differences in study protocols prevent comparisons between separate studies. Results should be considered in the context of each study design.***

# Manufacturer Post Approval Studies

| | Study | Redesign |
|---|---|---|
| **Allergan** | Large Post Approval Study | Breast Implant Follow up Study (BIFS) |
| | Core Study Continuation | N/A |
| **Mentor** | Large Post Approval Study | GLOW Combined Cohort |
| | Core Study Continuation | N/A |
| **Sientra** | US-PAS | N/A |
| | Core Study Continuation | N/A |
| **IDEAL** | Core Study Continuation | N/A |

# Study Overview

| | Allergan BIFS | Mentor LPAS | Sientra PACS | IDEAL Core |
|---|---|---|---|---|
| **Silicone** | Yes | Yes | Yes | No |
| **Saline** | Yes | Yes | No | Yes |
| **Textured** | Included | Included | Included | No |
| **Comparator** | Saline | Saline | None | None |
| **Indication** | Aug/Recon | Aug/Recon | Aug/Recon | Aug |
| **Follow up Period** | 7 years | 6-7 years | 10 years | 8 years |
| **Follow up %** | 78% | 15% | 51% | 94% |
| **Status** | Ongoing | Redesigned | Complete | Ongoing |

# Manufacturer Post Approval Studies - Allergan

| | Study | Redesign |
|---|---|---|
| Allergan | Large Post Approval Study | Breast Implant Follow up Study (BIFS) |
| | Core Study Continuation | N/A |
| Mentor | Large Post Approval Study | GLOW Combined Cohort |
| | Core Study Continuation | N/A |
| Sientra | US-PAS | N/A |
| | Core Study Continuation | N/A |
| IDEAL | Core Study Continuation | N/A |

# Allergan BIFS Protocol

- 2000 silicone and 257 saline patients selected from the original >40,000 in LPAS
  - Selected patients with compliant questionnaire follow up,  100% 4 year follow up guaranteed in both groups
  - Does not necessarily eliminate follow up bias

- Reported as percent of patients who did not have symptom at baseline who report symptom at any time point – denominator does not depend on follow up

| | Allergan BIFS |
|---|---|
| Silicone | Yes |
| Saline | Yes |
| Textured | Included |
| Comparator | Saline |
| Indication | Aug/Recon |
| Follow up Period | 7 years |
| Follow up % | 78% |
| Status | Ongoing |

# Allergan BIFS Results – Silicone

## >7 year follow up, 78% follow up, relation to national norms unknown

| Changes in Signs and Symptoms | Primary Augmentation n = 1519 | Revision Augmentation n = 209 | Primary Reconstruction n = 250 | Revision Reconstruction n = 22 |
|---|---|---|---|---|
| Aching of the arms and legs and arthritis in the hands and wrists | 9.2% | 19.1% | 17.6% | 18.2% |
| Achy joints arthralgia | 10.1% | 16.7% | 25.6% | 22.7% |
| Arthritis | 5.3% | 12.9% | 18.8% | 9.1% |
| Burning, tingling, or numbness in the fingers, toes, hands or feet | 11.7% | 20.1% | 18.8% | 13.6% |
| Changes in ability to think or learn | 5.3% | 8.6% | 7.2% | 18.2% |
| Confusion | 2.2% | 3.8% | 2.4% | 9.1% |
| Difficulty Concentrating | 8.9% | 9.1% | 11.2% | 22.7% |
| Difficulty speaking or understanding what is being said | 1.9% | 3.8% | 2.4% | 18.2% |
| Difficulty walking or manipulating small objects | 1.0% | 1.0% | 2.4% | 4.5% |
| Dry Eyes | 10.3% | 17.7% | 20.0% | 9.1% |
| Dry Mouth | 4.2% | 7.2% | 10.8% | 4.5% |
| Extreme Muscle Weakness | 2.0% | 3.3% | 3.6% | 4.5% |
| Generalized aching or stiffness of the joints and muscles, especially after sleep or after periods of rest | 10.7% | 14.8% | 21.6% | 36.4% |
| Insomnia | 8.2% | 12.9% | 13.2% | 22.7% |
| Memory Loss | 6.8% | 8.6% | 11.2% | 13.6% |
| Raynaud's phenomenon | 4.8% | 5.3% | 2.8% | 9.1% |
| Swelling of Muscles | 0.9% | 1.9% | 4.8% | 0 |
| Weakness | 3.5% | 5.3% | 4.4% | 18.2% |

# Allergan BIFS Results – Saline

## >7 year follow up, 78% follow up, relation to national norms unknown

| Changes in Signs and Symptoms | Primary Augmentation n = 218 | Revision Augmentation n = 20 | Primary Reconstruction n = 12 | Revision Reconstruction n = 7 |
|---|---|---|---|---|
| Aching of the arms and legs and arthritis in the hands and wrists | 7.3% | 30.0% | 41.7% | 0 |
| Achy joints arthralgia | 9.6% | 10.0% | 25.0% | 57.1% |
| Arthritis | 4.1% | 10.0% | 33.3% | 14.3% |
| Burning, tingling, or numbness in the fingers, toes, hands or feet | 8.7% | 15.0% | 25.0% | 14.3% |
| Changes in ability to think or learn | 2.8% | 5.0% | 16.7% | 14.3% |
| Confusion | 0 | 5.0% | 0 | 0 |
| Difficulty Concentrating | 6.4% | 5.0% | 16.7% | 14.3% |
| Difficulty speaking or understanding what is being said | 0.9% | 0 | 0 | 14.3% |
| Difficulty walking or manipulating small objects | 0 | 5.0% | 0 | 14.3% |
| Dry Eyes | 8.3% | 10.0% | 33.3% | 42.9% |
| Dry Mouth | 4.1% | 5.0% | 16.7% | 0 |
| Extreme Muscle Weakness | 0.9% | 5.0% | 8.3% | 0 |
| Generalized aching or stiffness of the joints and muscles, especially after sleep or after periods of rest | 8.7% | 15.0% | 33.3% | 28.6% |
| Insomnia | 8.7% | 10.0% | 16.7% | 14.3% |
| Memory Loss | 4.1% | 10.0% | 25.0% | 0 |
| Raynaud's phenomenon | 5.5% | 15.0% | 16.7% | 14.3% |
| Swelling of Muscles | 1.4% | 0 | 16.7% | 0 |
| Weakness | 1.8% | 0 | 0 | 0 |

# Manufacturer Post Approval Studies

| | Study | Redesign |
|---|---|---|
| **Allergan** | Large Post Approval Study | Breast Implant Follow up Study (BIFS) |
| | Core Study Continuation | N/A |
| **Mentor** | Large Post Approval Study | GLOW Combined Cohort |
| | Core Study Continuation | N/A |
| **Sientra** | US-PAS | N/A |
| | Core Study Continuation | N/A |
| **IDEAL** | Core Study Continuation | N/A |

# Mentor - LPAS

- After 21% 3-yr follow up in the original LPAS study, Mentor redesigned study with a new enrollment study – ongoing patient enrollment
  - At time of FDA request, most patients in new study had not reached 1 year follow up
  - Mentor received warning letter due to inadequate enrollment in new enrollment study
- Therefore, Mentor has submitted systemic symptoms data from the original LPAS study with limited follow up at 7 years

| | Mentor LPAS |
|---|---|
| Silicone | Yes |
| Saline | Yes |
| Textured | Included |
| Comparator | Saline |
| Indication | Aug/Recon |
| Follow up Period | 6-7 years |
| Follow up % | 15% |
| Status | Redesigned |

# Mentor LPAS Results – Silicone

## >7 years, 15% follow up, relation to national norms unknown

| Changes in Signs and Symptoms | Primary Augmentation Original n = 26.173 (n=3,633) | Revision Augmentation Original n = 8,382 (n=1,115) | Primary Reconstruction Original n = 5,023 (n=994) | Revision Reconstruction Original = 1,761 (n=301) |
|---|---|---|---|---|
| Persistent joint stiffness that lasts at least one hour, over a period of two weeks or longer | 274 (7.7%) | 121 (11.1%) | 137 (14.1%) | 50 (17.2%) |
| Persistent non-traumatic joint pain | 370 (10.4%) | 138 (12.7%) | 157 (16.2%) | 56 (19.3%) |
| Persistent joint swelling (more than 1 week) | 133 (3.7%) | 68 (6.3%) | 62 (6.4%) | 27 (9.3%) |
| Persistent muscle pain | 244 (6.9%) | 102 (9.4%) | 82 (8.5%) | 38 (13.1%) |
| Persistent sleep disorders at night, for example, waking up too early, not falling asleep for a long time, or awakening frequently | 717 (20.1%) | 313 (28.8%) | 286 (29.4%) | 94 (32.3%) |
| Persistent fatigue that kept you from working inside or outside the home | 136 (3.8%) | 69 (6.3%) | 48 (4.9%) | 23 (7.9%) |
| Fingers becoming unusually pale, numb, or uncomfortable in the cold | 369 (10.3%) | 128 (11.8%) | 116 (11.9%) | 28 (9.7%) |
| Excessively dry eyes or mouth | 233 (6.5%) | 130 (11.9%) | 131 (13.5%) | 47 (16.1%) |
| Persistent or recurrent tingling or numbness lasting at least several weeks | 156 (4.4%) | 65 (6.8%) | 64 (6.6%) | 24 (8.3%) |
| Episode of sudden visual loss or double vision | 71 (2.0%) | 15 (1.4%) | 23 (2.4%) | 1 (5.0%) |
| Persistent memory problems, difficulty concentrating on simple tasks, such as reading, television, etc. for at least 3 months. | 185 (5.2%) | 59 (5.4%) | 41 (4.3%) | 14 (4.9%) |
| Persistent weakness in your muscles lasting at least several weeks | 44 (1.2%) | 27 (2.5%) | 18 (1.9%) | 9 (3.1%) |

# Mentor LPAS Results – Saline

## >6 years, 12% follow up, relation to national norms unknown

| Changes in Signs and Symptoms | Primary Augmentation (n=101) | Revision Augmentation (n=11) | Primary Reconstruction (n=3) | Revision Reconstruction (n=2) |
|---|---|---|---|---|
| Persistent joint stiffness that lasts at least one hour, over a period of two weeks or longer | 8 (7.9%) | 3 (27.3%) | 0 (0.0%) | 0 (0.0%) |
| Persistent non-traumatic joint pain | 8 (7.9%) | 2 (18.2%) | 0 (0.0%) | 0 (0.0%) |
| Persistent joint swelling (more than 1 week) | 4(4.0%) | 2 (18.2%) | 0 (0.0%) | 0 (0.0%) |
| Persistent muscle pain | 8 (8.0%) | 8 (8.0%) | 0 (0.0%) | 0 (0.0%) |
| Persistent sleep disorders at night, for example, waking up too early, not falling asleep for a long time, or awakening frequently | 20 (19.8%) | 4 (36.4%) | 1 (33.3%) | 2 (100.0%) |
| Persistent fatigue that kept you from working inside or outside the home | 3 (3.0%) | 1 (9.1%) | 0 (0.0%) | 2 (100.0%) |
| Fingers becoming unusually pale, numb, or uncomfortable in the cold | 13 (12.9%) | 3 (27.3%) | 1 (33.3%) | 1 (50.0%) |
| Excessively dry eyes or mouth | 8 (7.9%) | 2 (18.2%) | 0 (0.0%) | 0 (0.0%) |
| Persistent or recurrent tingling or numbness lasting at least several weeks | 4 (4.0%) | 4 (4.0%) | 0 (0.0%) | 1 (50.0%) |
| Episode of sudden visual loss or double vision | 2 (2.0%) | 1 (9.1%) | 0 (0.0%) | 0 (0.0%) |
| Persistent memory problems, difficulty concentrating on simple tasks, such as reading, television, etc. for at least 3 months. | 3 (3.0%) | 3 (3.0%) | 0 (0.0%) | 0 (0.0%) |
| Persistent weakness in your muscles lasting at least several weeks | 1 (1.0%) | 1 (1.0%) | 0 (0.0%) | 0 (0.0%) |

# Manufacturer Post Approval Studies

| | Study | Redesign |
|---|---|---|
| **Allergan** | Large Post Approval Study | Breast Implant Follow up Study (BIFS) |
| | Core Study Continuation | N/A |
| **Mentor** | Large Post Approval Study | GLOW Combined Cohort |
| | Core Study Continuation | N/A |
| **Sientra** | US-PAS | N/A |
| | Core Study Continuation | N/A |
| **IDEAL** | Core Study Continuation | N/A |

# Sientra Post-Approval PMA Cohort Study

- Sientra ongoing US-PAS is only at 2 year time point at time of FDA request
  - Sientra received warning letter for insufficient follow up
- Sientra reported systemic symptoms from the Post-Approval PMA Cohort Study (PACS), which is the 10 year data from the original premarket Core Study

| | Sientra PACS |
|---|---|
| Silicone | Yes |
| Saline | No |
| Textured | Included |
| Comparator | None |
| Indication | Aug/Recon |
| Follow up Period | 10 years |
| Follow up % | 51% |
| Status | Complete |

# Sientra PACS Results – Silicone

## 10 Years, 51% follow up, relation to national norms unknown

| Changes in Signs and Symptoms | Augmentation Cohort (Primary and Revision) Original n = 1,479 (n=827) | Reconstruction Cohort (Primary and Revision) Original n = 309 (n=86) |
|---|---|---|
| **Muscle: muscle weakness/tenderness** | 18 (2.2%) | 1 (1.2%) |
| **Myalgias** | 3 (0.4%) | 0 (0.0%) |
| **Morning stiffness > 30 minutes** | 27 (3.3%) | 2 (2.3%) |
| **Rheumatoid Arthritis** | 14 (1.7%) | 0 (0.0%) |
| **Abnormal mental status** | 2 (0.2%) | 0 (0.0%) |
| **Pain: muscle weakness/tenderness** | 18 (2.2%) | 1 (1.2%) |
| **Chronic fatigue syndrome** | 6 (0.7%) | 0 (0.0%) |
| **Chronic malaise** | 0 (0.0%) | 0 (0.0%) |
| **Fibromyalgia: muscle weakness/tenderness** | 18 (2.2%) | 1 (1.2%) |
| **Dry eyes** | 45 (5.4%) | 5 (5.8%) |
| **Dry mouth** | 14 (1.7%) | 3 (3.5%) |
| **Sjögren's Syndrome** | 0 (0.0%) | 0 (0.0%) |
| **Raynaud's phenomenon** | 30 (3.6%) | 0 (0.0%) |

# Manufacturer Post Approval Studies

| | Study | Redesign |
|---|---|---|
| **Allergan** | Large Post Approval Study | Breast Implant Follow up Study (BIFS) |
| | Core Study Continuation | N/A |
| **Mentor** | Large Post Approval Study | GLOW Combined Cohort |
| | Core Study Continuation | N/A |
| **Sientra** | US-PAS | N/A |
| | Core Study Continuation | N/A |
| **IDEAL** | Core Study Continuation | N/A |

# IDEAL Post-Approval Study

- IDEAL PAS requirement was to follow core study patients to 10 years
- No requirement to collect systemic symptoms, but have to report referral to rheumatologist who have not been referred baseline at 1, 2, 3, 4, 7 years.

| | IDEAL Core |
|---|---|
| Silicone | No |
| Saline | Yes |
| Textured | No |
| Comparator | None |
| Indication | Aug |
| Follow up Period | 8 years |
| Follow up % | 94% |
| Status | Ongoing |

# IDEAL Post-Approval Study Results – Saline

## >8 Years, 94% follow up, relation to national norms unknown

| Cohort | CTD Sign/ Symptom | 1 Yr | 2 Yrs | 3Yrs | 4 Yrs | 7 Yrs | Cumulative rate |
|---|---|---|---|---|---|---|---|
| **Primary Augmentation** | Referral to board-certified Rheumatologist | 0.8% (3/382) | 1.3% (5/378) | 3.0% (11/371) | 3.6% (13/365) | 1.7% (6/344) | **7.8% (31/399)** |
| **Revision Augmentation** | Referral to board-certified Rheumatologist | 2.1% (2/96) | 5.3% (5/94) | 3.2% (3/94) | 3.3% (3/91) | 2.4% (2/83) | **9.7% (10/103)** |

# Conclusions

- The data from the PAS is limited by follow up and reporting issues.
- Differences in study protocols preclude any comparison between separate studies
- Symptoms consistent with the MDR reports and relevant to BII have been observed in these studies, although relation to national norms is unknown


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# Panel Deliberations – Question 1

1. Please discuss how to utilize breast implant registries for data generation characterizing longitudinal outcomes to better inform BIA-ALCL and BII patient care.

    a. Please list the highest priority questions to be addressed using breast implant registries.
    b. Please consider whether modifications to the existing registries are needed to address these questions. If so, what modifications do you recommend?
    c. Please discuss whether additional policies should be implemented such as mandatory reporting to registries, post-market surveillance requirements, etc. to promote data collection and analysis.

# Panel Deliberations – Question 2

2. Shortcomings cited by some people regarding the PROFILE registry and NBIR include data entry by physicians, limited data access, and data gathered being limited to reoperations. Others consider these shortcomings to be things that promote high quality, consistent data collection.

   a. In light of the high priority questions identified above to be addressed using breast implant registries, please discuss the extent to which each of the questions requires breadth (e.g. data entry by all, collection of all information) versus depth (e.g. data entry limited to certain individuals, collection of specific information).

   b. Please make recommendations on what information should be collected to address each of the high priority questions identified above.

# Panel Deliberations - Question 3

3. Some have identified implant surface texture as one modifiable risk factor for developing BIA-ALCL. While the majority of patients who develop BIA-ALCL have had textured implants, and most cases reported in the literature describe individuals who have had textured implants, there have been reports of BIA-ALCL in patients with smooth-surfaced implants and many reports do not include the surface texture of the implant at the time of diagnosis. The denominator for the number of textured and smooth implants in the U.S. is also not known to determine whether relatively more cases are observed with one implant type versus another implant type. Please discuss the following issues:

   a. Steps that should be taken to characterize the implant characteristics and patient factors associated with BIA-ALCL risk.
   b. Whether the benefit/risk profile for textured and smooth implants are different.
   c. What information breast implant manufacturers should report regarding number of implants placed in order to assess if there are certain breast implant characteristics affecting BIA-ALCL risk.

# Panel Deliberations – Question 4

4. In preparation for this advisory committee meeting on breast implants, FDA asked each breast implant manufacturer to provide its long-term data regarding a constellation of breast implant illness symptoms. FDA conducted this exercise because while there is not sufficient evidence to show an association between breast implants and connective tissue disease ***diagnoses***, there are numerous breast implant patients convening on social media to discuss a wide variety of ***symptoms*** that they are experiencing, and we have received an increasing number of Voluntary MDRs reporting these symptoms. While FDA doesn't have definitive evidence suggesting breast implants are associated with these conditions, we are looking to gain a full understanding of this issue to communicate risk, minimize harm, and help in the treatment of affected patients. Please discuss the following:
    a. Steps that should be taken by all stakeholders to characterize implant characteristics and patient factors to better understand the risk of a patient experiencing symptoms consistent with BII.
    b. Potential basic research questions warranting consideration to determine potential mechanisms of causation or association between breast implants and symptoms of breast implant illness, and, if present, the recommended studies (e.g., genetic, immunological, in situ allergy testing prior to and after implantation).
    c. How to characterize the relative risk for symptoms of breast implant illness (considering the wide variety of symptoms) in breast implant recipients compared to the general population.

# Panel Deliberations – Question 4 cont.

4. While FDA doesn't have definitive evidence suggesting breast implants are associated with Breast Implant Illness related symptoms, we are looking to gain a full understanding of this issue to communicate risk, minimize harm, and help in the treatment of affected patients. Please discuss the following:

   d. The work-up and evaluation of patients with breast implants possibly experiencing symptoms of breast implant illness and how this information should be used to inform both individual patient treatment decisions as well as our overall understanding of this issue.

   e. The extent of work-up and factors to be considered when breast implant removal surgery as a treatment for symptoms of breast implant illness is contemplated.

   f. Postoperative information that should be captured regarding patients who undergo breast implant removal surgery for preoperative symptoms of breast implant illness.

   g. Opportunities to leverage existing social media platforms and other technologies, e.g., artificial intelligence, text mining, mobile apps, and digital health, to collect and analyze data on BII symptoms.