



## **Postmarket Studies of Silicone Breast Implants**

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General and Plastic Surgery Devices Panel

Gaithersburg, MD

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- **Mentor's top priority has been and always will be patient safety**
- **We remain committed to investing in research aimed at further enhancing these medical devices and advancing surgical procedures to optimize patient outcomes**
- **We sincerely appreciate the opportunity to participate in this panel meeting and contribute ideas for future postmarket surveillance of silicone breast implants**

## **Objective of Post-Approval Studies**

**“to help assure continued  
safety and effectiveness of the approved device.”**

*(<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/PostApprovalStudies/ucm135263.htm>)*

**Mentor is fully committed to working with FDA  
to ensure that this objective is met.**

## **Post-Approval Clinical Studies for MemoryGel® Breast Implants**

- **Prospective, multi-center, clinical trials**
  - **MemoryGel® Core (1,008 total patients enrolled, 10yr)**
  - **MemoryGel® Large PAS (41,900 gel+1,000 saline enrolled, 10yr)**
- **Physician visits**
- **Patient questionnaires (Large PAS only)**
- **Very wide range of study endpoints**
- **Annual updates provided to FDA**

## Findings

*“The most frequent complications and adverse outcomes experienced by breast implant patients include capsular contracture, reoperation, and implant removal (with or without replacement).”*

[FDA White Paper (6/22/2011)]

Comparison of Cumulative Incidence of Complications: Core/PAS

Objectives	8 Years - Primary Augmentation	3 Years - Primary Augmentation		3 Years - Primary Reconstruction	
	Core	Core	Large PAS	Core	Large PAS
Capsular Contracture (III/IV)	10.9% (8.5-13.9)	8.4% (6.4-11.1)	5.3% (4.7-5.9)	9.3% (6.2-13.9)	9.1% (7.7-10.9)
Reoperation	20.1% (17.0-23.8)	15.3% (12.6-18.7)	10.8% (10.1-11.6)	26.2% (21.2-32.2)	20.4% (18.5-22.5)
Device Removal	7.3% (5.3-9.9)	4.6% (3.1-6.7)	5.0% (4.5-5.6)	12.6% (9.0-17.4)	13.5% (11.8-15.3)

## Findings

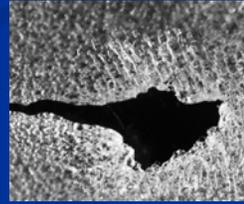
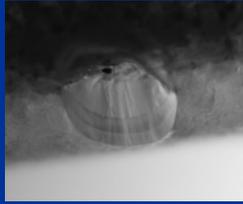
- “Reoperation for any reason” includes both:
  - device-related
    - contracture: 30% of all reoperations through 8 years  
*[primary augmentation]*
  - non-device-related
    - size change: 14% of all reoperations through 8 years  
*[primary augmentation]*
    - hypertrophic scarring: 11% of all reoperations through 8 years  
*[primary augmentation]*

## Findings

- Despite significant rates of reoperation
  - **satisfaction rates remain very high**  
(and similar for all study cohorts)
    - 97.5% of primary augmentation patients would have the surgery again
    - 97.4% of all reoperation patients indicated that they would have the surgery again

## Understanding Breast Implant Device Failure (Rupture)

- Source: Device Failure studies examining devices returned (worldwide)
- Lifetime product warranty ensures high return rate
- Majority of failures (63%) identified to have sharp instrument damage



## Detecting Breast Implant Rupture

- MRI is considered the most effective method for detecting rupture
- Current recommendations: start at 3 years, then every 2 years
- Estimated rupture incidence for primary augmentation at 3yr = 0.5%
- Patient compliance with recommendations are low (Large PAS)
- Of patients with suspected rupture identified by MRI (Core), only 29% opted to undergo reoperation for rupture in the 12 months following
- Surgeons have recommended revisiting these recommendations (McCarthy CM, Pusic AL, Kerrigan CL. 2008. *Plast. Reconstr. Surg.* 121(4):1127-1134.)

## Challenges of Current Large PAS

- Achieving adequate follow-up rates
- “The greater the deviation from standard practice in Post Approval Studies, the greater the challenges to be expected” :
  - Frequency of follow-up not part of some standard practices  
*[SBI Pts.: follow-up past 1 year is not standard practice for most]*
  - “Procedures or assessments beyond standard practice”  
*[SBI Pts.: 27p questionnaire in current Large PAS “arduous” & “intrusive”]*
  - “Length of study”  
*[SBI Pts.: 10yr duration is well beyond follow-up standard practice]*

*Todd Fonseca (Senior Clinical Research Director, Medtronic) at the June 2009  
FDA PAS Workshop*

## Follow-Up of Breast Implant Patients

- Young *et al.* 2004 explored “the reasons women did not schedule or keep follow-up appointments recommended by their surgeons”

### Finding:

- “the main reason for non-compliance is an absence of problems with implants”

Source: Young, V.L. *et al.* 2004. *Aesthetic Surgery Journal* 24:229-243.

## Strategies Used to Increase Follow Up

- “Dear Patient” letters from their physicians
- FDA Letters to Investigators
- >40,000 FDA letters to patients through investigators
- Modification/updating of patient study website
- FDA participation at society meetings to reinforce physician involvement to increase patient follow up

**FUTURE**

13

## Key Principles

- Different PAS objectives can be best addressed with:
  - different numbers of patients
  - different data sources
- Need to critically evaluate which endpoints already addressed (*e.g.*, expert panel reviews & published epidemiology studies)
- Focus resources (FDA, sponsor, physicians, patients) on remaining endpoints

## 12 Objectives of Ongoing Large PAS

1. Local Complications
2. Connective Tissue Disease (CTD)
3. Rheumatological Signs & Symptoms
4. Neurological Disease
5. Neurological Signs & Symptoms
6. Offspring
7. Reproductive
8. Lactation
9. Cancer
10. Suicide
11. Mammography
12. MRI Compliance & Results

## Myriad of Available Data Sources

- Medical literature (ongoing monitoring)
- Expert panel findings
- Continuation of prospective “Core” clinical trial (10 yr)
- Continuation of prospective “Continued Access” if applicable (10 yr)
- Registries (FDA Executive Summary-Table 7, T.O.P.S.)
- Administrative health databases
- Postmarket surveillance data (MDR & non-MDR)

## Promising Initiatives

- MDEpiNet

“to develop innovative methods in the medical device world to improve and enhance the understanding of device performance”

- Sentinel Initiative

“a national, integrated, electronic system (the Sentinel System) for monitoring medical product safety”

## Approach Going Forward

Objectives	Recommendation
Local Complications & Known Common Adverse Events	<i>Use Core and Continued Access studies with geographically diverse sites (10yr), Device Failure Study</i>
Connective Tissue Disease (CTD)	<i>Addressed by expert panels/literature/registries/meta-analyses</i>
Rheumatological Signs & Symptoms	<i>Use Core and Continued Access studies</i>
Neurological Disease	<i>Addressed by expert panels/literature/registries/meta-analyses</i>
Neurological Signs & Symptoms	<i>Use Core and Continued Access studies</i>
Offspring	<i>Addressed by expert panels / literature / registries</i>
Reproductive	<i>Addressed by expert panels / literature / registries</i>
Lactation	<i>Addressed by literature</i>
Cancer	<i>Addressed by expert panels / literature (ALCL ongoing)</i>
Suicide	<i>Addressed by literature / registries</i>
Mammography	<i>Use Core &amp; Adverse Event Reporting</i>
MRI Compliance & Results	<i>Use Core (results) &amp; Continued Access (compliance)</i>
Effectiveness	<i>Use Core study</i>

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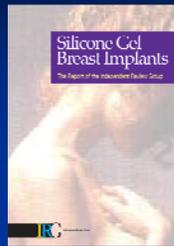
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## “Real World” Data Going Forward

- Objective of PAS: to evaluate the *real world* and long-term performance of devices after market approval
- Numerous examples of <20 study sites for pivotal trials associated with PMAs listed on FDA's Post-Approval Studies web page
- MemoryGel® Core study = 41 sites geographically distributed with 10yr follow-up
- Primarily private practice (non-academic) sites



## CTD Addressed by Expert Panels



IRG



NSP



IOM

### Example – Independent Review Group

- “no epidemiological evidence for any link between silicone gel breast implants and any established connective tissue disease”
- “cannot justify recommending further epidemiological studies to investigate this hypothesis”

## FDA Guidance & Literature

- *“Is there any other source of data (e.g., ... **literature**) ... or a combination thereof, that may be used to address the public health question?”*

*[FDA Guidance – 522 Postmarket Surveillance Studies]*

- *“We recommend you provide literature information specific to the subject breast implant type. However, **if no device type-specific information is available, you should provide pooled data** (e.g., silicone gel and saline data) from the literature.”*

*[FDA Guidance – Breast Implant PMAs]*

## CTD Addressed by Literature

- Berner et al. 2002
- Brinton et al. 2004
- Breiting et al. 2004
- Burns et al. 1996
- Edworthy et al. 1998
- Englert et al. 1996
- Englert et al. 2001
- Friis et al. 1997
- Fryzek et al. 2007
- Gabriel et al. 1994
- Gaubitz et al. 2002
- Giltay et al. 1994
- Goldman et al. 1995
- Hennekens et al. 1996
- Hochberg et al. 1996
- Hölmich et al. 2003
- Janowsky et al. 2000 (meta-analysis)
- Jensen et al. 2001
- Kjølner et al. 2001, 2004
- Laing et al. 2001
- Lee et al. 2011
- Lipworth et al. 2004 (meta-analysis)
- Nyrén et al. 1998
- Park et al. 1998
- Sánchez-Guerrero et al. 1995
- Schusterman et al. 1993
- Strom et al. 1994
- Weisman et al. 1988
- Wells et al. 1994
- Williams et al. 1997

N>38,000 unique patients

## Offspring Addressed by Literature

- Kjølner (2002, 1998) - Denmark (2,854 children)
- Signorello et al. (2001) - Sweden (5,874 children)
  - Findings:  
Either lower or no difference in adverse health endpoints in children born after (vs. before) cosmetic breast implant surgery

# Breast Cancer Addressed by Literature

## *Published Epidemiology Results (2000-present)*

>625,000 Total Patient-Years of Follow-Up

Study	Country	Total F/U (pt. yr.)	Mean F/U (yr.)	Risk Estimate (95% C.I.)
Brinton et al. 2000	U.S.	96,675	12.9	0.89 (0.8-1.1)
Pukkala et al. 2002	Finland	18,014	8.3	0.5 (0.2-1.0)
Brisson et al. 2006	Canada	366,608	14.9	0.64* (0.53-0.79)
Deapen et al. 2007	U.S.	42,314	15.5	0.69* (0.50-0.93)
Lipworth et al. 2009	Denmark & Sweden	103,565	16.6	0.73* (0.58-0.90)

\* Statistically  
significantly  
lower

# Other Endpoints Addressed by Literature

## *Neurological Disease*

- Brinton et al. (2004) 87,199 person-yr
- Englert et al. (2001)
- Winther et al. (2001) 24,034 p-yr
- Fryzek et al. (2007) 37,084 p-yr
- Nyren et al. (1998) 59,592 p-yr
- Hennekens et al. (1996) 10,830 p-yr
- Goldman et al. (1995) >1,416 p-yr
- Sanchez-Guerrero et al. (1995)  
11,170 p-yr
- Strom et al. (1994)

## *Lactation*

- Cruz and Korchin 2010

## *Other Cancers*

- Lipworth et al. (2009) 103,565 p-yr
- Deapen et al. (2007) 42,314 p-yr
- Brisson et al. (2006) 366,608 p-yr
- Pukkala et al. (2002) 18,014 p-yr

## *Suicide*

- Brinton et al. (2006) 248,952 p-yr
- Villeneuve et al. (2006) 277,289 p-yr
- Jacobsen et al. (2004) 31,842 p-yr
- Pukkala et al. (2003) 22,272 p-yr
- Koot et al. (2003) 39,735 p-yr
- Brinton et al. (2001) 187,483 p-yr

## Enhanced Postmarket Surveillance

• **Objective:** Identification of trends and safety signals (public health question)

- Monitor complaints and adverse events data (both MDR and non-MDR)
- Track usage through device tracking database to provide denominator
- Active monitoring and annual reporting of published literature (Case Reports & Epidemiology studies)
- Check for potential safety signals identified in case reports in the linked complaints/adverse events/device tracking data

• **Output:** Potential safety signal identified

• **Action:** Design targeted study in coordination with FDA to address

## Detecting Rare Signals

### Example – ALCL

- Initially identified by case reports in literature
- Followed by epidemiology study in Netherlands
- Further case reports and investigation
- Checked for occurrence in adverse event and complaints
- Expert panel convened
- Regulatory agency advisories issued
- Establishment of registry of patients with ALCL

Outcome: Successful identification and addressing of an extremely rare signal with our proposed approach to postmarket surveillance

## Summary

- In our view, many of the objectives of the original Large PAS have been addressed by literature, registries and expert panels
- Core (and Continued Access) studies should be continued through 10 years to provide both long-term outcomes and “real world” experience
- Enhanced post market surveillance is recommended to detect safety signals (public health issues)
- If safety signals are identified, Mentor proposes designing and implementing targeted studies in collaboration with FDA

**Thank You**

31