The Story of Silicone:
A Collision Course of
Breast Implants and the FDA

Akash Chandawarkar, MD
@AChandMD
DISCLOSURES

• Cypris Medical – Clinical Consultant (Stock Options)

• Not an regulatory expert, whatsoever!
Why this topic?

• Important to consider thresholds for risk/benefit with aesthetics

• History repeats itself

• The effects of historical events have lasting impact

• The power of the media vs. science is a recurrent theme (e.g. social media)
What is Silicone?

1930s-1940s

Frederick Kipping, PhD
What is Silicone?

Polydimethylsiloxane (PDMS)

1930s-1940s
What is Silicone?

Father of Silicones

Dr. J. Franklin Hyde in his laboratory

Dow Corning historic photo
Early Uses of Silicone

1943

“produced the grease that helped win the war”
Early Uses of Silicone

Chemically inert = biologically inert
Early Uses of Silicone

“...experiments showed that silicones as a group have a very low order of toxicity and so present an exceedingly minor hazard... Silicone resins are physically inert and present no hazards.”

Rowe VK, Spencer HC, Bass SL., J Indust Hygiene and Toxicology. 1948
“Use as permanent subcutaneous prostheses seems to be one of the greatest possibilities because of the silicones’ inertness, and there is hope of success.”
Early Medical Uses of Silicone

PERMANENT ARTIFICIAL (SILICONE) URETHRA

R. ROBERT DE NICOLA

From the Department of Surgery, Kadlec Hospital, Richland, Wash.

The case reported below is presented for two reasons: 1) for the unusual history of prolonged urethral mutilation resulting in a totally destroyed posterior urethra; and 2) this is the first report in the literature of apparently successful replacement of the human male urethra by artificial means.

A Father's Last-Chance Invention Saves His Son

Condensed from Town Journal
Howard La Fay

Little "Casey" and countless other infants will live because of John Holter's desperate persistence and patient skill
Breast prostheses

“Sponge” prostheses:
- Ivalon (polyvinyl alcohol)
- Polistan (polyethylene)
- Etheron (polyurethane)
- Hydron (polyglycomethacrylate)

Breast prostheses

Thomas Cronin  Frank Gerow

Braley SA. PRS 1973

1961
Breast prostheses
Breast prostheses
Brief History of US Regulation

1906: Meat Inspection Act and Pure Food and Drugs Act passed (T. Roosevelt)
1927: Bureau of Chemistry reorganized as Food, Drug, and Insecticide Administration (later FDA)
1938: Federal Food, Drug, and Cosmetic Act passed (FDR)
1958: Delaney Clause added to Food Additive Amendment
1976: Medical Device Amendments passed
Brief History of US Regulation

1906: Meat Inspection Act and Pure Food and Drugs Act passed (T. Roosevelt)
- Federal inspection of food products and medicines
- Halted sale of contaminated foods and called for truth in labeling

1927: Bureau of Chemistry reorganized as Food, Drug, and Insecticide Administration (later FDA)

1938: Federal Food, Drug, and Cosmetic Act passed (FDR)

1958: Delaney Clause added to Food Additive Amendment

1976: Medical Device Amendments passed
### Brief History of US Regulation

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1906</td>
<td>Meat Inspection Act and Pure Food and Drugs Act passed (T. Roosevelt)</td>
</tr>
<tr>
<td>1927</td>
<td>Bureau of Chemistry reorganized as Food, Drug, and Insecticide Administration (later FDA)</td>
</tr>
<tr>
<td>1938</td>
<td>Federal Food, Drug, and Cosmetic Act passed (FDR)</td>
</tr>
<tr>
<td>1958</td>
<td>Delaney Clause added to Food Additive Amendment</td>
</tr>
<tr>
<td>1976</td>
<td>Medical Device Amendments passed</td>
</tr>
</tbody>
</table>
Brief History of US Regulation

1906: Meat Inspection Act and Pure Food and Drugs Act passed (T. Roosevelt)
1927: Bureau of Chemistry reorganized as Food, Drug, and Insecticide Administration (later FDA)
1938: Federal Food, Drug, and Cosmetic Act passed (FDR)
   - Cosmetics and med devices under FDA control
   - Req to show new drugs to be safe prior to marketing
   - Limited to “adulteration” and “misbranding” for medical devices
1958: Delaney Clause added to Food Additive Amendment
1976: Medical Device Amendments passed
Brief History of US Regulation

1906: Meat Inspection Act and Pure Food and Drugs Act passed (T. Roosevelt)
1927: Bureau of Chemistry reorganized as Food, Drug, and Insecticide Administration (later FDA)
1938: Federal Food, Drug, and Cosmetic Act passed (FDR)
1958: Delaney Clause added to Food Additive Amendment
   - “… no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal”
   - ZERO tolerance; any dose level
   - In place until 1996
1976: Medical Device Amendments passed
Regulatory Implications for Silicone: Delaney Clause

Sarcomas Induced in Rats by Implanting Cellophane.

B. S. OPPENHEIMER, ENID T. OPPENHEIMER, AND A. P. STOUT.
From the Department of Cancer Research and the Department of Surgery, College of
Physicians and Surgeons, Columbia University, New York.


Malignant Tumors Resulting from Embedding Plastics in Rodents

B. S. Oppenheimer, Enid T. Oppenheimer, Arthur Purdy Stout, and I. Danishefsky
Institute of Cancer Research,
College of Physicians and Surgeons,
Columbia University, New York City


Further Studies of Polymers as Carcinogenic Agents in Animals*

B. S. OPPENHEIMER, ENID T. OPPENHEIMER, I. DANISHEFSKY,
ARTHUR PURDY STOUT, AND FREDERICK R. EIRICH


Solid State Carcinogenesis
Brief History of US Regulation

1906: Meat Inspection Act and Pure Food and Drugs Act passed (T. Roosevelt)
1927: Bureau of Chemistry reorganized as Food, Drug, and Insecticide Administration (later FDA)
1938: Federal Food, Drug, and Cosmetic Act passed (FDR)
1958: Delaney Clause added to Food Additive Amendment
1976: Medical Device Amendments passed
## Regulatory Implications for Silicone: Medical Device Amendments

### Medical Devices Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Risk</th>
<th>Examples</th>
<th>Safety / Effectiveness Controls</th>
<th>Regulatory Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Low</td>
<td>Tongue depressor, hospital beds</td>
<td>General Controls - With Exemption - Without Exemption</td>
<td>Self Registration Or 510(k)</td>
</tr>
</tbody>
</table>
| II    | Medium| Absorbable suture, blood pressure cuffs | General controls - With Exemption - Without Exemption Special controls - With Exemption - Without Exemption | • Most class II devices are approved under a 510(k) pre-market notification submission.  
• Few devices of class II are approve under PMA  
• 10-15% devices require clinical trial |
| III   | Highest| Implantable pacemaker, coronary stent | General controls Special controls Pre-market authorization             | Pre-market approval (PMA)  
Almost all require clinical Data |

**FDA:**  
“Grandfathered” in as Class II
Mounting “Evidence” that Silicone Implants are Harmful

Kumagai et al., Arthritis Rheum 1979

Augmentation Mammaplasty Associated with a Severe Systemic Illness
Barry F. Uretsky, M.D., J. James O’Brien, M.D., Eugene H. Courti ss, M.D., and Martin D. Becker, M.D.
Uretsky et al., Ann Plast Surg 1979

Van Nunen et al., Arthritis Rheum 1982

POST-MAMMOPLASTY CONNECTIVE TISSUE DISEASE
SHERYL A. VAN NUNEN, PAUL A. GATENBY, and ANTONY BASTEN

Case Report
POST-MAMMOPLASTY HUMAN ADJUVANT DISEASE
By M. A. Byron1, V. A. Venning2, and A. G. Mowat3
1Department of Rheumatology, Nuffield Orthopaedic Centre, Headington, Oxford OX3 7LD
2Department of Dermatology, Churchill Hospital, Headington, Oxford

Byron et al., Br J Rheum 1984

Adjuvant Breast Disease: An Evaluation of 100 Symptomatic Women with Breast Implants or Silicone Fluid Injections
Britta Ostermeyer-Shoaib, Bernard M Patten and Dick S Calkins1
Department of Neurology, Baylor College of Medicine and 1Krug Life Science, Houston, TX, USA
(Received for publication on December 7, 1992)

Ostermeyer-Shoaib et al., Arthritis Rheum 1982
"We have hordes of people who are willing to compromise. The world needs more people [like me] who won’t compromise"

"an epidemic of cancer afflicting thousands of unsuspecting women harboring the devices"

"This isn’t just about breast implants; this is about the empowerment of women!"
Ensuing Legal Battles

*Corley vs. Dow Corning* (1977): $170,000 award for rupture, pain, suffering
  Could not cite successful FDA review because had not happened

*Stern vs. Dow Corning* (1984): $1.7M award, $1.5 of which is punitive
  Gag order based on the fact that documents not representative of entire body of knowledge about silicone implants (later violated)

*Hopkins vs. Dow Corning* (1991): $7.3M award, $6.5M of which is punitive
  “Crossed fingers memo”
Scientific Evidence that Implants Are Safe

1. 1948: Dow Chemical toxicologists: silicone polymers well tolerated following injection, ingestion, and inhalation ($)
2. Studied in labs of leading surgeons and reported in respected journals ($)
3. 1974-1986: prospective cohort study from USC showed diminished (NS) incidence of breast cancer in patients with breast implants
4. 1970s: gel bleed showed silicone visible only on electron microscopy without clinical significance
5. 1980s: Immuno-toxicology studies showed negligible silicone influence on immunity
6. Cohort study and case control study show normally expected rates of connective tissue diseases
7. Experts in tumor biology and immunology explained to FDA why solid state carcinogenesis has nothing to do with human condition and that there are no validated reports of human adjuvant disease
# Regulatory Implications for Silicone: Medical Device Amendments

## Medical Devices Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Risk</th>
<th>Examples</th>
<th>Safety / Effectiveness Controls</th>
<th>Regulatory Pathway</th>
</tr>
</thead>
</table>
| I     | Low   | Tongue depressor, hospital beds | General Controls
- With Exemption
- Without Exemption                                                  | Self Registration
Or 510(k)                                              |
| II    | Medium| Absorbable suture, blood pressure cuffs | General controls
- With Exemption
- Without Exemption
Special controls
- With Exemption
- Without Exemption                                                  | • Most class II devices are approved under a 510(k) pre-market notification submission.
• Few devices of class II are approved under PMA
• 10-15% devices require clinical trial                              |
| III   | Highest| Implantable pacemaker, coronary stent | General controls
Special controls
Pre-market authorization                                                 | Pre-market approval (PMA)
Almost all require clinical Data                                     |

FDA: “Just kidding!”
You have 30 months to produce your data.
“Most of us know little about breast implants. We’ve seen the ads; we’ve heard the rumors about which celebrities have them and which don’t. But we don’t know anything about the dangers.”
Regulatory fallout

PMAs submitted (9):
- Dow Corning (2)
- Mentor (3)
- Inamed (1)
- Medical Engineering Corp/Surgitek (1)
- Cavon Corp (1)
- Bioplasty (1)

Advisory panel meeting: Nov 12-14, 1991 (Gaithersburg, MD)

Bioplasty seizure, July 1991
Moratorium

Nov 14, 1991: All PMA applications rejected – “none provided reasonable assurances that the devices were safe and effective under conditions of use described”; reserve availability for breast cancer reconstruction

Jan 6, 1992: Kessler asks for voluntary moratorium on further use of all silicone gel breast implants (including for reconstruction); emphasized FDA not urging to have removed

Feb 18, 1992: Advisory Panel meets again to consider new evidence

“How scientific is the FDA’s conclusion that no woman should have implants put in, and yet no woman should have them removed?
- Congresswoman Marilyn Lloyd

Apr 16, 1992: Kessler lifts moratorium; silicone gel implants limited to breast recon under approved protocol limitations
Path to Eventual Approval

March 1992: Allergan (McGhan) and Mentor only companies left after moratorium

Jan 8, 1993: Allergan and Mentor file safety and effectiveness for saline implants

May 1995: Dow Corning files for Ch 11 bankruptcy facing 20,000 lawsuits and 410,000 potential claims

July 1998: Dow Corning settles $3.2B from silicone implants to tens of thousands of claims

June 1999: Institute of Medicine release 400 page report concluding that silicone implants do not cause any major diseases by examining past research and other materials, conducting public hearings

Nov 1999: Mentor and Allergan receive approvals for saline implants for reconstruction and aug

Nov 2006: Allergan and Mentor receive conditional approval for silicone implants (15 years and 4 months after issuing call for PMAAs)

March 2012: Sientra gets approval for silicone gel implant
Connective Tissue Disease

The FDA has not detected any association between silicone gel-filled breast implants and connective tissue disease, breast cancer, or reproductive problems. In order to rule out these and other rare complications, studies would need to be larger and longer than those conducted so far.

www.fda.gov
Getting us here: ALCL
Getting us here: ALCL

Breast Implants: Update - Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

[Posted 03/21/2017]

AUDIENCE: Plastic Surgery, Oncology, Patient

ISSUE: FDA has updated its understanding of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) to reflect the agency’s concurrence with the World Health Organization designation of BIA-ALCL as a rare T-cell lymphoma that can develop following breast implants. At this time, most data suggest that BIA-ALCL occurs more frequently following implantation of breast implants with textured surfaces rather than those with smooth surfaces. BIA-ALCL is a rare condition; when it occurs, it has been identified most frequently in patients undergoing implant revision operations for late onset, persistent seroma. The exact number of cases remains difficult to determine due to significant limitations in world-wide reporting and lack of global implant sales data.

See the FDA Update for additional information, including a summary of Medical Device Reports and medical literature, and recommendations for patient care.
Getting us here: Breast Implant Illness
Establishment Labs Submits Investigational Device Exemption (IDE) Filing for Prospective Clinical Trial of Motiva Implants®

NEW YORK, Aug. 07, 2017 (GLOBE NEWSWIRE) — Establishment Labs, a global medical device company focused on aesthetic technologies with a strong emphasis on product development and innovation, announced today that it has submitted an Investigational Device Exemption (IDE) filing to the U.S. Food and Drug Administration (FDA) for its Motiva Implants®, the lead product in its portfolio of innovative aesthetic technologies. Upon acceptance, the IDE would enable the Company to initiate a clinical study in the U.S. to assess the safety profile and patient satisfaction of Motiva Implants.

“This is a very significant milestone for Establishment Labs and patient safety, and hopefully the start of many technologies that we can bring to market in the United States,” said Juan José Chacón-Quirós, CEO and founder of Establishment Labs. “Motiva Implants are already sold in over 60 countries worldwide and have been implanted more than 300,000 times over the past seven years. We are confident that a clinical study in the United States will confirm the safety profile we are seeing in all of our markets.”

The IDE submission for this Motiva Implants study proposes a single arm, multi-center study investigating female patients receiving primary breast augmentation, primary breast reconstruction, or revision surgery. Upon acceptance of the IDE, Dr. Caroline Glicksman, a board-certified plastic surgeon in the U.S., has agreed to lead the study as the principal.
What has happened since?

• 2006: Silicone implants back on market
  • Requirement of manufacturers for 10 year Post Approval Studies to maintain approval
What has happened since?

"Breast Implant Illness and Healing by Nicole". Facebook. Accessed 9/20/19
What has happened since?

September 2018

What has happened since?

November 2018
What has happened since?

December 2018

Watad A. Int J Epidemiol. 2018 Dec
What has happened since?

December 2018

Allergan's textured breast implants recalled by French authorities

More than 600 cases of cancer worldwide linked to a specific type of implant.

European CE marks are provided by accredited certification firms known as notified bodies. Until this week, CE marks for Allergan’s Microcell and Biocell textured surfaces were issued by a French notified body called LNE G-MED, which — unlike many notified bodies — is partially state-owned.

LNE G-MED was due to renew the CE marks as part of a five-yearly review, but did not. It wants to see further data from Allergan before re-issuing the safety certificate.

Allergan confirmed it had been forced to suspend European sales of products that no longer held a CE mark. It said it would continue to seek a renewed certificate from LNE G-MED, and planned to appeal if denied.
What has happened since?

March 2019

FDA issues warning letters to two breast implant manufacturers for failure to comply with post-approval study requirements

For Immediate Release
March 19, 2019
FDA Breast Implant Hearings
March 25-26, 2019

• Focus Areas:
  • BIA-ALCL
  • Breast Implant Illness
  • Surgical Mesh (ADM)
  • Silent Rupture Surveillance
FDA Breast Implant Hearings
March 25-26, 2019

• Day 1:
  • National and International Perspectives, Meeting Scope, Patient Perspective
  • Status of Industry Sponsored Breast Implant Studies and reports of BII and BIA—ALCL
  • The Use of Registries to Understand BII and BIA-ALCL
FDA Breast Implant Hearings
March 25-26, 2019

• Day 2:
  • Use of Surgical Mesh in Breast Reconstruction and Mastopexy
  • Utility of MRI for Breast Implant Silent Rupture Screening
  • Patient Education and Informed Consent
FDA Breast Implant Hearings
March 25-26, 2019
FDA Breast Implant Hearings
March 25-26, 2019

• Stakeholders: Industry
  • Efforts to improve PAS
  • Overall patient satisfaction
  • Relative rarity of ALCL, BII
FDA Breast Implant Hearings
March 25-26, 2019

- Stakeholders: Patients/patient advocates
  - Transparency of AE data
  - Insurance coverage of implant sequelae
  - Composition/ingredients of implants
  - Complete informed consent/checklist
  - (Ban of textured implants)
FDA Breast Implant Hearings
March 25-26, 2019

• Stakeholders: Professional societies (ASPS/ASAPS)
  • Facilitating patient choice
  • Commitment to collect data
    • PROFILE/NBIR
    • ANN
  • Efforts in ongoing and future research
  • Consideration of HRUS for implant rupture
FDA Breast Implant Hearings
March 25-26, 2019

• Asks from FDA to panel:
  • How to modify/utilize implant registries for BII/BIA-ALCL
  • Recommendations for next steps for characterization of BIA-ALCL incidence and risk factors
  • Methods for assessing and addressing BII
  • Risk/benefits of surgical mesh
  • MRI screening recommendations
  • Responsibilities for communicating breast implant risks and benefits to patients
FDA Breast Implant Hearings
March 25-26, 2019

• Panel discussions:
  • Salt loss method of texturing seems to have significant increased incidence of BIA-
    ALCL
  • Risk factors, genetics, commonalities between BII patients need to be studied
  • Registry maintenance is a large hurdle, but data is key
  • What are the benefits of mesh? Is there a good control group?
  • Is HRUS feasible? MRI recommendations have low compliance due to cost
  • Responsibility of informed consent lies with physician
FDA Breast Implant Hearings
March 25-26, 2019

• Panel prelim recommendations:
  • Easily understood consent form with BII/BIA-ALCL
  • Explant tissue should be analyzed by pathology
  • Establish criteria for “breast implant illness”
  • MRIs after 6 years may be more practical
  • No formal votes taken

• May 2010 official statement:
  • Labeling changes for manufacturers (possibly ingredient list, checklist, box warnings)
  • Changes to reporting of adverse events (ending summary reporting)
  • Expand participation in registries (PROFILE/NBIR)
  • No bans on any implants
Voluntary recall of BIOCELL
July 2019
Where do we go from here?

• Scientific discovery
• Database compliance
• Take care of affected patients
• Provide best informed consent and preventative measures for future patients
• All stakeholders at the table!
Breast Implant Illness: How Can We Help?

Patricia A McGuire, MD, Melinda J Haws, MD, Foad Nahai, MD, FACS


Published: 20 August 2019  Article history:

Breast Implant Illness: A Way Forward

Mark R. Magnusson, MBBS, FRACS
Rod D. Cooter, MBBS, PhD, FRACS
Hinne Rakhorst, MD
Patricia A. McGuire, MD
William P. Adams, Jr., MD
Anand K. Dova, BSc(Med), MBBS, MS, FRACS

Gold Coast, Queensland; and Sydney, New South Wales, Australia; St Louis, Mo.; and Dallas, Texas

Summary: The link between breast implants and systemic disease has been reported since the 1960s. Although many studies have looked at either supporting or refuting its existence, the issue still persists and has now been labeled “breast implant illness.” The rise of patient advocacy and communication through social media has led to an increasing number of presentations to plastic surgeons. This article summarizes the history of breast implants and systemic disease, critically analyzes the literature (and any associated deficiencies), and suggests a way forward through systematic scientific study. (Plast Reconstr Surg. 143: 74S, 2019.)