

Standards, Safety and Particulate Matter on Breast Implants: Bringing Data to the Discussion

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Preface

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The subject matter of this executive summary is of great interest to many plastic surgeons. I am a board-certified plastic surgeon with expertise in the science of breast implants and a breadth of experience in medical publication, research and analysis. I have no conflicts of interest with Sientra and was asked to review the in-depth analyses of testing performed by independent laboratories that assessed the presence of particulate matter on the surface of Sientra breast implants.

I reviewed the data and analyses in detail prior to submission to the FDA in December 2015. I have also reviewed the executive summary below, and it provides an excellent summary of the findings. The key conclusion from all of the testing and analyses is that **there is no increased risk to patients from any particulates on Sientra's breast implants**. The other key conclusions are:

1. The methodologies used in the analyses were sound and the testing identified none to very low levels of particulate matter.
2. The majority of particulates identified were almost exclusively components used in or during manufacturing of the breast implants.
3. The low level of particulates detected is small compared to, for example, the shedding from a laparotomy pad that a patient would be subjected to during any surgical procedure.
4. Typical breast implant practices, including breast pocket irrigation and irrigation of the implant itself prior to insertion, may further reduce the already low level of particulates that may be present on the surface.
5. There was NO evidence that any of the identified particulates would cause any related adverse events.

Introduction

The purpose of this paper is to provide a summary of particulate testing methodology and results related to Sientra breast implants, as well as to present long-term clinical study safety data, literature review results and clinical perspective, all of which confirm the continued safety of Sientra's breast implants. In September 2015, international regulatory agencies temporarily suspended the manufacturing and distribution of medical devices made by Silimed, based on an anonymous complaint regarding particulates found on the surface of some of Silimed's implants. In January 2016, ANVISA, the Brazilian regulatory authority, subsequently authorized Silimed to market and use its products concluding that the presence of particles in silicone implants do not represent additional risk.¹

Due to these events, Sientra voluntarily placed a hold on the sales of its devices in the United States and contracted independent third-party laboratories to conduct additional testing on their breast implants. Based on the analytical findings of the independent testing, along with the available toxicity data and existing regulatory safety standards for the various materials identified, margins of exposure (MOE) using worst-case assumptions were derived. The culmination of the extensive independent testing and analyses that was presented to the FDA revealed that Sientra's implants continue to meet established safety standards and do not pose an increased risk to patients. The authors of this white paper reviewed and approved the Risk Analysis submitted to FDA. This paper will summarize the testing and results as well as present clinical study safety data and our own clinical experience to confirm the continued safety of Sientra's breast implants.

What are particulates?

“Particulate matter” refers to particles that are present on a device.²

- Sterile particulate matter is found on all implantable medical devices. Manufacturing any implants (including all breast implants, orthopedic, cardiovascular, dental) that are completely free of particles is challenging because the presence of particulates remains unavoidable, even with current well-controlled manufacturing processes.³
- Particulate matter can come from many sources during device manufacturing and processing, including the raw materials, manufacturing processes and environment, product packaging, or the device itself.
- Although present on all types of implants, particle count limits are not defined for most implants. No standards or limits for particulates on the surface of breast implants have been established.

What testing was performed?

Two independent third-party laboratories employed two different test methods, the “rinse/wash” method and the “tape-lift” method, on 40 sterile, textured-surface Sientra Silicone Gel Breast Implants (20 implants per method). Textured-surface devices were tested as worst-case due to their irregular and increased surface area with the addition of the textured surface.

Rinse/Wash Method

Devices were rinsed with deionized water, then filtered through a tared 0.45 micron (μm) silver membrane filter. The dry membrane filters with captured particles were weighed to measure the quantity of particulate and inspected by optical microscopy using a range of magnifications to characterize the particulate detected, if any, followed by identification of the type of material.

Tape-Lift Method

Two sided carbon tape was used to lift off potential particles in multiple locations on each implant. The tape-lift method was selected because it had been used in the original TÜV SÜD analysis of Silimed implants. However, no data exists to support the appropriateness of this method for detecting particles on the surface of medical devices. This method appears to be meant for use in the aerospace industry – not for the sampling of medical devices. Due to the nature of this method, uncertainties exist about whether the tape is actually lifting materials from the medical device that would not be otherwise dislodgeable, e.g., “particles” of surface texturing. The tape-lift samples were characterized using Scanning Electron Microscopy (SEM) and Energy Dispersive X-Ray (EDX) Analysis techniques. Microscopic examination was performed at a magnification of 100x. It is estimated that this magnification allowed for the detection of virtually all particles down to approximately 5 microns in size and some particles down to approximately 2 microns. As a comparison, a human red blood cell is approximately 5 microns in diameter, and the cross-section of a human hair is approximately 17 microns as depicted in Figure 1.

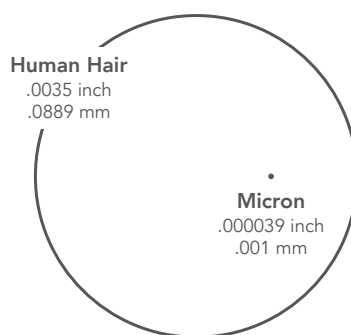


Figure 1. The cross-section of a strand of hair compared to a micron.

What were the results?

The results identified a low level of sterile, microscopic particulates via the two test methods. From the rinse method, the results showed particulate matter on 11 of 20 implants. Ten of those were comprised of small cotton fibers and one device had one protein particle. The protein particle was extremely small at 160 micrograms (one microgram = 1 millionth of one gram) and the sterilization process would denature any protein and would therefore have no enzymatic activity.

A greater number of particles were identified with the tape-lift method versus the rinse method, with particles characterized as fibrillar and non-fibrillar particles present on all 20 implants as summarized in Table 1.

Table 1. Types of Particulate Matter Detected via Tape-Lift Method

| 95% Non-Fibrillar <i>a solid particle with an irregular shape</i> | 5% Fibrillar <i>a solid particle with an elongated shape & parallel edges</i> |
|---|---|
| Polydimethylsiloxane (PDMS) <i>Biocompatible polymer makes up elastomers and gels</i> | Textile (cotton) <i>Chemically inert, natural and synthetic fibers</i> |
| Organic <i>Dominated by carbon</i> | Cellulose <i>Natural polymer, organic molecule</i> |
| Particulates Not Otherwise Specified (PNOS) <i>Too small and not definitively identifiable via chemical characterization</i> | Glass-like <i>Biocompatible, inert, synthetic vitreous fibers</i> |

Literature Review

A comprehensive literature review was also conducted in order to further evaluate the potential biological response associated with each of the types of particulate matter identified during the testing of the 40 implants and to identify published standards. No publications were found that revealed a recognized and proven association between adverse events and particulates on breast implants.

Clinical Performance

Sientra breast implants have been studied extensively. The Core Study is a 10-year, prospective, multicenter clinical trial that commenced in November 2002 and enrolled 1,788 patients for primary augmentation, revision-augmentation, primary reconstruction, and revision-reconstruction. In March 2012, the FDA approved the Sientra breast implants based on clinical data through three years from the largest pivotal silicone gel breast implant study to date. Currently, eight years of safety and effectiveness data are available for review, and these results provide further assurance of the long-term safety of Sientra breast implants (Table 2).⁴

Table 2. Primary Augmentation & Primary Reconstruction Key Complications through 8 years by Patient Kaplan-Meier Risk Estimates and 95% Confidence Intervals

| Complication | Primary Augmentation (N=1,116) | Primary Reconstruction (N= 225) |
|-------------------------------|--------------------------------|---------------------------------|
| Rupture – Overall | 4.9% (3.3%, 7.2%) | 1.4% (0.2%, 9.3%) |
| Rupture – MRI Cohort | 7.2% (4.8%, 10.8%) | 3.0% (0.4%, 19.6%) |
| Capsular Contracture (III/IV) | 11.2% (9.3%, 13.4%) | 12.8% (8.6%, 18.8%) |
| Reoperation | 20.7% (18.3%, 23.4%) | 46.3% (39.6%, 53.5%) |

In order to evaluate the potential clinical impact of particulates on implant safety and performance, clinical data from patients who received recently manufactured implants (enrolled in the US Post Approval Study (PAS)) were compared to clinical data from patients implanted almost a decade ago (enrolled in the Core Study). Because capsular contracture is one of the most common complications post-implantation, the incidence of capsular contracture in the US-PAS at 1 year follow-up (recently manufactured product) was compared to the incidence of capsular contracture at 1 year for the Core Study (product manufactured 10+ years prior). Results of the comparison revealed that, in all the cohorts, the incidence of capsular contracture was lower in the US-PAS than in the Core Study.

Clinical Perspective

Within the medical community it is universally recognized that there is some level of particulates on medical devices as well as further introduced in the operating room environment.⁵⁻⁶ There is no evidence in literature that there is any harm related to a low-level presence of sterile microscopic particulate on implants. Specifically, no association between particulates on breast implants and adverse events has been identified, and there is no elevated concern in the plastic surgery medical community.⁷⁻¹¹ Clinically, many products used in the operating room have more particulate matter that is shed into a surgical field, for example, laparotomy pads are well known to shed fibers into the surgical field. It is realistic to consider that even with the strictest and most controlled manufacturing processes, sterile, microscopic particulate matter at some low levels may be impossible to prevent. Additionally, it is standard practice in the United States to irrigate the surgical pocket and wash the implant prior to insertion, potentially further reducing any particulate matter that may have been on the surface of the implant. Collectively, the authors' clinical experience with these implants over the past four years confirms the evidence presented here: safe, predictable surgical results and extremely low complications in general. The combination of this extensive testing, literature safety review, and low complication rates as reported in pre and post market studies, all speak to the continued safety of Sientra Silicone Gel Breast Implants.

Conclusion

In summary, all of the evidence, including the independent laboratory testing, the long-term Core Study results and our own clinical experience shows that there is **no increased risk** to patients related to any particulates that may be present on breast implants and **reaffirms our full confidence in the Sientra breast implants**. As a result of the comprehensive series of testing and analyses reviewed by the FDA, Sientra has returned to the market, effective March 1st, 2016.



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