



**Research Indicates Long-Term Risk
To Women's Health Not Fully Addressed
In FDA Clinical Trials**

*Conclusions From Symposium
On the Safety And Effectiveness
Of Silicone Gel-Filled Breast Implants*

July 21, 2003

The National Organization for Women (NOW) was pleased to convene the recent symposium on the safety and effectiveness of silicone gel-filled breast implants. As an organization advocating on behalf of all women, we recognize that breast implants are an important public health issue, considering the escalating use of and demand for these devices and the long-standing and very public debate concerning their safety.

It was our goal to highlight recent research on silicone gel-filled breast implants in order to encourage a continued dialogue between scientists, plastic surgeons, physicians and federal regulators about the safety and effectiveness of these medical devices. The complex conclusions of the Institute of Medicine (IOM) report released in 1999 were misinterpreted by the popular press. It was erroneously suggested that past research had definitively proven the safety of these devices. However, NOW and many scientists viewed the IOM conclusions as a demand for better and more extensive research. In view of the growing body of research in this field, it was our goal to provide an opportunity to review the status of clinical, toxicological, and immunological studies on silicone gel-filled breast implants.

The relevance of this meeting was made more critical considering the fact that individuals engaged in research in this area meet resistance from scientific and medical journals in their effort to publish studies on silicone gel-filled breast implants. For many panel members, the symposium presented an opportunity to discuss the relevance of recent findings and make recommendations for future research.

The ongoing commitment of many scientists to study silicone gel-filled breast implants has included new research conducted at the National Institutes of Environmental Health Sciences at the National Institutes of Health and the Food and Drug Administration. These and other literature reports afford strong evidence of the need for a continued assessment of the growing body of information on the risks of these devices. We were privileged to have in attendance federal researchers from the Food and Drug Administration, the National Institutes of Health and the Armed Forces Institute of Pathology in addition to a number of prominent scientists from around the country.

An important part of NOW's mission is to ensure that women are provided with a thorough scientific basis for informed decisions about their health care, including the use of medical devices. New research in the area of silicone gel-filled breast implants has raised additional questions concerning the long-term safety of these devices and the need for frequent surgeries to correct complications. We, therefore, strongly encourage the Food and Drug Administration to consider both short- and long-term complications in a review of the clinical data on silicone gel-filled breast implants.

We would like to thank the panel members and presenters, as well as the many other individuals who helped to make this symposium possible.

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SUMMARY

The panel reached several overarching conclusions:

- The issue of long-term safety has not been adequately addressed in past research, specifically regarding the integrity of devices over time. The panel agreed that little regard has been given to the varying physical and chemical properties of the implant materials over time.
- Potential implications of long-term exposure to migrated silicone gel following gel-bleed or rupture of the breast implant device, specifically once silicone gel diffuses into surrounding tissues and into the lymphatic system, have not been adequately studied.
- New research continues to suggest that silicone may act as an adjuvant, a substance that nonspecifically enhances the immune response to an antigen, which may facilitate specialized immune responses.
- The panel agreed that clinical trials must be implemented in such a way as to capture long-term safety data, including indications of both local (inflammatory) and systemic responses.
- The panel concurred that the health implications of silicone gel in the lymphatic system and surrounding tissues is a serious concern and that dose response for exposure to silicone gel has not been adequately established, yet is critical to understanding the immunological implications of long-term exposure at varying levels.
- The high prevalence of so-called “local complications” such as hard capsules, chronic inflammation, frequent reoperation, and disfigurement has not been adequately discussed with women in informed consent.

Long-term effects were identified as one of the most important factors for future research on the safety and effectiveness of silicone gel-filled breast implants. This was a startling limitation of past research, specifically the studies reviewed by the Institute of Medicine in 1999. Research conducted by the Food and Drug Administration, published in 2000, found the median silicone gel-filled breast implant age at rupture was in the range of 10 years.¹ This is consistent with the largest data base for retrospective data analysis for almost 10,000 explanted implants. These studies demonstrate that the prevalence of rupture increases with time. The disregard for long-term effects has considerably limited the ability of past studies to fully explain the many complications associated with silicone gel-filled breast implants over time. The FDA’s *Guidance for Saline, Silicone Gel, and Alternative Breast Implants; Guidance for Industry and FDA* states “premarket approval applications may be filed with a minimum of 2 years of patient follow-up.”

Long-term properties are key to several safety issues. First, silicone gel-filled breast implants are known to have an increasingly high prevalence of rupture over time. Clinical evidence presented at the conference further suggested that silent rupture, or rupture that goes undetected by a woman, is a common phenomenon for silicone gel-filled breast implants. Due to the composition of silicone gel-filled devices, instantaneous deflation of the implant rarely occurs immediately following rupture. In contrast, saline-filled breast implants often rapidly

¹ Brown SL, MS Middleton, WA Berg, MS Soo, G Pennello. Presence of rupture of silicone gel breast implants revealed on MR imaging in a population of women in Birmingham, Alabama. *American Journal of Roentgenology*; 175:1057-1064, 2000.

deflate upon rupture. Therefore, following rupture of silicone gel-filled breast implants women are often exposed to the migration of silicone into surrounding tissues as well as regional sites, including the lymph nodes. Furthermore, removal of a ruptured implant may not remove all silicone especially that which has migrated to lymph nodes. The persistence of such silicone gel was of particular concern to the panel members. Clinical evidence suggests that silicone may persist in distant organs and lymph nodes for at least several years and may persist permanently in the reticuloendothelial system.

The migration of silicone beyond the fibrous capsule into lymph nodes and the persistence of even minimal, yet long-term, exposure to silicone has not been adequately investigated. The panel identified the dose or exposure level of silicone gel as critical in making an evaluation of the long-term health implications including potential immunological effects associated with silicone gel implantation. Past research investigating the potential association of silicone gel-filled breast implants and disease (in particular autoimmune diseases), including studies reviewed by the Institute of Medicine in 1999, often did not establish a direct “exposure” to the silicone gel through rupture or evidence of leakage through the migration of gel to connective tissue or lymph nodes.

While the general population may come in contact with minute levels of silicone, the exposure of the gel contained within a breast implant would be significant to the localized or systemic effects. Establishing a dose response curve is an essential next step in investigating the health consequences of silicone gel exposure. Another complicating factor is the escape or migration of silicone gel through an “intact” implant elastomer shell. The panel concurred that this phenomenon is well-documented and that, because elastomers are semi-permeable barriers, silicone gel can move into the capsule or surrounding tissue even in intact implants. Without an appropriate silicone dose response curve it is difficult to conclusively investigate the varying risk of long-term implantation.

However, research has documented risks associated with silicone exposure. Research conducted at the Food and Drug Administration and Armed Forces Institute of Pathology have focused directly on silicone gel exposure and migration. Studies published by the Food and Drug Administration have shown women exposed to “extracapsular silicone” gel escaping beyond the scar capsule that forms around breast implants were at higher risk for fibromyalgia.

Research conducted at the National Institute of Environmental Health Sciences (NIEHS) raised several questions central to the silicone debate. These include: under what conditions might silicone exposure possibly contribute to localized immune responses (i.e., in silicone breast implant capsules or axillary lymph nodes?) And, are localized immune responses shared with immune responses at remote sites of disease activity in some patients with silicone implants? The data suggest that shared, antigen-driven T cell responses may contribute to chronic inflammation in silicone capsules as well as systemic sites of immune pathology. Current and ongoing work by the Environmental Autoimmunity Group at NIEHS includes clinical, immunogenetic, and serologic studies of patients developing inflammatory muscle disease (myositis) following silicone implants. Preliminary data suggest “silicone may promote the development of atypical forms of systemic connective tissue disease that are immunogenically distinct from their idiopathic counterparts.” Taken together, the panel is concerned that these data support the notion that specific immune responses may be associated with silicone gel exposure in chronically inflamed capsular tissue where activated macrophages, lymphocytes and multinucleated giant cells are often observed surrounding silicone particles.

The panel further indicated that silicone gel may be working as a potent adjuvant, a substance that nonspecifically enhances the immune response to an antigen. Research using animal models demonstrated that long-term implantation of silicone resulted in both the production of autoantibodies to connective tissue antigens and increased susceptibility to an experimental model of autoimmune disease. A previous study by this same group investigating only short-term implantation found no increased incidence of disease. However, long-term implantation changed the ability to provoke the onset of disease and reflects the potential for biological activity associated with long-term implantation of silicone.

Another concern expressed by the panel centers around the ability to standardize all of the components of the silicone material used in each manufacturer's silicone gel-filled implants. Not all silicone gels and the "other components" that are added during manufacturing are "identical." The properties of a silicone gel tend to vary from manufacturer to manufacturer and even throughout a single manufacturer's production of a line of silicone gel-filled breast implant devices.

The panel concurred that the uniformity of any implanted material is critical to the development of a meaningful scientific investigation of potential health risks. The panel members recommended that the manufacturers of silicone gel-filled breast implants be required to clearly define all components used in the gel, including the quantities of such material. The manufacturers should also be required to take steps necessary to ensure that the silicone gel consistency remains constant throughout production. The uniformity of silicone elastomer shell thickness is also an important question as is acceptable levels of shell defects and impurities.

FDA traditionally considered the basic ingredients of a manufacturer's silicone gel proprietary information, including any changes to the formula during production. Therefore, this information was not shared with the FDA. Only now is this a required component of a pre-market approval application. Potential risks include the use of reactive metals for crosslinking silicone gel. Research has found that the chemical composition of silicone gels from breast implants contain detectable levels of platinum, a reactive metal catalyst used in the preparation of silicone gels. Platinum has also been observed to leak through intact implants into lipid-containing media. The rates at which platinum has been observed to leak from intact implants could lead to significant accumulation within lipid-rich tissues and should be investigated more fully in vivo.

A further limiting factor in the evaluation of safety data is that FDA does not require manufacturers of silicone gel-filled breast implants to stratify the different generations of devices or silicone gel during clinical trials or throughout the post-market surveillance timeframe. In addition, the shelf-life of silicone gel-filled breast implants has not been adequately established nor has there been an adequate evaluation of the physical and chemical aspects of the aging process of the gel either prior to implantation or throughout the life of the device once implanted.

Clinical and scientific evidence has shown that significant changes occur in the chemical and physical properties of a silicone gel due to aging of the gel. Observations have indicated that there are changes in gel properties and the potential for producing long-term health risks following explantation of both intact and ruptured devices and also in the particles of retrieved free silicone analyzed from patients' lymph nodes and tissues.

As a result, patient outcome data collected through clinical trials that should identify potential health risks are not often correlated with a specific generation or age of implant or silicone gel.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, the panel stressed the importance of research focused on the role of silicone in eliciting a specialized immune response over time. The panel concurred that there was adequate evidence to suggest that silicone may be acting as a potent adjuvant, and that the presence of free silicone gel in a female's lymphatic system and tissues was of particular concern.

Effects due to changes in silicone gel over time or "latency" was highlighted as a significant limitation to past research and the current clinical trials being conducted under FDA's guidance. While silicone gel-filled breast implants remain implanted in a woman's body the risk of exposure to silicone gel progressively increases through rupture or gel bleed through the semi-permeable membrane of intact implants. Clinical trials should therefore take into account not only the short-term complications (i.e., experience over the course of a few years) but also the long-term risk throughout the life of the device and the degree of migration of silicone following implant failure or explantation.

Considering the monetary expense of breast implants and risk of additional surgeries, it is clear that women do not consider implantation of breast implants as a short-term endeavor, with breast implants lasting only a few years before new implants are needed. Therefore, the FDA should require clinical trials that more accurately assess the long-term risk, otherwise the agency will fail to address the "intended use of the device" given the "intended patient population" and the "anticipated lifetime of the device" as stipulated by law.

The panel highlighted the following conclusions and recommendations:

- Clinical trial data collection should be extended to capture the latent complications. The panel agreed that as currently conducted in accordance with FDA regulation, clinical trials will generate no useful information on latent effects. Nor will they capture the majority of local complications (including rupture) or potential systemic implications of silicone gel leakage or migration. Panel members further recommended that clinical trials evaluate serological and tissue information on clinical trial patients as well as perform a comprehensive analysis of all signs and symptoms of autoimmunity, instead of evaluating only disease categories. The panel agreed that a long-term evaluation is warranted in order to ensure the safety of these devices and identify possible long-term risks of silicone gel-filled breast implantation.
- Considering the long-term health implications of rupture and migration of silicone gel, the FDA should require follow-up on all women who have had silicone gel-filled breast implant devices removed. This subset of the clinical population represents a critical missing component of a comprehensive evaluation of the long-term safety of silicone gel-filled breast implants. Otherwise, data collection may have the tendency to select for patients with the most benign outcomes. At present, the FDA only "recommends" and does not "mandate" this follow-up. FDA does not have a mechanism for actively monitoring long-term outcomes.

- Studies should be undertaken to investigate the change in silicone gel over time, taking into account the heterogeneity of silicone material used across devices and manufacturers. This analysis should determine the nature and rate of change in composition of silicone gel in intact and ruptured implants as well as migrated and displaced silicone gel.
- The panel felt that the FDA’s standard for implants of “reasonable assurance” of safety was ambiguous and did not accurately portray to the public assurance of safety and effectiveness.

Further, based on the intended use of the device, which is significantly longer than 2 to 3 years, “reasonable assurance” of safety and effectiveness could not be provided unless clinical data were collected for much longer periods of time than historically required by and acceptable to the agency for approval.

Please refer to the following definition of “reasonable assurance, according to the U.S. Congressional Federal Register (21 CFR 860.7 (d)).

(d)(1) Reasonable assurance that a device is safe when it can be determined, based on valid scientific evidence that the probable benefits to health from use of the device for its intended use and conditions of use, when accompanied by adequate directions of use, and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

- Further research should be conducted to examine the possible atypical forms of immune disease and specific immune responses related to silicone gel-filled breast implants. This research should examine the specific role of silicone gel as an adjuvant. Research using epidemiological techniques should assess the “exposure level” to silicone gel through rupture, extracapsular migration and the presence of silicone in distal sites such as lymph nodes.
- Product insert and informed consent requirements must also be addressed by the FDA to insure that more specific and quantitative data are conveyed to doctors and patients; especially complication data taken from manufacturers’ pre-market approval (PMA) clinical studies and from the literature for retrospective analytical studies.