

**MEMORANDUM**

To: Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

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**Docket Number 2004D-0002 "New Draft Guidance Document for Breast Implants"**

From: William E. Katzin, MD, PhD  
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Re: Draft Guidance for Industry and FDA Staff. Saline, Silicone Gel, and Alternative Breast Implants

Date: April 11, 2004

Dear Food and Drug Administration Representative:

I have reviewed the draft of the guidance for industry and FDA staff regarding saline, silicone gel, and alternative breast implants. I believe that this document represents a thoughtful and relatively comprehensive approach to a very complicated and controversial issue. There are several issues that I would like you to consider that may improve this effort.

1. Guidelines for the evaluation of gel bleed are quite specific. However, guidelines for evaluation of gel migration, particularly migration to regional lymph nodes, are poorly defined. For example, in sections 5.4 and 9.3 it is not clear how lymphadenopathy is defined nor is it clear how it should be identified. Ultrasound is one imaging method that may be useful in the identification of silicone migration to regional lymph nodes and MRI is another possibility. Ideally, abnormalities identified by either radiologic modality should be further evaluated by histopathologic and analytical chemical methods.
2. In Sections 6.1 and 6.5 it is suggested that implants be incubated in a lipid-rich medium in order to mimic the physiologic conditions to which implants are exposed. However, although the breast is largely fatty tissue, it is unlikely that implants themselves are exposed to free lipid. It is more likely that the immediate environment of implants *in vivo* is similar to interstitial fluid. It is also quite possible that implants *in vivo* are exposed to mediators of inflammation such as those released by macrophages and neutrophils. Chemically reactive species such

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as peroxides may therefore be more important in possible device degradation than are lipids.

3. Despite the Institute of Medicine report on the Safety and Effectiveness of Breast Implants, it should be emphasized that the science regarding possible associations between silicone gel containing breast implants and connective tissue diseases is still poorly developed. Implant manufacturers should be vigilant in their evaluation of the clinical data that they collect. Clinical and statistical analyses must be as broad as possible in scope and completeness. Potential manufacturers must demonstrate a willingness to expand the list of laboratory tests that will be routinely performed during patient follow-up as more disease markers become available and as the possible relationship between silicone gel and connective tissue diseases (or other diseases) becomes more clearly defined.
4. Finally, in Section 9.3 immunofixation electrophoresis (IFE) should be substituted for serum protein electrophoresis (SPEP) if the goal is to identify monoclonal proteins.