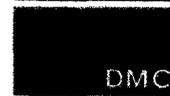


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3/19/04

**Docket Number 2004D-0002 "New Draft Guidance Document for Breast Implants"**

Dear Sirs:

I am submitting the following comments for consideration during your upcoming review of silicone-filled breast implants: I have concerns that fall under several pertinent areas:

- 1. Lengthening the follow-up in clinical trials.** Silicone gel-filled breast implants pose unique long-term risks associated with silent rupture, leakage and silicone gel migration. Clinical trials should be conducted in such a way to capture long-term data prior to approval, rather than relying upon post-approval reporting. I hold the position that a large study of patients over 10 years would provide the most convincing data, as problems that could arise due to latency need to be resolved. I recognize that this is going to be strongly resisted by the manufacturers, but as saline-filled implants are still available, I fail to appreciate the commercial need for a rush to market.
- 2. Design of the clinical trials.** The trial design should ideally be a blinded comparison between implant recipients using saline and silicone filled SBIs While this is not strictly a controlled comparison to normal (although a normal healthy cohort should be included as a third arm), it addresses the major concern of the safety of gel leakage. The clinical criteria should be developed by a rheumatologist familiar with mixed connective tissue disease, and should not be focused upon the classic diagnosis of recognized syndromes. MRI would appear appropriate for evaluation of implant status, provided the images are interpreted by a sufficiently skilled physician familiar with techniques to identify leaks, silent rupture and gel migration. MRI use should include all patients in the clinical trial, not a selected minority. The comparison of saline to gel should normalize the inherent bias that has been implied due

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to the social and mental status of patients seeking implants. It is important to remember that that Inamed Corporation's clinical trials demonstrated increases in CTD signs and symptoms in just over two years of clinical testing. Further, it will be critical to continue clinical and laboratory monitoring of patients that undergo explantation (particularly in the case of gel leakage), and include this data in the trial reporting.

3. **Relevant laboratory criteria for the assessment of clinical consequences.** Laboratory tests must provide a detailed evaluation of the status of the immune system, and the development of immunological abnormalities that are recognized as relevant to autoimmune and connective tissue disorders. All patients should be tested prior to entry into the trial, and at regular (annual) intervals thereafter. These tests should include (but not be limited to):
  - a. Anti-nuclear antibodies (full screen)
  - b. Total immunoglobulin levels
  - c. Screen for monoclonal gammopathies
  - d. Combined blood counts (CBC)
  - e. Natural Killer cell counts.
  - f. ESR and CRP
  - g. Rheumatoid factors
  - h. Anti-polymer antibodies. I am satisfied that Dr R. Wilson (Autoimmune Technologies) has developed a useful test for reactivity to implant silicone (this does not necessarily imply pathological consequences). This test appears to work in both SBI and VP shunt recipients in double blind trials. I have spoken to Dr Wilson and I understand that he will submit a response to the FDA under a separate cover. He and I have no commercial relationship.
4. **Retrieval studies.** These should be designed to account for three areas:
  - a. Material physical properties. A detailed investigation of mechanical reasons for failure.
  - b. Material chemical properties. There is a recognized need to address why implants become bright yellow after several years of implantation.
  - c. Material biological properties. A detailed investigation of the histopathology of the implant and the surrounding tissue to elucidate the nature of the inflammatory and/or immunological response. This should be cross-referenced to the laboratory parameters previously listed, and extended to include HLA typing of the patients with failed implants, and autoantibody responses to silicone bound proteins present on the surface of retrieved implants,

It would be seem most appropriate to harness the research expertise of NIEHS and other academic institutions well versed with silicone and materials research in order to obtain reliable information in an expedited manner. While I am aware that there is no current direct mechanism to accomplish this task, it seems foolish to ignore Government funded research in the performance of the FDA's task.

Yours truly,

Paul H Wooley, PhD.  
Professor, Director of Research