



Department of Materials Science and Engineering
Biomaterials Center

317 A MAE
PO Box 116400
Gainesville, FL 32611-6400
(352) 392-4907
Fax: (352) 392-3771

January 20, 2004/by Priority Mail

Division of Dockets Management (HFA-305)
FDA - 5600 Fishers Lane - rm 1061
Rockville, MD 20852

Re: New Draft Guidance Document: Docket No. 2004D-0002
for Breast Implants - COMMENTS & SUGGESTIONS

To FDA Breast Implant Guidance Document Staff:

In response to the recently issued revision of the "Saline, Silicone Gel, and Alternative Breast Implants" Draft Guidance Document published in the Federal Register (Docket Number 2004D-0002), I wish to provide the following comments and suggestions, as requested:

1. My comments to FDA Commissioner Dr. Mark McClellan in a letter dated 11-10-03 regarding the Inamed PMA notes a number of issues pertinent to revision of the guidance document and is enclosed with key points highlighted.
2. p. 3/#3: device description should note differences in shell/gel polymer composition, structure, physical and chemical properties and specs, compared to previous, i.e. the phenylsiloxane elastomer multiplayer shell in the Inamed PMA.
3. p.5/#4.2: add "amount of unreacted monomers, oligomers, and crosslinker"
4. p.5/#4.3: specify use of exhaustive extraction, i.e. in a Soxhlet extractor, add chloform to list of good solvents, and specify that extractions should be done on shells and gels from the finished product and on archived product.
5. p.7/#4.7: use exhaustive Soxhlet extraction as note above
6. p.8/#4.8: include measurements for chemical and physical stability (i.e. does mechanical structure and physical properties of gel change on cyclic stressing?). If filler is aqueous gel or solution, specify osmolarity and characterize in/out diffusion of metabolites and possibly pathogens.
7. p.11/6.1/par 3: testing on finished devices as well as (not just or) components.
8. p. 12/6.2: since all failures will result from stress concentration at defects, folds, tears, bubbles, particulate contaminants, etc., S/N cyclic stress fatigue testing of polymers should be done with a built in well defined defect (i.e. cut for tear strength, notch for impact strength, hole for stress fatigue failure in tension, etc.). Standard defect in shells should therefore be used. In this regard, specifications for "acceptable" bubbles, tears, particles, etc. must be defined for minimal risk.
9. p.14/#6.4: this section should include extraction data for % uncrosslinked silicone.
10. p.14-15/#6.5: bleed should also be measured after some non-destructive period of cyclic stress to measure changes in barrier properties due to mechanical stress.
11. p.15/#7: specs for shell defects should be noted here and the implant design must satisfy the mechanical manipulation stress/strain requirements of the implant procedure.

2004D-0002

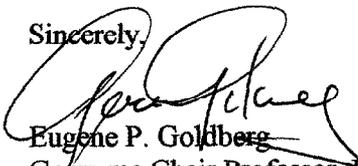
C1

12. p.17/#8: shelf life testing must include tensile and tear strength as well as % extractables and swelling for the shell.
13. p.26/#9.6: review of literature should include discussion of most pertinent references and data; especially must consider Brown et al. MRI study, Gabriel et al. local complications and additional surgery study, and Marotta et al. large cohort explant rupture data meta-analysis and frequency of additional surgery studies. These need full discussion. Papers concerning higher prevalence of lung and brain cancer and much higher prevalence of hospital admissions for breast implant recipients must also be fully discussed.

Also attached are some handwritten comments submitted to the Panel at the Inamed PMA Review with the more pertinent suggestions highlighted.

Your revised Guidance Document definitely appears to be a step in the right direction. I hope the foregoing suggestions will be helpful to preparing the final document.

Sincerely,



Eugene P. Goldberg

Genzyme Chair Professor, Biomaterials, Materials Science & Engineering

Director, Biomaterials Center

Faculty of Pharmacology & Therapeutics, McKnight Brain Institute, Biomedical Engineering Dept.

attachment



Department of Materials Science and Engineering
Biomaterials Center

317 A MAE
PO Box 116400
Gainesville, FL 32611-6400
(352) 392-4907
Fax: (352) 392-3771

Dr. Mark McClellan
Commissioner FDA
5600 Fishers Lane
Rockville, MD 20857

November 10, 2003/by FedEx (301)827-2410

Re: October 14-15, 2003 FDA Panel Review of Inamed Silicone Gel Breast Implant PMA

Dear Dr. McClellan:

As an academic scientist with fairly extensive teaching, research, and consulting experience in the fields of Biomaterials and Medical Device Development, including more than 20 scientific society lectures, and journal papers and letters concerning silicone gel breast implants, I traveled at my own expense to Gaithersburg to testify on October 14th on our research pertinent to the PMA. As a result of this experience, and what I consider to be an absurd outcome in the 9/6 vote of the Panel in favor of approval, I wish to respectfully bring two major issues to your attention for serious consideration before a final FDA decision is reached. These concern the (1) Review Process and (2) Scientific Data Evaluation. To help with your busy schedule, I will limit this letter to two pages and append additional documents should you wish to consider more specific supporting information. Overall, *I am strongly opposed to approval.*

1. The Review Process: I realize that Dr. Krause, who organized the Panel and the Review, had a thankless and difficult task given the controversy surrounding this PMA. However, depending on the PMA, and the various interest groups, and multidisciplinary science and engineering factors, I think it is important for the FDA to tailor each review so that there is a more appropriate balance of anecdotal personal testimony and scientific testimony than was allocated for this PMA. Furthermore, for an implant which was removed from general use in 1992 for lack of adequate safety data, shouldn't the Panel have had much broader pertinent scientific expertise, and shouldn't Inamed have been required by the FDA to provide long-term clinical data (more than 2-3 years) concerning the key local complication and immune safety issues that remain unanswered? Some comments and suggestions concerning this PMA follow:

1-A Testimony: Although 3 min. personal anecdotal talks may be adequate, I believe it essential to allocate at least 10-15 min to credible physical and medical scientists to present data and opinions of scientific value to the Panel. Additionally, since the PMA was not made available until the last minute, testimony from scientists should have been relegated to the 2nd day after the lengthy Inamed presentations on 10/14. The "process" was also strange. For my scientific testimony, PowerPoint and slide projection were not allowed. Isn't this ridiculous when virtually all Inamed and FDA staff presentations did use computer projection?

1-B Panel Expertise: Most disconcerting was the last minute selection of the majority of the Panel and the lack of balance of essential expertise. The Panel Chair, Dr. Whalen, was a superb selection. But why were there no experts from the fields of Polymers, Silicones, Biomaterials, Biocompatibility, Histopathology, Implant Engineering Design & Development, Quality Assurance, Device Manufacturing, and Product Specifications? Why no expertise concerning the Physical, Chemical, and Biological Properties of Silicones? Astonishing! As a member of the Society for Biomaterials, and a Fellow of the American Institute for Medical and Biological Engineering, I find it incredible that eminent scientists from the fields of Biomaterials and Bioengineering could not be found to serve on this Panel!

2. Scientific Evaluation: After an 11 year moratorium, the voluminous PMA was superficial concerning implant engineering design, gel and shell materials properties, and testing, with absolutely no comparison with data for the best 1992 Silastic-II type gel implants. What were they doing for the past 11 years?

Indeed, on what basis could the FDA possibly have agreed to even review this PMA based on only 2 year clinical data? At the review, Dr. Whalen (the Panel Chair) indicated that he was "flabbergasted" by only 2-3 year data. Isn't it also reasonable for the FDA to wonder if this development was conducted with the same thoroughness as Inamed's apparently ill-fated experience in the UK with Soybean Oil filled implants; touted as safer breast implants but reported to have serious safety problems in 2000?

Some further scientific comments and questions which I believe the FDA must consider include:

(1) **Rupture & Frequency of Reoperations:** The only large cohort statistical meta-analysis of data, for almost 10,000 gel implants, indicated 30% shell failure at 5 yrs, 50% at 10 yrs, and 70% at 17.5 yrs using data from 42 different explant studies. This meta-analysis from my laboratory was published in peer reviewed journals in 1999 and 2002. It indicated that 33% of women had at least one reoperation (some 2-6) within 6 years of primary implantation. Results are in excellent agreement with a Mayo Clinic paper by Gabriel et al and with the non-invasive MRI study by Brown et al from FDA/NIH. *Why did the PMA fail to discuss all of these papers which so clearly implicate Local Complications as a major safety problem with extraordinary risks of rupture and reoperation (and need for >2-3 years of clinical data)?*

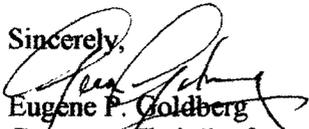
(2) **Implant Gel & Shell Polymers:** Did the Panel actually understand that a totally new shell (and gel?) was used? The PMA states that the shell is a new trilayer phenylsiloxane elastomer structure (not the polydimethylsiloxane of pre-1992 gel implants) and provides no data for tensile and tear strength nor any product specifications (see PMA presentation chart attachment). Furthermore, the fact that phenylsiloxanes are reported to be carcinogenic is mentioned but discounted as unimportant without meaningful discussion. Little composition data are presented for the gel but it is evident that the gel is still predominantly silicone fluid and therefore will "bleed" silicone into surrounding tissues as did pre-1992 gel products. Routine extraction testing of gels is not proposed to assure control *nor do we know what Product Specifications and routine Quality Assurance product testing will be done for Shells and Gels.*

(3) **ASTM and In Vitro Testing:** ASTM tests are in fact arbitrary and have little functional relevance. Hence, during the Inamed presentation, in response to a Panel question, it was stated that there was no correlation between all the *in vitro* testing and the actual clinical performance and safety of the device. *Astonishing!* They had a decade to do better engineering design, polymer selection, and improve control of manufacturing and testing to produce an improved product. *Based on the PMA, this was not done!*

(4) **Uncertainties Regarding Immune Disease, Cancer, and Frequent Hospitalization:** The "local" complication of *chronic inflammation* (an immune response) is well established but no PMA data on this is presented, especially histopathology of tissues surrounding explants. It is of course likely that such continuous local inflammation will have long term adverse systemic immune effects. The much higher prevalence of *brain and lung cancer* for gel implant recipients is also indicated without consideration of the important long term safety implications. Finally, we now have the benefit of a breast implant study by Dr. A. Tweed of the Canadian B.C. Centre for Disease Control which provides the startling result that *women with breast implants were 4X more likely to be hospitalized than women without these devices.*

(5) **Numerous Other PMA Problems:** There are so many other questions concerning detailed scientific inadequacies of this PMA that it is impossible to recite them all here. Suffice it say that this PMA offered no evidence of adequate safety for this cosmetic implant beyond what we knew in 1992 when the FDA moratorium was imposed for lack of adequate safety data. Inadequate *informed consent* by plastic surgeons using company information in the face of our current knowledge of the high prevalence of *Capsular Contracture, Disfigurement, Pain, Infection, Chronic Inflammation, Loss of Nipple Sensation, Gel Bleed, Rupture, and Reoperation* is inexcusable and virtually unenforceable if this implant were to be approved by the FDA for clinical use. I URGE THE FDA TO REJECT THIS GEL IMPLANT PMA.

Sincerely,


Eugene P. Goldberg

Genzyme Chair Professor, Biomaterials, Materials Science & Engineering

Director, Biomaterials Center

Faculty of Pharmacology & Therapeutics, McKnight Brain Institute, Biomedical Engineering Dept.

cc: Dr. Krause, Dr. Feigel, Dr. Whalen,
and appropriate members of the Congress

attachments

SGBE

FURTHER QUESTIONS FOR FDA

FROM DR. EUGENE GOLDBERG
UNIVERSITY OF FLORIDA

11

GIVEN TO DR. KRAUSE FOR DISCUSSION BY PAPER

12:45 PM
10-15-03

1. GIVEN THE IMPROVED MECHANICAL AND BARRIER PROPERTIES OF THE 3rd GENERATION SILASTIC-II GEL IMPLANTS USED IN 1992 BEFORE THE MORATORIUM, DOES INAMED BELIEVE THAT ITS NEW PHENYLSILOXANE SHELL + GEL IMPLANT IS BETTER THAN THAT DISCONTINUED IMPLANT, ESPECIALLY IF THE SILASTIC-II TYPE WERE MADE WITH A 0.020" SHELL? I.E. BETTER WITH REGARD TO RUPTURE + REOPERATIVE COMPLICATIONS?
2. IN VIEW OF THE FACT THAT THE INAMED SHELL IS A NEW PHENYLSILOXANE MULTI-LAYER COMPOSITION AND THAT PHENYLSILOXANES HAVE BEEN SHOWN TO BE CARCINOGENIC, ISN'T INAMED CONCERNED ABOUT THE POTENTIAL THAT THIS NEW SHELL POLYMER WILL INDUCE CANCER IN SOME PATIENTS IN THE LONG-TERM?
3. WHY HASN'T INAMED MEASURED BLEED ON FINISHED PRODUCTS? IT HAS BEEN DONE BY OTHERS. SEE: YU ET AL., PLASTIC RECONSTR SURG, 1996; 97: 756-764.
4. WHAT ARE THE SPECIFICATIONS FOR THE TENSILE, ELONGATION, AND TEAR STRENGTH FOR THE ACTUAL SHELL + WHAT ARE THE SPECIFICATIONS FOR BUBBLE, TEAR, PARTICULATE CONTAMINANTS WHICH FREQUENTLY OCCUR IN THE DIP COATING MANUFACTURING PROCESS? HOW DO THESE SPECS COMPARE WITH PRE-1992 SPECS WHICH OFTEN ALLOWED DEFECTS AS LARGE AS 1/16 - 1/32"?
5. AS CORRECTLY POINTED OUT IN THE INAMED PRESENTATION, THE ASTM TESTS REALLY HAVE NO CORRELATION WITH CLINICAL PERFORMANCE AND ARE IN FACT ARBITRARY. HAS INAMED DEVELOPED ANY MORE CLINICALLY RELEVANT TESTS TO ASSURE BETTER PERFORMANCE? AND WHY ARE BOTH SMOOTH AND TEXTURED SURFACES BEING PROPOSED?
6. THE SUBJECT OF CHRONIC LOCAL INFLAMMATION SEEMS TO HAVE BEEN IGNORED IN INAMED'S CLINICAL STUDIES. HAVE THEY DONE HISTOPATHOLOGY ON TISSUES SURROUNDING EXPLANTS TO LOOK FOR A LOCAL IMMUNE RESPONSE VIA MACROPHAGES + GIANT CELLS?

IN PMA