2004D-002
April 8, 2004

COMMENT ON THE DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF
ON SALINE, SILICONE GEL, AND ALTERNATIVE BREAST IMPLANTS

BY
THE NATIONAL CENTER FOR POLICY RESEARCH FOR WOMEN & FAMILIES

We appreciate the opportunity to comment on the FDA's January 2004 Draft Guidance on breast implants. The National Center for Policy Research for Women & Families is an independent, nonprofit research and educational organization that gathers, evaluates, and explains health research, to promote the health and safety of women, children, and families.

Our Center strongly supports the FDA's new emphasis on research to explain the causes and consequences of implant rupture, and research that evaluates a wide range of complications and symptoms among women with implants. However, we are concerned that the FDA Draft Guidance de-emphasizes the Core Study and other clinical trials and epidemiological research and seems to shift the research focus to biomaterials testing and retrieval studies.

We support the recommendations that mechanical testing be improved so that it predicts clinical outcomes and more accurately predicts rupture rates. We also support the FDA recommendation that sponsors develop a new gel bleed test that more closely mimics conditions in the body.

However, we believe that a comprehensive pre-market Core study, supplemented with other clinical trials and epidemiological research, are absolutely essential for understanding the safety of any breast implants. Previous research and reports, including the Institute of Medicine (IOM) report, have not conclusively determined whether systemic diseases are linked to breast implants, and well-designed federally-funded research conducted since the IOM report have raised questions about systemic diseases that may be associated with the long-term use of breast implants.

In addition, our Center makes specific suggestions for reform to section 9 (Clinical Studies), section 10 (Clinical Data Presentation), and Section 11 (Labeling).

BACKGROUND

Implants that are intended for long-term use must be studied on women who have had them for many years, in order to determine their safety. Two of the best-designed

studies on breast implants, led by Dr. Lori Brown of the FDA and Dr. Louise Brinton of the National Cancer Institute (NCI), evaluated the health of women who had implants for a minimum of seven or eight years, respectively. The women with documented silicone gel breast implant leakage in the FDA study reported a statistically significant increase in fibromyalgia and several other autoimmune diseases, whereas the women with breast implants in the NCI study were more likely to die from brain cancer, lung cancer and other respiratory diseases, and suicide, compared to other plastic surgery patients.

Autoimmune diseases and cancers develop over a period of many years, and even more years are likely to pass before they are diagnosed. Statistically significant increased risks of these diseases are documented in the FDA and NCI studies cited above. In contrast, other implant studies, many of which were funded by implant makers and serve as the major epidemiological studies in the IOM report, included large numbers of patients who had implants for short periods of time, even as short as a few months. Although the patients in those studies may have had implants for an average of six years or more, the sample sizes were relatively small, so that few women had implants for more than seven years and there was therefore insufficient statistical power to detect increased health risks.

The studies conducted on implant patients thus far suggest that breast implants rarely cause systemic disease in the short-term but may do so in the long-term, either because the diseases develop over several years after exposure, or because implants break and leak over time and that increases the likelihood of health problems. The research therefore indicates that the FDA should require carefully designed prospective or retrospective studies to answer the lingering questions on the long-term safety implications of breast implants.

Studies of women with ruptured implants are especially important because of concerns about how exposure to leaking silicone may affect women's health. Research conducted by Dr. Noreen Aziz, Dr. Frank Vasey, and their colleagues document that breast implant patients with rheumatological symptoms improve when their implants are removed and not replaced. In contrast, patients frequently became more ill if their implants were not removed, or were removed and replaced with new implants.

Improvements are needed in biomaterials testing and retrieval studies, but they should supplement a more comprehensive Core study and other clinical trials and epidemiological studies. As Drs. Feigel, Schultz and Wood implied in the January 8, 2004 Stakeholder Conference Call Advisory, we still need to discern the clinical consequences of not treating silent ruptures, determine a threshold for safety, and require the sponsor to establish its product as safe and effective.

Since FDA officials state that they cannot enforce any recommendations for post market requirements for medical devices, the only window of opportunity to compel a well-designed clinical trial or retrospective study to track diverse subpopulations of women over a minimum of ten years is **prior** to approval. In cases where a type of breast implant has been on the market for at least ten years, the Center calls for a primary focus

on long-term clinical trials or retrospective research with medical records and clinical exams to measure health outcome. These studies should be supplemented with well-designed biomaterials research and retrieval studies. The latter becomes more important in PMAs involving a newly developed type of breast implant; however, even these should require prospective clinical trials lasting at least five years, in addition to well-designed biomaterials research and retrieval studies.

DRAFT GUIDANCE 9. Clinical Studies

It is essential that women of color be included in the safety studies of breast implants, in numbers that are sufficient for meaningful data analysis. Since capsular contracture is caused by scarring, which can vary in different ethnic groups, there is reason to believe that race or ethnicity may influence complication rates among implant patients. In addition, African American women are more susceptible to autoimmune diseases, so race could influence the development of systemic diseases or symptoms.

Breast augmentation is increasingly popular among Asian American women and other women of color. Breast cancer touches women in all ethnic groups and African American women are more likely to undergo mastectomies than white women. It is therefore especially important that women of color be included in studies of breast reconstruction.

Section 9.1

In cases where a type of breast implant has been on the market, either in this country or abroad, prior to the submission of the PMA, the Center calls for a primary focus on long-term clinical trials or retrospective research with medical records, clinical exams, and self-reported symptoms to measure health outcome. If the device has been on the market for more than ten years, the Center calls for a minimum of ten years of patient follow-up **prior** to approval. Since implant rupture is difficult to detect and the risks of extracapsular and migrated silicone gel are of concern, it is reasonable and essential that long-term clinical studies address chronic illnesses and health risks, including but not limited to autoimmune disorders, respiratory diseases, brain cancer, and suicide.

A literature review and post-market approval requirements are no substitute for long-term clinical or epidemiological data and provide no assurance of safety and effectiveness of the breast implant. As described earlier, many previous studies included women who had implants for short periods of time. Most do not have the statistical power to determine whether implants cause a doubling or even tripling of relatively rare diseases.

When the breast implant has been on the market for less than ten years prior to the PMA, the FDA should require pre-market studies for a period that is almost as long as the product has been in use. New breast implants should be studied in clinical trials for at least five years, with very low loss to follow-up. Health risks should be assessed by

clinical exams at the end point, as well as on an analysis of medical records and self-reported symptoms.

Section 9.2

The FDA guidance indicates that women with approved saline breast implants are an appropriate control group. We disagree. FDA-approved saline breast implants have very high complication rates, especially for reconstruction patients. Saline breast implants are encased in a shell made from silicone and other chemicals. In addition, FDA approval for saline breast implants was based on research on complications but did not include evaluation of signs, symptoms or diagnosis of systemic diseases. A review of the transcript from the public advisory committee meeting on saline breast implants indicates that young women with saline breast implants complained of hair loss, fatigue, joint pain, memory loss, and other symptoms similar to those reported by women with silicone gel breast implants. If women with saline breast implants are used as a control group, another control group without silicone or implants should also be included.

Women who receive breast implants for reconstruction after mastectomy are much more likely to have complications within three years than augmentation patients. Data from the FDA advisory panel meeting on Inamed's silicone breast implants in October of 2003 indicated that 46% of reconstruction patients and 20% of augmentation patients had to have at least one additional operation within three years of receiving implants. Despite the tens of thousands of reconstruction patients who have had silicone gel implants as part of the FDA approved adjunct studies, few have been studied for more than a few months. This should be unacceptable to the FDA. Instead, the FDA should require well-conducted long-term research to determine why reconstruction patients experience more complications than augmentation patients, regardless of whether the implants are silicone or saline. In addition, a thorough assessment of the health effects of silicone gel leakage and migration is essential for augmentation and reconstruction patients.

We support the draft guidance recommendation that sponsors provide a description of cancer treatments on all reconstruction patients and on reconstruction and augmentation patients who develop breast cancer during the course of the study.

We are concerned about the statement in the draft guidance that seems to imply that high loss to follow-up is acceptable. Since breast implants can stay in a woman's body for many decades, the FDA should expect sponsors to pay for follow-up visits and find other strategies to ensure that very few patients are not lost to follow-up.

Section 9.3

We support the recommendation in the draft guidance that sponsors collect information on incidence, timing, and type of new breast cancer diagnosis after implantation, including interference with mammograms or delayed diagnosis.

Previous studies on the possible health effects of breast implants on breastfeeding and offspring are inadequate. Data on lactation complications are needed and breast milk

should be carefully tested to discover if it has been contaminated with chemicals from breast implants. The breastfed children of implanted women need to be studied for several years to determine if there are any adverse reactions compared to an appropriate control group, such as siblings breastfed before implants.

We are concerned that the guidance states that "the Core study is not designed to examine a potential linkage between breast implants and the development of CTDs." A comprehensive Core Study should examine the impact of implants on health and mortality from all causes. Since well-designed research has indicated a statistically significant increase in deaths from suicide, brain cancer, and respiratory diseases among women with breast implants, as well as a possible link between leaking implants and autoimmune diseases, the FDA should recommend the use of an established measure of depression, brain function and disease, respiratory problems and diseases, and a wide range of autoimmune diseases, in addition to the other signs and symptoms included in the draft guidance.

DRAFT GUIDANCE 10. Clinical Data Presentation

The FDA seeks data on the primary reason for implant removal and toward that end suggests that the sponsor preemptively create a hierarchy of reasons so that it can compartmentalize the primary reason for removal in the situations where more than one reason is given for the implant's removal. This approach is presumably an effort to ensure that rupture or health risks are listed as primary reasons, rather than cosmetic considerations that may be secondary. For example, an implant may be removed because it is broken or painful, and replaced by a larger or smaller implant because the patient takes the opportunity to change the size. On the other hand, the hierarchy might diminish the weight of the patients' reasons (such as pain in the breast) in favor of a medical diagnosis (such as capsular contracture), or in other ways fail to capture all the reasons for implant removal. The Center recommends that all the data be collected as well as the hierarchy of reasons.

Section 10.3

The FDA recommends that the sponsors collect data on each woman's age, height and weight. We recommend the additional collection of data on each woman's race or ethnicity.

DRAFT GUIDANCE 11.4 Patient Labeling

The Center agrees with the FDA guidance that information for patients is crucial. The risk information that is currently provided in labels and in patient booklets developed by implant makers are not intelligible to many consumers. A recent Institute of Medicine report on Health Literacy points out that many adults are not able to understand health information because they have difficulty understanding tables, statistics, and other crucial types of information, in addition to difficulty reading or understanding technical jargon.

Our Center contracted with a health educator who regularly consults to the National Cancer Institute for a review of Inamed's "informed consent" booklet on breast implants. Her analysis indicated that the risk information was difficult to understand and essentially buried in a booklet that was filled with less important and sometimes extraneous information.

The Center therefore strongly recommends that "plain language" health educators, women contemplating breast implants, and women with implant problems be integrally involved in the development of product labels, patient booklets, and other materials designed to fairly inform them of the risks of breast implants. We should be mindful that a sponsor's product literature is primarily a sales pitch and women are likely to weigh it more favorably than information provided by regulatory agencies or consumer advocates.

Focus groups and pilot testing are necessary to improve these materials, but they must be targeted to the final product, to ensure that any changes made earlier in the process are effective at addressing concerns that were expressed. A sponsor's promotional materials are directed and delivered to the ultimate consumer of the breast implant-- the patient. Patients and consumer groups should be at the table to express their concerns about what constitutes reasonable, relevant, reliable and sufficient information upon which to give patients' knowing and intelligent consent.

Diana Zuckerman, Ph.D.
Jill M. Follows, J.D., M.S.N.

The National Center for Policy
Research for Women & Families
1901 Pennsylvania Avenue N.W.
Suite 901
Washington, D.C. 20006
(202) 223-4000
www.center4policy.org