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April 9, 2004

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

Re: Docket No. 2004D-0002; Draft Guidance for Industry and FDA Staff; Saline,
Silicone Gel, and Alternative Breast Implants

Dear Sir or Madam:

Pursuant to the Food and Drug Administration's ("FDA") notice in the Federal Register,^{1/} Mentor Corporation ("Mentor") respectfully submits these comments on the FDA's Draft Guidance for Industry and FDA Staff; Saline, Silicone Gel, and Alternative Breast Implants ("Draft Guidance"). Mentor is a leading medical device company that manufactures, develops, and markets specialized medical products for the urology and aesthetic surgery markets (including breast implants) around the world.

Mentor understands that the goal of FDA's new Draft Guidance is to provide recommendations for the type and amount of scientific data that the Agency believes is necessary to provide reasonable assurance of safety, and to allow women contemplating breast implantation and their physicians to make informed decisions about these devices. Mentor further understands and appreciates that a core objective of the new recommendations, is to allow FDA and the public to have a more complete understanding of device rupture. Specifically, through the new Draft Guidance, FDA is seeking more extensive information on rupture rates over time; device lifetime estimates; the modes by which implants rupture; gel migration; and the clinical consequences of rupture. Additionally, the new Draft Guidance provides recommendations concerning gel bleed testing; collection and presentation of clinical data; and PMA approval conditions. Provided below are Mentor's comments on selected new Draft Guidance recommendations concerning these issues.

^{1/} 69 Fed. Reg. 1988 (Jan. 13, 2004).

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RUPTURE INFORMATION

Published Literature (Draft Guidance Sections 7, 9.5, and 9.6):

FDA's new Draft Guidance requests additional information on rupture rates, both overt and silent; the expected lifetime of the device; the expected modes and causes of device rupture; gel migration; and health consequences that might be associated with rupture.

Mentor believes that FDA's request for long-term safety information with respect to rupture is best provided primarily through reports in the literature. Determining an accurate estimate of device rupture rate has been a key element of many clinical investigations of silicone gel-filled breast implants reported in the literature over the years. These studies, particularly those population-based studies that evaluated rupture of third generation implants, offer a number of important findings with respect to silent and overt rupture rates and life expectancy of silicone gel-filled breast implants. Mentor fully supports FDA's recommendation that would allow consideration of published clinical information on silicone gel-filled breast implants, and encourages this flexibility of informational sources to be considered, as suggested by the new guidance. In particular, Mentor believes that FDA should consider published well-designed epidemiological and other forms of studies on third generation breast implants as critical support for the PMA review process for all implants.

First generation implants, which were marketed from the early 1960s through the early to mid-1970s, had a thick elastomeric wall enclosing a firm gel. Second generation implants, marketed between the mid-1970s through the mid-1980s, had thinner shells and a less viscous gel, and third generation "low-bleed" implants, marketed from the mid- to late 1980s to the present, had a multi-layer shell with a barrier layer to reduce the diffusion of silicone gel. Mentor's PMA devices are third generation devices, and have been manufactured since 1985. Third generation devices, as reported in the literature, have been observed to demonstrate improved performance, including lower rupture rates, as compared to second generation devices.

As it considers clinical evidence of the safety and effectiveness of breast implants, FDA has suggested in the Draft Guidance that it should be flexible with respect to accepting retrospective and other types of data generated by manufacturers to address long-term outcomes of breast implants. Because sponsors have generated long-term data in prospective, multicenter trials (i.e., pivotal Core studies), and also have long-term published data to support the safety and effectiveness of breast implants, the use of additional manufacturer's data should be supplemental and not be held to Core study design standards. Mentor supports the flexibility suggested in the Draft Guidance, and

believes that any data generated by manufacturers outside of the Core Gel study to address long-term outcomes should be considered as supplemental.

Preclinical Testing of Device Life Expectancy (Draft Guidance Section 6.2):

In its new Draft Guidance, FDA has recommended that manufacturers provide mechanical test data to predict device life expectancy *in vivo*. In the new Draft Guidance, the Agency has recommended that a sponsor develop new *in vitro* rupture test methodologies that will correlate more closely with clinical rates of rupture over time.

Mentor believes that clinical data from both the published literature and manufacturer studies offer the most meaningful information for predicting device life expectancy of breast implants. Mentor is concerned that any *in vitro* rupture test methodologies that strive to mimic *in vivo* conditions might not be predictive of *in vivo* performance, in that they may not fully account for lifestyle and activity-related variables. Because development of these test methodologies is an ongoing, iterative process, and because of the current limitations of test methods in this area, Mentor does not believe that approval of breast implant PMAs should be contingent upon the development and conduct of more predictive *in vitro* mechanical tests.

While manufacturers should endeavor to develop new and improved testing methodologies, Mentor believes that FDA should acknowledge in guidance the potential limited clinical significance of these types of tests. Specifically, these tests should be described in guidance as useful primarily in establishing baseline parameters for fatigue and physical characteristics of materials.

Tissue Sampling and Health Consequences Following Rupture (Draft Guidance Section 9.3):

Release of silicone from gel-filled breast implants can occur as a result of either rupture of the envelope or diffusion of minute quantities of silicone through the intact elastomer envelope. The released silicone remains almost entirely within the confines of the fibrous capsule surrounding the implant. As described by the IOM expert Panel^{2/} report in its conclusions regarding the animal toxicology studies of silicone and silicone breast implants,

^{2/} The *Safety of Silicone Breast Implants*, a review conducted by the expert panel of the Institute of Medicine, and published in 2000, represents one of the most comprehensive examinations of the enormous body of published scientific and medical literature on the safety of silicone breast implants, including nearly 1,200 cited references, covering the overwhelming majority of literature published over the more than 30 years that silicone breast implants have been available in this country.

“depots of gel, whether free or in implants, remain almost entirely where injected or implanted. Even low molecular weight cyclic and linear silicone fluids appear to have low mobility” (Chapter 4).

These conclusions based on animal data are supported by the results of investigations where the presence of silicon was compared in tissue obtained from patients with silicone gel-filled breast implants to tissue from cadavers of women who did not have silicone gel-filled breast implants. These studies demonstrate that silicone released from implants is retained primarily within the capsule, with only very small amounts detected in surrounding breast tissue and no distant migration.^{3/}

Based on the evidence from published literature that silicone gel is predominantly restricted to the surrounding capsule and does not tend to migrate to remote sites in the body, and the lack of association between implant rupture and systemic disease, Mentor does not agree with the Draft Guidance recommendation that tissue samples be taken from women undergoing explantation of ruptured devices. Additionally, from a procedural perspective, tissue sampling presents a number of obstacles, including the need for manufacturers to obtain the right to access tissue from the patient.

FDA also recommends characterization of any local health consequences of ruptured implant (both silent and symptomatic), including severity and clinical course.

Aside from the need for reoperations in the event of rupture, potential concerns have been raised over whether migration of silicone gel after device rupture might be associated with the development of connective tissue diseases (“CTD”), rheumatic diseases, and/or related symptoms. The IOM expert panel concluded that the evidence does not support an association of silicone breast implants with defined or atypical connective tissue disease. The composite of well-designed, CTD and related population-based epidemiology studies that have evaluated this issue since the IOM report support this conclusion.^{4/} Based on the evidence from published literature pertaining to health consequences and the characterization of health consequences that will be reported in

^{3/} See e.g., Evans, G.R.D., and Baldwin, B.J. 1997. From cadavers to implants: silicon tissue assays of medical devices. *Plast. Reconstr. Surg.* 100(6):1459-65.

^{4/} See, e.g., Fryzek et al. 2001. Self-reported symptoms among women after cosmetic breast implant and breast reduction surgery. *Plast. Reconstr. Surg.* 107:206-213; Berner et al. 2002. Comparative examination of complaints of patients with breast-cancer with and without silicone implants. *Eur. J Obstet. Gynecol. Reprod. Biol.* 102:61-66; Hölmich et al. 2003. Self-reported diseases and symptoms by rupture status among unselected Danish women with cosmetic silicone breast implants. *Plast. Reconstr. Surg.* 111:723-732; Gaubitz et al. 2002. Silicone breast implants: correlation between implant ruptures, magnetic resonance spectroscopically estimated silicone presence in the liver, antibody status and clinical symptoms. *Rheumatology* 41(2):129-3; and Contant et al. 2002. A prospective study on silicone breast implants and the silicone-related symptom complex. *Clin. Rheumatol.* 2:215-9.

Mentor's Core study, Mentor believes that this body of knowledge adequately addresses this concern, and no additional data requirements should be recommended, other than to acknowledge that in post-approval Core Gel follow-up, data on local complications will be collected.

GEL BLEED (Draft Guidance Section 6.5)

The Draft Guidance recommends that a sponsor develop a new gel bleed test that more closely mimics conditions in the body (e.g., incubate the breast devices in a lipid-rich medium prior to testing and conduct the testing in a physiologic environment). Additionally, FDA recommends that, as part of these *in vitro* gel bleed tests, sponsors identify and quantify the chemicals that bleed out of the shell over time (including platinum species), and the rate at which they bleed out.

Mentor agrees that current gel bleed test methods do not closely replicate conditions in the body, but rather, significantly exaggerate bleed. Consistent with the intended objective of these tests as designed, the primary value of current gel bleed tests is to provide reproducible comparative performance results between different components and device models. The Draft Guidance recommendation to incubate devices in a "lipid-rich" medium prior to testing also would not replicate *in vivo* conditions. In the *in vivo* environment, the mammary implant is surrounded by a collagenous, fibrous capsule, and is not in direct contact with fatty breast tissue. Rather, the implant is in direct contact with aqueous extracellular fluid and the fibrous capsule, which are not significantly lipid in nature. It is well recognized that the components of silicone bleed, including low-molecular weight silicone extractables, are not appreciably soluble in water (most are, in fact, virtually insoluble in water). Therefore, "silicone bleed" tends to accumulate on the surface of the device, such that the process eventually slows or stops. This phenomenon occurs because diffusion is driven by a concentration gradient or difference through the shell, and *in vivo*, there is little diffusion gradient maintained.

As noted above, published studies demonstrate that silicone released from implants is retained primarily within the capsule, with only very small amounts detected in surrounding breast tissue, and no distant migration. Further, given that a number of well-conducted epidemiological studies have demonstrated no association between silicone gel from implants and adverse health effects, it is unclear what significant benefit would be gained from further focus on *in vitro* testing. Therefore, Mentor does not support the recommendation for further development of *in vitro* gel bleed test methods.

POSTAPPROVAL REQUIREMENTS (Draft Guidance Section 9.7)

The Draft Guidance discusses continued follow-up of Core study patients; additional studies to address modes and causes of rupture; patient education; labeling and informed consent; physician education; and a patient registry to facilitate long-term monitoring of patient outcomes and related data as recommended conditions of approval.

Continued Follow-up of Core Study Patients:

Although Mentor agrees that Core Study patients should be actively followed for 10 years which is consistent with Mentor's Core Gel protocol, we believe that the guidance should clarify that follow-up visits past 2 years may be conducted post-approval. As part of this post-approval process and consistent with Mentor's Core Gel protocol, the participants in the MRI substudy portion of Mentor's Core Gel Study will have MRI screenings at 2-year intervals.

Additional Studies to Address Modes and Causes of Rupture:

This recommendation, as written, will create uncertain interpretation for FDA and sponsors with regard to the types of studies that could be conducted. Mentor recommends that this bullet be clarified to refer to postapproval explant analyses. Mentor believes that its current and continuous complaint and explant analyses, as part of Mentor's comprehensive Quality Assurance program, will continue to provide information on the modes and causes of rupture. Additionally, Mentor suggests that the results of these evaluations be submitted to FDA in Annual Reports.

Physician Education:

Mentor agrees with the Draft Guidance recommendation that physicians involved in breast implantation be thoroughly trained in the procedure. Through the unique circumstances of silicone gel-filled breast implant use in Mentor's Adjunct studies during the 1990s, many physicians have significant experience with the implantation of silicone gel breast implants. Since 1992, a significant number of investigators have been enrolled in the Mentor Adjunct Study, which allows approved investigators to implant silicone gel implants into patients for reconstruction and revision indications. These physicians, through use over the years, have become well trained in the surgical techniques of implanting gel devices.

Currently available professional education initiatives augment this physician training and experience. For example, the American Society of Plastic Surgeons ("ASPS") has sponsored instructional courses and has held annual symposia to provide ongoing in-depth reviews of safety and outcomes data related to breast reconstruction and breast augmentation. In addition, ASPS has developed a web-based, outcomes data-collection tool, allowing for national benchmarking and comparison of an individual surgeon's outcomes against that benchmark. The society is also funding breast implant research to educate its membership, to ensure patient safety, and to improve patient outcomes. All of these initiatives are significant tools to training and maintaining surgical education and verification.

Mentor will work in conjunction with ASPS and other professional societies to develop surgical training seminars. These seminars will focus on surgical techniques, methods for the detection of ruptures, and the overall risks and complications associated with silicone gel-filled breast implants. Mentor will also provide support materials for this training, such as product labeling and relevant literature.

Patient Registry:

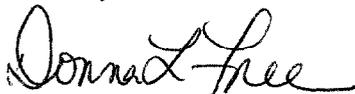
The recent Draft Guidance document indicates that the FDA may require, as a postapproval condition, the establishment of a patient registry. Mentor agrees with the concept of a *voluntary* breast implant patient registry, and believes that such a registry should be a secure database that has been developed and is administered by an independent unbiased source or group. Data from the registry should be accessible for analysis (redacted of patient identification) and periodic reports may be published discussing implant trends. Given the nature of this initiative, Mentor proposes that this element of the new Draft Guidance be implemented as part of PMA postmarket conditions of approval.

One example of such a database discussed during the October 2003 Advisory Panel meeting already has been established by the American Society of Plastic Surgeons (“ASPS”). Specifically, the ASPS has developed a Tracking Outcomes in Plastic Surgery (referred to as “TOPS”) registry, which collects plastic surgery procedural data, and clinical outcomes, and also is capable of collecting satisfaction data from patients themselves.

A breast implant registry is embedded within the Internet data-collection tool of TOPS. This registry (National Breast Implant Registry or “NBIR”) can track information, such as the number of implants placed or removed, clinical indications, type of facility, anesthesia administered, and short-term complications. The registry was designed to allow physicians to track implanted and explanted devices of their highly mobile patients. NBIR has been sufficiently successful in its design that it has attracted international interest. It has served as the template for IBIR, the International Breast Implant Registry, which is poised to become the standard for the European community, Australia, and South America. Thus, Mentor believes that TOPS and NBIR data collection efforts could be the registry of choice to trace implant-related data and outcomes.

Mentor appreciates your considerations of the aforementioned comments. If you have any comments or questions, please do not hesitate to contact us.

Sincerely,



Donna L. Free

Vice President, Regulatory Submissions