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

*Re: May 23, 2005 Citizen Petition, Docket No. 2005P-0204/CP1  
("May 23 Petition")*

Public Citizen; The National Women's Health Network; Breast Cancer Action; Command Trust; Consumer Action; Suzanne Parisian, MD; Sidney M. Wolfe, MD; The National Organization for Women; North Carolina Consumers Council; In the Know; the Massachusetts Consumers' Coalition; National Research Center for Women & Families; Our Bodies Ourselves; Breast Cancer Fund; The Women's Bioethics Project; Toxic Discovery; Women's Community Cancer Project; African American Women In Touch; Linda MacDonald Glenn; and Marc Heyison, President/Cofounder of Men Against Breast Cancer, petitioners in the above-captioned matter, hereby submit this supplement to their May 23 Petition in response to a July 28, 2005 press release from Mentor Corporation ("Mentor") that the Food and Drug Administration ("FDA") has issued an "approvable letter" to Mentor in connection with its pre-market application ("PMA") for silicone gel-filled breast implants ("silicone breast implants"). For the reasons stated below, petitioners respectfully request that FDA withdraw its approvable letter to Mentor, and reiterate their request that the Agency deny the company's PMA for silicone breast implants.

Dockets Management Branch  
Food and Drug Administration  
September 21, 2005  
Page 2

I. **As Noted in the May 23 Petition, Post-marketing Commitments Cannot Sustain a Finding that a Class II Medical Device Is Safe and Effective.**

FDA's "approvable letter" to Mentor is not a public document. However, according to a Mentor press release dated July 28, 2005, the letter "stipulates a number of conditions which Mentor must satisfy in order to receive FDA approval to market and sell silicone gel-filled breast implants in the United States." Mentor Press Release, July 28, 2005, "Mentor Receives Approvable Notification from FDA for its Silicone Gel-Filled Breast Implants." The Mentor press release also indicates that "the conditions outlined in the approvable letter are generally consistent with the . . . deliberations" of an FDA Advisory Panel that in April 2005 reviewed the Mentor PMA and recommended its approval to FDA. *Id.* The Advisory Panel's recommendation of approval was conditioned on Mentor's commitment to meet *nine* post-approval requirements. If Mentor's press release is accurate, the FDA approvable letter contains the same, or similar, post-marketing requirements as the Advisory Panel recommendation.

A central point of the May 23 Petition is that post-marketing commitments *cannot* substitute for an affirmative showing by Mentor, *before* FDA approval, that its silicone breast implants are safe and effective. Mentor's silicone implants are Class III medical devices and, as discussed in the May 23 Petition (at p. 2), the manufacturers of such devices bear the burden of affirmatively providing a reasonable assurance of their products' safety and effectiveness *before* the products are approved and sold on the market. Approval of the Mentor PMA on the basis of post-approval commitments to

Dockets Management Branch  
Food and Drug Administration  
September 21, 2005  
Page 3

conduct additional safety studies, in the absence of an adequate pre-approval showing by Mentor that its silicone breast implants are safe, would contravene the requirements of the Federal Food, Drug and Cosmetic Act (“FFDCA”) and would be inconsistent with FDA’s longtime treatment of silicone implant products. Such approval would therefore constitute arbitrary and capricious Agency action in violation of the Administrative Procedures Act (“APA”). Furthermore, as both the Agency and a report by the IOM have acknowledged, FDA has limited ability to enforce postmarket surveillance such as commitments made by Mentor to conduct safety studies after approval.

As discussed in detail in the May 23 Petition, Mentor has thus far failed to provide reasonable assurances of its products’ safety. The record demonstrates that the updated safety data on which the company relied to prove the safety of its breast implants — data submitted to FDA mere months after Mentor received a “major deficiency” letter from FDA highlighting the inadequacies of the company’s safety data — were insufficient to allay longstanding FDA and public concerns regarding the safety of silicone breast implants, and did not meet the criteria set forth in the FDA Draft Guidance incorporating the best and latest scientific thinking on the issue of silicone breast implant safety. *See* May 23 Petition at 14-25.

Specifically, as is made clear in the FDA Staff Review of the Mentor PMA, the Core Study and Sharpe-Collis Study on which Mentor principally relied were of limited or no value in resolving the three main safety concerns relating to silicone implants: (1)

Dockets Management Branch  
Food and Drug Administration  
September 21, 2005  
Page 4

implant ruptures over the lifetime of the device; (2) gel bleed and migration; and (3) regional and local health complications arising from ruptures and associated gel migration. This anecdotal, single physician study fails to sufficiently meet the standards for valid scientific evidence as set forth by the Draft Guidance document. Moreover, FDA scientists estimated that even if the very low rupture rate that Mentor estimated were accurate, that would result in 22,500 silent implant ruptures per year in the U.S. *Transcript of Advisory Panel Meeting on Mentor's PMA*, April 13, 2005 (“*Mentor Transcript*”) at p. 183 (testimony of FDA’s Dr. Sahar Dawisha).

The Advisory Committee purported to address these unresolved safety concerns by conditioning its approval recommendation on Mentor’s commitment to expand its Core Study data, *after approval and marketing of its silicone breast implant products*, in an effort for the Agency and an Agency’s Advisory Committee in 5 years to better assess the long-term safety effects of silicone breast implants. (May 23 Petition at 13-14, 26-27). FDA’s “approvable letter” to Mentor appears to take the same “cart before the horse” approach, permitting approval and marketing of Mentor’s breast implants despite the current absence of adequate safety data, on the theory that such data will be forthcoming from Mentor sometime in the future. The law, however, does not allow for this “approve first, test later” approach, which exposes consumers to potentially unsafe medical devices. Any uncertainties as to the safety of a Class III medical device *must* be resolved in favor of non-approval – especially where, as in the case of Mentor’s silicone

Dockets Management Branch  
Food and Drug Administration  
September 21, 2005  
Page 5

breast implants, the product confers very little benefit over approved alternate devices, such as saline implants.

Indeed, as discussed in the May 23 Petition, the nature and scope of the post-marketing conditions imposed by the Advisory Committee, and apparently adopted in some form by FDA itself, strongly support *denial* of the Mentor PMA. The fact that Mentor has indicated that it would voluntarily undertake, on a post-approval basis, important safety studies highlights the fact that the company failed to provide FDA with evidence of the safety of its products in its PMA, as set forth in the “major deficiency” letter and FDA Draft Guidance.

For example, the long-term post-marketing studies that the Advisory Panel recommended imposing on Mentor as a condition of approval are some of the very same studies that FDA, in its Draft Guidance and “major deficiency” letter, indicated were necessary if Mentor were to meet its pre-approval statutory burden and adequately address longstanding FDA concerns about the safety of silicone implants over the lifetime of the device, gel migration, and related regional and local health consequences. Similarly, Mentor’s agreement to include in its post-approval studies women whose implants have ruptured but have not been replaced simply confirms that the studies that Mentor conducted in response to FDA’s Draft Guidance and “major deficiency” letter were inadequate because of their exclusion of this important subpopulation and failure to capture the data prior to PMA submission. In short, the Mentor post-approval conditions

Dockets Management Branch  
Food and Drug Administration  
September 21, 2005  
Page 6

simply expose the deficiencies of its pre-approval scientific data. The law does not permit the company to remedy its pre-approval failures after approval during which consumers are exposed to a product of questionable safety.<sup>1</sup>

That the post-approval conditions identified by the Advisory Panel are an insufficient basis for FDA approval is further confirmed by the fact that these commitments are substantially similar to those made in a silicone breast implant PMA filed by Inamed Corp. that was rejected by FDA in January 2004, over the “approval with conditions” recommendation of another Agency Advisory Panel.<sup>2</sup> That 2003 Advisory Panel also recommended approval, but the FDA wisely rejected the recommendation because of the lack of long-term safety data and the unenforceable conditions of

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<sup>1</sup> Indeed, as noted in the May 23 Petition (at 28-29), some of Mentor’s post-approval commitments resemble the types of commitments made by manufacturers that qualify for an Investigational Device Exemption (IDE) from FDA. An IDE, which Mentor already has for its Core Study, allows sponsors of unapproved devices to ship their products lawfully in interstate commerce, in order to permit investigations of that device. An IDE requires submission to the Agency of an investigational plan including a study protocol, risk analysis, monitoring procedures, training of clinical investigators, valid informed consent forms, and other relevant information – in other words, precisely the kind of information the Advisory Panel has required Mentor to produce post-approval with respect to silicone implants, during which time Mentor’s implants will be aggressively marketed to women as reasonably safe and effective. The parallels between the Mentor conditions and the IDE requirements compel the conclusion that the Mentor products are most appropriately treated in the way they are currently treated, *i.e.*, as available only in the “stringently controlled” clinical setting reserved for IDE products.

<sup>2</sup> Inamed, like Mentor, submitted updated data on safety that was reviewed by the Advisory Committee Panel in April 2005. The Panel, however, voted *not* to recommend approval of the Inamed PMA. Inamed has since submitted a revised PMA for FDA’s consideration. The issue of Inamed’s revised PMA is the subject of a separate supplement to the May 23 Petition.

Dockets Management Branch  
Food and Drug Administration  
September 21, 2005  
Page 7

approval. There is no justification for FDA to reverse course and now approve Mentor's product based on the very same tenuous post-approval commitments that the Agency deemed to be an insufficient basis on which to approve the Inamed PMA.

The FDA Commissioner recently emphasized that the Agency must consider the enforceability of conditions of approval that it imposes on a product, when he discussed Barr Laboratory's application to sell Plan B over-the-counter. While petitioners are in no way endorsing the Agency's statements concerning the age restrictions at issue in the Plan B decision, the FDA should be consistent on the principle of enforceability. If the Commissioner states that the Agency should not approve a product with conditions that it is unable to enforce, that should apply to all the products that the FDA regulates — including silicone gel breast implants and other medical devices.

The May 23 Petition provides additional arguments as to why post-approval conditions are inadequate to satisfy the pre-market approval regime governing Class III devices. First, such conditions are rarely effective, and, historically, have not been effective when applied to Mentor itself. *See* May 23 Petition at 29-30 [citing Center for Radiological Devices and Health, "Condition of Approval Studies as a Postmarket Tool for PMA Approved Cohort 1998-2000" (March 2005), and noting that manufacturers *routinely* shirk their commitments to provide such studies, that FDA has limited means of enforcing fulfillment of these commitments, and Mentor's own history of non-

Dockets Management Branch  
Food and Drug Administration  
September 21, 2005  
Page 8

compliance with conditions of approval studies exemplifies the problem]. Second, the many flaws in the proposed post-market activities set forth in Mentor's own PMA further call into question the company's commitment to effective post-approval conduct. *Id.* at 30-31. And third, even if Mentor were willing to abide by the conditions imposed by the Panel, there would be significant practical impediments to the effective implementation of these conditions. *Id.* at 31.

In summary, post-market conditions are an ineffective, inadequate, and an unlawful proxy for pre-market safety determinations in cases involving Class III medical devices. FDA has already recognized this, having rejected the Inamed PMA for silicone breast implants over the "approval with conditions" recommendation of an FDA Advisory Panel. Indeed, because of its longstanding and unresolved concerns regarding the long-term safety of silicone implants, FDA has *never* approved a PMA for such implants. Approving Mentor's PMA on the basis of the company's post-market commitments, in the absence of pre-market data that reasonably establishes safety, would constitute an unwarranted, 180-degree departure from the Agency's longtime approach both to silicone breast implants in general and, in particular, to the use of post-market conditions as a means of establishing safety of such implants. Such an approval would therefore constitute arbitrary and capricious Agency action, in violation of the APA. *See* May 23 Petition at 37-39 (discussing APA standard and case law).

Dockets Management Branch  
Food and Drug Administration  
September 21, 2005  
Page 9

**II. Information Not Addressed During the Advisory Panel Meetings in April 2005 Also Supports Rejection of the Mentor PMA.**

There are two important pieces of information that were not discussed during the FDA Advisory Panel on silicone gel breast implants, and that further support withdrawal of the FDA approvable letter to Mentor and rejection of the Mentor PMA for silicone breast implants.

First, the Advisory Panel failed to consider important information bearing on the gel bleed rate of the Mentor implants. Specifically, although Mentor describes its silicone gel breast implants as low bleed, we have been informed that the patches in Mentor's silicone implants are *not* made of low bleed material. At the Advisory Panel meeting on April 13, Commander Samie Allen of the FDA stated that there were unresolved issues regarding gel bleed testing, but did not state what they were or what Mentor was doing to "adequately identify and quantify the gel bleed constituents and the bleed rate of those constituents." *Mentor Transcript* at 142. The fact that Mentor has never resolved the gel bleed issue makes it all the more incumbent on Mentor to resolve these

Dockets Management Branch  
Food and Drug Administration  
September 21, 2005  
Page 10

unanswered questions and to provide FDA with accurate analysis of the amount that the patch and shell will bleed inside a woman's body over the lifetime of the implant.<sup>3</sup>

Second, the Advisory Panel failed to consider important facts that call into question the relevance and generalizability of the European Sharpe/Collis data provided by Mentor as their long-term rupture data. Dr. Dawisha of the FDA pointed out at the Advisory Panel meeting on April 13, 2005 that there were several fundamental differences in the Sharpe/Collis sample compared to the U.S. core study: "because of the differences in patient characteristics, implant type, implant placement compared to the U.S. Core Study; and because one, rather than serial, MRI was performed, the ability of these data to predict a long-term rupture rate or a rate over time is limited." *Mentor Transcript* at 175.

However, neither Dr. Dawisha nor anyone from Mentor or the FDA pointed out a further aspect of the Sharpe/Collis data that undermines the generalizability of the Sharpe/Collis study: the silicone breast implants used in the Sharpe/Collis study *may have been made differently* than the silicone gel breast implants made in the United States. It is our understanding that for the last several years, silicone gel breast implants used in the U.K. have not been made in the U.S., and are instead made in Leiden, Netherlands. No information was provided to the Advisory Panel about where the silicone breast implants

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<sup>3</sup> We understand that Mentor's demonstrator silicone implant models *are* made with a low bleed patch, but the silicone implant models marketed by Mentor and used for surgery are not. FDA should investigate this discrepancy.

Dockets Management Branch  
Food and Drug Administration  
September 21, 2005  
Page 11

in the Sharpe/Collis study were made; their exact design and material specifications; or the process specifications for their manufacturing, assembling, packaging, and sterilizing, compared to implants in the Core Study. Control systems for implants used in the U.K. compared to the U.S. were also not specified. Even if the implant components were made in the U.S., the final product may differ from U.S. implants, and the FDA needs to examine any differences.

In addition, the FDA should also statistically quantify the expected 10-year rupture rate of Mentor silicone gel breast implants, extrapolating from the data provided, as it did for Inamed's product. This would require adjusting the rupture rate to take into account significant subpopulations that were not included in the Sharp/Collis study, including women with capsular contracture, women whose implants were removed, and women with implants for reconstruction and revision, as well as differences in surgical procedures in the study compared to the U.S., differences in the manufacture of the implants, and other significant differences. In addition, FDA should also require Mentor to supply long-term data on the effect of the Mentor implants on breast cancer patients.


The new information discussed at pages 9-10 raises serious questions regarding both Mentor's failure to meet certain FDA concerns on issues such as gel bleed, and regarding the relevance of those studies that Mentor has pointed to in support of the safety and effectiveness. At a minimum, this information compels further FDA review of the Mentor application. In our view, it compels outright denial of that application.



Dockets Management Branch  
Food and Drug Administration  
September 21, 2005  
Page 12

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To summarize, any decision to approve Mentor's PMA in the face of (1) the statutory framework requiring a PMA applicant to affirmatively demonstrate safety and effectiveness *before* the marketing of its product, and (2) the new information bearing on the gel bleed issue and the relevance and generalizability of the Sharpe/Collis European study would be arbitrary and capricious and contrary to law. See May 23 Petition at 37-39. We therefore urge the Agency to reconsider its approvable letter to Mentor, to withdraw that letter, and to deny Mentor's PMA.

  
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