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May 23, 2005

**VIA MESSENGER**

Dockets Management Branch  
Food and Drug Administration  
Room 1061  
5630 Fishers Lane  
Rockville, MD 20852

Dear Sir or Madam:

Please find enclosed an original and four copies of a Citizen Petition we have submitted to the FDA on behalf of several organizations and individuals.

This petition urges FDA, pursuant to 21 U.S.C. § 360e(d) of the Federal Food, Drug, and Cosmetic Act, to deny the pre-market approval applications of Mentor Corporation and Inamed Corporation for approval of silicone-gel filled breast implant products.

If you have any questions concerning this Petition, please call Bill Schultz at (202) 778-1820 or Carlos Angulo at (202) 778-1811.

Thank you for your attention to this matter.

Sincerely,

William B. Schultz  
Carlos T. Angulo

Enclosure

2005 P-0204

CPI

May 23, 2005

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

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Docket No. \_\_\_\_\_

**CITIZEN PETITION**

Public Citizen; The National Women’s Health Network; Breast Cancer Action; Command Trust; Eugene Goldberg, PhD; Suzanne Parisian, MD; Sidney M. Wolfe, MD; The National Organization of Women; The National Research Center for Women and Families; Consumer Action; In the Know; the League of United Latin American Citizens; the Massachusetts Consumers’ Coalition; Men Against Breast Cancer; The North Carolina Consumers Council Inc.; Our Bodies, Ourselves; The Breast Cancer Fund; The Women’s Bioethics Project; Toxic Discovery; and the Women’s Community Cancer Project (“Petitioners”) hereby submit this Citizen Petition under 21 C.F.R. § 10.30. Petitioners request that the Food and Drug Administration (“FDA” or “the Agency”), pursuant to 21 U.S.C. § 360e(d), deny Mentor Corporation’s (“Mentor”) and Inamed Corporation’s (“Inamed”) pending applications for premarket approval (“PMAs” or “applications”) to market silicone gel-filled breast implants (“silicone implants”).<sup>1</sup>

**A. Action Requested**

This Petition requests that FDA determine that neither Mentor nor Inamed has met its statutory burden of providing a reasonable assurance that its silicone implant products are safe, and that the Agency therefore deny both companies’ PMAs. This decision would be consistent

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<sup>1</sup> A brief description of the individuals and organizations joining this petition is set forth as Appendix A hereto.

with FDA's previous determinations regarding Mentor's and Inamed's PMAs, and with longstanding Agency policies and practices regarding silicone implants.

**B. Statement of Grounds**

**1. Introduction and Summary**

Under FDA regulations, silicone implants are classified as Class III medical devices, which must receive FDA approval before they may be marketed. 21 C.F.R. § 878.3540. The Federal Food, Drug, and Cosmetic Act ("FFDCA"), in turn, *requires* FDA to deny any application for approval of a Class III device if "there is a lack of showing [by the applicant] of reasonable assurance that [the device] is safe under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 360e(d)(2)(A). It is clear from the statute that the manufacturer bears the affirmative burden of providing "reasonable assurance" of safety. *See also* 49 Fed. Reg. 50878 (December 31, 1984) (noting that, in general, "the laws and regulations under which [FDA] operates place the burden of proof of safety . . . on the manufacturer, except for traditional foods and cosmetics [and, now, dietary supplements].").

In general, in determining whether a Class III device is safe, the risks of using the device are balanced against the device's therapeutic benefits. 21 U.S.C. § 360c(a)(2)(C). In other words, where a Class III device confers some therapeutic benefit, safety may be established even if the device presents certain health risks, if the benefits outweigh those risks. The silicone implants at issue in this case, however, confer very little benefit over approved alternative breast implant products. In these circumstances, *any* concerns regarding potential health risks associated with the device must be resolved in favor of denial of approval. It is not enough for a manufacturer to show that the evidence of health risks is inconclusive or does not clearly support

a finding that a product is unsafe. Rather, the manufacturer must be able to demonstrate that the data affirmatively support the conclusion that its product does not entail significant risks.

As demonstrated in detail below, neither Mentor nor Inamed has satisfied its burden under the statute of affirmatively providing reasonable assurance that its silicone implant products are safe. Their PMAs must therefore be denied.

Any determination by FDA that the Mentor or Inamed products are in fact safe would represent an unwarranted, 180-degree departure from FDA's longstanding and consistent treatment of this issue, and would constitute arbitrary and capricious conduct in violation of the Administrative Procedures Act ("APA"), 5 U.S.C. §§ 701 *et seq.* During the last decade and a half, FDA has repeatedly identified significant long-term safety issues with respect to silicone implants. Most recently, in a January 2004 Draft Guidance that represents FDA's latest and best scientific learning on the subject, the Agency again identified these safety issues and set forth exacting standards for the approval of PMAs for silicone implant products.<sup>2</sup> In fact, FDA has *never* approved any PMA for a silicone gel breast implant product,<sup>3</sup> a testament to the heavy burden of proof placed on applicants to fully address FDA's and the public's longstanding and significant safety concerns, and to the applicants' failure to present evidence adequately addressing these concerns.

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<sup>2</sup> "Draft Guidance for Industry and FDA Staff: Saline, Silicone Gel, and Alternative Breast Implants," Center for Device and Radiological Health, January 13, 2004 ("Guidance" or "Draft Guidance").

<sup>3</sup> See June 2004 FDA Breast Implant Consumer Handbook ("*FDA Consumer Handbook*"), at 15 ("As of the date of this handbook, no company has PMA approval for a silicone gel-filled breast implant. . . . [*A*]ll silicone gel-filled breast implants are considered investigational." (Emphasis in original)).

FDA approval of the Mentor and/or Inamed applications would also constitute a dramatic reversal of the Agency's position regarding those applications in particular – a position that thus far has been fully consistent with longstanding FDA policies and practices, and with the latest and best Agency science. As to Inamed, FDA in January 2004 declined to follow the recommendation of an FDA Advisory Committee Panel that the company's PMA be granted and issued a "not approvable" letter in January 2004. As to Mentor, FDA in March 2004 issued a "major deficiency" letter.<sup>4</sup> While these letters are not publicly available, the Agency's descriptions of the letters in its Staff Summaries of the pending PMAs indicate that FDA premised its decisions on the failure of the manufacturers to provide long-term safety data that meets the standards set forth in the Draft Guidance and that adequately addresses longstanding FDA safety concerns regarding silicone implants. Both Mentor and Inamed have submitted updated data that they claim meets FDA's standards. But the Agency's own review of that updated data clearly has concluded that Mentor and Inamed still have not addressed the concerns that formed the basis for the Agency's past refusals to approve their respective applications.<sup>5</sup>

On April 12-13, 2005, an FDA Advisory Panel voted to recommend Agency approval of the updated Mentor PMA, but voted against recommending approval of the updated Inamed PMA. FDA should decline to follow the Panel's Mentor recommendation, which has no basis in the data, is inconsistent with longstanding FDA policies and practice, and improperly substitutes

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<sup>4</sup> The "not approvable" letter to Inamed and the "major deficiency" letter to Mentor are hereafter referred to collectively in this Petition as the "previous rejection letters."

<sup>5</sup> See FDA Summary Panel Memorandum to General and Plastic Surgery Devices Advisory Review Panel Regarding Mentor Corporation Silicone Gel-Filled Breast Implants, March 2, 2005 ("*FDA Mentor Summary*"); FDA Summary Panel Memorandum to General and Plastic Surgery Devices Advisory Review Panel Regarding Inamed Corporation Silicone Gel-Filled Breast Implants, March 2, 2005 ("*FDA Inamed Summary*").

post-marketing conditions for the statutory requirement that a Class III device be deemed safe *before marketing*. While the Panel's recommendation as to the Mentor application should be rejected by FDA, the Panel decision to recommend denial of the Inamed application is consistent with the FDA precedents, policies, and science, and should be followed. Indeed, the Panel's decision on *Inamed*, which submitted data that was in many ways superior to Mentor's, is compelling evidence that the Panel's *Mentor* recommendation was inconsistent with the scientific data and incorrect.

In short, neither Mentor's nor Inamed's updated data can support an FDA decision to reverse course and determine, after already declining to approve these very same applications and for the first time ever, that a PMA for silicone implants demonstrates "reasonable assurance that the device is safe." Even if interpreted in the manner most favorable to Inamed and Mentor, the data regarding safety are inconclusive, and FDA therefore *must* deny both applications.

2. **Factual Background and Regulatory History**

a. **FDA's Decision to Require Pre-Market Approval of Silicone Implants**

FDA's policies and practices for the last three decades reflect a continued concern with the safety, especially the long-term safety, of silicone implants. As a result, *no* silicone gel breast implant product has ever been approved by the Agency as safe and effective for general use. Indeed, FDA has never approved any PMA application for injectable liquid silicone for a cosmetic indication.

Until 1976, there was no formal mechanism for FDA regulation of any kinds of breast implants, although such products were available on the market at that time. That year, FDA acquired a specific statutory basis for the regulation of medical devices, including breast implants, with Congress' enactment of the Medical Device Amendments of 1976. 90 Stat. 539

(1976), *subsequently codified at* 21 U.S.C. § 360c *et seq.* In 1978, an FDA Advisory Panel recommended characterizing breast implants as “Class II” devices, which would not have required Agency premarket approval. However, recognizing the health risks associated with silicone implants, FDA declined to follow the Advisory Panel recommendation, first proposing in 1982 and finalizing in 1988 the recharacterization of breast implants as “Class III” devices under the statute. 47 Fed. Reg. 2829 (January 19, 1982) (proposed rule); 53 Fed. Reg. 23874 (June 24, 1988) (final rule); 21 C.F.R. § 878.3540. This recharacterization meant that even manufacturers of already-marketed breast implants products had to submit by 1991 new PMAs demonstrating their products’ safety and effectiveness. 56 Fed. Reg. 14620 (April 10, 1991) (final rule)). As discussed above, a Class III device manufacturer bears the burden of *affirmatively demonstrating* safety and effectiveness. Manufacturers submitting PMAs for silicone implants in 1991 had had at least *10 years* -- since first notice of the reclassification of these products to Class III in 1982 -- to prepare safety and effectiveness data for their products.

Nevertheless, in April 1992, after extensive reviews of manufacturers’ safety and effectiveness data, FDA ruled on pending PMAs for *silicone* implants by restricting the use of such products to participants in clinical observational (known as “adjunct”) studies who sought the implants for reconstruction or revision (replacement of an existing implant), as opposed to cosmetic augmentation, purposes. The Agency determined that while the availability of silicone implants for reconstruction or revision, under strict controls, was appropriate, PMA applicants had not made the safety showing needed to support general approval of their applications. This state of affairs exists today. At no time has FDA determined that silicone implants satisfy the statutory safety and efficacy requirements for Class III devices. Silicone breast implants are considered investigational, and such products are therefore not generally available on the market.

In contrast to its decision on silicone implants, FDA in 2000 approved the use of *saline* breast implants as safe and effective. These implants are generally available on the market today.

**b. The IOM Report, FDA Rupture Study, and Other Literature**

Subsequent studies confirmed FDA's view regarding the safety of silicone implants. These studies focused on, among other things, three issues that remain among the Agency's principal safety concerns regarding silicone implants and are central to the question of whether Mentor and/or Inamed's PMAs should be approved: first, the issue of rupture frequencies over the lifetime of silicone implant products; second, the issue of whether, as a result of rupture, there is "migration" of the silicone gel outside the implant shell through the body; and third, the issue of the health consequences of ruptures and associated risks of gel migration.

In 1999, the Institute of Medicine of the National Academy of Sciences published a government-sponsored report entitled "Safety of Silicone Breast Implants", Institute of Medicine (National Academy Press (2000)) ("IOM Report"). On the issues of implant ruptures, local and regional complications, and health consequences, the IOM Report was unequivocal, finding that:

- reoperations and local and perioperative complications are frequent enough to be a cause for concern (IOM Report at 5, 10);
- these complications have "significant implications for the safety" of silicone implants, because they involve risks themselves, such as pain, disfigurement, and serious infection, and may also lead to medical and surgical interventions, such as reoperations, that also have risks (*id.* at 3, 10);
- the risks posed by these complications accumulate over the lifetime of the product, but the long-term data are deficient (*id.* at 5, 10);

- “[i]nformation concerning the nature and relatively high frequency of local complications and reoperations is an essential element of adequate informed consent for women undergoing breast implantation.” (*id* at 5, 10);
- the prevalence of silicone implant ruptures for implants five years old or less was “perhaps less than 10 percent”, but would “continue to accumulate and [rupture] prevalence would increase in ensuing years.” (*id.* at 141); and that
- “[r]upture frequencies, in the past, have been considerable, and the rupture rate of current models has yet to be measured over a long period of time.” (*id.* at 4).

In 2000, FDA researchers released a study focusing on the frequency of implant ruptures.<sup>6</sup> This study identified ruptures as an important issue because of, among other reasons, the possibility of gel migration.<sup>7</sup> Indeed, as noted above, FDA has never approved injectible liquid silicone for cosmetic purposes because of safety concerns associated with migration. The FDA Study reviewed implants of an average age of 17 years and concluded that over two-thirds (69 percent) of the women studied had ruptures in one or more breasts, and that 21 percent of these women experienced gel migration outside the implant. FDA Rupture Study at 2.

Other studies of silicone implants have confirmed that ruptures are common, that they increase over time, that they are clinically initially silent, that gel migration is a common consequence of rupture, and that such gel migration has significant local and regional health consequences. In particular, a series of studies from Denmark focusing on so-called “third

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<sup>6</sup> Brown, S.L., *et al.*, “Prevalence of rupture of silicone gel breast implants revealed on MR imaging in a population of women in Birmingham, Alabama,” *Am. J. Roentgen.* 2000; 175(4): 1057-1064.

<sup>7</sup> See “Study of Rupture of Silicone Gel-filled Breast Implants (MRI Component),” May 22, 2000, Summary prepared by Center for Devices and Radiological Health, FDA (“Rupture Study Summary”), at 1, available at <http://www.fda.gov/cdrh/breastimplants/studies/birupture.html>.

generation” implants -- the most recent versions of these products, which have been on the market since the 1980’s -- have addressed such critical safety issues as silicone implant rupture rates and the related local and regional health consequences.<sup>8</sup> Another study has concluded that “[t]he prevalence of multiple surgeries necessitated by capsular contracture, pain, disfigurement, various disease symptoms, implant failure and patient anxiety” resulting from ruptures is “disturbingly high” and that one-third of implants required at least one additional surgery within a mean implant duration of six years. Marotta, *et al.*, “Silicone Gel Breast Implant Failure and Frequency of Additional Surgeries: Analysis of 36 Studies Reporting Examination of More Than 8000 Explants,” *J. Biomed. Materials – Applied Biomaterials* 1999:48(3):354-364.

Most recently, in April 2005, a study published in the *American Journal of Surgical Pathology* focusing on the gel migration issue reported that 90% of 96 women who had had silicone implants showed silicone droplets in their lymph nodes, and that 95% of these 96 women showed abnormal cells in their lymph nodes, as compared to only 33% of women who had had breast cancer surgery without the addition of silicone implants. Katzin, W., *et al.*, “Pathology of Lymph Nodes from Patients With Breast Implants,” *Am. Surg. Pathol.* 2005; 29(4): 506-510 (“Katzin”) (noting, at p. 510, that “[o]nce outside the implant, silicone is apparently able to migrate via lymphatic channels to gain access to regional lymph nodes” and

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<sup>8</sup> *E.g.*, Holmich, L.R., *et al.*, Incidence of silicone breast implant rupture, *Arch. Surg.* 2003; 138: 801-806; Holmich, L.R., *et al.*, Self-reported Diseases and symptoms by rupture status among unselected Danish women with cosmetic silicone breast implants, *Plast Reconstr. Surg.* 2003; 111(2): 723-732; Holmich, L.R., *et al.*, Untreated silicone breast implant rupture, *Plast Reconstr. Surg.* 2004; 114(1): 204-214. These studies are hereafter referred to collectively as the “Danish Studies”.

reporting evidence of silicone migration “from breast implants to various distant sites, including the upper extremity, the groin, [and] the liver . . . .”).<sup>9</sup>

**c. Inamed’s and Mentor’s PMAs, the FDA Draft Guidance, and the Recent Advisory Panel Recommendations**

Notwithstanding the accumulated evidence indicating that silicone implants, including third-generation implants, are unsafe (or, at the very least, that significant safety concerns regarding these products remain unresolved), Inamed filed a PMA seeking approval of its third-generation silicone implant products in December 2002. In October 2003, an FDA Advisory Committee Panel voted 9-6 to approve the Inamed PMA, provided that Inamed agree to undertake extensive post-market commitments as a condition of approval. *FDA Inamed Summary* at 10. In January 2004, however, FDA declined to follow the Panel’s recommendation and issued a “non-approvable” letter denying the Inamed PMA. While the contents of the “non-approvable” letter are not public, FDA has indicated in subsequent public documents that among the principal deficiencies in the initial Inamed PMA were its failure to adequately describe the rates and rates of change of implant rupture over the lifetime of the product, to describe the incidence of gel migration resulting from ruptures, and to characterize the health consequences of ruptures and associated migration. *FDA Inamed Summary* at 12, 17, 52, 62.

In December 2003, Mentor filed *its* PMA for third-generation silicone implants. The following month, and a week after FDA had denied Inamed’s PMA, the Agency released its

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<sup>9</sup> A range of other health issues associated with silicone implants also exists. One health issue that has been identified as a clear problem is the fact that silicone implants interfere with mammographies, and therefore increase the risk that breast cancer will go undetected. *FDA Consumer Handbook* at 37 (“Implants increase the difficulty of both taking and reading mammograms.”); IOM Report at 284 (noting that implants “interfere with screening mammography . . . , making a proper examination of the breast more difficult and occasionally impossible.”); *FDA Mentor Summary* at 64 (describing silicone implants’ interference with mammography as “a potential risk.”)

Draft Guidance on breast implants, including silicone implants. In that Guidance, which FDA characterized as “reflect[ing] the latest thinking in science and medicine pertaining to breast implants” (p. 1), the Agency identified the principal safety issues related to silicone implants and laid out exacting criteria for those manufacturers seeking approval of silicone implant products. For example, FDA identified device rupture and associated gel migration as “one of the primary safety concerns presented by breast implants” (*id.* at 22) and recommended that manufacturers provide the Agency with detailed, *long-term* clinical data (*i.e.*, data that can be projected out to 10 years) on the modes, causes, and rate of ruptures, and the incidence of associated gel migration. *Id.* at 23. FDA also noted that information about “complications” associated with implants “is important in determining [their] safety” and recommended that manufacturers supply it with detailed, long-term information regarding “the incidence, timing, and reasons” for all device removals, reoperations, additional surgical procedures, and other complications. *Id.* at 21.

Both Inamed and Mentor filed comments with FDA objecting to significant provisions in the Draft Guidance. Among other things, Mentor argued that FDA’s request for additional, long-term safety information regarding ruptures and related complications “is best provided primarily through reports in the [existing] literature” and that “the use of additional manufacturer’s data should be supplemental and not be held to Core study design standards.” Letter from Donna Free, Vice President, Regulatory Submissions, Mentor Corporation, to FDA Dockets Management Branch, April 9, 2004, at 2. In essence, therefore, Mentor argued that it should not be required to develop any new long-term safety data to address FDA’s concerns and, by implication, that it did not have the data and would not expend significant time and resources to develop it. Inamed went even further, essentially arguing the new standards reflected in the

Draft Guidance were unfair, because they constituted an unwarranted departure from past Agency Guidances and the treatment of the issue by the 2003 Advisory Panel, in addition to being “unnecessary and misguided in their approach.” Letter from JoAnn M. Kuhne, Senior Director, Regulatory and Clinical Affairs, Inamed Corporation, to FDA Dockets Management Branch, May 25, 2004, at 2. Neither company suggested in its comments that it intended to even attempt to meet the standards set forth in the Draft Guidance, or, certainly, that it could comply with the Guidance in a short period of time.

On March 14, 2004, FDA issued a “major deficiency” letter to Mentor declining to approve the company’s PMA for silicone implants. While the contents of that letter are also not public, FDA has indicated in subsequent public documents that the primary deficiencies in Mentor’s PMA included the company’s failure to provide sufficient long-term data to the Agency regarding (1) the rupture rate over the anticipated lifetime of the device, (2) the incidence of associated gel migration, and (3) the local and regional health consequences of implant rupture and related migration. *FDA Mentor Summary* at 87. Thus, FDA determined Mentor’s application to have been deficient in some of the very areas characterized by FDA in its Draft Guidance as among the most important in determining silicone implant safety, and in many of the areas in which the Inamed application had also been found deficient.

Notwithstanding their criticisms that the Draft Guidance imposed significant new data development and collection requirements on silicone implant manufacturers, both Mentor and Inamed returned to FDA, only months after issuance of the Draft Guidance, with updated Core Study and other data purporting to demonstrate the safety of their products. These applications were submitted (in Inamed’s case, resubmitted) for review to an FDA Advisory Panel.

Given Mentor's and Inamed's representations that they did not have, and would not develop, the data identified in the Draft Guidance, the updated data provided by the companies merely months after the Draft Guidance was published could not possibly have been adequate to meet the Guidance's standards. In anticipation of the Panel's consideration, FDA Staff reviewed both applications. As discussed in detail below, FDA determined in each case that the manufacturer's additional data was "of limited value" in addressing the major FDA safety concerns set forth in the Draft Guidance and in FDA's previous responses to the Mentor and Inamed PMAs: rupture rates, gel migration issues, and local and regional health consequences of ruptures and migration. *FDA Inamed Summary* at 40; *FDA Mentor Summary* at 79, 87.

On April 12, 2005, the FDA Advisory Committee voted to recommend that FDA deny the Inamed PMA. On April 13, however, the Panel voted to recommend that FDA approve the Mentor application, which, as discussed below, contained even less clinical and safety data than Inamed's application. Significantly, the Panel's Mentor recommendation was conditioned on Mentor's commitment to meet *nine* post-approval requirements. These requirements were similar to those imposed as conditions of the Advisory Panel's recommendation of approval for the Inamed PMA – a recommendation FDA ultimately declined to follow based on the sponsor's failure to provide a reasonable assurance of safety – and included:

- that patients sign consent forms acknowledging implant risks, including the risk of rupture and reoperation;
- that Mentor sell its product only to board certified plastic surgeons who must undertake special hands-on training in an effort to minimize the risk of rupture;
- that Mentor establish a registry to track long-term patient welfare;

- that Mentor’s labeling advise patients to get regular MRIs to identify so-called “silent” (undetected) ruptures, which make up the majority of all silicone implant ruptures;
- that Mentor complete ongoing studies to determine rupture rates up to and including 10 years, and that these studies be reviewed by an independent data monitor;
- that Mentor’s study include analysis of women whose implants have been removed, but not replaced;
- that FDA review Mentor’s post-approval data in five years; and
- that Mentor’s implants be linked to their recipients by a tracking number, in order to better study any problems that arise.

3. **Analysis**

FDA’s issuance in 2004 of a “non-approvable” letter to Inamed and a “major deficiency” letter to Mentor was consistent with the Agency’s longstanding safety concerns regarding silicone implants and with the latest and best scientific thinking on the subject, as embodied in the FDA January 2004 Draft Guidance. Any decision by FDA to reverse that course would be completely without basis, and would constitute arbitrary and capricious agency action in violation of the Administrative Procedures Act.

- a. **The updated Mentor and Inamed data failed to meet the standards identified by FDA in its Draft Guidance and previous rejection letters, and gives FDA no basis for determining that either company has now demonstrated a reasonable assurance of safety of its product.**

The crux of the matter is whether the updated data submitted by Mentor and Inamed only a few months after the FDA’s previous adverse actions on the companies’ PMAs provides FDA with a basis for reversing its position and finding that Mentor and/or Inamed has now met its statutory burden of providing reasonable assurance of the safety of its products. The answer is no. As FDA itself has already determined upon review of the updated Mentor and Inamed data,

that data are in every respect “of limited value” in responding to the principal concerns set forth in FDA’s previous rejection letters to the two companies.

FDA focused on three principal safety issues in rejecting the original Mentor and Inamed PMAs: (1) the incidence and rate of implant ruptures over time; (2) the potential for “gel migration” resulting from implant ruptures; and (3) the local and regional health consequences of rupture and gel migration. The Mentor and Inamed data submitted to FDA after the earlier denials purported to address these concerns in a manner that would satisfy the requirements of the FDA letters and Draft Guidance and would affirmatively demonstrate product safety, as required by the statute. However, the updated data remain scientifically and clinically deficient and provide no basis for an FDA reversal of position on either the Mentor or the Inamed PMA.

*i. Rupture Data*

FDA made clear in the Draft Guidance that a manufacturer seeking a PMA for silicone implants must provide long-term (*i.e.*, 10-year-projected) rupture data that will affirmatively demonstrate the safety of silicone implants over the anticipated lifetime of the device. As reflected in the IOM Report, the FDA Rupture Study, the Draft Guidance, and FDA’s previous rejection letters to Mentor and Inamed, determining the frequency of silicone implant ruptures, and whether rupture rates increase over the lifetime of the implant, has long been an important factor in efforts by FDA and others to determine the long-term safety of silicone implants.

The independent data predating the Mentor and Inamed studies indicate both that there is a significant risk of implant rupture overall, and that this risk increases over time. For example, the Danish Studies focused on women receiving implants for augmentation purposes and reported a rupture incidence rate, including both definite and possible ruptures, of 8.9 ruptures per 100 implants per year – which, using 2003 U.S. annual surgical breast implant figures and

assuming (conservatively) that only half of American women receiving implants for augmentation purposes would elect to receive *silicone* implants, would add up to 22,500 ruptures per year in patients receiving implants for augmentation purposes. An incidence rate of 9% per year would translate into an alarming and unacceptable number of ruptures at the conclusion of 10 years. As to the question of whether the rupture rate increases with device age, the Danish Studies determined that for “third-generation” implants (the category to which the Mentor and Inamed products belong), the rupture rate at 5 years was 2%, while the rate at 10 years was 15%,<sup>10</sup> although that report also suggested that the actual rates were higher, because, among other things, the data did not include any implants that had ruptured within the first three years. *FDA Mentor Summary* at 84.<sup>11</sup>

The data presented in the updated Core and adjunct studies submitted by Inamed and Mentor purported to project rupture rates over a 10-year period, in order to attempt to establish the long-term safety of the companies’ products. These data, however, were woefully inadequate to allay the concerns set forth in the IOM Report, FDA Draft Guidance, and elsewhere. For example, as to Inamed, the FDA staff review found that:

- The Inamed Core Study’s reliance on full 3-year MRI data and partial fourth-year data on clinically observed ruptures made it “difficult to reasonably predict the probability of rupture through year 10.” *FDA Inamed Summary* at 40; *see also Transcript of Advisory Panel Meeting on Inamed’s PMA Application*, April 12, 2005 (“*Inamed Transcript*”), at 162 (FDA staff presentation noting sponsor’s own recognition that “three to four year

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<sup>10</sup> Holmich, L.R., *et al.*, Incidence of silicone breast implant rupture, *Arch. Surg.* 2003; 138:801-806.

<sup>11</sup> FDA also noted that the Danish Studies assumed a linear rupture rate curve, which could not be assumed with only two data points used, a further possible source of underestimates. *Id.*

data [are] insufficient to describe the rate of rupture over the expected lifetime of the device”). Specifically, FDA noted that the “limited” data created significant uncertainty in the rupture rate curve over 10 years and used its own analysis to demonstrate how dramatically different rates, including rates much higher than those estimated by Inamed, could be extrapolated from the company’s data. *Id.* at 33-40 (comparing rate changes using constant, linear, and quadratic formulas).

- Additionally, Inamed’s use of only two data points -- MRIs at the first and third years -- for so-called “silent” (undetected) ruptures made the 10-year projection even more difficult. *FDA Inamed Summary* at 38 (noting “the difficulty of predicting the percentage of ruptures per year having silent rupture data from the year-1 and year-3 MRI.”); *Inamed Transcript* at 214-215 (exchange between Advisory Panel member Dr. Miller and FDA staff reviewer Dr. Dawishi noting that it is “impossible” to extrapolate long-term rupture rates based on two data points).
- Inamed’s adjunct study, begun in the early 1990’s with reconstruction and revision patients, was “of limited value” to characterize the rupture rate [and] rupture rate over time” (*FDA Inamed Summary* at 40) because (1) the adjunct study did not employ MRIs, the *only* way to detect “silent” ruptures, which in turn, make up the overwhelming majority (86%) of overall silicone implant ruptures, and (2) the sponsor’s follow up was inadequate. *See also, Inamed Transcript* at 164. (FDA presentation describing Inamed adjunct study to be “of minimal utility in describing the rupture rate.”)

The Mentor Core Study data purported to show significantly lower rupture rates than the Inamed data. However, the FDA Staff review concluded that Mentor’s data, like Inamed’s, was flawed because:

- The Mentor Core Study, which FDA staff has characterized as “constitut[ing] the majority of the clinical safety and effectiveness prospective data” (*Transcript of Advisory Panel Meeting on Mentor’s PMA*, April 13, 2005 (“*Mentor Transcript*”), at 154) did not include *any* data on four of the six product models for which Mentor sought approval. *FDA Mentor Summary* at 1, 50;
- The Mentor Core Study was even more deficient than Inamed’s in terms of its utility in establishing rupture rates over time, containing MRI rupture data for only *two full years and clinically observed rupture data for part of a third year* (as compared to the Inamed 3-4-year data), and was therefore “of limited value to address the rupture rate over time due to the short duration of the follow-up.” *FDA Mentor Summary* at 79.
- Mentor, unlike Inamed, which had attempted to use its Core study data to project long-term rupture rates and to determine whether these rates increased over time, did not even “use [the Core Study] data to address the rupture rate over the lifetime of the device,” *id.* at 87, completely ignoring the issues identified in the Draft Guidance and major deficiency letter.
- Mentor’s Adjunct Study, which like Inamed’s Adjunct Study was also begun in the early 1990s for reconstruction and revision patients, was of “*no value* in determining the rupture rate and the rate over the lifetime of the device” (*id.* at 91 (emphasis added)) because, like Inamed, Mentor did not use MRIs -- the only reliable method of identifying silent ruptures -- in its Adjunct Study and because extremely low follow-up rates made the data “difficult to evaluate.” *Id.*
- The Sharpe/Collis Study from England, on which Mentor heavily relied for rupture and long-term rupture rate data, was also determined by FDA to be “of limited value in

characterizing the rupture rate and the rupture rate over the lifetime” of the Mentor product for a wide variety of reasons, including that the study (1) included no women who had reconstructive or replacement implants, the two groups shown to have the highest rupture rates; (2) excluded women who had had implants placed below the muscle, the more common placement in recent years and which, according to the IOM Report, more frequently results in ruptures; (3) excluded women with capsular contracture, which increases the risk of rupture; (4) was based on one MRI, rather than serial MRIs; (5) described data from only one surgeon’s practice; (6) did not review rupture rates over time; (7) did not include three of the six silicone implant models in Mentor’s PMA; and (8) excluded patients whose implants had been removed four years or less from the time of implantation, thereby underestimating the overall rate. *FDA Mentor Report* at 79-83, 88; *Mentor Transcript* at 175 (FDA staff presentation concluding that “the ability of [the Sharpe-Collis data] to predict a long-term rupture rate or a rate over time is limited”), 197 (presentation of FDA Statistical Reviewer concluding that “the estimate of long-term risk of rupture from the Sharpe and Collis data is limited in its ability to apply to the overall Mentor Core Study patients”). Moreover, FDA determined that the entry criteria used for the Sharpe/Collis study was so restrictive that most of the women who were the subjects of the Mentor Core Study would not have even satisfied them. *Id.* at 81.

ii. *Gel Bleed and Migration Data*

In its “not approvable” letter to Inamed and its “major deficiency” letter to Mentor, FDA highlighted the need for the companies to provide additional data on gel bleed and gel migration – *i.e.*, the extent to which silicone gel escapes from the implant shell, both in cases of rupture and

in cases where the shell remains intact, and migrates to the regional lymph nodes and other distant parts of the body. *FDA Mentor Summary* at 43, *FDA Inamed Summary* at 62 (both noting that gel bleed information “is needed to fully characterize the device and its interaction with the body over its expected lifetime” and that “it is also needed so that women may be informed of the identity and quantity of chemical constituents that leak out of an intact implant”); *FDA Mentor Summary* at 74, *FDA Inamed Summary* at 17 (both noting the need for studies addressing the incidence of gel migration). Both these issues were highlighted in the Draft Guidance. *See* Draft Guidance at 14 (recommending gel bleed testing that mimics in vivo conditions), and 22 (recommending clinical studies relating to gel migration)). The April 2005 Katzin study has confirmed that gel bleed and migration may have an adverse effect on the immune system, and that “the possibility that silicone frequently migrates to regional lymph nodes of patients with silicone breast implants *must be* considered in assessing the safety of these medical devices.” Katzin at 510 (emphasis added).

Despite FDA’s recommendation, however, the Mentor and Inamed updated applications were, again, thoroughly deficient in their treatment of these important issues and provided *no* assurance, much less a *reasonable* assurance, of the safety of the Inamed and Mentor products.

As to the issue of gel bleed data, FDA determined the Mentor and Inamed updated Core Studies to both be “of limited value” because of, among other things, the studies’ failure to accurately mimic in vivo conditions, or to provide diffusion rates for each gel bleed constituent. *FDA Mentor Summary* at 48, *FDA Inamed Summary* at 64. *See also Inamed Transcript* at 209 (FDA staff presentation noting that FDA had “a lot of problems with the [Inamed gel bleed] test methodology”), 210 (exchange between Advisory Panel member Dr. Li and FDA staff reviewer Dr. Arepali noting that Inamed gel bleed data likely underestimated bleed rates); *Mentor*

*Transcript* at 138 (FDA staff presentation noting that Mentor gel bleed testing was “of limited value”), 141-142 (noting that there “outstanding issues” as to Mentor gel bleed testing that the company must address “in order to adequately identify and quantify the gel bleed constituents and the bleed rate of those constituents”).

Similarly, FDA found that both the Mentor and Inamed Core and Adjunct Studies were “of limited value” in assessing the extent of gel migration as a result of ruptures. Specifically, FDA determined that because the data relied on by Mentor and Inamed were of limited duration (in Inamed’s case, three full years of MRI data and a partial fourth that included only clinical observation, in Mentor’s case, two full years and a partial third only of clinical observation), an insufficient number of ruptures was observed to support any conclusions on this point. *FDA Mentor Summary* at 79; *FDA Inamed Summary* at 40. FDA also concluded that the English Sharpe/Collis study, on which Mentor also relied to address gel migration issues, provided “limited information” of use on the issue of gel migration. *FDA Mentor Summary* at 82.

*iii. Local and Regional Health Consequences of Implant Ruptures*

A third principal concern expressed by FDA in its denial letters to Inamed and Mentor was the companies’ failure to meet the recommendations of the FDA Draft Guidance that manufacturers provide “a detailed description of the local health consequences” of silicone implant ruptures and associated gel migration. Draft Guidance at 23; *see also, FDA Inamed Summary* at 40; *FDA Mentor Summary* at 87.

As noted in the IOM Report and elsewhere, local and regional health complications have “significant implications for the safety” of silicone implants, because they involve risks themselves, such as pain, disfigurement, and serious infection, and may also lead to medical and surgical interventions, such as reoperations, that also have risks. IOM Report at 3, 10. These

latter concerns are compounded by the fact that removal of the implant is recommended in *any* case of rupture, even “silent” ruptures, because of concerns about gel migration and capsular contracture (*i.e.*, contracture of scar tissue around the implant, potentially causing pain and implant disfigurement). IOM Report at 131 (“Careful explanation and direct visual examination are the standard for diagnosis of silicone gel-filled implant rupture, both unsuspected or silent, and for confirmation of rupture.”)

The Danish Studies indicate some of the health risks posed by silicone implant ruptures and associated gel migration, noting that women with extracapsular ruptures were six times more likely than women with intact implants to experience breast hardness and were also more likely to report connective tissue diseases, pleuritis, or fatigue. *See FDA Mentor Summary* at 88 (citing Danish Studies). One of the Danish Studies (Holmich, *et al.*, 2004) concluded that gel migration can cause or increase capsular contracture and the development of silicone granulomas. *Id.* (citing Holmich study). The 2005 Katzin study also provides evidence of significant local and regional health consequences resulting from gel migration. Katzin at 510 (noting “the potential for adverse health consequences of silicone migration to regional lymph nodes” and that the phenomenon of gel migration “does provide a rational basis for suggesting that silicone gel implants may have an impact on the immune system”); *id.* (“Finally, the role of silicone in the development of lymphoma at least deserves mention since there are several case reports describing primary breast lymphoma in patients with silicone gel implants as well as patients with co-existent silicone lymphadenopathy and lymphoma in the same lymph node.”)

FDA’s own review of the existing literature confirms these findings. *See also Inamed Transcript* at 170 (FDA staff presentation noting studies showing the presence of silicone granulomas from ruptured implants “in auxiliary lymph nodes and in the chest area, as well as in

distant areas such as the eyelid and abdomen” and also noting the disproportionately high presence of silicone in the liver of women suffering “silent” (undetectable) ruptures); FDA Summary Panel Memorandum to General and Plastic Surgery Devices Advisory Review Panel regarding Inamed Corporation Silicone Gel-Filled Breast Implants, September 12, 2003 (“[There] are several studies that report that, in some cases, there is gel migration outside of the fibrous scar capsule (extracapsular rupture) following rupture. Cases of distant migration of gel to breast, axillary lymph nodes, abdomen, groin, arms, and fingers have been reported, some with serious consequences and deformities (e.g., extensive migratory granuloma formation and contracture, and scarring from gel extrusion and ulceration) described as a consequence of gel migration.”).

Once again, however, FDA’s review of the updated Inamed and Mentor data found the manufacturers’ updated Core Studies to be wholly inadequate, principally because neither study was of sufficient scope or duration to provide enough rupture data from which to assess local and regional complications. *FDA Inamed Summary* at 40 (“[Inamed’s] data are of limited value to address the local health consequences of rupture due to the small number of patients with confirmed ruptures and because all patients had not yet had follow-up after rupture”); *FDA Mentor Summary* at 79, 87 (“[Mentor’s] data are of limited value to address the local health consequences of rupture due to the small number of ruptures observed.”) FDA’s review also pronounced the Sharpe/Collis study -- also relied on by Mentor on the issue of local and regional health consequences -- to be of similarly limited value in this area as it was in the areas of rupture rates and gel migration. *Id.* at 82. *See also Mentor Transcript* at 179 (FDA staff presentation concluding that “[d]ue to the small numbers of women with ruptured implants in

both the Core Study and the Sharpe-Collis case series, the ability to address the rupture health consequences specifically for Mentor implants is limited.”)

Dr. William Katzin, a pathologist at the Case Western Reserve School of Medicine and author of the recent American Journal of Surgical Pathology article cited above, provided highly relevant testimony on the gel migration issue before the Advisory Panel on April 12, 2005:

The presence of silicone in macrophages cells whose function includes antigen presentation in lymph nodes, lymph nodes whose function it is to coordinate and amplify activities of the immune system provides a rational basis for a model in which silicone has a *direct impact* on the immune system in patients with silicone gel-filled implants. Considering the *certain access* of silicone to regional lymph nodes in patients with gel-filled breast implants, *I would conclude that such implants should not be considered safe until the molecular details of that potential impact have been thoroughly assessed using lymph node tissue.*

Inamed Transcript at 360 (emphasis added). It is also significant that despite its statements that silicone was inert, Dow Corning sought to sell silicone in the 1970s to vaccine manufacturers to boost the immune response to the vaccines’ antigens. Boley W., *et al.*, “Immunological enhancing activities of organosilicon compounds and non-functional fluids,” Report no. 4319, Midland, Mich.: Dow Corning, Oct. 2, 1974 (internal Dow Corning document obtained in civil discovery).

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Inamed’s and Mentor’s hastily assembled, “updated” data fails to provide FDA with *any* sufficient scientific information in *any* of the areas of concern identified by FDA in its initial rejection letters to the two companies. These data fail to meet the recommended standards set forth in the FDA Draft Guidance, or to provide FDA with a basis on which to reverse its previous position and conclude that either Inamed or Mentor has met its statutory burden of

affirmatively providing “reasonable assurance of [the] safety” of its silicone implant product.<sup>12</sup>

This is particularly true of the Mentor application. As noted in the FDA presentation before the Advisory Panel on April 13, 2005, Mentor relied almost exclusively on published medical literature, such as the Danish studies, as a substitute for its own lack of clinical U.S. data to establish the long-term safety and performance of its device(s). *Mentor Transcript* at 181-182 (noting limitations in Core Study and Sharpe-Collis data and Mentor’s reliance on the published literature to address rupture rates, gel migration, and the health consequences of rupture). However, this published medical literature did not specifically address Mentor’s products or study women with implants for reconstructive or replacement indications; *nor* did it provide FDA with any *new* information beyond what had already been available to the Agency when it issued its “major deficiency” letter to Mentor in March 2004. Finally, the published medical literature relied upon by Mentor contained many of the shortcomings of the Core Study and Sharpe-Collis data, since only one of these studies “describe[d] the health consequences of women specifically with ruptured implants followed over time” and even that study only used a two-year follow-up period. *Id.* at 182.

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<sup>12</sup> Mentor and Inamed have argued, and will no doubt continue to argue, that one basis for FDA approval is that the more recent, “third-generation” implant models demonstrate lower rupture rates than earlier models, suggesting that these versions of silicone implant products are safer than the earlier models. But as noted by one FDA staff reviewer, the lower rupture rates associated with the third generation implants may be due to the fact that these devices have not been implanted in women's bodies for as long a time as earlier models, not to their superior design. *Inamed Transcript* at 207 (Comments of Medical Officer Dr. Dawisha) (“[I]f you look at the duration of implantation, it’s . . . the shortest in the third generation implants. So it’s difficult to conclude that the reason the rupture rate is lower in the third generation is because of the design. You could also conclude that the reason the rupture rate is lower is because these implants have been in less, a shorter duration of time.”). There is no basis on which to conclude that the long-term safety of these third-generation implants has been demonstrated *over their lifetime*. Certainly, the Inamed and Mentor studies have failed to make this critical showing.

**b. Post-marketing conditions cannot substitute for an affirmative FDA determination that a Class III device manufacturer has met its statutory burden of proving safety.**

The April 13, 2005 decision of the FDA Advisory Panel to recommend approval of the Mentor silicone implant products was conditioned on Mentor's commitment to undertake extensive post-marketing activities designed to help address the safety concerns surrounding its products, including:

- Mentor's commitment that patients who might use their implant products be required to sign special, updated product consent forms that would acknowledge implant risks and include information regarding risks of rupture and reoperation;
- Mentor's commitment to sell its product only to board-certified plastic surgeons who have first undertaken special hands-on training regarding surgical implantation techniques to be used with the Mentor implant in an effort to minimize the risk of rupture;
- Mentor's commitment to open a registry to track long-term patient welfare and device performance and to tie the registry to the product warranty;
- Mentor's commitment to include in its product labeling and informed consent form a recommendation for an MRI after 5 years, and additional MRI's every 2 years thereafter, to identify "silent" ruptures;
- Mentor's commitment to complete its ongoing Core study with MRI subset to determine rupture rates after 10 years, and to have these studies reviewed by an independent data monitor;
- Mentor's commitment to include within its Core study population women whose implants are removed, but not replaced;

- Mentor’s commitment to agree to participation in a public FDA Advisory Panel that will be convened in 5 years to review the outcome of the company’s post-approval safety data, including rupture rate, gel migration, product performance over time, and health consequences for augmentation, revision, and reconstruction patients; and
- Mentor’s commitment to link its implant products to actual implant recipients by use of tracking numbers, in order to better study any problems that arise.

These post-approval conditions, however, provide no basis for approval of Mentor’s silicone implant products.

Most fundamentally, as discussed above, the statutory regime enacted by Congress to cover Class III devices is a *premarket* approval regime that requires a Class III device manufacturer to provide reasonable assurance of the safety of its product *before* marketing the product. This premarket approval regime has been specifically applied to silicone implants, even though those products were for a time allowed to remain on the market without a determination of safety and effectiveness. If there are uncertainties as to the safety of a Class III device, including silicone implants, these uncertainties cannot be resolved by approving the product and then allowing the manufacturer to try to meet its statutory burden afterward.

The law does not allow for an “approve first, test later” approach that exposes consumers to potentially unsafe medical devices; uncertainties as to the safety of a Class III device *must* be resolved in favor of non-approval, especially where, as here, the product confers very little benefit over approved alternative devices. The Advisory Panel ignored this basic principle in recommending approval based on Mentor’s representations that it would conduct post-market studies in an effort to resolve such basic issues as the long-term safety of its products.

If anything, the nature and scope of the post-marketing conditions in this case strongly supports *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 draft Guidance. For example, the long-term post-marketing studies that the Advisory Panel have imposed on Mentor as a condition of approval are some of the very same studies that FDA, in the Draft Guidance and “major deficiency” letter, indicated were necessary if Mentor was to meet its *pre-approval* statutory burden and adequately address longstanding FDA concerns about the safety of silicone implants over time, 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 Guidance and rejection letter were deficient in their exclusion of this important subpopulation. In short, the Mentor post-approval conditions expose the deficiencies of its pre-approval scientific data. The law does not permit the company to remedy its pre-approval failures after approval, while in the meantime exposing consumers to products of questionable safety.

Indeed, 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. 21 U.S.C. § 360j(g); 21 C.F.R. § 812.1 *et seq.* An IDE allows sponsors of unapproved devices to ship their products lawfully in interstate commerce, in order to permit investigations of that device. *See In re Orthopedic Bone Screw Prods. Liab. Litig.*, 159 F.3d 817, 819 (3<sup>d</sup> Cir. 1998) (noting that an IDE “allows limited use of an experimental medical device to gather the type of data necessary to support a [PMA]”), *reversed on other grounds, sub*

*nom. Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001). An IDE, which Mentor already has for its Core study, 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 Mentor is expected 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. *See* 21 C.F.R. § 812.25. 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. *Dyer v. Danek Med., Inc.*, 115 F. Supp. 2d 732, 736 (N.D. Tex. 2000).

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 the original Inamed silicone implant PMA, which was rejected by FDA in January 2004, over the “approval with conditions” recommendation of an Agency Advisory Panel. There is no justification for FDA to reverse course and now approve Mentor's product based on the very same post-approval commitments that the Agency deemed to be an insufficient basis on which to approve the Inamed PMA.

A further reason why the Mentor conditions cannot support an approval is that such conditions are rarely effective. In a recent study, FDA's Center for Device and Radiological Health (“CDRH”) reported that “performance of Condition of Approval of Studies is suboptimal” and that “CDRH has limited procedures for monitoring manufacturer's progress and results from [such studies].” Center for Radiological Devices and Health, “Condition of

Approval Studies as a Postmarket Tool for PMA Approved Cohort 1998-2000” (March 2005), at 2, 9. As the study demonstrated, manufacturers *routinely* shirk their commitments to provide such studies, and FDA has limited means of enforcing fulfillment of these commitments. Mentor’s own history of compliance with condition of approval studies exemplifies the problem. As noted at the FDA public meeting on 5-year data for saline breast implants in 2002, Mentor lost 95% of its post-approval saline implant study patients to follow-up after 5 years. In response to FDA pressure, the company managed to increase follow-up to 24% after six years, but the data remained so weak that it could not support an adequate quality of life analysis.<sup>13</sup>

The proposed post-market activities set forth in Mentor’s PMA further calls into question its commitment to effective post-approval conduct. The FDA Mentor Summary noted, for example, that Mentor’s proposal for a patient registry was flawed because Mentor proposed not to create its own registry, but rather to obtain reports from the already existing Tracking Outcomes in Plastic Surgery (TOPS) registry and the National Breast Implant Registry (NaBIR). FDA pointed out that while Mentor “provided a description of what data are collected in the TOPS and NaBIR registries, Mentor did not provide their plans for analyzing the data.” *FDA Mentor Summary* at 102. Similarly, while Mentor indicated that it was working with various plastic surgeons’ groups to develop a comprehensive physician training program, the Agency reviewers noted that the proposed training “does not appear to include any specific information with regard to rupture screening method and frequency or removal after confirmed intracapsular

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<sup>13</sup> See FDA Panel Memorandum to General and Plastic Surgery Devices Advisory Review Panel regarding Mentor Corporation Saline-Filled and Spectrum Mammary Prostheses Status of PMA Conditions Approval, June 11, 2002, *available at* [http://www.fda.gov/ohrms/dockets/ac/02/briefing/3876b2\\_02-Saline%20BI%20Panel%20Memo-Mentor%206-11-02.doc](http://www.fda.gov/ohrms/dockets/ac/02/briefing/3876b2_02-Saline%20BI%20Panel%20Memo-Mentor%206-11-02.doc).

or extracapsular rupture, as well as modes and cause of rupture findings, which should be based on the Mentor data.” *Id.* at 104.

Given Mentor’s poor track record with post-approval studies, the Agency simply cannot responsibly allow the company to escape its obligation to provide reasonable assurance of safety *before approval* by simply promising to try to do so *after approval*. There is no basis for concluding that Mentor’s commitments will prove any less empty than its past commitments, or than those of many other Class III device manufacturers.

Finally, even if Mentor did comply with its conditions of approval, there are significant practical impediments to making those conditions clinically effective in terms of public health. For example, while Mentor has agreed to make a labeling recommendation that women receiving silicone implants undergo periodic MRIs (the first after 5 years, and then every 2 years thereafter) to identify any silent ruptures, the cost of MRIs – approximately \$1890 per procedure<sup>14</sup> – makes such precautions unrealistic, particularly for young women who are not typically receiving routine breast imaging such as mammography, or by women of any age who do not have MRIs covered by their health insurance. Because MRIs are currently the only reliable means of detecting silent ruptures, which, in turn, constitute the majority of all silicone implant ruptures, Mentor’s post-approval conditions provide little in the way of practical assurances that any safety problems associated with its products can be quickly and effectively diagnosed and addressed. In fact, many MRI facilities may not have the breast coils necessary to perform MRIs for women with breast implants, and few radiologists are trained to read them.

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<sup>14</sup> See <http://www.febblue.org/toyourhealth/tyhhwcostsfamily.html#2>.

**c. Neither the alleged benefits of implants nor the concept of “freedom of choice” supports FDA approval of the Mentor and Inamed products.**

Proponents of approval of silicone implants have argued that implants have salutary effects on the health of some women by improving their self-esteem and quality of life, and that therefore women should be free to evaluate for themselves the risks and benefits of silicone implants. There are three basic reasons why FDA approval of the Mentor and Inamed products cannot be premised on the alleged benefits of silicone implant products or on amorphous concepts of “freedom of choice.”

First, FDA itself has determined, in the context of its consideration of the Mentor PMA, that “the literature *does not* provide strong scientific support that breast implants have measurable psychological and psychosocial benefits for women seeking breast augmentation.” *FDA Mentor Summary* at 70 (emphasis added). FDA further concluded that “assessing psychological or quality of life after breast cancer reconstruction with implants is complicated by numerous factors” and that Mentor had not provided FDA with any scientific “[l]iterature that adequately evaluates the short-term or long-term psychological or psychosocial benefits of breast implants as a reconstructive procedure using appropriate control group.” *Id.* at 73. Thus, the data simply do not support the contention that implants, in general, confer recognizable health and quality of life benefits. *See also Mentor Transcript* at 168 (FDA staff presentation noting various problems relating to “quality of life” studies provided by Mentor).

Second, in any event, even if breast implants *were* found to confer such benefits, that is not a basis for approval of silicone implants that, at best, are of uncertain safety. FDA has previously determined that *saline* implants are reasonably safe and these products are widely available on the market. Thus, consumers already have available to them FDA-approved implant

products that can provide any benefits breast implants confer on their recipients. Moreover, those women who seek silicone implants *may* receive the implants as part of the ongoing core and adjunct studies. Thus, FDA has already struck the proper balance between the risks and benefits of silicone implants.

Third, even if silicone implants were found to confer tangible health and quality of life benefits on their recipients (which has not been proven), *and* even if saline implants were not a safe and adequate alternative (which they are), it does not follow that consumers may be left to evaluate for themselves the risks and benefits of using silicone implants. The FDCA could not be clearer: a PMA for a Class III device bears the burden of *affirmatively demonstrating safety*, and FDA cannot approve a Class III device absent such a showing. It is not left to the individual consumer to decide, in her particular case, that the risks of silicone implants are acceptable. This regime stands in contrast to the regime governing, for example, dietary supplements, where there is no burden on the manufacturer to demonstrate safety before marketing (as long as the manufacturer does not make health claims and includes certain statutorily-required disclaimers). *E.g., United States v. Lane Labs-USA, Inc.*, 324 F. Supp. 2d 547, 564 (D.N.J. 2004) (explaining regulatory regime for dietary supplements and how these products are, to a certain degree, outside “the reach of the FDA’s preauthorization scheme”) (internal quotation, citation omitted).

In any event, the argument that women should be free to choose silicone implants is fundamentally flawed because it operates on the incorrect presumption that women considering these products fully understand *all* their risks and benefits and can make an informed decision about whether the risks outweigh the benefits. As discussed above, there is *at best* a lack of reliable information regarding the long-term safety of silicone implants – a situation that Mentor’s and Inamed’s PMAs have not remedied. Under these circumstances, there is no

possibility of *informed* consumer decisionmaking. What Inamed and Mentor and their supporters seem to mean by “freedom of choice” is not the right to make an *informed* decision, but rather a world of “buyer beware” in which silicone implant manufacturers shirk the pre-approval obligations placed on them by FDA, and uninformed consumers are forced to bear the consequences. The law does not allow this approach with respect to silicone implants and other Class III devices.

**d. FDA should decline to follow the Advisory Panel’s recommendation that it approve the Mentor PMA.**

An Advisory Panel recommendation that a Class III medical device be approved is not binding on FDA. Moreover, FDA has three times previously rejected Advisory Panel recommendations of approval in the area of silicone implants: First, when it rejected an Advisory Panel’s recommendation to classify implants as a Class II medical device and instead determined that safety concerns instead counseled in favor of classification as a Class III device; second, in 1992 when the FDA rejected PMAs for silicone implants from Inamed, Mentor, and Dow Corning despite Panel recommendations of approval; and, most recently, in January 2004, when the Agency rejected Inamed’s PMA over an Advisory Panel approval recommendation. In April 2005, an Advisory Panel recommended denial of Inamed’s updated PMA, but recommended approval of Mentor’s PMA. There is nothing in the Advisory Panel’s Mentor recommendation to alter the conclusion that the company has again failed to sustain its statutory burden and to address longstanding FDA concerns about the safety of silicone implants. Indeed, the Panel’s recommendations regarding Mentor and Inamed are inconsistent. The Panel declined to recommend the Inamed product for approval in large part because the company’s data was too limited, both in time and in scope, to address FDA’s concerns regarding long-term rupture rates, gel migration, and their health consequences, and because Inamed’s reliance on outside studies,

such as the Danish Studies, as a substitute for their own clinical data. The following comments by the Panel members are illustrative:

- “[T]he [rupture] data doesn’t really allow us to project out past the length of time that the data is collected at this point [*i.e.*, three years, plus a partial fourth year].” Comments of Advisory Panel member Dr. Li (*Inamed Transcript* at 283-284).
- “I don’t recognize any characterization [of rupture rates] that I can feel comfortable with beyond the three year point.” Comments of Advisory Panel member Dr. Newburger (*id.* at 285);
- “I think that the rupture data have been adequately represented with respect to the limitations of the study design. The projections beyond where the data end are very risky.” Comments of Advisory Panel member Dr. Blumenstein (*id.* at 286);
- “I have trouble extrapolating from beyond the solid data . . . . And after that the projected data seems to have weaknesses that we may not have talked about.” Comments of Advisory Panel member Dr. Doyle (*id.*)
- “I don’t see that the frequency of observed intracapsular gel, extracapsular gel, migrated gel and destination of these have been characterized because of the lack of sampling local tissue.” Comments of Dr. Newburger (*id.* at 288);
- “I’m extremely uncomfortable using the Danish data, especially on clinical type of related issues as projections of how these implants do as the devices were from different manufacturers, the chemistry of the gels were different, failure mechanisms, perhaps were different. So although the Danish studies give us some indication, I think it’s extremely risky to say that those same numbers would apply here.” Comments of Dr. Li (*id.* at 294).

- “[We] don’t have what is expected lifetime. I don’t know whether you’re telling me ten or 20 years, and I’m not even comfortable beyond three years based on the data we have.” Comments of Dr. Doyle (*id.* at 340).

Given that these concerns led the Advisory Panel to decline to recommend that FDA not approve the *Inamed* application, the Panel’s decision to recommend approval of the *Mentor* application is truly baffling. The record is clear that Mentor was afflicted with the very problems identified by the Advisory Panel as the basis for its decision not to recommend approval of Inamed’s PMA. Each application was plagued by a lack of long-term Core Study data – indeed, Mentor’s application relied on data of a duration *one year less* than Inamed’s. Both Mentor and Inamed relied heavily on published literature that was not specific to the applicant and that had been available to FDA when it initially declined to approve the companies’ respective applications in early 2004. Both applications contained adjunct studies that were of no value because they did not use MRIs to identify silent ruptures and because follow up was poor. Indeed, the only real difference between the two applications was that Mentor, unlike Inamed, relied on outside reports -- specifically, the English Sharpe-Collis reports -- to bolster their other long-term safety data. Yet these reports, as discussed above, were thoroughly discredited by the FDA staff reviewers as failing to provide valid scientific evidence of safety.

In short, there was no adequate or objective scientific basis for the Advisory Panel to recommend approval of the Mentor application, while not recommending approval of the Inamed application. The Panel’s decision on Inamed, moreover, is consistent with the FDA’s January 2004 decision on the previous Inamed application, the “major deficiency” letter issued to Mentor in March 2004, the Draft Guidance that the FDA issued in January 2004, the concerns voiced by FDA staff regarding both updated applications, and with the Agency’s longstanding policies and

practices regarding silicone implants in general. It is that recommendation, not the inexplicable recommendation on Mentor, that should guide FDA at this stage in the process.

**e. FDA approval of the Mentor and/or Inamed PMAs would violate the Administrative Procedures Act.**

Any decision by FDA to approve the Mentor and/or Inamed PMAs would be an unwarranted, 180-degree departure from the Agency's longstanding approach to silicone implants, and from FDA's past treatment of the Mentor and Inamed PMAs themselves, and would therefore constitute arbitrary and capricious action in violation of the Administrative Procedures Act.

The APA requires that administrative agencies engage in "reasoned decisionmaking." *E.g., Puerto Rico Higher Educ. Assistance Corp. v. Riley*, 10 F.3d 847, 853 (D.C. Cir. 1993) ("One of the fundamental principles of administrative law is that an agency's actions must be supported by reasoned decisionmaking."). In order for an agency action to be the product of "reasoned decisionmaking," the action must be consistent with past precedents and policies, unless the agency provides a satisfactory explanation for its decision to depart from those precedents and policies. *Wisconsin Valley Improvement Co. v. Fed. Energy Regulatory Commission*, 236 F.3d 738, 748 (D.C. Cir. 2001) ("[A]n agency acts arbitrarily and capriciously when it abruptly departs from a position it previously held without satisfactorily explaining its reason for doing so."); *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 57 (1983) ("[A]n agency changing its course must supply a reasoned analysis . . .") (citation omitted). A satisfactory explanation for an agency's reversal of course is one that articulates a "rational connection between the facts found and the choice made." *Dart v. United States*, 848 F.2d 217, 231 (D.C. Cir. 1988) (internal quotation, citation omitted).

Approval of the Mentor and/or Inamed PMAs under these circumstances would be the antithesis of the “reasoned decisionmaking” required by the APA. FDA’s longstanding position on silicone implants, a position bolstered by the best available science and most recently set forth in the Draft Guidance, is that there are substantial long-term safety issues concerning these products and that only by conducting detailed, long-term studies regarding such issues as rupture rates, gel migration, and local and regional health consequences can a manufacturer hope to meet its statutory burden. The fact that *no* PMA for silicone implants has *ever* been approved is a testament both to the appropriately rigorous standards set by FDA in this area, and to the manufacturers’ inability to resolve the Agency’s longstanding safety concerns. FDA’s treatment of the Mentor and Inamed PMAs has thus far been completely consistent with its decade-old treatment of silicone implants in general. In its previous rejection letters and draft Guidance, FDA has once again made clear its continuing concerns regarding the long-term safety of silicone implants and has called upon Mentor and Inamed to provide detailed long-term data to allay these concerns.

As set forth above in detail, and as FDA staff have already made clear, neither Inamed nor Mentor has provided FDA with the scientific data necessary to satisfy the Draft Guidance standards. In the absence of any such data from Mentor or Inamed, there is no basis whatsoever on which FDA can justify a decision to reverse course and approve either PMA. Nor can there be found any rational connection between, on one hand, FDA’s findings that the updated Mentor and Inamed data are of “limited” or no value in addressing critical safety issues regarding silicone implants, and, on the other, a decision to approve either PMA on the basis of the new data. FDA’s findings and the APA *compel* the conclusion that the Mentor and Inamed PMAs should be denied.

**C. Conclusion**

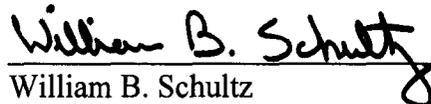
For the foregoing reasons, FDA should decline to approve the Mentor and Inamed PMAs for silicone implants. More research must be conducted on the safety of silicone implants before the safety of these devices can be reasonably assured, and before the lives and health of women using silicone implants can be adequately protected.

**D. Environmental Impact**

The action requested in this petition will have no impact on the environment.

**E. Certification**

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioners that are unfavorable to the Petition.

  
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