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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 request the Food and Drug Administration ("FDA") (1) to reopen the record of the Inamed Corporation ("Inamed") application to market silicone gel-filled breast implants, (2) to make any new data and FDA analysis of the new data publicly available, and (3) to permit public comment on Inamed's recent amendments to its application. An FDA Statement issued today indicates that Inamed has received an approvable letter from FDA, although the statement says that "[t]he approvable letter does not mean that Inamed's device is approved for marketing in the United States at this time." Accordingly, petitioners also



request that FDA withdraw its approvable letter. As explained below, a refusal to grant this request would constitute arbitrary and capricious Agency action, in violation of the Administrative Procedure Act.

### **Background**

The revised Inamed application raises important issues concerning the adequacy of Inamed's data set for the Core Study after the removal of more than 25% of the total sample and two-thirds of the breast cancer patients in the sample. As discussed in the May 23, 2005 Petition, FDA has consistently invited public participation in the Agency's evaluation of the safety of silicone gel-filled breast implants. In 1978, shortly after Congress conferred on FDA the responsibility to regulate medical devices, the Agency convened an Advisory Committee to recommend the appropriate classification of silicone gel-filled breast implants. The Advisory Committee's consideration of this issue was open to the public. In 1982, the Agency issued a proposed rule to classify breast implants, and issued the final rule in 1988, after receiving public comment. In 2003, the Agency adopted a public process to consider Inamed's application to market breast implants and made an extensive staff summary available to interested members of the public, who were permitted to make presentations at the public Advisory Committee meeting held in October 2003. After that application was denied and Inamed submitted a revised application in 2004, the Agency once again adopted a public process, convening another Advisory Committee meeting, making an extensive staff analysis of Inamed's



data available to the public prior to the meeting, and hearing 12 hours of public testimony on the Inamed application at the meeting. On April 12, 2005, the Advisory Committee voted to recommend that FDA deny the Inamed PMA.

On July 18, 2005, Inamed announced that it had substantially modified its application. According to Inamed's Press Release, the company has removed the request to market Style 153 implants from its application as well as all data pertaining to Style 153, and it has added new, 10- to 12- year European data for its other styles of breast implants. Today FDA announced that it has issued an approvable letter to Inamed for its application to market silicone gel-filled breast implants.<sup>1</sup>

For the reasons stated below, petitioners respectfully request that the FDA withdraw its approvable letter to Inamed and reiterate their request that the Agency deny the Inamed's pre-market approval application ("PMA") for silicone gel-filled breast implants.

### **Discussion**

It is clear that these changes fundamentally altered Inamed's most recent application to market silicone gel-filled breast implants and raise fundamental questions about the adequacy of the sample size and generalizability of the data on which Inamed is now relying to prove safety. In particular, the removal of Style 153 substantially weakens the "Core Study," the key study relied on by Inamed. The Core Study data are

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<sup>1</sup> Inamed Press Release, July 18, 2005; FDA Statement, September 21, 2005.



central to Inamed's case for approval, because it is the only meaningful, prospective data provided; moreover 86% of ruptures in the implants are "silent" and can be detected only with an MRI, and the Core Study provides the only Inamed MRI data that can be used to measure incidence of rupture.

In their summary memo for the Inamed PMA, FDA staff concluded that the data provided by the company were inadequate to answer the questions posed by the Agency in the draft guidance. Although the Agency's Draft Guidance on standards for breast implant applications had requested data that could be projected for 10 years, the MRI data in the Core Study contained only two data points (MRI tests were given at years 1 and 3) and, therefore, according to FDA staff and the Advisory Committee, were inadequate to project data over 10 years. In addition, the FDA Advisory Committee expressed concern that the short-term rupture data for the Inamed sample, which included Style 153, was unacceptably high.

Inamed has now modified the Core Study results by removing Style 153 from the analysis data. This strategy raises fundamental questions about the Company's data. Inamed's post-hoc (after-the-fact) manipulation of the Core Study is contrary to basic principles on how clinical studies should be conducted. However, it is based on the company's appropriate acknowledgement that different implant styles have different rupture rates. It is therefore appropriate for the company to determine that Style 153 is a defective implant because of its high rupture rate, and to remove it from the PMA and from the data analysis of the Core Study. In doing so, it becomes essential that all



subsequent data analyses separately evaluate the rupture rate of each of the other implant Styles for which Inamed seeks approval, to ensure that each style is safe.

The PMA analysis was based on the analysis of three groups of patients: augmentation, reconstruction, and revision. Inamed did not study the safety of each implant style within those three groups or across those three groups. The removal of Style 153 from the Core Study data results in a much smaller sample of reconstruction and revision patients. It results in even smaller samples of reconstruction and revision patients in the MRI subsamples, making it impossible to meaningfully evaluate rupture rates in two out of three Core Study samples. Inamed's amended PMA therefore results in a Core Study that includes too few reconstruction and revision patients to provide adequate, short-term or long-term safety data.

In addition, Inamed has indicated that it amended its application to include new European data for the styles on which it seeks approval. No other information has been provided about the quantity or quality of this data. These developments raise a number of important questions that are appropriate for public airing. Once the new data and any FDA staff summaries are made available, the public should be given 60 days to comment on the following issues, as well as other issues that may arise.

1. Post-Hoc Analysis. In conducting a clinical trial, it is normally not permissible to redesign the trial to exclude unfavorable data after the trial has begun. In its PMA, Inamed provided aggregate rupture data for all its implant styles combined, assuming rupture rates would be similar across the styles and that therefore there was no



need to study the safety of each style separately. It was only after the rupture rate was determined to be very high for reconstruction patients and revision patients that Inamed examined the rupture data of specific styles, and discovered that one of the styles, Style 153, had a higher rupture rate than the other styles. After their PMA was rejected, Inamed proposed to remove the data from Style 153 from its application, to improve their overall implant rupture rate. Is it appropriate as a matter of clinical trial design to remove the data from the Style 153 implants from the Core Study? If it is appropriate to treat Style 153 as a separate data set, then it is not appropriate for Inamed to combine data from the four remaining styles (Styles 40, 45, 110 and 120) in the Core Study. Based on the Style 153 data, it is no longer possible to assume that the rupture rate and safety data of all Inamed's implant styles are similar and that the data can be analyzed for all styles together. Instead, the data from each style should be analyzed separately.

Since we have not seen the revised Inamed PMA data, we do not know if Inamed has now provided separate statistical analysis for each style. However, we know from the Inamed PMA data discussed at the April 2005 Advisory Committee meeting that when Style 153 is excluded only 4 of the 8 remaining implant styles were included in the Inamed Core Study. Inamed is therefore requesting approval for 8 implant styles based on data for only half of those styles. When each style is considered separately, the number of subjects is not sufficient in many of the styles. For example, Inamed seeks approval for four styles (Styles 10, 15, 20 and 115) which each have a sample size of 0 in the Core Study. And, the samples for the other four styles are sometimes too small for



inferential statistics as well: for example, in the breast cancer reconstruction sample, Style 45 has a sample size of only 5 implants and Style 120 has a sample size of only 15 implants; the number of patients is even smaller. Clearly, the sample sizes for the specific implant styles are too small in the reconstruction sample for inferential statistical analysis, and several of these samples are too small in the revision and augmentation samples as well.

2. Inadequate Size of Core Study When Style 153 Is Removed. The Inamed Core Study included 494 augmentation patients, 221 reconstruction patients, and 225 revision patients. The removal of Style 153 substantially reduces the size of the Core Study current sample by 26% to 691 patients, and, even more importantly, would reduce the initial sample sizes of the reconstruction and revision groups to approximately 80 and 159, respectively. As women drop out of the Core Study, those sample sizes decrease over time. However, it is not possible for us to calculate the exact sample size in the most recent data analysis, because we do not know if the women with Style 153 are more or less likely than other women to be lost to follow-up. Based on Inamed's 2000 data indicating that Style 153 compromised two-thirds of the reconstruction sample and approximately 30% of the revision sample, it is reasonable to conclude that when Style 153 is deleted, these samples are much smaller than the sample sizes requested by the FDA and much too small to provide meaningful inferential statistical safety data, even for the four different models of breast implants included in the Core Study.



3. Inadequate Size of MRI Subsamples and Reconstruction and Revision Samples. The MRI subsamples within the Core Study are approximately one-third the size of the Core Study, and those subsamples are also substantially reduced when patients with Style 153 implants are deleted. Breast implants are touted as an important option for breast cancer patients, and without Style 153, the MRI component of the Inamed Core Study breast cancer reconstruction sample is now much too small to provide meaningful safety data, *even when all styles are combined*. According to the FDA staff memorandum on Inamed's data (p. 16), Inamed provided third-year MRI data on fewer than 52 reconstruction patients and fewer than 60 revision patients. According to our estimate, Inamed's removal of the Style 153 data probably leaves the company with fewer than 30 reconstruction patients. Even as a total sample, this is much too small to calculate safety with any confidence. Moreover, since the sample includes women with 4 different implant styles, each should be evaluated separately to ensure that they do not have high rupture rates. This is virtually impossible, especially for Style 45 and Style 120, as noted in subsection 1, above, *even when MRI and non-MRI samples are combined*. Obviously, it is not possible to generalize from MRI rupture data based on just one or two women, or even five or ten women with each implant style. These samples are much too small to provide meaningful data, even at 3 years, and would be even smaller at 5 years or 10 years. Moreover, the total reconstruction sample of approximately 80 patients in the Core Study is too small, given expected loss to follow-up, to provide meaningful data at year 5 or year 10. In fact, Inamed told the FDA several years ago that 580 implants were

needed to provide sufficient numbers for safety and effectiveness analysis in a six-year study.<sup>2</sup>

The revision sample is also a very important part of the PMA, since as FDA points out in its summary memo (Inamed FDA Summary Panel Memorandum, pages 17-18 ), many augmentation and reconstruction patients will eventually be revision patients. When Style 153 patients are deleted from the analyses, we calculate that the total revision sample is approximately 159 women, substantially smaller than the sample size approved by the FDA. Given the percentage of patients lost to follow-up, the sample size is too small for a 5-year or 10-year study. We estimate that there would be fewer than 40 revision patients undergoing the third-year MRI; these MRI data are crucial since most ruptures have no symptoms, and 40 revision patients with MRIs is much too small. And, as previously noted, the MRI sample size of 40 is expected to decrease substantially in later years, resulting in even less meaningful analysis.

4. Long-term Core Study Data. The FDA Draft Guidance on breast implants indicated that applicants should submit data from which 10-year breakage rates could be projected. The FDA staff and the Panel concluded that the duration of the Inamed Core Study was inadequate to project over 10 years, particularly since there were only two data points (at one and three years) for MRI results. Removal of Style 153 does not remedy the deficiency in the Core Study, but rather adds to the deficiency by substantially

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<sup>2</sup> McGhan Mammary Implant PMA, July 1991, pp. IVB-128, IVB-136-137



reducing the sample size available for 5-year and 10-year post-market follow-up. In light of Inamed's track record in post-market study of saline breast implants, it is clear that there will be too few women in any long-term data analysis of reconstruction patients, even if the four styles could appropriately be combined into one sample.

5. New European Study Data. Inamed has stated that it amended its PMA application to include new European data. It did not indicate in its public announcement whether the data provide rupture information on all 8 implant styles, and whether each style has been analyzed separately. Any surgical or manufacturing differences between Inamed implants in Europe and the U.S. would need to be taken into consideration in determining the relevance of these data to the PMA. And, of course, the data need to be analyzed separately for reconstruction, revision, and augmentation patients.

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The FDA has determined on several occasions to adopt an open, public process for the consideration of applications to market silicone gel-filled breast implants. This is obviously an issue that is vitally important to members of the public, as demonstrated by the broad public participation in the April 2005 Advisory Committee meeting. To allow Inamed to make a major amendment to its application without providing interested members of the public the new data or affording them an opportunity to comment would be an abrupt departure from the Agency's consistent, past practice. The Agency has offered no explanation for such a departure and we submit that there is no explanation that would justify such a course of action. Adopting this approach makes the Advisory



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Committee and all the work undertaken by interested members of the public in connection with that meeting a complete sham. It is highly unusual for the FDA to have convened an advisory committee, invited public participation, and then, after the Advisory Committee recommended against approval, to allow Inamed to selectively exclude unfavorable data, and then, without making the new data available to the public or affording the public an opportunity to comment, to reject the recommendation of the Advisory Committee and to approve the application.

This course is a clear arbitrary and capricious agency action and therefore would violate the Administrative Procedure Act, 5 U.S.C. § 706(2)(A). *See* May 23, 2005 Petition, pp. 37-38.

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