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

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Hand Delivery [or By Facsimile]

Docket No. _____

CITIZEN PETITION

The National Organization for Women, Public Citizen's Health Research Group and the National Women's Health Network submit this petition under 21 C.F.R. 510.30 and 10.35 to request that the Commissioner of Food and Drugs stay its review of and decision on any and all Premarket Applications ("PMAs") for silicone gel-filled breast implants until the actions described below are taken with respect to such implants .

A. Action Requested.

This petition requests that the Commissioner of Food and Drugs refrain from completing the review of the PMA submitted by Inamed Corporation ("Inamed") for McGhan silicone gel-filled breast implants, until an amendment to such PMA is submitted to the Food and Drug Administration (FDA) responding to the deficiencies identified in this petition and consisting of adequate data demonstrating a reasonable assurance of safety or effectiveness of such implants. This petition further requests that, pursuant to 21 C.F.R. 14.7 (2), "the Commissioner will expedite the review of the petition and make a reasonable effort to render a decision before the action concerned in the petition."

B. Statement of Grounds.

1. The Core clinical study in the Inamed PMA does not include adequate data to provide a reasonable assurance of safety, particularly data substantiating the long-term safety of

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silicone gel-filled breast implants in relation to rupture, gel migration and increases in connective tissue disease signs and symptoms as seen at two years follow-up. The panel decision to recommend approval with considerable and unfeasible postapproval conditions including labeling requirements to warn of the limited safety data is tantamount to a complete denial of choice – since an informed choice can not be made in the absence of data that demonstrates even minimum standards of safety.

The Inamed PMA purports to demonstrate the safety and effectiveness of McGhan silicone gel-filled breast implants in seven styles for breast augmentation, reconstruction and revision. The application relies largely upon a Core clinical trial. There was also an "adjunct" study that collected safety (local complications data) and an AR90 study that collected safety and effectiveness data on saline-filled and silicone gel-filled implants. The adjunct and AR90 clinical studies are incomplete, underpowered and of inadequate duration to substantiate that the implants are safe for their intended uses.

The clinical data in the Core clinical trial is based only on one complete year of follow-up and the partial completion of follow-up at 2 and 3 years for several parts of the study. Therefore, the data fails to address substantial long-term problems that can affect women's health. Because silicone gel-filled breast implants were first commercially distributed before enactment of the 1976 Medical Device Amendments, the FDA is aware of historical data on the type of complications that are associated with these devices and the timeframes in which they occur. Both anecdotal and scientific evidence demonstrates that the onset of the majority of complications occur after a considerable period of latency.

Because of the late onset of local, regional and systemic complications, substantial evidence of long-term complications, and the long and controversial history of these devices, Inamed's core clinical trial and other studies did not produce sufficient clinical data to provide a reasonable assurance of safety. Nevertheless, the limited data reflect high complication and reoperation rates: 20.6% reoperation and 7.5% removal/replacement rate for augmentation patients and 45.5% reoperation, 25.3% removal/replacement and 6.3% rupture rate for reconstruction patients.

As one member of the General and Plastic Surgery Devices Panel stated in the panel's October 14 - 15, 2003 meeting, "A decade has passed and we sat here today talking about two and three-year data. I'm flabbergasted."[1] Another member of the panel observed "it simply boggles the mind" that the PMA did not substantiate greater safety, effectiveness and durability after years of experience with such health complications and device failures.

The panel was ambivalent in its assessment of the adequacy of Inamed's literature review of long-term risks of cancers, connective tissue disorders, reproductive or teratogenic effects, interference with breast feeding or detection of tumors through mammography. Inamed publicly conceded at the panel meeting that its preclinical mechanical data is not clinically meaningful. Absent substantiating clinical experience with its products, the company's reliance on historic literature, consisting of case reports and studies of non-Inamed product, and on preclinical animal testing fails to provide a reasonable assurance of safety.

The FDA has publicly acknowledged that "there are additional safety issues that apply to the silicone implants that do not apply to the saline implants, such as silent rupture and gel migration, which will need to be evaluated."[2] Research has consistently demonstrated that the onset of the majority of complications related to silicone gel-filled breast implants occur between seven to ten years and, unlike saline breast implants, are often not detected by women for many years after they occur. Research conducted at the FDA by S. Lori Brown, Ph.D., verified the latency of developing complications associated with silicone gel-filled breast implants, including rupture and gel migration.[3]

Indeed the Summary Panel Memorandum, dated September 12, 2003, prepared by the FDA's Inamed PMA Review Team noted, "one consequence of implant rupture is gel migration." According to the memorandum, "there are several studies that report that, in some

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[1] Dr. Thomas Whalen, acting chairman of the panel, quoted in the Associated Press, October 15, 2003.

[2] Letter from Amit K. Sachdev, Associate Commissioner for Legislation, Department of Health and Human Services, to Senator Edward M. Kennedy, July 2, 2003.

[3] Brown SL, MS Middleton, WA Berg, MS Soo, G Pennello. Presence of rupture of silicone gel breast implants revealed on MR imaging in a population of women in Birmingham, Alabama. American Journal of Roentgeonology; 175: 1057-1064, 2000.

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 result of gel migration."

These long-term adverse medical consequences specifically include an elevated risk of an immunological response, potentially contributing to the development of systemic illness following long-term implantation of silicone gel-filled breast implants. Recently published and ongoing research continues to demonstrate the real potential of an immunological response to long-term implantation of silicone gel-filled breast implants, particularly in the presence of significant rupture or verifiable gel migration. Research at the National Institutes of Environmental Health Sciences and published research by the FDA has demonstrated the presence of immunological responses to silicone gel-filled breast implants including a significant association with fibromyalgia.[4]

The Core clinical study reconstruction and augmentation cohorts demonstrated increased frequencies of connective tissue disease signs and symptoms through year 2 of patient follow-up. When asked by the advisory panel whether the association between connective tissue disease and silicone breast implants was "closed", Dr. Sahar Dawisha of the FDA responded that the question of a relationship "has not been resolved at this time." (emphasis added)

2. The Inamed PMA fails to provide adequate data on the rate of asymptomatic or silent rupture of silicone gel-filled breast implants, making a complete assessment of the resulting safety consequences impossible.

According to the Summary Panel Memorandum dated September 12, 2003, "in their review, Inamed provided no discussion of the significance of implant rupture. Because implant age is a factor in rupture, it is not clear whether later generations of implants have improved with respect to rupture, since these implants have not achieved the age of earlier generations."

[4] Brown SL, Duggirala HJ, Pennello G. An Association of Silicone-Gel Breast Implant Rupture and Fibromyalgia. Current Rheumatology Reports, 2002; 4:293-298.

As one method of investigating asymptomatic rupture, more than 108 of 221 patients from the reconstruction cohort (48 percent) and 166 of 331 patients from the augmentation cohort (50 percent) in the Core study were intended to be subject to serial MRI screening to determine asymptomatic or silent rupture.[5] Complete MRI screening data was completed one year post-operatively for all three indications of augmentation, reconstruction and revision, and partial three-year data was available for the augmentation cohort. Only 2 implants from the reconstruction cohort were followed to the second screening at three years. As such, the panel concluded that there was limited data and no relevant information on asymptomatic rupture.

The absence of this longer-term data from the PMA makes a rigorous assessment of safety impossible. Of the 15 implant ruptures reported by Inamed at the time of database closure, a majority of nine (60 percent) were initially detected by MRI screening and were asymptomatic. And with less than half of the reconstruction patients enrolled in this screening subset, FDA recognized that "had a larger proportion of patients undergone MRI screening, the rupture rate would likely be higher."

As a result, the design and execution of the Core study clearly understates the frequency of asymptomatic or silent rupture. Additionally, published literature on silicone gel-filled breast implant rupture, although not specific to Inamed, substantiates the fact that rupture rates increase significantly with implant age, with between 26 percent (median implant age of 12 years) and 55 percent (median implant age of 16 years) of such implants assessed by MRI for evidence of rupture.

These deficiencies were also clearly identified by the General and Plastic Surgery Devices Panel, whose members discussed extensively the absence of reliable information on asymptomatic rupture. There was a panel consensus that Inamed had failed to provide adequate information to provide a reasonable assurance of safety with respect to such ruptures. The Inamed PMA consequently lacks adequate safety data on the rate of asymptomatic or silent rupture of the McGhan silicone gel-filled breast implants.

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[5] Dr. Sahar Dawisha (FDA), Inamed Clinical Summary memorandum, September 12, 2003, pp 36-37.

3. The Inamed PMA includes little if any clinical data in support of the safety or effectiveness of two of the seven proposed styles of silicone gel-filled breast implants.

The FDA's summary memorandum for the General and Plastic Surgery Devices Panel baldly acknowledges that the Inamed Core clinical study "does not include Style 10 or 20, which are two implant styles for which Inamed is seeking approval. This is the primary clinical data set for this PMA."[6] Although Inamed claims that data is available from the adjunct study to support the safety and effectiveness of these two styles, which differ in important design features as volume, shell surface, shape and profile from the other five styles, the adjunct study cannot provide more than 1 month of actual data underlying the use and observation of these two styles. The adjunct study was initiated in 1998[7] and closed in August of 2003. According to Inamed Styles 10 and 20 were introduced into the adjunct study in July of 2003.

4. Unreliable mechanisms of post-marketing surveillance and proposed conditions of use susceptible to noncompliance cannot provide the clinical data or remedy deficiencies in the Inamed PMA to provide a reasonable assurance of safety.

In the absence of actual clinical data in the Inamed PMA, the proposed reliance on mechanisms of post-marketing surveillance which have historically yielded incomplete or unreliable data, and on conditions of use which are highly susceptible to noncompliance, cannot provide the clinical data to provide a reasonable assurance of safety, nor remedy the deficiencies of the Inamed core clinical study. Dr. Lori Brown from the FDA acknowledged in her presentation to the panel "surveillance is not the equivalent of a clinical study."[9]

Inamed proposed a series of postapproval conditions to the General and Plastic Surgery Devices Panel that would consist of loosely monitored post-market surveillance and provider education programs that would serve marketing and promotional purposes more than they would

[6] FDA Inamed PMA Review Team, Summary Panel Memorandum, September, 12, 2003.

[7] Dr. Sahar Dawisha (FDA), Inamed Clinical Summary memorandum, September 12, 2003.

[9] FDA presentation to the advisory panel, October 14, 2003, Slide 87.

assure patient safety. The proposal to require annual MRIs to detect implant rupture was attenuated into an ineffectual "strong recommendation" rather than an actual condition of use of the devices. Celia Whitten from the FDA acknowledged at the advisory panel meeting that the FDA does not have the ability to provide oversight of postapproval conditions to ensure compliance.

The FDA's historic post-market surveillance of breast implants has been inadequate and the agency has acknowledged that it is unrealistic to rely upon such scrutiny to generate data that could supplant long-term safety data collected through rigorous clinical investigation. As early as 1995, the Center for Devices and Radiological Health (CDRH) determined that breast implant manufacturers did not need to identify the age of the device in reporting adverse events. As a result, the failure rate and susceptibility to complications are not discernible for different "generations" of breast implants in patients and on the market.

As of March 13, 2003 erroneous reports – filed under incorrect identifiers by both Inamed and Mentor Corporation ("Mentor") – were removed. Whether these reports have been refiled under the correct identifiers has not been determined. Moreover, as divulged during the FDA's criminal investigation of Mentor, the problems of inadequate manufacturer adverse event reporting, the use of incorrect identifiers for hundreds of such MDRs, the FDA's waiver of filing of additional MDRs for issues that were "well characterized", and the significant loss of patients to follow-up for saline-filled breast implants were not remedied by the FDA, nor was the potential recurrence of such problems fully addressed by the agency. Unless the FDA can undertake steps to dramatically improve and ensure the accuracy of adverse event reporting by breast implant manufacturers and user facilities, reliance on this method of surveillance is not a satisfactory method of assuring the safety of silicone gel-filled breast implants.

C. Conclusion.

For the aforementioned reasons of law, regulation and policy, the Commissioner should refrain from completing the review of and the decision concerning the Inamed PMA for silicone gel-filled breast implants, until a PMA amendment is submitted responding to the deficiencies identified in this petition.

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 petitioner that are unfavorable to the petition.

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