

May 25, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket Number: 2004D-002 – “Draft Guidance for Industry and FDA Staff: Saline, Silicone Gel, and Alternative Breast Implants”

Dear Sir or Madam:

Inamed Corporation (“Inamed”) submits the comments below in response to FDA’s “Draft Guidance for Industry and FDA Staff: Saline, Silicone Gel, and Alternative Breast Implants” (“Draft Guidance”) issued January 8, 2004. Over a decade of discussion on silicone breast implants (SBIs) preceded the consideration of Inamed’s premarket approval application (“PMA”) for SBIs.

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Background

Issues surrounding SBIs were initially brought into focus when FDA convened the General and Plastic Surgery Device Panel (“the Panel”) on November 12-14, 1991. The 1991 Panel met to assess the safety and effectiveness of SBIs, reviewing the first SBI PMAs, following FDA’s classification of all breast implants as Class III devices. On January 6, 1992, FDA called for a voluntary moratorium on the use of SBIs, to allow the Panel to thoroughly review issues such as breast cancer detection, contracture, rupture, gel bleed, and silicone migration. These concerns were revisited by the Panel on February 18-20, 1992, with additional information provided by implant manufacturers, and the added topics of autoimmune and connective tissue disease.¹ On April 16, 1992, FDA announced that, consistent with the recommendations of the Panel, SBIs would be allowed on the market in limited circumstances under controlled clinical studies.²

It has now been over 12 years since FDA removed SBIs from the open market, making them available only through controlled clinical studies. When FDA issued its Draft Guidance on January 8, 2004, then-Commissioner Mark McClellan stated that “[t]he FDA, sponsors, and the clinical community have learned a great deal about...silicone gel-filled breast implants” in the past decade, and that “based on this knowledge” the Draft Guidance provides FDA’s view on the information needed to demonstrate safety and effectiveness.³

¹ Transcript of General and Plastic Surgery Devices Panel Meeting (February 18, 1992) at 7-9.

² “Chronology of FDA Breast Implant Activities” (Updated August 29, 2000) at 2. Available at: <http://www.fda.gov/breastimplants/bichron.html>.

³ “FDA Provides Pathway for Sponsors Seeking Approval of Breast Implants” (January 8, 2004) at 1. Available at: <http://www.fda.gov/bbs/topics/NEWS/2004/NEW01003.html>.

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What FDA fails to explain is how, despite 12 years of discussion about well known issues surrounding SBIs, it allegedly made new discoveries between the General and Plastic Surgery Devices Panel meeting on October 14-15 of 2003 ("the 2003 Panel") and January 8, 2004 that warranted substantial changes to its Guidance on SBIs. The issues considered at the 2003 Panel meeting have been widely discussed since the first SBI PMAs were considered in 1991-1992. There were no surprises presented at the 2003 Panel, and based on the data presented in accordance with FDA's "Guidance for Saline, Silicone Gel, and Alternative Breast Implants: Guidance for Industry and FDA" issued February 11, 2003 ("2003 Guidance"), Panel members voted 9-6 to recommend approval of SBIs, finding reasonable assurance of safety and effectiveness.

I. Inamed Based its PMA Submission on FDA's 2003 Guidance, and the Drastic Changes Proposed in the 2004 Guidance are Not Justified, Nor are They Necessary to Provide Reasonable Assurance of Safety and Effectiveness.

Since 1992, FDA has offered SBI manufacturers guidance on how to demonstrate the safety and effectiveness of their devices.⁴ At the 2003 Panel meeting, FDA explained the intended flow of information between the Agency and manufacturers. Dr. Celia Witten, Division Director of ODE's Division of General, Restorative, and Neurological Devices, offered Panel members a regulatory overview of SBIs, explaining that "FDA has provided Guidance to manufacturers both in written form and direct discussions to assist them in developing the data needed to support a PMA."⁵

Due to the history of SBIs, FDA Guidance has been of exceptional importance to SBI manufacturers in understanding FDA's expectations for PMAs. We fundamentally disagree with the process that resulted in the proposed changes to the FDA's Guidance on SBIs in January of 2004. More importantly, we disagree with the content of the changes, and do not believe that they are necessary to demonstrate safety and effectiveness, or even that they are capable of producing the suggested answers. Inamed met the criteria for approval, following the 2003 Guidance, which FDA issued with all the knowledge gained in the decade since the moratorium. The Panel Meeting did not raise any new issues necessitating a change in the guidance, and there is no justification for imposing new criteria at this time.

While FDA's actions to drastically change the Guidance on SBIs at this late date are unfair to Inamed, more importantly, we believe that the proposed changes are unnecessary and misguided in their approach, for the reasons that will be described below. It is true that the Panel recommended certain of the proposed requirements, but they recommended them as *post-approval* requirements. Useful information may be gained through certain post-approval studies, and we welcome the opportunity to provide this information in post-approval studies, but the fact remains that reasonable assurance of safety and effectiveness has already been provided consistent with the FDA Guidance in effect at the time Inamed's PMA was submitted, and based on the recommendation of the 2003 Panel.

⁴ See "Draft Guidance for Preparation of FDA Submissions of Silicone Gel-Filled Breast Prostheses" (May 11, 1992).

⁵ Transcript of General and Plastic Surgery Devices Panel Meeting (October 14, 2003) at 261.

II. The Proposed Changes to the Guidance Would Hold SBIs to a Higher Standard than Any Other Device, Imposing Requirements Beyond Those Necessary to Provide Assurance of Safety and Effectiveness, with a Misplaced Emphasis on Rupture.

Over the past decade, FDA has provided the roadmap for manufacturers to follow in developing data for SBI PMAs. Inamed assiduously followed FDA's Guidance in designing and conducting clinical and preclinical studies, the results of which were included in Inamed's PMA. FDA's February 2003 Guidance provided specific recommendations on clinical study design, how to demonstrate sufficient sample size, and also recommended the safety assessments that a sponsor should make in the clinical study, listing complications that FDA considers crucial to determining risks for all breast implants.⁶ In addition, FDA suggested frequencies for follow up evaluations of implant patients.⁷ Based on concerns raised regarding breast implants, the Guidance recommended that a sponsor collect safety data regarding potential connective tissue disease, the silent rupture rate for silicone implants, and mammographic changes and detection difficulties.⁸ Inamed followed the recommendations of the 2003 Guidance in its PMA submission.

A. It is Unreasonable to Hold SBIs to a Higher Standard for Premarket Clinical Data than Any Other Device.

According to the 2003 Guidance, a sponsor may submit clinical data after 2 years of study, and neither the Guidance nor Inamed's communications with FDA indicated that SBIs would be treated differently from other implants with regard to the length of follow-up required for PMA submission to support a reasonable assurance of safety and effectiveness. There should be a reasonable expectation that if a sponsor has followed the Guidance provided by FDA, and the Panel votes to recommend approval, the recommendation will be upheld. Contrary to this logical expectation, the Draft Guidance proposes that SBIs be held to a higher standard than other implantable devices, as FDA may require more than 2 years of premarket clinical data.

If a sponsor cannot use FDA's Guidance as a benchmark for sufficiency, sponsors will have to blindly guess at what data they should provide in a PMA, without knowing how to focus resources to provide the best information possible. The situation created when FDA changes the

⁶ "Guidance for Saline, Silicone Gel, and Alternative Breast Implants: Guidance for Industry and FDA" (February 11, 2003) at 17. The Guidance indicates that information should be collected on the following: the incidence, timing, and reason(s) for all implant removals, for removal with replacement with Sponsor's device, another manufacturer's device, and for removal without replacement; the incidence, timing, and reason(s) for any reoperation; the incidence, timing, and type(s) of additional surgical procedures; the incidence, timing, and resolution of all other complications; the incidence, timing, and severity of alterations in nipple or breast sensation; the incidence, timing, and severity of interference with lactation; the incidence, timing, and nature of difficulties with pregnancy; the incidence, timing, and cause of patient deaths from post-mortem examinations; the incidence, timing, and type of new breast cancer diagnosis post-implantation.

⁷ *Id.* at 18.

⁸ *Id.* at 19.

standard for sufficiency in the midst of considering a PMA, without basing this decision on any new information, is arbitrary and antithetical to FDA's role in assisting manufacturers to develop PMA data.

At the 2003 Panel meeting, Cdr. Samie Allen of FDA advised Panel members that the 2-year data were not to be considered alone, but that the ultimate question was "whether this short-term study, coupled with the other information will be enough to provide reasonable assurance of safety for this product."⁹ The majority of the 2003 Panel was convinced that the totality of the information provided this assurance.

B. FDA's Focus on Rupture Rates, Gel Bleed, and Silicone Migration is Misplaced, as the Essential Question is Whether There are Long-Term Health Effects Associated with SBIs--the Overwhelming Evidence is that There is No Link to Adverse Health Effects.

Many of the proposed changes to the SBI guidance relate to concerns over rupture, gel bleed, and silicone migration, and recommend that new mechanical testing methodologies be developed, additional data be gathered from retrieval studies, and supplemental clinical information be provided *prior to approval*. Despite the Draft Guidance's implication that these areas represent newly warranted concern, this is not the case. When the 1992 Panel met to consider additional information on SBIs, the primary areas of interest were diagnosis of cancer, capsular contracture, rupture, gel bleed, silicone migration, and whether there was a causal link to autoimmune or connective tissue disease.¹⁰ When these issues were raised over 12 years ago, then-Commissioner David Kessler identified that while we want to gain information about rupture rates and determine how ruptures should be detected and treated, a key question was what the *consequences* of rupture were--that is, whether escaped gel material would have an adverse health effect.¹¹ Safety and effectiveness are well established for SBIs. There are massive amounts of data on this subject, as SBIs are the most-studied device in U.S. history. SBIs have a 30-year history in numerous European markets and continue to be marketed in these countries without any substantiated evidence or even significant allegations of systemic disease that some individuals in this country have made.

The currently proposed requirements are misguided in their focus on rupture and silicone migration. While rupture is an unintended patient outcome, the more important question is whether ruptures result in health problems. The overwhelming evidence gained over the past decade is that there are no significant long-term health effects linked to SBIs. Neither the extensive toxicological studies or chemical evaluations, nor long-term epidemiological data have indicated that silicone poses any additional systemic health risks compared to saline implants. Moreover, the short term complications of SBIs have also been well established, both as to frequency and severity. The 2003 Panel agreed by a vote of 9-6 that the cumulative evidence provided reasonable assurance of safety and effectiveness, and that additional studies on rupture were not needed prior to approval. While rupture may be an appropriate topic for post-approval

⁹ 2003 Panel (October 14) at 554.

¹⁰ 1992 Panel (February 18) at 7-9.

¹¹ *Id.* at 22.

study, and we would welcome any knowledge gained in this way, such additional studies are not necessary to demonstrate safety and effectiveness of SBIs. In addition, in some cases the methods proposed will not effectively capture relevant information.

III. Comments on Draft Guidance

The issues raised in the Draft Guidance have been the subject of over a decade of discussion and consideration, and no newly-gained information supports the drastic changes proposed. Below, we have provided our specific comments on the draft guidance.

4.2 Extent of Crosslinking

The Draft Guidance requires that manufacturers confirm the uniformity of the degree of crosslinking across manufacturing lots of the shell. In addition, FDA also recommends that the manufacturer perform Fourier Transform Infrared Spectroscopy (FTIR) analysis on the cured polymer to confirm the presence of silicone functional groups.

Inamed believes the requirement for an FTIR scan is inappropriate and has not been adequately justified. FDA has not provided a scientifically valid rationale explaining the need for the information requested.

6.2 Fatigue Rupture Testing of Total Device

FDA's Draft Guidance requires manufacturers to develop a new test methodology that replicates clinical failure modes and approximates the rate of rupture during the expected life of the device.

Inamed recognizes that implant rupture and the rate of rupture is a safety concern; however, this concern is not new. The issue of implant rupture and rupture rate was raised during the 1992 Panel Meeting. The current 2003 Guidance, which was developed to address the concerns raised at the 1992 Panel Meeting, includes appropriate and scientifically proven methods for analyzing the fatigue resistance of breast implants. The agency has not presented any new, scientifically valid evidence that supports the need for new fatigue test methodologies.

Further, it is not feasible to design an *in vitro* fatigue test that will exactly mimic the *in vivo* conditions to which a breast implant will be exposed. The stresses placed on a breast implant *in vivo* will vary with each patient depending on factors such as pre- and post-operative handling of the device, the patient's physical characteristics, the patient's activity level, and the patient's medical history. The rupture rate of Inamed's SBI is approximately 1%, as established through clinical studies. This rupture rate is also supported by the scientific literature. Requiring manufacturers to design a test methodology to replicate and adequately predict a 1% rupture rate is unreasonable and not relevant to assessing the safety or effectiveness of the product.

It is clear that the mechanical performance of a breast implant can be adequately demonstrated through bench testing using currently available and validated test methods. The

pertinent question is whether ruptures result in health problems. The suggested revisions to the fatigue testing will not, and cannot, provide the answer to this question. The overwhelming evidence gained over the past decade is that there are no significant long-term health effects linked to SBIs. Neither the extensive toxicological studies or chemical evaluations, nor long-term epidemiological data have indicated that silicone poses any additional systemic health risks compared to saline implants.

Additionally, by requiring such testing to be conducted prior to approval, FDA is holding breast implants to a higher standard of “a reasonable assurance of safety and effectiveness” than other permanent implants, including life-supporting and life-sustaining implants. For example, the Draft Guidance states that changes to the fatigue testing requirements are predicated on clinical indications that devices do rupture, and concludes that, based on these indications, the current test methods are not valid. Clinical information has also shown that other permanent implants, such as permanent pacemaker electrode leads, fail prematurely, and such failures have occasionally led to patient death. FDA was fully aware of this information and the clinical experience when developing a guidance document for the types of data needed to support a PMA for these devices, yet the agency did not require manufacturers of these devices to develop new test methodologies for predicting the rate of failure nor are such data required for approval. The agency has adopted the use of post-marketing studies to assess the long-term safety of permanent pacemaker leads and other implants, and the same policy should be applied to breast implants.

For these reasons, Inamed believes the criteria for fatigue testing of devices should remain unchanged from the 2003 Guidance and that information regarding the long-term rupture rates and clinical consequences of rupture be assessed through post-approval studies.

6.5 Bleed Testing

The Draft Guidance requires manufacturers to develop a new test methodology that mimics *in vivo* conditions that can be used to quantify gel bleed and identify the gel bleed constituents.

As with the question of fatigue resistance and rupture, the questions regarding gel bleed are not new, and over the past decade FDA has provided manufacturers with guidance on the type of the information that would be needed to support PMA approval for silicone breast implants, including guidance on gel bleed testing. FDA has not presented any new valid scientific evidence that warrants a change from the current recommended test methodologies.

Additionally, such testing is not necessary to establish a reasonable assurance of the safety and effectiveness of silicone breast implants. Inamed has assessed gel bleed and migration in patients who have experienced rupture. The data demonstrate that the silicone gel does not migrate beyond the capsule. A traumatic rupture may cause gel migration outside the capsule; however, replicating a traumatic rupture during a clinical study is not feasible or ethical. There is a significant body of evidence, including the Institute of Medicine’s report “*Safety of Silicone Breast Implants*” (IOM Report) that conclude silicone breast implant materials pose no clinically relevant risk and no increased risk of systemic disease or conditions. Extensive

toxicological studies, chemical evaluations, and long-term epidemiological data also demonstrate that no health hazards are associated with silicone breast implant material.

The gel bleed requirements for PMA approval should remain unchanged from the 2003 Guidance. Improvements in test methods and issues of scientific interest are more appropriate for postmarket research studies.

7.0 Modes and Causes of Rupture

FDA recommends that a Retrieval Study include the analysis of local tissue/capsule. It is not ethically appropriate to collect tissue samples from a healthy patient, nor has FDA provided a valid scientific or clinical rationale for the need to conduct such testing. Such testing is not feasible or ethically appropriate without meaningful scientific or clinical rationale. Research in this area spans several decades, and to date no validated technologies have been developed. No new scientific evidence has been presented that supports FDA's recommendation that manufacturers conduct research and develop new technologies for analyzing local tissue/capsule in healthy patients.

Further, the data obtained from such testing is not necessary to establish a reasonable assurance of the safety and effectiveness of silicone breast implants. There is a significant body of evidence, including the IOM Report that concluded silicone breast implant materials pose no clinically relevant risk and no increased risk of systemic disease or conditions. Extensive toxicological studies, chemical evaluations, and long-term epidemiological data also demonstrate that no health hazards are associated with silicone breast implant material. Therefore, it is Inamed's opinion that the Retrieval Study should exclude analysis of local tissue/capsule.

9.1 Clinical Studies, General Information

The Draft Guidance recommends that data be analyzed on both a per patient and per device basis. The Draft Guidance further recommends that patients and devices be classified by the initial indication at study entry. For example, if a reconstruction patient undergoes contralateral augmentation, that *patient* would be classified as a reconstruction patient. As for the devices used, one would be classified as a reconstruction device and the other one as an augmentation device. The same approach is used for revision patients.

Inamed disagrees with FDA's proposed classification schemes. A patient who undergoes reconstruction in one breast with contralateral augmentation in the other breast should be classified as a reconstruction patient, and both devices should be classified as reconstruction. A patient's entire body and physiological system may have been subjected to reconstructive therapies such as mastectomy with chemotherapy or radiation treatment. As such, both breasts, not just the reconstruction breast, are different from the normal population. It is inappropriate to report outcomes associated with contralateral augmentation in a revision patient, such as asymmetry, along with device outcomes in the normal augmentation population. Indications should be applied to patients as a whole, not to individual breasts. The classification of revision patients should be similarly defined.

9.3 Safety Assessment, Rupture of Silicone Gel-Filled Breast Implants

The Draft Guidance states that if a silicone breast implant ruptures, gel can migrate outside of the capsule and into the breast area, the lymph nodes, and distant locations. FDA, therefore, recommends tissue sampling from the surrounding breast tissue and capsule to confirm whether or not device constituents are present. FDA also recommends that manufacturers use MRI to detect silent ruptures. If MRI is not adequate to detect silent ruptures, manufacturers are required to develop a new imaging modality as an alternative to MRI.

Inamed believes that it is neither feasible nor ethically appropriate for a manufacturer to collect patient tissue samples without a demonstrated scientifically or clinically valid rationale for doing so. Currently, there are no validated analytical methods available for quantifying or identifying silicone from breast implants. Additionally, patients are exposed to silicone and silicone products in their everyday lives. There are no proven methods for differentiating silicone from breast implants from that to which may be present from normal exposure, thus the information that would be obtained from tissue sampling would be inconclusive.

Additionally, the tissue sampling FDA recommends will not provide answers about the long-term health consequences that may be associated with silicone gel migration, if such migration were to occur. The pertinent question is whether ruptures result in adverse health effects. Inamed's clinical studies demonstrated a rupture rate of approximately 1% and gel migration was assessed as part of the study. The data demonstrate that the silicone gel does not migrate beyond the capsule. The overwhelming evidence gained over the past decade indicate that there are no significant long-term health effects linked to SBIs. Neither the extensive toxicological studies or chemical evaluations, nor long-term epidemiological data have indicated that silicone poses any additional systemic health risks compared to saline implants.

The development of a new imaging modality as an alternative to MRI is overly burdensome and beyond the scope of a premarket requirement. MRI is the state-of-the-art imaging technique and took years to fully develop. It is unreasonable to require a manufacturer to develop such technology to support market approval of a device.

Inamed believes that the requirement for tissue sampling and development of new analytical methods for detecting silent rupture should be omitted from the guidance.

9.3 Safety Assessment, Connective Tissue Diseases ("CTDs")

The Draft Guidance recommends that manufacturers provide information on numerous CTD diseases/conditions as part of the overall safety assessment of its device. FDA also recommends that "if indicated" patients should have a follow-up examination by an appropriate specialist.

As previously stated, there is a significant body of evidence indicating that silicone gel materials do not present any long-term adverse health effects, and that there is no causal link between silicone gel and CTDs. In fact, FDA acknowledges in the Draft Guidance that the "Core Study (the study suggested by FDA to support approval) is not designed to examine a

potential linkage between breast implants and the development of CTDs.” Therefore, it is inappropriate and against FDA policy to require such information as part of the premarket evaluation of SBIs.

Many of the symptoms the Draft Guidance recommends be followed will manifest or increase with patient age and may selectively increase with age in individuals who have high awareness of their body. As written, in the Draft Guidance, the symptoms requiring follow-up are very non-specific and most will increase inherently with patient age. Therefore, the specific symptoms and circumstances that would require follow-up should be identified.

9.4 Effectiveness Assessment

As part of the effectiveness assessment for breast implants, FDA has recommended collecting Health Related Quality of Life (“HRQL”) information on patients at the preoperative timepoint and 1, 2, 4, 6, 8, and 10 year timepoints.

Inamed fundamentally disagrees with the need for 10-year data as a premarket requirement. According to the 2003 Guidance, a sponsor may submit clinical data after 2 years of study. Specific to the requirement of long-term HRQL data, Inamed believes that collection of this data should not occur beyond the 2 year follow-up. The validity of HRQL data and/or other Quality of Life (“QOL”) data beyond the 2 year timeframe has not been established. Statistical and psychometric phenomena such as regression to the mean and practice effects become increasingly likely as patients are administered the same questionnaire repeatedly. Two years is a sufficient timeframe over which to obtain a reasonable assessment of the effect of breast implant surgery on patients’ quality of life. Quality of life data obtained beyond two years is increasingly likely to be affected by a myriad of unrelated events occurring in patients’ lives, such as aging or weight gain. Furthermore, patients will likely have already completed a Quality of Life questionnaire multiple times after their two year visit, decreasing the validity of the data collected.

10.4 Safety Data Presentation – Complications

The Draft Guidance recommends that the overall sum of all complications as well as the total number of events be provided at each follow-up timepoint. It is possible that multiple events may be part of a single complication. Inamed believes there is no value in counting the total number of events at each visit due, and that this requirement should be omitted from the guidance.

10.5 Safety Data Presentation – Rupture

The Draft Guidance recommends that when a device ruptures and is explanted, manufacturers provide tissue sampling data of the patient’s surrounding breast tissue and capsule to confirm whether device constituents are present.

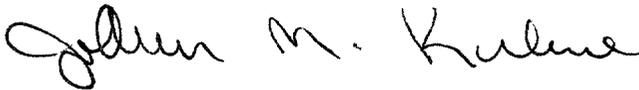
Inamed believes that the proposal to require manufacturers to collect patient tissue samples without a demonstrated scientifically or clinically valid rationale for doing so is

unsupportable. Currently, there are no validated analytical methods available for quantifying or identifying silicone from breast implants, and due to other sources of exposure to silicone, testing of this tissue would not provide conclusive evidence.

Conclusion

We respectfully submit the above comments to FDA's Draft Guidance on SBIs and submit that compliance with the 2003 Guidance provided adequate assurance of the safety and effectiveness of SBIs.

Sincerely,

A handwritten signature in black ink, appearing to read "JoAnn M. Kuhne". The signature is written in a cursive style with a large initial "J" and "K".

JoAnn M. Kuhne, M.S.N., R.A.C.
Senior Director, Regulatory and Clinical Affairs