PMA P020056
Silicone-Filled Breast Implants

BRIEFING DOCUMENT

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TABLE OF CONTENTS

1. INTRODUCTION ............................................................................................................................................3
2. REGULATORY HISTORY .....................................................................................................................................4
3. EXECUTIVE SUMMARY ....................................................................................................................................4
4. DEVICE DESCRIPTION ......................................................................................................................................6
5. PRECLINICAL STUDIES ......................................................................................................................................7
   A. GEL CONSTITUENT TESTING...........................................................................................................................8
      1. Chemical Analyses of Low Molecular Weight Components in the Device ..............................................8
      2. Gel Bleed Testing ........................................................................................................................................8
      3. Toxicological Implications of Gel Bleed .....................................................................................................10
   B. PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING .................................................................11
   C. PHYSICAL/MECHANICAL TESTING ...........................................................................................................13
      1. Static Rupture Testing (Ultimate Burst Testing) .......................................................................................13
      2. Fatigue Rupture (Cyclic Fatigue Testing) .................................................................................................13
6. CLINICAL STUDIES .........................................................................................................................................14
   A. OVERVIEW OF STUDIES .............................................................................................................................14
   B. EFFECTIVENESS .........................................................................................................................................14
      1. Quality of Life ..........................................................................................................................................15
      2. Patient Satisfaction .................................................................................................................................15
   C. SAFETY .......................................................................................................................................................16
      1. Rupture Rate ............................................................................................................................................17
      2. Modes and Causes of Rupture ...............................................................................................................22
      3. Health Consequences of Rupture ..........................................................................................................24
         a. Local Complications ...........................................................................................................................24
         b. Silent Rupture Progression to Symptomatic Rupture .....................................................................25
         c. Intracapsular Rupture Progression to Extracapsular Rupture .........................................................26
         d. Connective Tissue Disease ..............................................................................................................27
         e. Patient Satisfaction ...........................................................................................................................27
   7. POSTAPPROVAL PLAN .................................................................................................................................27
      A. CORE POST APPROVAL STUDY .............................................................................................................27
      B. PHYSICIAN EDUCATION AND TRAINING ............................................................................................27
         1. INAMED Education and Training .....................................................................................................27
         2. INAMED Continuing Education Series Publications .....................................................................28
         3. Labeling and Patient Education ......................................................................................................29
      C. VOLUNTARY PATIENT REGISTRY .....................................................................................................29
   8. CONCLUSION ..................................................................................................................................................30
1. Introduction

Silicone breast implants are an important option for women seeking augmentation, reconstruction or revision implantation surgery. They have particular importance in the context of reconstructive surgery because they enable surgeons to more closely match natural breast shape and feel. These same advantages of silicone breast implants should also be available to women seeking breast augmentation, thus providing a choice for women between the currently approved saline-filled breast implants and the silicone-filled implants that are the subject of this PMA. Despite the current controversy surrounding their availability in the United States, silicone-filled breast implants were available to women from the early 1970s through 1991, and since then have been provided to tens of thousands of U.S. women through clinical studies. They have also been widely available for the past 30 years throughout most of Europe and in many other countries around the world.

The current PMA seeks to supply the necessary safety and efficacy data so as to make Inamed silicone implants available on a much less restrictive basis. The current silicone-filled breast implant represents a generational advancement over the implants of a decade ago, with greater safety and durability due to several improvements in design and manufacturing. This safety has been demonstrated in a series of clinical trials, including an ongoing 10-year large-scale prospective study with close to 1,000 patients, supplemented by a 5-year prospective study of over 46,000 patients. The safety is further supported by approximately 100 published research papers that have appeared in peer-reviewed journals around the world.

Seemingly, the FDA’s primary basis for concern about the safety of silicone breast implants is the exposure to silicone gel material after a potential rupture of the implant. In addition to its clinical studies, Inamed has conducted extensive non-clinical research to assess the safety of the silicone gel and to determine the modes and causes of rupture. The results show that the gel material is biocompatible and nontoxic. Further, Inamed’s mechanical testing and post-explantation testing of retrieved implants has determined the structural integrity of the implant and identified primary causes of rupture. This information has guided and is continuing to guide labeling, education, and implant design to better characterize rupture and further reduce its occurrence.

Though Inamed’s ultimate goal is to eliminate the possibility of rupture, ruptures do still occur. Therefore, Inamed has fully investigated any potential health consequences of rupture. The results show that the primary consequences of rupture are cosmetic, though local complications such as pain can occur. Importantly, Inamed’s clinical studies and the extensive peer-reviewed literature have demonstrated no serious or systemic complications associated with rupture. In this light, because most ruptures result in explantation and a new implantation, the greatest risks associated with rupture are the known risks of additional surgery and not the exposure to the silicone gel material.
2. Regulatory History

In December 2002, Inamed submitted our silicone gel-filled breast implant PMA (P020056), seeking approval for augmentation, reconstruction, and revision indications for several implant styles.

In October 2003, FDA presented this PMA to the General and Plastic Surgery Devices Advisory Panel. The Panel recommended, in a 9 to 6 vote, that the PMA was approvable with conditions. FDA subsequently determined that the PMA was not approvable, and a not-approvable letter was issued on January 7, 2004.

In August 2004, Inamed submitted responses to the January 7, 2004 not-approvable letter for this PMA. This briefing document contains a summary of the data/information submitted in response to FDA’s not-approvable letter, which will be the subject of the April, 2005 General and Plastic Surgery Devices Advisory Panel meeting.

3. Executive Summary

Since the October 2003 meeting, Inamed has generated substantial data to address the concerns raised by the Committee and subsequently by the FDA. FDA’s revised 2004 guidance document added requirements to provide information on the expected rupture rate over the lifetime of the device, modes and causes of rupture and health consequences of rupture. Inamed responded by amassing significant scientific data that address these concerns and further demonstrate the safety of our silicone-filled breast implants. Inamed is committed to working with FDA to further their evaluation of these devices and reach a safety and effectiveness determination.

Inamed now has additional information regarding the frequency of ruptures observed and a description of the potential local health consequences associated with device rupture. Because there is now more clinical information available from our studies, along with information from published reports in peer-reviewed journals, we can now better characterize implant rupture. Our extensive retrieval study of explanted devices has also enabled us to more thoroughly characterize the modes and causes of implant rupture.

Inamed has addressed a primary issue regarding long term risk of implant rupture and its associated complications, and has calculated an overall risk of silent and symptomatic rupture in the Core Study of 2.5% at 3 years, and estimated to be 13.9% at 10 years after implantation. This estimate of a long term rupture rate is consistent with that of the failure rate of Inamed’s saline-filled breast implants, which yielded an 8-year deflation rate of 7.3% in Inamed’s 1995 Saline Augmentation Study. Though the shells of Inamed’s saline and silicone-filled implants are similar, saline failures should be considered the worst case because saline failure rates include valve failures that do not occur in gel-filled devices. The majority of the ruptures identified in the Core Study were for the Style 153 implant, a uniquely shaped device with an
inner bladder/ lumen that has a higher incidence of rupture than the other silicone-filled implants. Removing the Style 153 implants from the rupture rate calculations provides a rupture rate of 0.9% at 3 years, and estimated to be 5.1% at 10 years after implantation.

An expert materials scientist performed an independent re-analysis of Inamed’s retrieval data and found no data to support a concern that implants will “wear out” over time, consistent with the clinical data demonstrating that rupture rates are relatively constant over the duration of implantation. Thus, a linear progression of rupture rates is to be expected based on retrieval analysis, as well as data from Inamed’s Core Study, saline shell failure rates and 10-year surveillance data for Inamed’s silicone-filled implants.

Modes and causes of implant rupture were identified based on improved analytical tools and data obtained from both the independent expert’s re-analysis of retrieval data and Inamed’s comprehensive additional investigations of our retrieved devices. With the improved retrieval analysis, Inamed was able to successfully identify rupture failure modes for more than 90% of analyzed devices. The retrieval analyses conducted by both Inamed and the independent expert show that the primary cause of implant rupture in retrieved devices is due to surgical damage.

In order to reduce implant ruptures caused by surgical damage, physician education will be a key factor. Inamed recognizes its duty to provide surgeon education through continuing medical education, as well as via device labeling, that incorporates warnings on surgical practices that may lead to rupture. INAMED Academy and our other educational initiatives will ensure that physicians are equipped with the most current clinical outcome and risk information to provide to their patients and will offer a structured opportunity for surgeons to share their experiences with each other in an ongoing effort to evolve “best practices”.

To address concerns regarding local health consequences associated with rupture, Inamed examined over 100 patients with implant ruptures in the Core and Adjunct Studies. Only 6 of these ruptures involved extracapsular gel or gel migration. It was also determined that the complications experienced concomitant with rupture, as well as the complications experienced after removal of the ruptured implant, were the same types of complications and the same frequency of complications experienced by women with non-ruptured implants.

In order to address FDA’s concern that gel implant constituents could be present in patient tissues, Inamed has developed the Physiologically Based Pharmacokinetic (PBPK) model for selected molecular weight silicone constituents present in silicone-filled breast implants. The PBPK methodology offers an appropriate pathway for obtaining meaningful data, given the complexities and constraints associated with patient tissue collection and the lack of valid scientific methodologies for analyzing human tissue samples for silicone constituents. Inamed has determined that the PBPK model will be a viable scientific methodology to help characterize any potential health consequences of exposure to gel implant constituents, with findings to date supporting the safety of silicone implants.
Inamed is committed to demonstrating the safety and effectiveness of its silicone-filled breast implants in order to bring these devices to market and make them available to the women seeking them. Furthermore, the new data collected by Inamed contributes to the body of knowledge which will enable women and their physicians to make informed decisions regarding the use of these devices.

4. Device Description

Inamed’s silicone-filled breast implant shells are constructed from medical grade silicone elastomer, surrounding a viscous, lightly crosslinked silicone gel with a silicone patch positioned on the posterior side. The shell and patch have a barrier layer to reduce the rate and amount of gel bleed. Round or shaped implants are available in a variety of sizes and projections with either a smooth or textured surface. All implants are provided sterile and are single use devices.

The round implants have shells made from a single lumen and are available with either a smooth or textured surface. The shaped implants have shells made from a double lumen and are available only with a textured surface. The BIOCELL® texturing covers the entire shell except for the patch area. Choosing a smooth or textured surface is a matter of surgeon and patient preference; BIOCELL® texturing promotes mild tissue adherence which helps maintain implant position within the surgical pocket.

Figure 1 illustrates the width, height and projection of both round and shaped responsive gel implants.

**Figure 1: Implant Shapes.** Enlargement shows structured barrier layer with an inner and outer layer of silicone sandwiching silicone barrier layer.
Breast implants are for the following indications:

- Breast Augmentation
- Breast Reconstruction
- Revision of existing breast implants

The gel breast implant styles are as follows:

<table>
<thead>
<tr>
<th>Style No.</th>
<th>Surface Texture</th>
<th>Shape</th>
<th>Profile</th>
<th>Sizes (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Smooth</td>
<td>Round</td>
<td>Moderate Projection</td>
<td>120-800cc</td>
</tr>
<tr>
<td>15</td>
<td>Smooth</td>
<td>Round</td>
<td>Midrange Projection</td>
<td>158-752cc</td>
</tr>
<tr>
<td>20</td>
<td>Smooth</td>
<td>Round</td>
<td>Full Projection</td>
<td>120-800cc</td>
</tr>
<tr>
<td>40</td>
<td>Smooth</td>
<td>Round</td>
<td>Standard (Moderate) Projection</td>
<td>80-560cc</td>
</tr>
<tr>
<td>45</td>
<td>Smooth</td>
<td>Round</td>
<td>Full Projection</td>
<td>120-800cc</td>
</tr>
<tr>
<td>110</td>
<td>BIOCELL® Textured</td>
<td>Round</td>
<td>Moderate Projection</td>
<td>90-510cc</td>
</tr>
<tr>
<td>115</td>
<td>BIOCELL® Textured</td>
<td>Round</td>
<td>Midrange Projection</td>
<td>150-716cc</td>
</tr>
<tr>
<td>120</td>
<td>BIOCELL® Textured</td>
<td>Round</td>
<td>Full Projection</td>
<td>180-650cc</td>
</tr>
<tr>
<td>153</td>
<td>BIOCELL® Textured</td>
<td>Shaped</td>
<td>Full Height, Full Projection</td>
<td>360-720cc</td>
</tr>
</tbody>
</table>

Changes made to the implants since 1991 include increasing the thickness of the shell by more than 50%, increasing the cohesivity of the gel and implementing tighter manufacturing specifications. These improvements are designed to improve the durability of the devices.

5. Preclinical Studies

Inamed has conducted extensive preclinical assessments of its breast implants and their constituent materials. The tests assess the safety of the constituents of the gel material along with the potential for the material to bleed from the implant into surrounding tissue. Inamed has further characterized the safety of the implants by assessing the potential for gel constituents to move within the body. Inamed has also assessed the durability of the implant when subjected to extreme or repetitive forces simulating super-physiologic stresses. In conjunction with the results from the retrieval study, these results support the safety and reliability of the devices.
A. Gel Constituent Testing

The potential for the silicone gel material to bleed from an intact implant has been evaluated in both \textit{in vitro} and \textit{in vivo} animal testing. The resulting positive assessment of the safety of the gel constituents also addresses concerns related to possible exposure to gel material subsequent to rupture of the shell.

1. Chemical Analyses of Low Molecular Weight Components in the Device

To determine the amount and identity of silicone constituents that could potentially bleed from the implant into the patient, testing is conducted to assay the extractable silicone constituents using vigorous extraction conditions. This provides the worst case scenario for gel bleed. Finished sterilized devices were analyzed for extractables (the amount of silicone oil that can be removed from the gel, shell or patch, by extraction in hexanes, a good solvent for silicones). Under these extraction conditions, the shell ceases to act as a resistant barrier to diffusion of the silicones in the gel.

The techniques used to detect these components include solvent extraction followed by gas chromatography, using both a mass spectrometer (GC-MS) and a flame ionization detector (GC-FID), and by gel permeation chromatography. Complete metal analyses were performed on the extracts. With the exception of platinum and tin (Table 1), metals were generally below detection limits.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Identification & Implant Shell (ppm) & Patch (ppm) & Gel (ppm) \\
\hline
Tin & 0.05 & 6.60 & 0.06 \\
Platinum & 3.30 & 2.60 & 4.00 \\
\hline
\end{tabular}
\caption{Concentrations of Catalyst Metals Detected (in ppm by component weight)}
\end{table}

The concentrations of catalyst metals detected in the implant shell, patch and gel have never been shown to be cytotoxic in Inamed’s testing.

2. Gel Bleed Testing

Gel bleed testing was conducted to determine the maximum exposure a patient could expect \textit{in vivo} of the silicone gel constituents. These conditions are much milder than those used for extraction (Section 5A1) and, as anticipated, only a fraction of the available materials actually underwent bleed. The shell acts as a barrier membrane, so gel bleed was assessed using implants meeting the minimum shell thickness specifications. The diffusion rates of low molecular weight silicone gel constituents
through the shell were assessed for standard production Style 40 and Style 110 implants. The study design was consistent with ASTM F703 and involved the use of silicone disk methodology. In essence, this test measures the facility of the silicone oil to move from gel, across the barrier layer, into a dimethylsilicone elastomer disk. Because the oil is very compatible with the receiving dimethylsilicone elastomer, transfer is efficient, and this test represents an accelerated, worst case scenario for gel bleed. The cumulative average bleed rates from the devices over the 8 week course of the study were 0.0019 g/cm²/wk for smooth surface gel devices (Style 40) and 0.0006 g/cm²/wk for textured surface gel devices (Style 110).

*In vivo*, the implant will be exposed to a primarily aqueous environment, which contains many other constituents, the most significant with respect to gel bleed likely being organic lipids. Inamed developed a new gel bleed test that better mimics a lipid-like environment. In this case, silicone oil transfer into commercially available Extraction Disks, which are comprised of silica coated with octadecyl groups (C-18), was measured. In general, the study design followed the ASTM F703 gel bleed methodology, which calls for incubating implants on test disks for 8 weeks at 110°F, a worst case temperature condition. However, instead of using silicone disks as in the ASTM standard, the testing employs high surface area disks with a C-18 layer that is closer in nature to the hydrophobic lipids encountered in the body. After a gel-filled breast implant is placed over a disk for a given period of time, the implant is removed and the disk evaluated for bleed constituents, which are identified and quantified by gas chromatography-mass spectrometry (GC-MS). Style 40 implants were used for this testing as they were the worst case implant model in the ASTM testing.

The silicone species identified on the disks matched species identified in silicone disk samples from the ASTM study. There were only small differences in the relative concentrations of silicone species in bleed found in the disks, when compared to the silicone disks.

The rate of the bleed determined by employing disks with Style 40 implants was 0.0003 gm/cm²/wk, which is approximately six times less than in previous ASTM gel bleed testing of the Style 40 implant.

The rate of change in bleed over time was determined to be minimal after approximately 1 month of exposure and was less than the rate of change determined for the ASTM silicone disk methodology throughout the testing period. That is, bleed slows as equilibrium is reached between the silicone oil in the shell and the silicone outside the shell surface. As anticipated, the silicone shell to silicone disk interface enhances silicone bleed, compared to the silicone shell to C-18 coated disk of the disk method, reflecting the preference of silicone to associate with itself even in a hydrophobic, lipid-
like environment. We note that the physiological environment for the implant is mostly water, and, thus, both of these *in vitro* assays will overestimate bleed to be expected *in vivo*.

There was no evidence that either of the catalysts used in implant manufacture, platinum or tin, were contained in the constituents of silicone gel bleed as detected on either the silicone or disks.

### 3. Toxicological Implications of Gel Bleed

Silicones are widely used in daily life. Exposure occurs through inhalation (e.g., silicone carriers in personal care products), topical exposure (e.g., hair conditioners, hand creams), ingestion (e.g., antacids, colic medication) and injection (e.g., lubricants in syringes). Additional adventitious exposure occurs through contact with the many silicone based commercial products: baby bottle nipples, shoe polish, window sealants, lubricants, waterproofing materials, etc. They are amongst the most, if not the most, studied synthetic materials with respect to biocompatibility. The scientifically credible data continues to show the absence of a relationship between disease and silicones.

Several major studies have assessed the toxicological risks associated with silicones, focusing in particular on breast implants. The most notable studies in the area of breast implants are the comprehensive reviews conducted by the U.S. National Science Panel, the British Independent Review Group (IRG) and the Institute of Medicine (IOM) report, commissioned by the U.S. Congress. These reports, which reflect scientifically based assessments, conclude (quote taken from the IOM report) “that a review of the toxicology studies of silicones known to be used in breast implants does not provide a basis for concern at expected exposures.”

Several agencies and some researchers continue to be concerned about silicone bleed from implants, particularly the lower molecular weight material, which is expected to be the fraction of gel constituents with the most mobility *in vivo*. Inamed has undertaken a series of studies to address the partitioning of silicones *in vivo* (see Section 5B). While the evidence for safety is overwhelming, these studies provide a better understanding of silicones in the human body.

Attempts have previously been made to relate the biological activity of the platinum catalyst used to crosslink implanted silicones to that of anticancer drugs. Regarding the platinum catalyst, the IOM Report concluded, “evidence currently available suggests that platinum is present only in the zero valence elemental state,” and the IRG reported, “stable platinum compounds are most commonly used, typically up to 10 ppm. These have

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different properties, particularly in terms of biochemical reactivity, and are much less toxic than platinum used as cytotoxic drugs."

The FDA has examined the biological impact of platinum in silicone breast implants. Studies on implanted women, compared to women who had never had implants, demonstrated no differences in urinary platinum levels. The FDA notes that there is a large difference in the bioactivity of metallic platinum and platinum salts. The former, they note is neither associated with allergic reactions, nor other diseases. The latter may cause progressive allergic reactions, as noted above. They conclude, and concur with the IOM report, that with respect to allergic reactions, “there are no epidemiological studies providing evidence linking platinum residues from breast implants with these symptoms, any of which may occur without exposure to platinum.”

Some recent reports have proposed, without scientific evidence, that the platinum in implants is in a highly bioactive form and delivered in large amounts. These reports ignore fundamental chemical principles and are not credible.

B. Physiologically Based Pharmacokinetic Modeling

To address the concerns regarding how the silicone from a ruptured implant, or from bleed from a nonruptured implant, impacts a patient, Inamed believes that the most scientifically valid approach is to establish a Physiologically Based Pharmacokinetic (PBPK) model for selected molecular weight silicone constituents present in silicone-filled breast implants. PBPK modeling has been reported to examine numerous compounds as they are actively metabolized, processed or partitioned among various anatomical compartments. Such a model is robust and allows the direct determination of compound levels in any designated body compartment (liver, blood, brain, skin, breast tissue, etc.) at any time under a number of various inherent (gender, age, etc.) conditions or environmental challenges (fasting, hypertension, etc.).

PBPK modeling represents the current state-of-the-art tool for integrating and describing pharmacokinetic data. The resulting PBPK model can therefore be used to make informed decisions about the disposition of silicones that may migrate from intact or ruptured gel implants. Because of its underlying biological basis, PBPK models are also a method of choice for decreasing the uncertainties associated with extrapolating across species, routes of exposure and dose in human health risk assessments. This capability is especially important:


for situations where it is neither ethical nor technically or statistically feasible to obtain the necessary data in humans.

Inamed’s initial PBPK model is based on published PBPK modeling developed for D₄, octamethylcyclotetrasiloxane, a mobile and extensively studied silicone constituent, to describe possible silicone movement from a breast implant depot. Additional animal tissues (blood and fat) and human tissues (blood and breast) partition coefficients data have been determined to describe an implant based exposure PBPK compartment. PBPK modeling can express the absorption, tissue distribution, metabolism and elimination of a compound, as well as the biological interaction of a compound with tissues and systems of the body, especially for situations where it is not ethical or possible to obtain necessary data in humans. Compared to time and research efforts associated with generating meaningful data without the assistance of PBPK modeling, use of PBPK simulations allow the data associated with a smaller sample size to be accurately extrapolated and become predictive of the movement of silicone species into and out of the human body.

Specific PBPK modeling for octamethylcyclotetrasiloxane (D₄) is described in the literature⁶,⁷,⁸,⁹. As FDA scientists have stated, “PBPK models will reduce the uncertainties in the human risk assessment process … [and] will provide a much needed scientific basis to the traditional human risk assessment for medical devices⁸.”

As stated in the summary of the interim report describing the work completed to date to develop a physiologically based pharmacokinetic (PBPK) model for octamethylcyclotetrasiloxane (D₄) that may migrate from intact or ruptured silicone breast implants into surrounding tissues,

“The resulting implant site simulations were based on both a young adult (pre-menopausal) woman and a matured (post-menopausal) woman using worst-case exposure conditions (i.e., no shell to simulate complete rupture of the largest available implants; maximum levels of D₄ in silicone; and a range of assumed breast tissue fat contents from very low to virtually all fat). The resulting simulations indicate that D₄ is cleared primarily by exhalation with highest concentrations achieved briefly in breast tissues of a post-menopausal

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woman due to the very high assumed fat content. D₄ is predicted to be cleared to levels below 1 ppm within ~30 days. Thus, it is unlikely that D₄ would be detected in any tissue of the body within a few weeks of receiving an implant, even if immediately ruptured, under the assumptions used in this initial PBPK model.”

C. Physical/Mechanical Testing

Inamed’s physical/mechanical testing is designed to stress the implants beyond the maximum stress expected in vivo to ensure their durability. The smallest implants with the thinnest shells (Style 40 smooth gel implants and Style 110 textured gel implants) were tested, providing the worst case scenario in testing. Inamed’s testing demonstrated that the implants are unlikely to rupture even in the worst case repetitive physical activity undertaken by the patient or the forces encountered during normal daily life.

1. Static Rupture Testing (Ultimate Burst Testing)

The amount of force required to induce failure with a single compression of an implant is assessed by ultimate burst testing. In summary, the implant is squeezed between two plates until it ruptures (see Figure 2). This testing was performed on three devices of each Style (40 and 110), using a 5,000 lb load cell. The measured minimum force at failure for all tested devices exceeded 1,000 pounds of force. By comparison, a standard mammogram exerts about 32 pounds of force. Thus, it is expected that the implants would not rupture under in vivo squeezing pressure.

![Figure 2: Demonstration of static rupture testing](image)

2. Fatigue Rupture (Cyclic Fatigue Testing)

Fatigue rupture testing assesses the number of cycles at specific applied loads that a device can endure without rupture. This testing represents an in vivo activity such as walking or running. The worst case scenario would be running by a patient with the largest size implants (800cc). That scenario would produce 3.6 pounds of applied load. The testing was performed on three implants of each Style (40 and 110). At an applied load of 30 pounds, well above the maximum expected 3.6 pounds in vivo, all implants
withstood 6.5 million cycles without failure. Thus, it is expected that the implants would not rupture under \textit{in vivo} cyclic fatigue activities.

6. Clinical Studies

A. Overview of Studies

The primary clinical data on Inamed’s silicone-filled breast implants comes from 2 prospective multi-center trials. The Core Study implanted 940 patients (approximately 50% augmentation, 25% reconstruction and 25% revision). The Adjunct Study is a large safety study, implanting over 45,000 patients to date in reconstruction and revision cohorts.

The Core Study was designed as a prospective study of patients aged 18 years or older seeking silicone-filled breast implants for augmentation, reconstruction or revision of an existing implant. Over 80% of patients were Caucasian and most study participants were married. Approximately half were employed in professional occupations, and more than three fourths had at least some college education. The median patient age was 34 years for augmentation patients, 50 years for reconstruction patients and 44 years for revision patients. Patient medical history including breast disease and breast cancer information was collected at baseline. Follow-up visits occur post-operatively at 0-4 weeks, 6 months and annually through 10 years. Serial MRI to detect silent rupture of the implant for a subset of patients occurs subsequent to the annual follow-up visits at 1, 3, 5, 7 and 9 years post-implant. Safety assessments consist of complication rates and rates of reoperation. Additionally, post-implant reports of connective tissue disease and breast disease were obtained. Effectiveness assessments consist of patient satisfaction, breast size change (augmentation patients only) and measures of patient quality of life. Patient follow-up is currently ongoing. Complete 3-year data is available for the Core Study with a compliance rate of 86% for augmentation patients, 94% for reconstruction patients and 87% for revision patients.

The Adjunct Study was designed as a prospective 5-year open enrollment study to assess safety outcomes. Patients are those seeking breast reconstruction or revision of an existing implant for medical reasons. Follow-up visits occur post-operatively at 1, 3 and 5 years. Safety assessments consist of complication rates and rates of reoperation. Patient enrollment and follow-up in the Adjunct Study are currently ongoing.

B. Effectiveness

The effectiveness of Inamed’s silicone-filled breast implants is not in question. The silicone material has unique characteristics that make the implant feel and look more like natural breast tissue, and in Europe and other nations where women can choose from among all options for breast implants, they choose silicone 9 to 1 over saline implants. The
effectiveness of the silicone implants is reflected not only in their popularity but is also demonstrated in Inamed’s clinical trials.

The Core Clinical Study includes Quality of Life and patient satisfaction measures. The Inamed implants consistently generated higher scores for Quality of Life measures associated with the breasts. The satisfaction measures demonstrated the highest levels of satisfaction with the implants. Even among the fraction of patients whose implants failed during the trial, the majority sought reinplantation and most of them chose an Inamed silicone-filled implant as a replacement.

The advantages of silicone-filled breast implants are particularly evident in the context of reconstruction. Only silicone has the properties that enable surgeons to precisely match reconstructed breasts to the patient’s original breast. While this is particularly important in unilateral surgeries, it can also be important in reconstruction following mastectomy for a woman who wants to more closely approach a restoration of her original breasts in both appearance and feeling. Although nothing can make up for the loss associated with mastectomy, silicone breast implants can aid in recovery.

Women who are seeking a cosmetic procedure also benefit from the advantages of silicone. The more natural look and feel of Inamed’s silicone-filled implant makes it the device of choice for this procedure.

1. Quality of Life

Examining quality of life issues for patients in the Core Study, we find no change post-implant for general items such as overall self-esteem. These patients have above average self-esteem pre-implantation and, thus, are not undergoing implantation to increase their self-esteem but to change one aspect of their body. Augmentation patients do show a significant increase post-implantation in physical self concept and in body esteem related to sexual attractiveness. All patients showed a significant increase in the quality of life measures for patient satisfaction related to breast size and breast shape.

2. Patient Satisfaction

Patient satisfaction post-implant was uniformly high across all cohorts in the Core Study, with rates at 3 years of 96% for augmentation patients, 92% for reconstruction patients and 88% for revision patients. For those patients who expressed dissatisfaction, the most common reason was capsular contracture.
C. Safety

The clinical safety of Inamed’s silicone-filled breast implants has been extensively studied and thoroughly characterized. Inamed has collected surveillance data spanning the entire ten years that these third generation devices have been available to patients around the world. In addition, Inamed has data on over 47,000 patients enrolled in prospective clinical studies, including the ongoing 10-year Core Clinical Study. Further, there is extensive data published in respected peer-reviewed journals supporting the safety of these implants.

All of these sources of data together paint a single picture of the safety of the devices. The data show that the primary risk to women undergoing implantation with Inamed’s devices is the risk of surgery itself. As the implant is not a lifetime device, there is typically an additional risk of explantation or revision surgery. The risks associated with these surgeries are well-known and are primarily local complications.

The data Inamed has gathered along with that in the peer-reviewed literature supports the safety of the devices themselves. The implant is inert, composed of nonreactive, nontoxic biocompatible material that typically remains contained within the implant.

Despite the safety of the material of the implant, there is a concern over the potential for the implant shell to fail. In the event of a failure of the shell, the gel material usually remains inside the shell though this is still designated as a rupture. Most ruptures are asymptomatic and are called silent ruptures.

There is the potential for the shell of the breast implant to fail with the possibility of exposing the gel material to the inner surface of the tissue capsule formed around the implant creating an intracapsular rupture. Under certain rare circumstances, it is also possible for the gel to migrate from within the implant capsule to the surrounding tissues and body compartments creating an extracapsular rupture.

It is important to note that the rate of complications in patients whose implants rupture is no greater than the background rate of complications seen in patients with intact implants. While the patients in Inamed’s studies had no systemic consequences of rupture, they were advised to discuss explantation with their doctors and most of them chose to explant the ruptured implants. Neither before nor after explanation did these patients have any serious complications associated with the rupture of the implant.

FDA’s revised 2004 guidance document added the requirement to provide information on the rate and rate of change of rupture over the expected lifetime of the device, modes and causes of rupture and health consequences of rupture. Inamed has obtained this additional requested data and summarized it below.
1. Rupture Rate

Establishing a long-term rupture rate for silicone-filled breast implants has been a fundamental concern of the FDA. Inamed used a variety of approaches to accomplish this task. By examining the 3-4 year Core Study data in combination with 10-year surveillance data of Inamed’s silicone-filled breast implants and 8-year clinical study data for Inamed’s saline-filled breast implants, we are able to provide a likely estimate of a slope for the long-term rupture rate.

Beginning with the Core Study, Inamed was able to obtain an estimate of overall rupture that does not suffer from underestimation by weighting the non-MRI cohort with the expected number of silent ruptures, had the non-MRI cohort also undergone MRI screening.

The Core Clinical Study enrolled a total of 1,782 implants; 663 implants (37%) were enrolled in a simultaneous MRI cohort while 1,119 implants were not routinely screened with MRIs. Within the MRI cohort, 30 silent ruptures were identified (4.5% = 30/663). In order to obtain the same percentage of silent ruptures among the 1,119 implants, the non-MRI cohort was weighted with expected silent ruptures. Weighting was adjusted for enrollment indication as described in the following table. For example, 1.5% of the augmentation implants in the MRI cohort experienced silent rupture; therefore, 10 (1.5% of 656 enrolled) implants in the augmentation non-MRI cohort were expected to have a silent rupture.

<table>
<thead>
<tr>
<th>Enrollment Indication</th>
<th>MRI Cohort</th>
<th>Actual Silent Rupture Results</th>
<th>NON-MRI Cohort</th>
<th>Expected Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of Implants</td>
<td># of Silent Ruptures</td>
<td>% Silent Ruptures</td>
<td># of Implants</td>
</tr>
<tr>
<td>Augmentation</td>
<td>331</td>
<td>5</td>
<td>1.5%</td>
<td>656</td>
</tr>
<tr>
<td>Reconstruction</td>
<td>182</td>
<td>17</td>
<td>9.3%</td>
<td>179</td>
</tr>
<tr>
<td>Revision</td>
<td>150</td>
<td>8</td>
<td>5.3%</td>
<td>284</td>
</tr>
</tbody>
</table>

* Current results through partial 4 year data.

After determining the expected number of implants with silent rupture in each cohort, the distribution of failure times for the expected silent ruptures in the non-MRI cohort was determined by using the distribution of failure times seen in the MRI cohort. The result in the non-MRI cohort for augmentation was 2 patients at each of 5 failure time points. The result in the non-MRI cohort for reconstruction and revision was 1 and 2 patients, respectively, at each of the failure time points identified from the MRI cohort.

Out of the 43 expected silent ruptures in the non-MRI cohort, 7 were identified via explantation for a non-rupture reason (e.g., exchange to increase size) and, therefore,
only 36 implants needed to be weighted with a silent rupture status (43 expected silent ruptures minus 7 identified silent ruptures = 36 silent ruptures to be weighted).

After identifying the total number (and failure time points) of the weighted silent ruptures, all ruptures were combined and a Kaplan-Meier analysis was performed. The analysis contained 36 weighted silent ruptures in addition to the reported ruptures described in Table 2 (37 silent ruptures and 6 symptomatic ruptures).

Table 2: Core Study Reported Ruptures: 4 Years

<table>
<thead>
<tr>
<th>Cohort (MRI/Non-MRI)</th>
<th>Population</th>
<th>Type (Silent/ Symptomatic)</th>
<th>Number of Implants ¹⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Augmentation (N = 331)</td>
<td>Silent</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Reconstruction (N = 182)</td>
<td>Silent</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Revision (N = 150)</td>
<td>Silent</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td><strong>Total MRI</strong></td>
<td><strong>Silent</strong></td>
<td><strong>30</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Symptomatic</strong></td>
<td><strong>2</strong></td>
</tr>
<tr>
<td>Non-MRI</td>
<td>Augmentation (N = 656)</td>
<td>Silent</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Reconstruction (N = 179)</td>
<td>Silent</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Revision (N = 284)</td>
<td>Silent</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>Total Non-MRI</strong></td>
<td><strong>Silent</strong></td>
<td><strong>7</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Symptomatic</strong></td>
<td><strong>4</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Total MRI &amp; Non-MRI</strong></td>
<td><strong>Silent</strong></td>
<td><strong>37</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Symptomatic</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

Estimates of rupture risk obtained from the analysis are summarized in Table 3.

¹⁰ Only confirmed and unconfirmed ruptures were included in the analysis. All suspected ruptures later found to be non-ruptures are not included.
Table 3: Core Study Preliminary Risk of Rupture Overall (Silent & Symptomatic)

<table>
<thead>
<tr>
<th>Statistic/Population</th>
<th>Risk of Rupture at 4 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk of Rupture (Overall)</strong></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>5.5%</td>
</tr>
<tr>
<td>Augmentation</td>
<td>1.7%</td>
</tr>
<tr>
<td>Reconstruction</td>
<td>15.1%</td>
</tr>
<tr>
<td>Revision</td>
<td>7.7%</td>
</tr>
<tr>
<td><strong>Risk of Silent Rupture</strong></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>5.2%</td>
</tr>
<tr>
<td>Augmentation</td>
<td>1.4%</td>
</tr>
<tr>
<td>Reconstruction</td>
<td>14.7%</td>
</tr>
<tr>
<td>Revision</td>
<td>7.5%</td>
</tr>
<tr>
<td><strong>Risk of Symptomatic Rupture</strong></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>0.3%</td>
</tr>
<tr>
<td>Augmentation</td>
<td>0.3%</td>
</tr>
<tr>
<td>Reconstruction</td>
<td>0.4%</td>
</tr>
<tr>
<td>Revision</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

The estimates of rupture risk in the above table are overestimated because they contain many unconfirmed ruptures suspected via MRI; this causes overestimation because Inamed’s data has shown that ~36% of all ruptures suspected via MRI have been determined to be intact. This ~36% false positive rate includes the Style 153. To obtain more informative estimates of rupture, ~36% of the unconfirmed ruptures (5 implants out of 14) were assumed to be intact and the risk was recalculated. Every combination of 5 out of 14 was used to calculate an adjusted risk (2002 combinations). The range of risks is reported in Table 4.

Table 4: Core Study Adjusted Risk of Rupture Overall (Silent & Symptomatic)

<table>
<thead>
<tr>
<th>Population</th>
<th>Range Obtained from Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>5.1% – 5.2%</td>
</tr>
<tr>
<td>Augmentation</td>
<td>1.6% – 1.7%</td>
</tr>
<tr>
<td>Reconstruction</td>
<td>12.3% – 15.1%</td>
</tr>
<tr>
<td>Revision</td>
<td>6.0% - 7.7%</td>
</tr>
</tbody>
</table>

Therefore, the overall rupture rate is estimated to be 5.2% at 4-years post-implantation. This estimate has been adjusted to address the issue regarding underestimation of rupture
from the non-MRI cohort and over-estimation of rupture due to false positive MRI results for unconfirmed ruptures.

Although the rupture rate in the reconstruction cohort is higher than the rupture rates in the other 2 cohorts, Inamed believes this is primarily based on the increased use of Style 153 implants in this cohort. Style 153 is the only double lumen implant and is subject to a particular type of failure at the site where the inner lumen attaches to the outer lumen. As the Style 153 is the only shaped implant, it is particularly effective in providing a reconstruction patient with a reconstructed breast that matches her natural breast. In the reconstruction cohort, 64% of the devices used were Style 153, whereas patients in the augmentation and revision cohorts were not as likely to receive Style 153 devices (8% of augmentation devices and 30% of revision devices).

Inamed constructed a curve indicating a 2.5% overall rupture risk at 3 years and projecting a 13.9% overall rupture risk at 10 years. The 10-year risk was derived by considering the following:

- Partial 4-year data shows a risk of 0.2% at 1 year, with an increase of 1.7% between 1 and 2 years, another increase of 0.6% between 2 and 3 years, and finally another increase of 3.0% between 3 and 4 years.
- Average increase equates to approximately 1.4% per year.
- Given that the Core Study currently shows a 5.5% rupture rate at 4 years it is anticipated at 5 years there would be a 1.4% increase resulting in the 6.9% 5-year risk of rupture, and at 10 years there would be a 13.9% risk of rupture [6.9% + (5 years * 1.4%)].

Another confirmation of the appropriateness of Inamed’s estimated 10 year rupture rate for the silicone-filled implants subject to this PMA, is the comparability to the long term rupture rate in Inamed’s 1995 saline study, in which the implant shells are essentially the same as the shells for Inamed’s gel implants. The 4-year rupture rate for the Core augmentation cohort is similar to the 4-year deflation rate for the saline augmentation cohort with 1.7% vs. 3.1% respectively. Saline deflation should be considered the worst case failure rate for Inamed’s implant shells because saline deflation rates include valve failures that do not occur in gel-filled devices. At 8 years the augmentation deflation rate is 7.3%, leading to the conclusion that the rupture rate for augmentation patients with silicone-filled breast implants would be similar at 8 years, with a progression at 10 years in line with the 10-year estimate described above.

Finally, long term rupture rate data is available from Inamed’s product surveillance out to 10 years for the Style 153 implant and out to 5 years for Inamed’s other PMA gel styles. Based on 20,434 Style 153 devices implanted in the United States between 1993 and 2003, the rupture rate was 5.4% at 10.3 years. For 74,905 other PMA gel style devices
implanted in the United States between 1998 and 2003, the rupture rate was 0.68% at 5 years. While Inamed recognizes that this data relies upon voluntary reporting of device failures and theoretically could be subject to underreporting, the company’s warranty program provides financial incentives for reporting failed devices. Inamed believes these financial incentives provide for reporting that is not grossly misrepresentative of actual device failures in the field.

By plotting the rupture data from the Core Study with the rupture data from Inamed’s saline study and surveillance of silicone implants, we see in Figure 1 that the slopes are all similar and show a linear progression through 10 years. This suggests that Inamed’s 3-4 year Core Study data can be used to predict a 10-year rupture rate of 13.9% with reasonable accuracy. Calculating a failure rate excluding the Style 153 implants provides a 4-year rate of 2.1% and a 10-year estimate of 5.1%.

![Figure 3: Implant Rupture Rates](image-url)
2. Modes and Causes of Rupture

As described in Section 5C, Inamed’s physical/mechanical testing shows that our silicone breast implants are unlikely to rupture under conditions simulating worst case \textit{in vivo} repetitive physical activity or the forces encountered in daily life. Therefore, to fully examine the issue of rupture, it is critical to understand how ruptures occur \textit{in vivo} and the role played by various contributing factors. Based on feedback from noted expert materials scientist [insert name] and leading plastic surgeons, Inamed instituted a myriad of improvements in the methods of analysis for the Retrieval Study. Subsequently, Inamed analyzed 442 explanted Core and Adjunct Study devices and successfully identified the modes and causes of rupture for 91\% of the 133 implants evidencing rupture. For the devices identified with ruptures, it is unknown whether they were ruptured \textit{in vivo} or during explantation. In addition to increasing the level of understanding regarding why and how ruptures occur, Inamed also assessed the durability of the silicone devices and determined that durability is not a significant concern for these implants.

Surgical damage has been found to be the leading cause of failure in Inamed’s silicone-filled breast implants returned for analysis. The modes of failure identified in the Retrieval Study are summarized in Table 5.

<table>
<thead>
<tr>
<th>Failure Mode</th>
<th>Ruptured Implants (N=133)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Surgical Damage</td>
<td>63</td>
</tr>
<tr>
<td>Posterior Opening (Style 153 implant)*</td>
<td>48</td>
</tr>
<tr>
<td>Surgical Impact**</td>
<td>5</td>
</tr>
<tr>
<td>Manufacturing Defect</td>
<td>4</td>
</tr>
<tr>
<td>Fold Flaw Failure</td>
<td>1</td>
</tr>
<tr>
<td>Unknown (openings where the failure mode could not be identified)</td>
<td>12</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>133</td>
</tr>
</tbody>
</table>

*potential design change identified  
**shell was strained (or stretched) causing a change in the physical characteristics of the shell in the area of the failure

FDA’s revised 2004 guidance document added the requirement to assess surgical techniques that increase the risk of rupture to better guide physicians on the best way to implant the devices. Based on direct analysis of explanted ruptured silicone-filled breast
implants, observation of implantation surgeries and the published literature\textsuperscript{11,12}, the surgical techniques associated with device rupture are:

- Use of sharp instruments, such as scalpels, suture needles, forceps etc. in close proximity to the device. This can result in unintentional damage to the device and immediate or subsequent device rupture, i.e. surgical damage.

- Creation of a fold in the surface of the device during implantation, which allows the surface of the device to abrade against itself and result in the creation of a hole in the device shell. While the occurrence of fold flaw failure is low for silicone-filled breast implants (only 0.8\% of rupture cause), surgical technique is suspected as a contributing factor.

- Straining the shell by forcing the implant through a small opening. Surgical technique is suspected to be a cause of localized weakening of the shell, which could make the device more subject to rupture.

Inamed has confirmed the hypothesis that localized strain, below the ultimate rupture limit and imparted to the device when forced through a small opening, measurably changes the stress-strain response curve for the shell elastomer. Additionally, when devices are intentionally strained beyond ~400\% elongation through a small opening and then subjected to extreme and accelerated cyclic loading, the devices rupture and exhibit failure characteristics very similar to those observed in explanted ruptured devices that have been classified as having a “sharp edged” opening.

While Inamed has experience analyzing and testing returned devices, comprehensive assessment of surgical techniques in relation to the risk of rupture, would not be considered complete without feedback from surgeons familiar with the use of these devices. Therefore, Inamed approached 5 leading plastic surgeons for their assessments of the impact of surgical technique on risk of device rupture. The plastic surgeons queried are acknowledged experts in the field who serve as faculty and directors for INAMED Academy, an educational program that provides a forum for the exchange of information and best practice ideas among plastic surgeons.

Survey results showed that the surgeons ranked incision size as having the highest impact on implant survivability, with size of dissected pocket and transaxillary approach both ranked as having a moderate impact. With one exception, the surgeons were unaware that the majority of implant ruptures analyzed by Inamed had evidence of surgical damage. In

\textsuperscript{11} Young, V.L. and Watson, M.E. 2001. Breast implant research. Where we have been, where we are, where we need to go. Clin. Plast. Surg. 28(3): 451-483.
order to promote improved implantation techniques, Inamed apprised the faculty of the Retrieval Study findings and introduced an element concerning iatrogenic damage into the curriculum of INAMED Academy.

3. Health Consequences of Rupture

a. Local Complications

In the Core Clinical Study, 43 confirmed and unconfirmed ruptured implants have been identified in 42 patients. Overall, these patients do not show any unexpected adverse events or consequences (i.e. local complications). The complications experienced most frequently after confirmed rupture were redness, infection and swelling. All of these are common complications following surgery. No patterns developed, and no complications appeared with an alarming frequency to suggest a relationship with rupture. This is consistent with the published literature findings and Adjunct Study results, which show that the local complications experienced by women with ruptured implants were not significantly different from the local complications experienced by women with intact implants.

Underlying the analysis for comparison of consequences for patients with ruptured implants versus patients with non-ruptured implants is the fact that all patients who have a confirmed rupture have also undergone implant removal. Therefore, many of the outcomes (e.g., redness, swelling) seen after confirmed rupture may be due to the implant removal procedure itself. In order to evaluate the role of rupture in causing future outcomes (i.e., consequences), it is most useful to compare explants that have been confirmed ruptured (25 patients, 25 implants) to those that have been confirmed intact (131 patients, 208 implants).

As shown in Figure 4, the percentage of patients who experienced complications is virtually identical for those patients with confirmed ruptures (52.9% = 9/17) versus those with confirmed intact implants (53.1% = 42/79).
Figure 4: Local Complications Flow Diagram

The most common local complications experienced after removal of confirmed ruptured implants are redness (24%, n=4), swelling (18%, n=3) and infection (18%, n=3). The most common local complications experienced after removal of confirmed non-ruptured implants are capsular contracture (14%, n=11), breast pain (14%, n=11) and swelling (13%, n=10). Although the length of follow-up for the confirmed rupture patients (average 1.3 years) was less than the length of follow-up for confirmed intact patients (2.5 years), many of the complications seen in the confirmed rupture group were post-operative sequelae that occurred shortly after explantation.

b. Silent Rupture Progression to Symptomatic Rupture

As seen in the Core and Adjunct Studies as well as in the published literature, standard clinical practice is to explant a device when rupture is identified, resulting in little data on silent ruptures that progress to symptomatic ruptures.

In the Core Study 59 implants were suspected of silent rupture, and 45 underwent explantation, revealing 23 confirmed ruptures and 22 confirmed non-ruptures. Fourteen implants have not yet undergone explantation, owing to recent identification of the suspected rupture or other circumstances such as additional evaluations still pending.
In the Adjunct Study of 144 confirmed or unconfirmed ruptures, 22 implants were suspected of silent rupture. Nineteen (19) of these implants were explanted soon after identification of the suspected rupture, and 2 were recently identified. In 1 implant a suspected silent rupture was identified via CT scan ordered by the patient’s oncologist. At follow-up visits with her plastic surgeon 6 months and 1 ½ years later, the patient presented with moderate asymmetry. This suspected rupture has not yet been confirmed because the patient has lymphoma and does not wish to undergo surgery at this time.

c. Intracapsular Rupture Progression to Extracapsular Rupture

In both the Core and Adjunct Studies no cases were noted of intracapsular ruptures that progressed to extracapsular ruptures. Indeed, of the four extracapsular ruptures reported in the Adjunct Study, two were due to wound dehiscence and implant extrusion with the silicone gel leaking out of the incision site, and a third was most likely due to the physician nicking the capsule and possibly the implant during a nipple reconstruction procedure. The instance of extracapsular gel in the Core Study occurred following an incision made during an exploratory surgery to check the implant status. The physician created an incision large enough to insert his finger through to feel the implant surface for signs of rupture or free gel. At the time of the exploratory surgery, free gel was found only on the implant surface, and the physician noted the absence of extracapsular gel. Replacement surgery was scheduled for a later date. Before the replacement surgery could occur, extracapsular gel was found oozing through the incision site, and the physician believes this was a result of his opening the capsule during the digital exploration.

As noted above in Section 6C3b, standard clinical practice is to explant a device when rupture is identified, resulting in little data regarding intracapsular ruptures that progress to extracapsular ruptures. Literature shows that extracapsular rupture is generally caused by a trauma to the breast and not a progression from an intracapsular rupture. However, a recent prospective follow up study on the Danish cohort, Holmich et al. (2004), performed a second MRI two years after the first screening MRI to assess the changes over time in untreated ruptures. Results showed that 9% of intracapsular ruptures progressed to extracapsular ruptures over a 2 year period, although the progression was minor in most cases. For the intracapsular ruptures that developed into extracapsular ruptures, 3 of the 7 women reported trauma to the affected breast between the first and second MRI, and an additional woman underwent a mammogram during that time period.
d. Connective Tissue Disease

None of the Core Study patients with confirmed or unconfirmed ruptures experienced a connective tissue disease (CTD) post-implant. Inamed examined CTD signs/symptoms (S/S) experienced by patients post-implant and found some increases in both the confirmed rupture and confirmed intact patients. However, when compared to patients from Inamed’s clinical study for saline-filled breast implants, the increase in CTD S/S were not significantly different for patients having silicone gel-filled breast implants.

e. Patient Satisfaction

Patient satisfaction remained high for patients experiencing an implant rupture. In fact, at 3 years post-implantation, 100% of patients with confirmed rupture in the Core Study were satisfied. This is consistent with the Adjunct Study findings, which revealed that very few patients expressed dissatisfaction with their breast implants even following a confirmed rupture.

7. Postapproval Plan

A. Core Post Approval Study

Inamed will continue full data collection in the Core Study through completion of the 10 year studies. Annual office visits will be used to assess local complications, rupture, CTD, breast cancer, reproduction and lactation problems and quality of life for all patients. In addition, patients enrolled in the MRI cohort will continue to undergo MRI screening for silent rupture every 2 years. Furthermore, patients who are explanted of all study devices without receiving replacement implants will be followed annually through telephone follow-up with their physician to assure that complications occurring after explantation are captured. Inamed provides financial incentives to encourage a high level of compliance with the follow-up requirements, thus allowing for complete and accurate data collection.

B. Physician Education and Training

1. INAMED Academy

There are three overarching goals of Inamed’s educational initiatives: 1) to provide a forum for Inamed to convey important information to physicians from our multicenter clinical studies and implant retrieval analyses, 2) to ensure that physicians are equipped with the most current clinical outcome and risk information to provide to their patients, and 3) to provide a structured opportunity for surgeons to share their experiences with each other in an ongoing effort to develop “best practices” such as surgical practices that can reduce implant
rupture.

INAMED Academy is held at convenient locations around the country and provides an avenue to report on device specific information gleaned from sources such as our retrieval evaluations, multicenter clinical trials and complaint database. Current content of INAMED Academy includes discussion of local risks and complications associated with breast implant surgery. Specific complications discussed include rupture (both symptomatic and asymptomatic), leakage, gel bleed, gel migration and capsular contracture. These risks are presented in the context of literature review as well as the experience from Inamed Corporation’s multicenter clinical studies. Systemic effects considered in association with silicone breast implants are also covered, with a review of published literature and a discussion of the types of studies that examine the association between breast implants and systemic complications. This provides a better understanding of the frequency of these effects and the strength of the associations.

INAMED Academies also cover the topic of silicone technology, which provides a general understanding of the chemistry of silicone and its use in medical products. Medico-legal issues are part of the curriculum as a component of silicone breast implant surgery. Also provided is discussion on the importance of the informed consent process and suggestions for rendering patient informed consent. Examples are provided of multiple methods for delivering risk information to patients, including the use of documents such as “Making an Informed Decision, Saline Filled Breast Implant Surgery.” This topic includes discussion of issues identified by the American Society of Plastic Surgeons (ASPS) as either implant related risks or risks related to breast surgery.

The strength of the surgeon faculty and their acknowledged expertise with the peer audience, along with the modular flexibility of the INAMED Academy curriculum allow the content to be adjusted frequently to include timely discussion on such issues as patient monitoring and management of complications, e.g. suspected rupture.

2. INAMED Continuing Education Series Publications

Augmenting the educational opportunities provided by INAMED Academy is the Continuing Education Series. This series provides an opportunity for respected surgeons to share their thoughts on a particular issue related to the practice of plastic surgery. In addition, the series provides a forum for Inamed to share the plastic surgery community information related to clinical updates, new product innovation, data on device analysis and post approval experience that may be relevant to their practice. While this same information may also be provided in the updated Directions for Use document that accompanies each device, it is our belief that periodic direct mail Continuing Education Series publications are more likely to be read and incorporated into practice. Furthermore, this provides yet an additional opportunity for Inamed to re-
emphasize to the surgeons the importance of informing their patients of relevant new clinical information.

3. **Labeling and Patient Education**

To facilitate the informed consent process, Inamed intends to supply a patient informed decision booklet, “Making an Informed Decision”, which is tailored to each indication for implantation: augmentation, reconstruction and revision. The booklets will include all information necessary for a patient to evaluate the risk and benefits of breast implant surgery. In addition to an overview of surgery and a summary of long term and systemic risks based on literature review and presentation of the results of Inamed’s clinical studies, the booklets will include recommendations to patients for monitoring their breast implants following surgery, as well as the toll-free number to use in the event they wish to discuss issues related to their breast implants with company representatives. The booklets will include a page for patients and surgeons to sign stating that the information has been reviewed and questions addressed by the physician. Focus groups will be conducted to ensure that the booklets present the information clearly to the target audience.

C. **Voluntary Patient Registry**

The purpose of Inamed’s current Registry is to provide a database that identifies and tracks patients who use Inamed’s silicone-filled breast implants. It is not designed to collect prospective outcome data, but rather to collect demographic and contact information for patients who are implanted with Inamed’s silicone-filled implants. The registry also tracks patient willingness to participate in third party studies, as designated by each patient on the Breast Implant Registration Form.

To facilitate the collection of rupture data, Inamed will link the registry system with our warranty programs that provide substantial financial incentives to report implant ruptures. Linking the two systems electronically will allow Inamed to potentially contact patients who have reported a device rupture in an effort to collect additional clinical outcome data, as well as conduct analyses on the demographic information. These warranties supply between $1,200 and $2,400 toward surgical costs and free replacement product, which provides a financial incentive for patients and physicians to report implant ruptures. Linking the two systems provides an added value for the patient registry.
8. Conclusion

Inamed’s preclinical and clinical data demonstrate a favorable risk benefit profile for its silicone-filled breast implants. The risks are few and relate primarily to the complications of surgery or the potential need for additional surgery. Rupture rates are low, with a 3-year rate of 2.5% and a discernible linear progression allowing for prediction of a 10-year rate of 13.9%. Excluding the Style 153 implants provides an even lower rate of 0.9% at 3 years and a prediction of 5.1% at 10 years. Further, the vast majority of these ruptures are expected to be intracapsular, with a small percentage of extracapsular ruptures and an even smaller percentage evidencing migrated gel. Inamed’s Core and Adjunct Clinical Studies, as well as the literature also show that patients with ruptured implants experience the same types of complications experienced by women with non-ruptured implants.

Patient satisfaction is uniformly high across all studies and cohorts. An additional indication of patient satisfaction with the implants is that most patients undergoing explantation choose to be reimplanted with Inamed’s silicone-filled breast implants.

Inamed’s silicone-filled breast implants provide a safe and effective option for patients who desire breast reconstruction, breast revision or cosmetic augmentation. The choice is a personal one that the patient makes with the guidance of her physician. Women in the United States should have access to the best possible implants to meet their needs. The Inamed silicone gel-filled breast implants offer an important range of options to women and their doctors, and should be available as an option for women in the United States who are considering breast implantation.

To assure patient safety, Inamed will continue to conduct extensive physician education programs and continue to improve device labeling to incorporate warnings on surgical practices that may lead to rupture, as well as provide accurate and complete information to women on the safety of silicone-filled breast implants. Beyond that, Inamed is unwavering in its quest to continue clinical and laboratory studies of the implants in the post-approval period in order to provide a growing knowledge base to surgeons and to continually improve the informed decision process for women considering breast implants.

Thank you again for the opportunity to share our data with FDA’s General & Plastic Surgery Expert Advisory Panel.