FDA SUMMARY PANEL MEMORANDUM

TO: **General and Plastic Surgery Devices Advisory Panel Members**

FROM: FDA's Inamed PMA Review Team

DATE: March 2, 2005

SUBJ: P020056 - Inamed Corporation
Silicone-Filled Breast Implants

In December 2002, Inamed submitted their silicone gel-filled breast implant PMA P020056. Inamed is seeking approval for augmentation, reconstruction, and revision indications for several implant styles. The Inamed Silicone-Filled Breast Implants are composed of silicone gel encased in a silicone elastomer envelope (shell). They are available in smooth and textured surfaces in round and shaped versions, with gel volumes between 80 and 800cc. A more detailed device description is provided in Section II of this memo.

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 because the data did not provide a reasonable assurance of the safety of the device. A not-approvable letter was issued on 1/7/04.

In August 2004, Inamed submitted responses to the 1/7/04 not-approvable letter for this PMA. This package contains the data/information submitted in response to the 1/7/04 not-approvable letter and FDA's analyses of these data/information. We are asking the Panel to review and discuss these new data/information and to consider the FDA's current Panel questions regarding this new data/information submitted in Inamed's response. A copy of the FDA's current Panel questions is provided in Tab 2 of your Panel package.

Section I of this review memo provides a summary of the October 2003 Advisory Panel's deliberations.

Section II of this review memo provides an overview of the device description, including changes made to the device since the October 2003 Panel meeting. The changes to the device were not in response to any specific deficiency in the 1/7/04 not-approvable letter.

Section III of this review memo provides an overview of the prospective clinical studies presented in this PMA. Although this section does not discuss Inamed's specific responses to the 1/7/04 not-approvable letter, we do provide a basic description of the clinical studies and what has changed in terms of the information provided since the October 2003 Panel meeting.

Section IV of this review memo provides a summary of Inamed's responses to the 1/7/04 not-approvable letter. This section is organized by each topic covered in the 1/7/04 not-approvable letter. However, the last topic in this section, **Device Effectiveness**, was not an issue in Inamed's 1/7/04 not-approvable letter for this PMA. FDA provided this information for your convenience because you will need to consider the risks and benefits, as a whole, for Inamed's product when providing your final recommendation for the PMA (approvable, approvable with conditions, or not approvable).

For completeness sake, in Tab 5 of your Panel package, we have also included copies of the two FDA review memos provided to the October 2003 Panel.

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I. BACKGROUND ON THE OCTOBER 2003 ADVISORY PANEL MEETING

In October 2003, FDA presented this PMA to the General and Plastic Surgery Devices Advisory Panel. The Panel meeting agenda, Panel package, Panel roster, FDA slides, meeting summary, and Panel transcript are available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=388. A Panel transcript summary is also provided in Tab 5 of your Panel package. FDA's review memos from the October 2003 Panel meeting are also included in Tab 5.

The primary clinical data set presented at the October 2003 Panel meeting were the results of the Inamed Core Study. The Core Study is being conducted under investigational device exemption (IDE) [redacted] and is a 10-year study designed to evaluate the safety and effectiveness of Styles 40, 45, 110, 120, and 153 for augmentation, reconstruction, and revision patients. A subset of the total number of patients receives MRIs to prospectively evaluate asymptomatic or silent rupture at the specified times of 1, 3, 5, 7, and 9 years after implantation. This group, referred to as the MRI cohort, consists of approximately one-third of the total number of patients in the Core Study. Note that the terms "silent rupture" and "asymptomatic rupture" are used synonymously throughout this document.

The Core Study data presented to the October 2003 Panel involved a total of 494 augmentation, 221 reconstruction, and 225 revision patients. At that time, there was complete physician follow-up data through 2 years for all patients with partial 3-year data (only some of the patients had reached their 3-year follow-up timepoint at that time). For the MRI cohort, there was complete MRI data for all patients at the 1-year screening. There was MRI data for some patients at 3 years because only some of the patients had reached their 3-year follow-up timepoint.

A. OCTOBER 2003 PANEL DISCUSSION OF FDA QUESTIONS

Below are FDA's questions asked to the October 2003 Panel with a summary of the Panel's responses to those questions. A copy of FDA's questions from the October 2003 Panel meeting is also provided in Tab 5 of your Panel package.

1. ***Prospective MRI screening for asymptomatic rupture was conducted in a subset of Core Study participants (approximately 34%). Complete MRI screening data are available for the 1-year post-operative timepoint for each indication and partial 3-year data are available for the augmentation indication at the time of database closure. Continued MRI screening of this Core Study subset is planned for at years 3, 5, 7, and 9 after implantation.***

   Of the 15 implant ruptures that Inamed reports as confirmed at the time of database closure, the majority--9 implants (60%)--were initially detected by MRI screening and were asymptomatic:
   - ***Core Augmentation, 0 of 3 ruptures***
   - ***Core Reconstruction, 6 of 8 ruptures***
   - ***Core Revision, 3 of 5 ruptures.***

   Additionally, published literature on silicone gel implant rupture, although not specific to Inamed's implants, indicates that rupture rate increases with implant age and that depending on implant type, manufacturer, and age, between 26% (median implant age 12 years) and 55% (median implant age 16.4 years) of implants assessed by MRI had MRI evidence of rupture.

   Please discuss the adequacy of the information to determine the safety of this product with respect to asymptomatic rupture.

   The Panel was not in agreement as to whether they believed there were adequate data to determine the safety of the product. Some believed there were adequate data to assess short-term (i.e., 1-year) safety with respect to asymptomatic rupture but that long-term data were lacking. Other Panel members believed that the asymptomatic rupture data was insufficient to assess the short-term safety of the device based on the fact that only 1-year and with partial 3-year data were provided and that only one-third of the patients in the Core Study were screened with MRI. Some Panel members noted the rupture rate and shape of the curve over time was not known. A Panel member voiced disappointment that Inamed had not improved their device since the 1992 Panel meeting so that it would have a lower rupture rate. A Panel member expressed disappointment that the PMA did not contain longer patient follow-up data. Many Panel members acknowledged that the consequences of asymptomatic rupture are unknown. One panel members stated that there was uncertainty as to whether patients would be harmed by a silent rupture. Other questions were raised regarding the monitoring the patients (e.g., How should patients be monitored for asymptomatic rupture? Who pays for the MRI costs? How are patients identified who are at high risk for asymptomatic rupture?).

2. Potential long-term and general health effect issues for these implants include the risk of cancer(s), connective tissue disorders (typical and atypical), gel migration, interference of implant on ability of mammography to detect tumors in implanted breasts, interference with breast feeding, reproductive/teratogenic effects, and the later effects on offspring from women with implants. To address these issues, Inamed utilized historical published literature, which is not specific to Inamed's implants, as well as animal studies on their product. Please discuss the adequacy of the literature and preclinical testing to determine the safety of this product with respect to long-term and general health effects.

The Panel members were not in agreement as to whether there were adequate literature and preclinical testing to assess safety with regard to the long-term and general health effects. Some Panel members did not believe that the preclinical testing was helpful in that it did not mirror what happens in-vivo and because the mechanism of rupture of these devices is not understood. With regards to the literature submitted by Inamed, comments were made that the literature was not specific to Inamed's devices; however, many Panel members believed the historical literature was adequate to address the risks of connective tissue disease (CTD) and cancer. Others commented that the literature and preclinical data do not provide long-term implant rupture information or much information regarding gel migration and extracapsular rupture. Another Panel member commented that we do not know how having silicone gel breast implants affects a woman's decision to seek mammography. Lastly, another Panel member commented that there are issues about the ability to interpret mammography results for women with silicone gel breast implants.

3. Considering the safety data reported for the augmentation group:

- ***local complications reported in Core Study, Adjunct Study, and AR90 Study***
- ***asymptomatic/silent rupture information based on approximately 30% of the patients in the Core Study with only the first of 5 prospective serial screenings with complete data***
- ***published historical literature and animal data to address long term and general health effects.***

Given these data, and that the augmentation patient generally has breast implant surgery at a younger age which includes childbearing years compared to the other indications, is there reasonable assurance that the device is safe for augmentation patients?

The Panel members were not in agreement as to whether a reasonable assurance of safety was established for women seeking breast implants for augmentation. Many Panel members raised concerns about local complications, including asymptomatic rupture, and reoperation rates, in both augmentation and reconstruction patients. Many of the same concerns raised in question 1 above regarding silent rupture were raised again. These issues included not understanding the prevalence of asymptomatic rupture over time, not understanding the best way and most cost effective way to detect asymptomatic rupture, and not understanding the implications of asymptomatic rupture. Some expressed concerns about long-term local complication rates, as a result of asymptomatic rupture. Other Panel members commented that the local complication data presented by Inamed was within the range of that presented for similar studies of saline-filled breast implants.

One Panel member expressed concern about ability to provide adequate informed consent without longer term follow-up, particularly to educate a young woman choosing to have implants when she may not understand her lactational interests 10 year later or the importance of breast cancer screening. One Panel member expressed concern about local complications, especially in young women who will have this implant for a long time and will probably have, even if nothing goes wrong, repeated surgeries for replacement because they do not last. One Panel member expressed concern about the lack of data regarding potential health concerns for offspring of women with breast implants.

4. ***Considering the safety data reported for the reconstruction and revision groups:***
   - ***local complications reported in Core Study, Adjunct Study, and AR90 Study***
   - ***asymptomatic/silent rupture information based on approximately 30% of the patients in the Core Study with only the first of 5 prospective serial screenings with complete data***
   - ***published historical literature and animal data to address long term and general health effects.***

   Given these data, and that reconstruction and revision patients generally undergo breast implantation at an older age than augmentation patients, is there reasonable assurance that the device is safe for reconstruction and revision patients?

   The Panel did not comment specifically on the safety data for women who receive breast implants for reconstruction and revision. This question was discussed as part of the deliberations for question #3 above.

5. ***To evaluate device effectiveness, Inamed collected data on patient satisfaction and health status/quality of life (e.g. SF-36, MOS-20, Body Esteem Scale, etc.). Based on these data, has Inamed adequately demonstrated reasonable assurance of effectiveness of the implants for each of the augmentation, reconstruction, and revision indications?***

   The Panel was in agreement that effectiveness was established. However, there was some concern raised by a few Panel members that the quality of life (QoL) parameters were worse from pre-op to 2 years, particularly for augmentation patients.

6. ***Given the information in question 1, please address the following with respect to labeling for the device:***
   a. ***Provide your recommendations for the frequency and method of screening for asymptomatic rupture, given that prospective screening for asymptomatic rupture in not currently routinely performed.***
   b. ***Provide your recommendations for the necessity of explantation of asymptomatic implant ruptures.***

   With regard to the method of screening, some Panel members believed that MRI was the gold standard (i.e., the only way to pick up a true asymptomatic rupture). However, some Panel members argued that physical exam, mammography, and ultrasound were other viable methods. Comments were made that MRIs are expensive and it is unrealistic to think that

the physicians and/or patients would recommend MRIs based on the financial burden.

With regard to the recommendations for the frequency of screening, the majority of the Panel believed that annual or biennial physician visits were necessary, at least out to 10 years; however, the Panel did not clearly state that this was specific to the screening for asymptomatic rupture. In fact some Panel members stated that there should be annual or biennial physician visits and then, if necessary, do MRI screening for suspected rupture. Some Panel members believed that any recommendation for a diagnostic test should be data driven but that there are no longitudinal data about the incidence of rupture to determine how significant a problem it is and how it should be monitored.

The Panel expressed frustration over the lack of data with which to make recommendations regarding silent rupture, and they were unable to reach consensus on whether and when to screen for silent rupture, what method to use to screen for silent rupture, and how often to screen for silent rupture.
With regard to whether the device would be explanted if an asymptomatic rupture were detected, the Panel agreed that if there was extracapsular gel, the device should be explanted. Most of the Panel agreed that a ruptured device, even an asymptomatic or silent ruptured device, should be removed. They made this recommendation because the clinical implications of rupture are unknown and because an asymptomatic rupture can progress to a symptomatic rupture.

Other Panel members commented that patients receiving breast implants for augmentation or reconstruction need to understand that the treatment will involve a series of surgeries, not one, each with a danger of rupture.

7. Inamed provided a brief description of their postapproval study plan. The Core Study protocol, as well as informed consent, currently requires yearly follow-up with a physician. Inamed is now proposing a change to the study requirements as follows. More specifically, Inamed is proposing a 2-phase postapproval study. Phase I involves continued physician evaluation as per the IDE protocol through a patient's 5-year follow-up timepoint. Phase II involves mail-in surveys completed by the patient from their 6 to 10-year follow-up timepoints. In the proposed Phase II protocol, for example, MRI screening for asymptomatic rupture would not be captured. Given this proposal:

a. Please comment on the method of data collection (mailed survey) from the 6 to 10-year timepoints.

b. Please describe any other specific endpoints which should be captured as part of the postapproval study.

Most of the Panel agreed that physician follow-up through 10 years was necessary for a postapproval study. The Panel recommended that the post approval study should collect data on silent rupture, clinical consequences of rupture, and reoperation rates. Some Panel members stated that the postapproval study should include additional retrieval studies of explanted devices to assess the mechanism of rupture. Some Panel members stated that data on capsular and extracapsular tissues should be captured. Some Panel members stated that long-term health effects in women and children should be captured.

B. OCTOBER 2003 PANEL RECOMMENDATION

In a 9 to 6 vote, the October 2003 Panel recommended approvable with conditions for this PMA. Below is a summary of the conditions of approval proposed by the Panel.

Post-approval data collection:

1. Continued evaluation of Core Study patients for 10 years via physical examinations and MRIs at 5, 7, and 9 years. Panel members were not in agreement as to whether MRIs should be required versus another method of silent rupture assessment.

2. An independent third party should audit the Core postapproval study annually.

3. The Panel discussed the types of data/information to capture in a postapproval study but did not agree on whether that data/information was specific to the proposed Core Study postapproval study or to a registry. The data/information discussed included follow-up after explantation, rupture data, data on children of women with silicone gel breast implants, and data on CTD.

4. The Panel members stated that the current Inamed patient registry should be modified to capture more information. Note that at the time of the October 2003 Panel meeting, the Inamed's registry did not collect prospective data, but, instead, collected device serial and catalog numbers, patient indication and date of implantation, physician contact information, and patient contact information at the time of surgery for patients who receive their silicone gel product. Some Panel members recommended a 3rd party monitor for the registry. Some Panel members recommended that all implants, not just Inamed's be included. Some Panel members recommended that the registry be expanded to include clinical data, data after explantation, and data for the lifetime of the patient. Some Panel members recommended that Inamed's registry also be expanded to collect lactation and reproductive adverse events, as well as adverse events in children of women with silicone gel breast implants. There was not complete agreement among the Panel members as to the type of data to be included in the expanded registry.

Device Retrieval Studies:

5. The Panel stated that a 3rd party should review the current device retrieval study data because the data as analyzed by Inamed were inconclusive.

6. The Panel stated that Inamed should conduct a new device retrieval program, with 3rd party oversight, to study changes that occur in product over time and investigate failure modes.

Labeling:

7. The Panel stated that Inamed should develop a model informed consent form with FDA, Panel, and public input.

8. The Panel stated that Inamed should develop and distribute patient education information in various mediums (e.g., booklet, CD ROM, video). Inamed should partner with professional organization(s) to develop it, and also utilize focus group studies. Some Panel members recommended that the educational material should include information on silent rupture and the need to monitor for it.

9. The Panel recommended that the labeling include statements that any patient with silicone gel-filled breast implant should have regular physician follow-ups, as long as they have the device. Overall, the Panel agreed on recommending/encouraging 1 to 2-year physician follow-up intervals.

10. With regard to the surgeon educational materials or labeling, the Panel members were not in agreement as to (1) whether it should be recommended that MRI be used when rupture is suspected and (2) whether device removal should be recommended if silent rupture is confirmed.

Hotline/Outreach and Training:

11. The Panel stated that Inamed should produce patient guidance materials and establish toll-free telephone number for patients regarding how to monitor their breasts after implantation with a silicone gel-filled breast implant.

12. Some Panel members stated that Inamed should develop a surgeon education and certification program to train surgeons on technique-related issues for implanting silicone gel-filled breast implants, that it should be developed with a professional educational organization, that they Inamed should list certified physicians on website, and that Inamed should require physician certification to obtain their silicone gel-filled breast implants.

C. FDA'S DECISION ON INAMED'S ORIGINAL PMA

FDA considered all scientific safety and effectiveness data provided in the PMA, as well as the Panel's deliberations on that scientific data. FDA determined that the PMA was not approvable because the data did not provide a reasonable assurance of the safety of the device. Therefore, FDA issued a not-approvable letter on 1/7/04.

The deficiencies that were the bases for the not-approvable letter were:

1. Inamed should provide data from the Core Study (including the MRI cohort), with follow-up of sufficient duration, to describe the rate and rate of change of local complications over the expected lifetime of the device, to describe the frequency of ruptures observed (intracapsular, extracapsular, and migrated gel), and to characterize the potential local health consequences of ruptured implants. For example, the study duration should be sufficient to measure or reasonably estimate how the shape of the curve for the percentage of ruptured implants versus time changes over the expected lifetime of the device.

2. Inamed should provide data from supplemental sources (e.g., retrospective or prospective data from Adjunct Study and/or European studies, literature) to further characterize the local health consequences of rupture.

3. Inamed should provide data to characterize the modes and causes of clinical rupture of their devices.

In August 2004, Inamed provided responses to the 1/7/04 not-approvable letter in [redacted] of their PMA. A summary and review of the additional information submitted by Inamed is provided in Sections II-IV of this memo, with the specific responses discussed in Section IV.

II. DEVICE DESCRIPTION OVERVIEW

Since the October 2003 Panel meeting, Inamed modified their device to include 2 new styles – Styles 15 and 115. No specific clinical or preclinical testing was provided for these particular styles because they contain no new materials and because the dimensions of these styles fit within those already tested. Below is a summary of the device description for all the styles, including those recently added to the PMA.

The Inamed Silicone-Filled Breast Implants are available in smooth and textured surfaces in round and shaped versions. The minimum shell thickness is [redacted] for the smooth implants and [redacted] for the textured implants. All styles are single lumen devices with the exception of Style 153. The Style 153 is a double lumen device consisting of an inner bladder within the outer lumen. Both the inner bladder and outer lumen are silicone filled. The inner bladder is located at the lower pole of the breast implant and its function is to maintain the curved profile of the style. All implants are dry heat sterilized.

The Inamed Silicone-Filled Breast Implants under PMA review are:

Style	Shape, Profile	Shell Surface	Volume (cc)
10	Round, Moderate Projection	Smooth	120-800
15	Round, Midrange Projection	Smooth	158-752
20	Round, Full Projection	Smooth	120-800
40	Round, Standard Projection	Smooth	80-560
45	Round, Full Projection	Smooth	120-800
110	Round, Moderate Projection	BIOCELL	90-510
115	Round, Midrange Project	BIOCELL	150-716
120	Round, High Projection	BIOCELL	180-650
153	Shaped, Full Height, Full Projection	BIOCELL	360-720

The implant is composed of silicone gel encased in a silicone elastomer envelope (shell). The shell contains a patch, made from silicone elastomer, which covers the hole in the posterior shell that results when the shell is removed [redacted] during manufacture. During manufacture, the gel is injected through the patch and the fill hole is sealed using a small amount of [redacted] silicone adhesive. Thus, the primary components of the subject implants are the shell, patch, silicone gel filler, and silicone adhesive. Below is a detailed description of each of the primary components, including the materials.

[redacted]

consists of an inner and outer layer sandwiched around a "barrier layer" designed to impede the diffusion of components of the gel through the shell. All layers of the shell are produced using a [redacted] siloxane. [redacted]

Fourier Transform Infra-Red (FTIR) spectra of the shell material showed infrared spectral peaks that are characteristic of siloxane.

The texturing covers the entire shell except for the patch.

The **patch** is manufactured from two types of silicone elastomers.

The following table summarizes the material information:

Component	Material
Shell, middle (barrier) layer	
Shell, inner/outer (base) layers	
Patch, outer layer	
Patch, inner (barrier) layer	
Silicone gel	
Silicone adhesive	

III. CLINICAL STUDIES OVERVIEW

There were 3 prospective studies that were reviewed as part of the original PMA and presented to the October 2003 Advisory Panel – the Core Study, the Adjunct Study, and the AR90 Study. The Core Study is considered the primary clinical data set to support approval of this PMA. Below is a description of each of these prospective studies and any new information provided by Inamed for these in response to the 1/7/04 not-approvable letter.

Core Study

The Core Study was conducted under [redacted]. The Core Study is a 10-year study designed to evaluate the safety and effectiveness of Styles 40, 45, 110, 120, and 153 for augmentation, reconstruction, and revision patients. The IDE study was approved in June 1998 for 940 patients (500 augmentation, 220 reconstruction, and 220 revision). Evaluation timepoints include preoperative, operative, 0-4 weeks, 6 months, and 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 years. A subset of patients (150 augmentation, 101 reconstruction, and 73 revision) was to be enrolled in a cohort to undergo serial MRIs to screen for silent rupture at 1, 3, 5, 7, and 9 years after implantation.

The original set of Core Study data presented to the October 2003 Panel involved a total of 494 augmentation, 221 reconstruction, and 225 revision patients enrolled across 46 investigational centers (sites) with implant Styles 40, 45, 110, 120, or 153. The first patient was enrolled on 1/6/99 and the last was enrolled on 6/30/00. The date of database closure was 3/27/03, so there were 2 years of physician follow-up data on all patients, with some patients having up to ≈4½ years of physician follow-up data. The Core Study data presented at the October 2003 Panel meeting was based on: (1) physician follow-up data through 2 years for all patients, and data through 3 years available for some patients; and (2) MRI data on the complete cohort of patients in the MRI subset at 1 year with MRI data for some patients at 3 years. The patient follow-up compliance for the 1-year MRI screening was 87% for augmentation, 94% for reconstruction, and 94% for revision. The silent rupture rate (reported only for the MRI cohort) was higher than the overall rupture rate (overall includes both silent and symptomatic and in the MRI and Non-MRI Cohorts combined) for each of the three indications because silent rupture information was not collected in the Non-MRI group. Refer to the "Inamed Clinical Summary Memorandum" in Tab 5 of your Panel package for a detailed summary of the Core Study data presented to the October 2003 Panel.

As noted in Section II above, PMA styles under review are Styles 10, 15, 20, 40, 45, 110, 115, 120, and 153. Styles 40, 45, 110, 120, 153 were part of the Core Study. Styles 10 and 20 were added when the original PMA was submitted. Styles 15 and 115 were added as part of their August 2004 submission. Styles 10, 20, 15, and 115 were added to those styles under PMA review with no specific clinical or preclinical testing because the materials are the same and the dimensions of these 4 styles fit within those already tested.

Inamed responded to the 1/7/04 not-approvable letter in August of 2004. The date of database closure for this response is 5/19/04, which is ≈1 year later than that discussed at the October 2003 Panel meeting. In this response, Inamed did not provide a complete set of updated clinical data. Instead, they provided clinical data that focused on addressing the issues raised in the 1/7/04 not-approvable letter. Inamed's dataset now includes: (1) physician follow-up data on all

patients through 3 years with some patients at 4 years and (2) 1 and 3-year MRI data for augmentation patients and 1-year and partial 3-year MRI data for reconstruction and revision patients. The patient follow-up compliance for the second Serial MRI was 87% (of 166) for augmentation, 83% (of 61) for reconstruction, and 81% (of 70) for revision. Refer to Section IV below for details.

Adjunct Study

The Adjunct Study is a 5-year study that is designed to address the public health need of reconstruction and revision patients for silicone gel-filled breast implants. The concept of a public health need study was established in 1992 when no silicone gel breast implant PMAs were approved, yet FDA believed that reconstruction and revision patients should have access. Inamed's Adjunct Study was approved in 1998 and remains ongoing. The Adjunct Study follow-up timepoints are 1, 3, and 5 years. Local complications and satisfaction data are collected. There is no MRI cohort in the Adjunct Study; therefore, silent rupture is not assessed. There is no limit on the number of reconstruction and revision patients or sites.

The original set of data from the Inamed Adjunct Study presented to the October 2003 Panel involved a total of 15,465 reconstruction and 9,881 revision patients enrolled across 2,355 sites. Although all styles under PMA review are now part of the Adjunct Study, the clinical data submitted in the PMA involved only Styles 10, 20, 40, 45, 110, 120, and 153. The date of database closure for the information presented at the October 2003 Panel meeting was 8/30/02. For the reconstruction patients, the 1-year and 3-year follow-up rates were 54% and 27%, respectively. For the revision patients, the 1-year and 3-year follow-up rates were 44% and 20%, respectively. Refer to the "Inamed Clinical Summary Memorandum" in Tab 5 of your Panel package for a summary of the Adjunct Study results presented to the October 2003 Panel.

In their August 2004 response to the 1/7/04 not-approvable letter, Inamed provided rupture rate and health consequences from their Adjunct Study with a date of database closure of 7/2/04 in response to the 1/7/04 not-approvable letter. Refer to Section IV below for details.

AR90 Study

The AR90 Study was a 5-year prospective study that collected safety (local complications) and effectiveness data on saline-filled and silicone gel-filled implants for augmentation and reconstruction. The AR90 Study involved silicone gel Styles 40, 80, 110, 120, 148, 153, and 246, as well as silicone/saline Styles 46, 156, 178, and 278. Of these 11 styles, only Styles 40, 110, 120, and 153 are under review in this PMA. The other styles are not being manufactured today. The 5-year follow-up rates were 70% for augmentation and 78% for reconstruction. The AR90 study did not include an assessment for silent rupture. Refer to the "Inamed Clinical Summary Memorandum" in Tab 5 of your Panel package for a summary of the AR90 Study results presented to the October 2003 Panel.

Inamed's August 2004 response to the 1/7/04 not-approvable letter did not include any new information from the AR90 Study.

IV. RESPONSES TO DEFICIENCIES IN 1/7/04 NOT-APPROVABLE LETTER

This section provides a summary of each of the topics covered in Inamed's 1/7/04 not-approvable letter.

As stated above, the last topic in this section, **Device Effectiveness,** was not an issue in Inamed's 1/7/04 not-approvable letter for this PMA. FDA provided this information for your convenience because you will need to consider the risks and benefits, as a whole, for Inamed's product when providing your final recommendation for the PMA (approvable, approvable with conditions, or not approvable).

A. RUPTURE RATE AND HEALTH CONSEQUENCES

Implants can be suspected of rupture because of symptoms such as flattening of the implant or pain (suspected symptomatic rupture) or because of definite or indeterminate findings of rupture on MRI (suspected silent rupture). FDA believes that confirmation of rupture status occurs at explantation (implant removal). At explant, suspected implant ruptures are identified as either confirmed intact or confirmed ruptured. Some implants are removed for reasons other than suspected rupture (e.g., to correct a cosmetic complication, to treat capsular contracture, to change implant size), and the implants may be found to be ruptured at the time of explant.

When a silicone gel-filled breast implant ruptures, the patient and the physician may be unaware of it, the body does not have a mechanism for eliminating the silicone gel, and the gel can migrate outside of the capsule into the breast area, the lymph nodes, and distant locations. Accordingly, FDA recommends that a sponsor provide data with follow-up of sufficient duration to adequately describe the rate and rate of change of local complications over time (with specific concern with rupture), to describe the frequency of ruptures observed (intracapsular, extracapsular, and migrated gel), and to characterize the potential local health consequences of their ruptured implants. The study duration should be, for example, sufficient to measure or reasonably estimate how the shape of the curve for the percentage of ruptured implants versus time changes over the expected lifetime of the device. These data may come from the Core Study or other sources, such as the Adjunct Study and literature. These concerns were conveyed by FDA in Inamed's 1/7/04 not-approvable letter. Below is a summary of the information provided by Inamed to address these issues, stratified by data source, followed by FDA's rupture analysis and conclusions.

It is important to note that all 4-year data referenced below are partial data because not all patients were due for their 4-year follow-up at the time of database closure (May 2004) for submission of their August 2004 response.

It is also important to note that the clinical data in this Panel review memo are shown with data separately for primary augmentation, primary reconstruction, and revision indications. FDA believes that it is important to consider the data for revision patients within the context of the augmentation or reconstruction patient populations, which are the original indications for which patients receive breast implants. For example, when considering the safety for augmentation patients, 21 (4%) patients of 494 had revision surgery (i.e., device removal with study device

replacement) through 3 years, converting their risk to that of revision patients, who have different risks and benefits to consider. Therefore, the clinical data collected on revision patients should be considered in your determination of whether the data demonstrates a reasonable assurance of safety of the device for augmentation and reconstruction patients (question 5 of the Panel questions provided in Tab 2 of your Panel package).

1. Inamed Core Study – Rupture Rate and Rate Over Time

In responding to the issue of rupture rate and rate over the lifetime of the device, Inamed included ≈1 additional year of rupture data than that presented at the October 2003 Panel meeting, with a new date of database closure of 5/19/04. There is now: (1) physician follow-up data for all patients through 3 years and physician follow-up for some patients at 4 years; and (2) MRI data for the subset of patients in the MRI cohort at the 1 and 3-year timepoints.

The number of implant ruptures reported in the Core Study, as of 5/19/04, is summarized in Table 1 below. Note that there were silent ruptures reported in the Non-MRI Cohort, which is the two-thirds of Core Study patients who were not undergoing serial MRI screening. Silent ruptures were reported in the Non-MRI Cohort when, for example, an implant was removed for a size change and found to be visibly ruptured at the time of explant/revision surgery. Note that some of the silent ruptures reported in the MRI cohort have not yet been "confirmed."

There were 6 augmentation implants and 1 revision implant, which Inamed claims are confirmed as non-ruptured; however, this confirmation is based on mammogram, ultrasound, or a second MRI following the MRI that showed suspected rupture. These 7 implants are not included in the rupture information and are discussed following Table 6 below. FDA believes that until confirmatory explantation is performed, these implants should be included in the rupture rate as a worst case.

In the event that the explanted device is sent to Inamed's laboratory, it is the explanting surgeon's visual assessment at the time of explantation which has determined the final rupture status – either intact or ruptured – for the purposes of the Core Study. There were 2 implants in which the laboratory results indicated ruptured implants, but the explanting physician identified the implants as intact, which are not included in this rupture rate: Patient [redacted] (1 augmentation implant) and [redacted] (1 reconstruction implant). However, there were also 2 implants ([redacted] and [redacted]) in which the laboratory results indicated as intact, but the explanting physician identified as ruptured; these are included in the rupture rate.

Additionally, there were 3 implants (2 in the MRI Cohort and 1 in the Non-MRI Cohort) that were ruptured after removal of the original study device and replaced with another study device, which are not included in the rupture information below: [redacted] (augmentation MRI); [redacted] (reconstruction MRI); and [redacted] (reconstruction Non-MRI).

Table 1: Summary of silent and symptomatic ruptures reported in the Core Study MRI Cohort and Non-MRI Cohort on a by-implant basis.

	MRI Cohort N = 663 Implants			**Non-MRI Cohort N = 1119 Implants**	
	Silent	**Symptomatic**		**Silent**	**Symptomatic**
Augmentation	5	1		2	3
Reconstruction	17	1		4	0
Revision	8	0		1	1
Total	30	2		7	4
Total Rate	4.5%	0.3%		0.6%	0.4%

Recall that the MRI Cohort consists of approximately one-third of the total Core Study Patients. It is clear that the silent rupture rate is higher than the symptomatic rupture rate for both the MRI Cohort and the Non-MRI Cohort. Even in the Non-MRI Cohort, which is not undergoing serial screening for silent rupture, silent ruptures are reported more frequently than symptomatic ruptures.

Table 2 below summarizes the by-implant follow-up compliance for the MRI Cohort. Note that as patients have their implants removed for any reason, whether or not they are replaced, those implants are removed from the available pool of implants in the MRI Cohort. Therefore, the available pool of patients/implants for the MRI cohort is decreasing over time. This is particularly evident in the augmentation cohort, in which there were 32 discontinuations (22 due to removal and 10 due to MRI issues) at the second (of 5) MRI screenings. Therefore, at the second MRI screening at 3 years, 10% of the initial augmentation MRI Cohort is no longer available for participation in the MRI study.

Table 2: By-implant compliance for the MRI cohort in the Core Study.

1st MRI at 1 year	**Augmentation**	**Reconstruction**	**Revision**	**Total**
Theoretical	331	182	150	663
Deaths	0	0	0	0
Implant Removals	12	0	0	12
Expected	319	182	150	651
Actual	277	170	142	589
% Follow-up	86.8%	93.4%	94.7%	90.5%
2nd MRI at 3 years				
Theoretical	331	109[b]	134[b]	574
Deaths	0	1	0	1
Implant Removals	22	9	0	31
MRI Discontinuations[a]	10	2	0	12
Expected	299	97	134	530
Actual	263	79	108	450
% Follow-up	88.0%	81.4%	80.6%	84.9%
Mean Duration of Implantation at 2nd MRI	2.5 years	4.1 years	4.2 years	

[a]Includes patients with metal implants or claustrophobia.

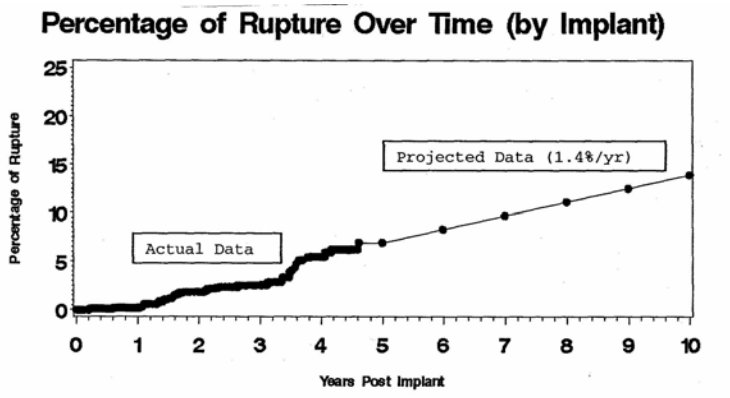
[b]Theoretical for reconstruction and revision patients is lower at the second MRI because MRI screening began in these cohorts later than for augmentation. Therefore, all reconstruction and revision patients have not yet reached the timepoint for their second MRI screening.

As noted above, complete data from the Core Study is available up to 3 years with partial data at 4 years. Inamed attempted to use these available data from the Core Study to estimate the long-term rupture rate (i.e., at 10 years) from their 3 to 4-year data. To do this, they used the proportion of silent ruptures observed in the MRI Cohort by indication to "estimate" the number of silent ruptures in the Non-MRI Cohort by indication. Because Inamed believes that MRI has a false positive rate of 36% based on their MRI Cohort, the hypothetical "estimated" number of silent ruptures were reduced by 36% in the Non-MRI Cohort. Because there were a few silent ruptures observed in the Non-MRI Cohort (as described above), they additionally reduced the estimated number of silent ruptures in the Non-MRI Cohort to avoid double counting. They then pooled the data from each separate indication into one group by weighting the proportion of patients for each indication.

To construct a hypothetical Kaplan-Meier (KM) rupture rate curve at 10 years for the entire Core Study population, Inamed then applied the time points when silent rupture was reported for the MRI Cohort to the Non-MRI Cohort. Without data beyond 4 years, Inamed assumed that the rupture rate will remain constant and averaged the cumulative rupture rate observed by the number of years of observation. For example, using the rupture rates for this extrapolated and weighted group through 4 years, Inamed estimated changes of 0.2% between years 0 and 1; 1.7% between years 1 and 2; 0.6% between years 2 and 3; and, 3.0% between years 3 and 4.

Using this approach, Inamed determined that the rupture rate increases by a rate of 1.4% per year. The constructed curve shown below in Figure 1 was provided by Inamed and shows the hypothetical rupture rate in the total Core Study population extrapolated out to 10 years based on the above approach. The curve shows a by-implant, rupture rate of **13.9% at 10 years** for all indications combined. Note that what Inamed refers to as "actual data" in this figure is their actual data for the MRI Cohort combined with the estimated data for the Non-MRI Cohort.

Figure 1: Hypothetical[1] by-implant rupture curve provided by Inamed - Core Study[2].



[1]Actual data shown here through 4 years is actual data observed in the MRI Cohort combined with hypothetical, estimated data in the Non-MRI Cohort. Projected data is shown beyond 4 years, assuming a constant rate of increase.
[2]All 3 indications of augmentation, reconstruction, and revision were combined into one curve.

There were several assumptions made in utilizing this approach:

- That it is appropriate to estimate the silent rupture rate in the Non-MRI group using data from the MRI group.
- That it is appropriate to reduce this estimated rate by excluding hypothetical unconfirmed false positive MRI ruptures in the Non-MRI group.
- That it is appropriate to pool the separate indications of augmentation, reconstruction, and revision together.
- That the rupture rate will remain constant, resulting in a straight line for the shape of the rupture curve.

Focusing on the existing, actual data without hypothetical extrapolation, Table 3 below shows the by-implant Kaplan-Meier risk rates of silent rupture in the MRI Cohort through 4 years in the Core Study. Recall that not all reconstruction and revision patients had reached their 4-year follow-up, and only some of the reconstruction and revision patients had their second MRI to screen for silent rupture. Table 3 only reports silent ruptures in the MRI Cohort. It does not include symptomatic ruptures.

Table 3: By-implant Kaplan-Meier risk rates of first occurrence of silent rupture[1] through 4 years[2] - Core Study, MRI Cohort - actual data.

Indication	**Rate (95% CI)**
Augmentation (N = 331 implants)	1.5% (0.0, 3.0)
Reconstruction (N = 182 implants)	14.2% (7.5, 20.8)
Revision (N = 150 implants)	6.0% (1.9, 10.0)

[1]MRIs were performed to screen for silent rupture at approximately years 1 and 3 following implantation.
[2]Based on complete 3-year and partial 4-year data. Not all reconstruction and revision patients had their second MRI.

Tables 4-6 below show the total rupture rate (total rupture rate = silent + symptomatic ruptures), by indication, through 4 years in the Core Study. Recall that these tables are based on complete data 3-year data and partial 4-year data. The total rupture rate is shown for the MRI and Non-MRI cohorts separately because silent rupture is under-ascertained in the Non-MRI cohort, which does not undergo serial MRI to screen for silent rupture. Recall that annual physical examinations of the breasts and implants occurred at 0-4 weeks, 6 months, and then annually thereafter. Complete MRI data is available for the first MRI at 1 year, and only partial MRI data is available for the second MRI at year 3.

Table 4: By-implant KM total[1] rupture rate through 4 years in **Augmentation** patients - Core Study MRI Cohort and Non-MRI Cohort - actual data.

	MRI Cohort		**Non-MRI Cohort**	
	By-Patient N = 166	By-Implant N = 331	By-Patient N = 320	By-Implant N = 640
Rate (95% CI)	3.4% (0.5, 6.3)	1.7% (0.2, 3.2)	1.1% (0.0, 2.2)	0.5% (0.0, 1.1)

[1]Total rupture rate refers to both symptomatic and silent ruptures.

Table 5: By-implant KM total[1] rupture rate through 4 years in **Reconstruction** patients - Core Study MRI Cohort and Non-MRI Cohort - actual data.

	MRI Cohort		Non-MRI Cohort	
	By-Patient N = 107	By-Implant N = 182	By-Patient N = 113	By-Implant N = 177
Rate (95% CI)	20.5% (11.3, 29.7)	13.1% (7.2, 19.0)	4.9% (0.2, 9.6)	3.2% (0.1, 6.2)

[1]Total rupture rate refers to both symptomatic and silent ruptures.

Table 6: By-implant KM total[1] rupture rate through 4 years in **Revision** patients - Core Study MRI Cohort and Non-MRI Cohort - actual data.

	MRI Cohort		Non-MRI Cohort	
	By-Patient N = 78	By-Implant N = 150	By-Patient N = 138	By-Implant N = 264
Rate (95% CI)	10.9% (3.8, 18.1)	5.7% (1.9, 9.6)	1.7% (0.0, 4.1)	0.9% (0.0, 2.1)

[1]Total rupture rate refers to both symptomatic and silent ruptures.

Inamed attributed the observed silent rupture rate to over-diagnosis of rupture via MRI in the Core Study. Inamed provided the data to support this contention. Of the 38 implants with suspected rupture in the MRI Cohort, Inamed stated that:

- 15 were confirmed ruptured at explantation
- 2 were confirmed as intact at explantation
- 7 were categorized as confirmed intact based on a subsequent MRI, mammogram, or ultrasound showing no rupture
- 14 have not yet been confirmed ruptured or intact.

The 7 implants which Inamed claims are confirmed intact based on MRI, mammogram, or ultrasound were initially suspicious of rupture via MRI. A subsequent imaging study (either mammogram or ultrasound or MRI) showed no rupture. Six of these were augmentation and 1 was a revision implant. These 7 implants are NOT included in the rupture rates shown in Tables 4-6 above. However, without explantation, FDA considers these as "unconfirmed," and we believe they should be included in the rupture rates above.

By categorizing these 7 implants as intact, Inamed believes that 24 implants have a confirmed status: 15 as ruptured as determined at explantation; 2 as intact as determined at explantation; and 7 as intact as determined by MRI, mammogram, or ultrasound. Inamed calculated a false positive rate of 37.5% for MRI (9 intact divided by 24 confirmed, with 7 of the 9 intact never having been explanted). This rate of ≈38% was used to reduce the estimated rate of silent ruptures in the Non-MRI Cohort.

However, if only the 17 explanted implants are considered confirmed, then the false positive rate of MRI is 11.8%, with 2 confirmed intact implants out of 17 total implants confirmed by explant.

The **specificity** of MRI in determining rupture (1 minus the false positive rate) for the Core Study is therefore 88.2%, if explant is used as the method for confirming implant status. This specificity of 88.2% for MRI in detecting implant rupture is within the published range of 86-94% for MRI based on a meta-analysis of 18 studies.[1] In a more recent publication, the specificity of MRI in detecting rupture was reported to be 100% in Hölmich, et al. in 2001.[2] And,

a subsequent publication by Hölmich (2005)[3] found a specificity of 97% for MRI in detecting rupture. In the literature, it is explantation which is used to confirm the rupture status.

An issue related to the specificity of MRI in detecting rupture is the **sensitivity** of MRI in detecting implant rupture. Inamed's product labeling claims that the sensitivity of MRI to detect rupture is 64% (Scaranelo, et al. 2004).[4] However, unless explantation is performed on all implants in the MRI Cohort, including those read as negative for rupture via MRI, Inamed cannot determine the sensitivity of MRI to detect rupture using the Core Study. The sensitivity of MRI (which is the ability to detect a true positive rupture) in Hölmich, et al. in 2001[2] was 86%. In the subsequent publication by Hölmich (2005)[3], MRI yielded a sensitivity of 89%, a specificity of 97%, a positive predictive value of 99%, and a negative predictive value of 79% for detecting a rupture, confirmed at the time of explantation. For the diagnostic ability of MRI to accurately detect rupture, these are excellent values; however, this does mean that MRI missed 11-14% of the implant ruptures in the Danish Registry. The sensitivity of MRI published in the literature ranges from 71-83%.[1]

Inamed also attributed the observed rupture rate for reconstruction patients to the fact that many of the ruptures were of Style 153. In the reconstruction population, 64% of the patients used Style 153, compared to 8% for augmentation and 30% for revision. As discussed in Section B (**Modes and Causes of Rupture)**, analysis of retrieved implants showed that Style 153 had [redacted] rupture. Of the 15 confirmed ruptured implants in the MRI Cohort, all of the 10 confirmed ruptured reconstruction implants were Style 153, and all of the 3 confirmed ruptured revision implants were Style 153. Of the 14 unconfirmed ruptured implants in the MRI Cohort, 6 reconstruction and 3 revision implants are Style 153.

2. Inamed Core Study – Health Consequences of Rupture

To address the local health consequences of rupture in the Core Study, Inamed compared the local complications, patient satisfaction, and CTD signs and symptoms (CTD S/S) reported in patients with confirmed ruptured implants to those with confirmed intact implants. Note that these data included the local complications, patient satisfaction, and CTD S/S AFTER the explantation which confirmed the implant as ruptured or intact. In the suspected but unconfirmed cases (i.e., no explantation has occurred), the local complications, patient satisfaction, and CTD S/S are reported AFTER the date of estimated rupture (i.e., after the MRI date showing a suspected rupture).

The Core Study enrolled 1,782 implants in 940 patients. As of the 5/19/04 date of database closure, 248 implants have been explanted for any reason. At the time of explant, 223 implants in 131 patients were reported as confirmed intact, and 25 implants in 25 patients were reported as confirmed ruptured. (As a side note, of these 25 confirmed ruptured implants, 15 (60%) were silent ruptures found in the MRI cohort).

Of these 25 confirmed ruptured implants occurring in 25 patients in the Core Study, 23 were intracapsular (5 augmentation, 13 reconstruction, 5 revision implants), 1 was extracapsular (1 augmentation implant in 1 patient), and 1 involved detachment of inner lumen of a Style 153 implant, which was categorized as neither intracapsular or extracapsular rupture by Inamed. Inamed reported no cases of migrated gel in these 25 confirmed ruptured implants. However,

because the surgeons are not sampling local lymph nodes, surrounding breast tissue, or even more distant sites, it is possible that gel migration may not have been discovered.

Table 7 below summarizes the **patient satisfaction data** reported through 4 years for patients with confirmed intact (N = 131 patients) versus confirmed ruptured implants (N = 25 patients). Note that there are significant amounts of missing information, with at least half of the patient data missing, particularly at 3 years, making the data difficult to interpret.

Table 7: Summary of patient dissatisfaction for Core Study patients with confirmed intact or confirmed ruptured implants through 4 years.

Status	N	% Definite or Somewhat Dissatisfied	Mean (SD)
Confirmed Rupture	11/25	9.1%	4.2 (1.0)
Confirmed Intact	54/131	13.0%	4.2 (1.2)

Table 8 below compares **selected local complications** reported after explant (i.e., after confirmation) in patients with confirmed rupture and with confirmed intact implants. Note that approximately 30% of patients have not had a follow-up visit to assess for local complications after explantation (i.e., confirmation). Also note that Inamed combined the three indications of augmentation, reconstruction, and revision, all of which have unique complication rates. An important note is that the mean duration of follow-up between these two groups of patients is different, with longer follow-up in patients with confirmed intact implants. These confirmed intact implant patients with longer follow-up would be expected to have higher complication rates because of their longer follow-up. However, despite their 1-year less follow-up, patients with confirmed ruptured implants had higher rates of infection, lymphadenopathy, redness, seroma, skin rash, and swelling, which are shown shaded in Table 8 below. Lymphadenopathy, redness, skin rash, and swelling are physical signs generally associated with an inflammatory reaction and/or with infection. However, it should be noted that these data are based on a small number of patients, especially in the confirmed rupture group, which makes it difficult to draw definitive conclusions.

Table 8: Selected local complications reported after explant in Core Study patients with confirmed ruptured implants (N = 25 patients) and confirmed intact implants (N = 131 patients).

	Confirmed Ruptured Implants	Confirmed Intact Implants
	N=17 patients[1]	N=79 patients[2]
No complication	8 (47%)	37 (47 %)
Asymmetry	0	7 (9%)
Breast pain	2 (12%)	11 (14%)
Bruising	1 (6%)	6 (8%)
Capsular contracture	2 (12%)	11 (14%)
Infection	3 (18%)	2 (3%)
Lymphadenopathy	1 (6%)	2 (3%)
Redness	4 (24%)	8 (10%)
Seroma	2 (12%)	4 (5%)
Skin rash	1 (6%)	1 (1%)

	Confirmed Ruptured Implants	Confirmed Intact Implants
	N=17 patients[1]	N=79 patients[2]
Swelling	3 (18%)	10 (13%)
Wrinkling	0	6 (8%)

[1] 17 of the 25 patients with a confirmed ruptured implant have had a follow-up evaluation after explantation. The mean duration of follow-up is 1.3 years (range 14 days to 4.6 years).
[2] 79 of the 131 patients with confirmed intact implants have had a follow-up evaluation after explantation. The mean duration of follow-up is 2.5 years (range 5 days to 4.9 years).

With respect to CTD S/S, 11 of the 25 women with confirmed ruptured implants had at least one CTD questionnaire after confirmation (i.e., removal), and 72 of the 131 women with confirmed intact implants had a CTD questionnaire after confirmation. These data are summarized in Table 9 below. Note that approximately 50% of patients have not had a follow-up visit with a CTD questionnaire to assess for CTD S/S after explantation (i.e., confirmation). Also note that Inamed combined the three indications of augmentation, reconstruction, and revision, all of which have unique CTD S/S reporting. Also note that the mean duration of follow-up between these two groups of patients is significantly different, with longer follow-up in patients with confirmed intact implants. These confirmed intact implant patients would be expected to have higher CTD S/S reporting rates due to their longer follow-up. However, despite their 1 year less follow-up, patients with confirmed ruptured implants had a higher percentage of reports of new GI, General, Muscle, and Skin complaints, as shown in Table 9. Only the Muscle category was statistically significantly higher for patients with confirmed ruptured implanted compared to patients with confirmed intact implants (Fishers Exact test, p=0.426). It should be noted that these data are based on a small number of patients, especially in the confirmed rupture group, which makes it difficult to draw definitive conclusions.

Table 9: CTD S/S categories reported after explantation (i.e., confirmation) in Core Study patients with confirmed ruptured implants (N = 25 patients) and confirmed intact implants (N = 131 patients).

	Confirmed Ruptured Implants N = 11 patients[1]	Confirmed Intact Implants N = 72 patients[2]
	N (%)	N (%)
Gastrointestinal	3 (27%)	17 (24%)
General	2 (18%)	10 (14%)
Joint	0	14 (20%)
Muscle	5 (45%)	12 (17%)
Neurological	1 (9%)	15 (21%)
Other	2 (18%)	14 (19%)
Skin	3 (27%)	13 (18%)
Urinary	0	5 (7%)

[1] 11 of the 25 patients with a confirmed ruptured implant have had a follow-up CTD evaluation after explantation. The mean duration of follow-up is 1.6 years (range 173 days to 3.7 years).
[2] 72 of the 131 patients with confirmed intact implants have had a follow-up CTD evaluation after explantation. The mean duration of follow-up is 2.4 years (range 19 days to 4.3 years).

3. Inamed Adjunct Study

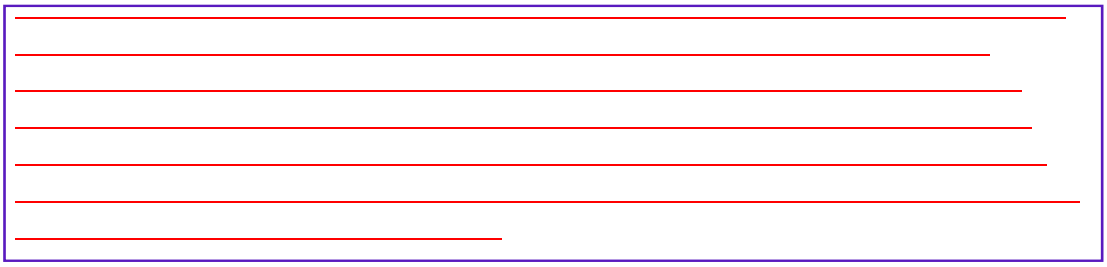
Of the 8/30/02 date of database closure for the original submission, 15,465 reconstruction and 9881 revision patients have received Inamed gel-filled breast implants through their Adjunct Study. The follow-up rates through 3 years were 27% for reconstruction and 20% for revision. Follow-up rates through 5 years were not provided in the original report.

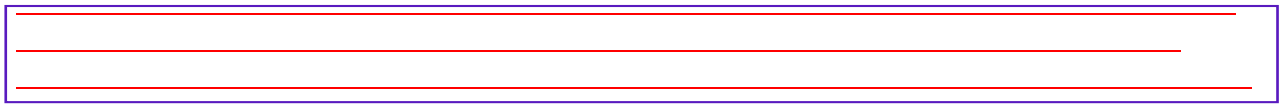
In their August 2004 submission (with a date of database closure of 7/2/04), Inamed reported that a total of 46,314 patients had been implanted in their Adjunct Study. The 5-year KM rupture rates were 3.0% for reconstruction (based on 355 patients available for analysis) and 2.7% for revision (based on 468 patients available for analysis). However, because of the low follow-up rates and the lack of MRI screening for silent rupture, data from the Adjunct Study [redacted] are not useful for determining the rupture rate over the lifetime of the device.

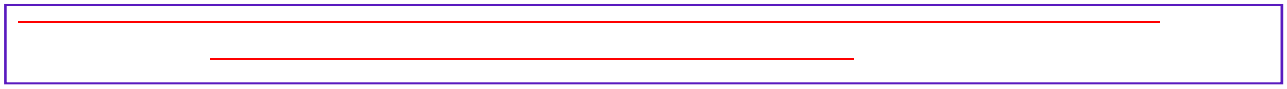
Of the limited number of patients available for analysis, Inamed reported 105 patients with ruptures. The majority of these ruptures are symptomatic ruptures because the Adjunct Study patients do not undergo MRI screening. Of these 105 reported ruptures, 99 have been confirmed with explant, and 6 have not yet undergone surgery to confirm the status of the suspected rupture. Of the 99 confirmed ruptures, 95 were intracapsular, 1 was extracapsular with resulting migrated gel, and 3 implants (in 3 patients) had silicone gel leaking from their wounds.

One reconstruction patient categorized as having an intracapsular rupture had gel migration to the axilla which the physician reported as due to multiple needle procedures to the breast. As a worst case analysis, situations in which silicone gel is leaking from a wound or from a nipple or is found in distant sites such as the axilla, should be classified as extracapsular. Therefore, of the 99 confirmed ruptures, 94 are intracapsular and 5 are either extracapsular or resulted in migrated or extruded gel. The patient numbers for patients with extracapsular or migrated/extruded gel according to Inamed are shown below. The patient numbers that are **bolded** are classified as extracapsular by Inamed.

[redacted]







Therefore, of the 99 confirmed ruptures in the Adjunct Study as a worst case, 93 were intracapsular and 6 (6%) were extracapsular. Inamed acknowledges that the 6% frequency of extracapsular rupture in Inamed's Adjunct Study is lower than the 25% rate reported in the Danish literature data because MRI was used in the Danish Registry to detect extracapsular rupture. This suggests that MRI is more sensitive in detecting extracapsular rupture than gross examination of ruptured implants by the physician at the time of explant. Another reason why the frequency of extracapsular rupture is lower for the Adjunct Study than the Danish Registry is because the duration of implantation for the Adjunct Study, a maximum of 5 years, is significantly lower than that of the Danish Registry, which is a median of 12 years.

To evaluate the consequences of rupture, Inamed examined the local complications reported concomitant with implant rupture (at the time of rupture) and local complications reported following rupture.

There were no local complications reported at the time of rupture for ≈31% of these 99 patients. The most frequently reported complications were capsular contracture (35%), asymmetry (20%), breast pain (14%), implant palpability (14%), implant malposition (12%), and wrinkling (10%), with all other complication rates <10%.

Of the 99 patients with a confirmed rupture in the Adjunct Study, follow-up after rupture was performed for 63 of the 99 patients (64%). Of these 63 available patients, no complications were reported following rupture in 67%. The most frequent complications after rupture were asymmetry (16%), implant palpability (16%), capsular contracture (11%), implant malposition (11%), and wrinkling (11%), with all other complication rates <10%. Of these 63 patients, 18% underwent implant removal, 11% underwent a capsule procedure, and 16% underwent other procedures such as breast biopsy, pocket/wound revision, or nipple reconstruction.

The Adjunct Study has no data on silent rupture progression to symptomatic rupture because there was no MRI cohort in the Adjunct Study. Inamed stated that it is clinical practice to remove the implant when rupture is confirmed, and they acknowledge that no data exists on silent ruptures progressing to symptomatic ruptures from their Adjunct Study data.

The Adjunct Study also has no data on intracapsular rupture progression to extracapsular rupture. Inamed stated that it is clinical practice to remove the implant when rupture is confirmed.

Given the low follow-up rate in the Adjunct Study and the lack of screening for silent rupture, the Adjunct Study data are of limited value to characterize the rupture rate, rupture rate over time, and the health consequences of rupture because of the under-ascertainment of rupture and inadequate patient follow-up.

4. Danish Breast Implant Registry

A summary of the types of data that are collected in the Danish Breast Implant Registry (Danish Registry) are provided in the **Inamed's Postapproval Plans** section below. The Danish Registry includes 1472 women with breast implants and 560 women with breast reduction as of November 2001[5], of which 263 are Inamed devices that are the subject of this PMA. The median duration of implantation of these 263 Inamed implants is 3.78 years (range of 18 days to 4.8 years). Inamed stated that none of these implants have ruptured; however, none of these patients are included in the MRI studies of the Danish literature data below. *These Danish Registry data have limited value in characterizing the rupture rate and rate over time, health consequences of rupture, silent ruptures progression to symptomatic ruptures or intracapsular ruptures progression to extracapsular ruptures specifically for Inamed devices.*

5. Danish Literature Data – Rupture Rate

Below is a summary of several publications of Danish data regarding the incidence and prevalence of silent rupture rate.

Hölmich, et al. in 2001[2] reported on the prevalence of rupture via MRI of a subset of augmentation patients. Patients who had their surgery between 1973 and 1997 were randomly selected to undergo MRI in 1999 for rupture detection. There were 271 women with 533 implants reported, with 183 of these implants identified as "third generation" (i.e., implanted after 1988), 130 identified as "second generation" (i.e., implanted 1979-1987), 9 identified as "first generation" (i.e. implanted 1974-1978), and 211 with missing identity. The median duration of implantation was 12 years (range 3 to 25 years). The youngest implants are 3 years old. Therefore, the data are applicable only to implants which survive without removal for at least the first 3 years following implantation.

There were 141 of the 533 implants with definite rupture (26% of implants) observed in 97 of the 271 women (36% of women). Of the 141 ruptures, 110 implants (78%) were intracapsular and 31 (22%) were extracapsular. An additional 32 implants were determined to be possibly ruptured. If definite and possibly ruptured implants are considered, then 173 of 533 implants (32%) were ruptured. The prevalence of rupture was highest for second generation implants (N = 130 implants), lowest for first generation implants (N = 9), with third generation implant (N = 183) prevalence rates low.

The manufacturers included in this study were as follows: McGhan/3M (n = 146), Dow Corning (n =101), Surgitek/Bristol (n = 78), Nagor/Remploy (n = 43), Eurosilicone (n = 18), Misty/Bioplasty (n = 18), Heyer Schulte/Baxter (n = 13), CUI/Cox-Uphoff (n = 10), Kocken (n = 6), and unknown (n = 100). Some of these implants are only available in Europe. Note that one

of the three MRI centers, which involved 203 of the 533 implants, utilized an MRI machine with a magnet which was not sufficiently strong enough to provide reliable scans. This may have biased the data, resulting in an underestimation of the rupture rate. The applicability of these data to predict the rupture rate and rate over time for the Inamed product is limited.

In a subsequent study, Hölmich, et al. (2003)[6] reported on the incidence of implant rupture based on the results of a second MRI performed in 2001 on the above women who still had their implants and who agreed to a second MRI. The one center described above which utilized an underpowered magnet was excluded for the second MRI. The patients therefore underwent serial MRI over a two year period, once in 1999 and once in 2001 at 2 centers.

The median duration of implantation was similar to that of the previous study: 12 years (range 3 to 25 years). There were 317 implants in 186 women included. Approximately two-thirds of the implants (N = 197) were "third generation" (i.e., implanted in 1988 or later); 91 implants were "second generation" (i.e., implanted 1979-1987), and 29 were "first generation" (i.e., implanted 1974-1978). The youngest implants are 3 years old; therefore, the data are only applicable to implants which were not removed within the first 3 years of implantation. Therefore, the data are only applicable to implants which survive without removal for at least the first 3 years following implantation.

There were 33 total definite ruptures, 26 of which were diagnosed by MRI and 7 which were incidentally found at repeat surgery. Of the 26 MRI-diagnosed ruptures, 6 were extracapsular. There were 23 total possible ruptures, 22 of which were identified by MRI and 1 which was reported at surgery as "sticky" but intact. The total rupture incidence for definite rupture was 5.3 ruptures per 100 implants per year (95% confidence interval 3.5 – 7.1). For MRI-diagnosed ruptures, the rate of definite rupture is 4.4 per 100 implants/year (95% CI 2.7–6.1). The total rupture incidence rate for definite or possible ruptures was 8.9 ruptures per 100 implants per year (95% confidence interval 6.6 – 11.3). Because the authors state in the discussion section that they believe that the true rupture rate is closest to the combined group of definite and possible ruptures, it is 8.9 ruptures/100 implants/year that is the more realistic value to address the rupture rate because it includes both definite and possible ruptures.

For third generation implants which do not rupture in the first 3 years, the authors estimate a rupture rate of 2% at 5 years, and 15% at 10 years. This is based on 197 of the 317 implants which they categorized as "third generation" (i.e., implanted at year 1988 or later). They point out that a survivor bias may have influenced this estimate, yielding a rupture estimate which is too low, because the implants included had to remain intact for 3 years and because implants explanted before the first MRI were excluded. Another limitation which the authors fail to point out is that this projected estimate over time is based on the assumption of a linear shape for the rupture curve. With only two time points for MRI assessment, the shape of the rupture curve cannot be assumed to be linear. The authors describe a prior small pilot study in which the sensitivity of MRI was 86% with a specificity of 100%, and they acknowledge that because of the high specificity relative to sensitivity, some ruptures may have been missed.

In a more recent publication, Hölmich, et al.[3] in 2005 found a specificity of 97%, sensitivity of 89%, positive predictive value of 99%, and negative predictive value of 79% for MRI in detecting rupture. For the diagnostic ability of MRI to accurately detect rupture, these are excellent values; however, this does mean that MRI missed 11-14% of the implant ruptures in the Danish literature data.

6. Danish Literature Data – Health Consequences

Below is a summary of several publications of Danish data to characterize the incidence of intracapsular gel and extracapsular gel rupture, progression of intra to extracapsular rupture, and local breast symptoms associated with implant rupture for silicone gel-filled breast implants, in general. These literature references are not specific to Inamed devices.

Hölmich, et al.[2] in 2001 reported that of the 141 implant ruptures noted on MRI, 31 implants (22 %) were noted to be extracapsular. In 2003, Hölmich, et al.[6] reported that of 26 MRI-diagnosed ruptures, 6 (23%) were described as extracapsular. In both the 2001 prevalence and 2003 incidence studies, approximately one-fourth of the ruptures were noted to be extracapsular with three-fourths of the ruptures as intracapsular. Recall that the 2001 study reported on the prevalence of rupture in 271women who underwent a singe MRI screening of their cosmetic implants (median in-vivo age of implants 12 years, range 3 – 25 years) in 1999. The 2003 study reported on the incidence of rupture in 186 of these women at 2 of the 3 MRI centers from the 2001 study who still had their implants, and who underwent a second MRI screening in 2001.

Hölmich, et al. (2003)[7] reported the results of self-administered questionnaires from the patients who underwent the first MRI screening 1999. The questionnaires were completed, on average, 1 year before this (first) MRI examination. Women with intact implants (N = 146 women) were compared with women with MRI-diagnosed ruptures (N = 92 women), and there were no statistically significant differences in self-reports of local breast symptoms or generalized symptoms in women with intact versus ruptured implants when adjusted for age, placement, and type of implant. Women with evidence of extracapsular rupture on MRI were, however, 6 times more likely to report breast hardness than women with intact implants (OR 6.3, 95% CI 1.7-23.5). Although not statistically significant, women with extracapsular rupture were 3 times more likely to report a connective tissue disease (OR 3.8, 95% CI 0.4-35.1), 2 times more likely to report pleuritis (OR 2.2 95% CI 0.1-39.4), and 1.7 times more likely to report fatigue (OR 1.7, 95% CI 0.5-5.9) than women with intact implants, when adjusted for age, placement, and type of implant.

In 2004, Hölmich, et al.[8] reported that of 96 implants definitely ruptured at the first serial MRI in 1999, 19 (20%) were extracapsular and 77 (80%) were intracapsular. Among the 19 implants in 14 women with extracapsular silicone noted at the first MRI, the extracapsular silicone appeared to remain stationary in 16 implants, appeared to effuse marginally in one implant in one patient, and appeared to effuse significantly in 2 implants in one woman. This latter woman with significant extracapsular silicone gel effusion noted on the second compared to the first MRI, reported intermittent pain in the left lateral area. Explant surgery in this latter patient confirmed significant effusion of extracapsular silicone. Neither of the 2 women with effusion of extracapsular silicone reported any trauma.

Of the 77 intracapsular definite MRI ruptures at the first MRI screening in 1999 reported in Hölmich, et al. (2004), 69 (90%) showed no changes at the subsequent MRI screening in 2001. Of the 8 implants (10%) which showed a change between the first and second MRI screening, 1 which was suspicious for extracapsular silicone was actually a herniated capsule and all gel was reported to be intracapsular at explant. Of the remaining 7 implants suspicious for progression from intracapsular to extracapsular gel on MRI, all implants did, indeed, have evidence of extracapsular rupture at the time of explant. Three of these 7 women reported trauma to the affected breast between the first and second MRI examination, and one woman reported mammography.

The authors also reported the serologic findings and self-reported symptoms of a cohort 206 Danish women (405 implants) who had augmentation implants implanted between 1973 and 1998 (median duration of implantation 12 years; range 3 to 25 years), who still had their original implants, who had two serial MRI examinations in 1999 and in 2001, and whose implants were either intact at the time of both MRI examinations (N = 98 women with 193 implants) or who had at least one implant read as definitely ruptured at the first MRI screening in 1999 (N = 64 women with 96 implants). It is these two groups of women: intact (98 women with193 implants intact at both MRI screenings) and ruptured (64 women with 96 implants with at least one definitely ruptured implant at the first MRI in 1999) which were compared for self-reported local breast symptoms and autoantibody status. With respect to autoantibodies, women with ruptured implants were not more likely to test positive for autoantibody tests such as ANA, RF, and ACL. Patients whose implant ruptures progressed from intracapsular to extracapsular did not have progression of autoantibody production. Women with ruptured implants were 2 times more likely to report non-serious pain to the affected breast (odds ratio 2.2; 95% CI 1.2 to 4.2) compared to women with intact implants. Women with ruptured implants were 2.5 times more likely to report a change in breast shape (OR 2.5; 95% CI 1.3-4.8).

The authors concluded that among 11% of ruptured implants, there appeared to be progression of silicone seepage, with some instances attributable to trauma while others seemed spontaneous. They believe that "intracapsular/extracapsular implant rupture is not a permanent condition and that the fibrous capsule, although solid and sometimes even calcified, is not impermeable to silicone." The authors also assert that untreated silicone rupture may entail the risk of silicone migration, which can remain unnoticed in many cases, but which can cause or increase capsular contracture and development of silicone granulomas.

7. Other Literature

Inamed referred to the literature for the questions of frequency of intracapsular gel, frequency of extracapsular gel, frequency of migrated gel and destination of migrated gel, frequency of intracapsular and extracapsular gel and gel migration beyond breast tissue, local complications associated with implant rupture, progression of silent to symptomatic ruptures, and progression of intracapsular to extracapsular ruptures. These references describe, for the most part, small case series of implants, and in some cases use mammography, which is inferior to MRI, for determining rupture status. Additionally, these references are not specific to Inamed's devices and are, therefore, of limited value in estimating the rupture rate for the implants in this PMA.

The literature cited described local complications of ruptured breast implants as silicone granuloma, axillary adenopathy, pain or tenderness, arm or neck pain, chest wall pain, breast size change, breast deformity, itching, joint swelling, and myalgia. There are reports of the presence of silicone using spectroscopy, in the surrounding capsule, axillary lymph nodes, and liver of women with intact implants.

Brown, et al. (2000)[9] studied a cohort of 344 women with 687 implants from a NCI study who under went MRIs. The median implant age was 16.4 years (range 6.4 to 28.0 years). Of the 687 implants, 378 (55%) were definite for rupture via MRI and 50 (7.2%) were indeterminate for rupture. Extracapsular ruptures were found in 85 of the 678 implants (12.4%) and involved 73 of the 344 women (21%).

Another study in which 90 women with 142 silicone gel-filled breast implants underwent MRI to detect implant rupture status, ANA testing, rheumatic symptom reporting, and magnetic resonance spectroscopy (MRS) to determine the presence of silicone in the liver, was reported by Gaubitz, et. al. (2002).[10] The mean duration of implantation was 9 years (range 1-26 years) with 24% of the women having implants for cosmetic reasons and 76% for reconstructive reasons. Twenty-four of the 90 women had implant rupture (27%) with 11 of the 90 women with evidence of extracapsular rupture on MRI (12% of the women; 46% of the 24 ruptures). Thirteen of the 24 women with ruptured implants (54%) had evidence of silicone in the liver, compared to 15 of 51 women without implant rupture (23%), which was statistically significant ($p=0.006$). The authors believe that the positive MRS noted in women with intact implants could be due to gel bleed. Compared to a comparison group of 113 women without implants (62 with a history of breast cancer and 51 with hormone replacement therapy), there were no differences in ANA positivity for the entire group of 90 women with implants. For the patients with evidence of silicone in the liver via MRS, statistically significantly higher levels ($p=0.033$) of ANA positivity were noted (13 of the 28 MRS positive patients) compared to MRS-negative women (15 of 62). With respect to self-reported rheumatic disease symptoms, there were no statistically significant differences between women with intact versus ruptured implants. However, patients with MRS evidence of silicone in their livers complained more frequently of tingling and numbness in the fingers compared to women without MRS evidence of silicone in the liver.

In summary, besides the articles published using the Danish data summarized in items 5 and 6 above, the literature provides limited information on silent rupture progression to symptomatic rupture, intracapsular rupture progression to extracapsular rupture, and health consequences of rupture.

8. Inamed Complaint Database

The voluntary Inamed complaint database indicates 491 ruptures reported for 95,339 implanted between 1993 and 2003. Inamed constructed a curve showing the duration of implantation for each ruptured implant, calculating a KM rupture rate of 4.1% at 10.4 years. The shape of this curve appears linear until 5 years, at which time the curve appears more exponentially shaped. Inamed recognizes that these data rely on voluntary reporting but believes the financial incentives are such that there would not be gross misrepresentation of rupture. *However, because this is based on voluntary reporting and does not include an active follow-up, including*

assessment of rupture, FDA believes these data cannot be used to estimate the rupture rate of Inamed's gel-filled breast implants.

9. Inamed Saline-Filled Breast Implant Data

Inamed referred to their 4-year, by-implant saline-filled breast implant deflation rate of 3.1% for augmentation as comparable to their 4-year, by-implant silicone gel-filled breast implant rupture rate of 1.7% for augmentation. (As a note, the 8-year, by-implant rupture rates for Inamed's saline-filled breast implants are 7.3% for augmentation and 11.7% for reconstruction.)

It should be noted that saline-filled breast implant deflation is almost always symptomatic, while silicone gel-filled breast implant rupture is most often asymptomatic (i.e., silent). In addition to the differences in the materials and design of saline-filled versus gel-filled breast implants, there are significant differences in operative techniques such as incision size (gel-filled implants are pre-filled necessitating a larger incision) and the degree to which surgeons handle the implant during placement (gel-filled implants are handled to a greater extent because they are pre-filled). *Therefore, FDA believes that saline-filled and gel-filled breast implants cannot be compared with respect to rupture because of these differences to estimate the rupture rate of Inamed's gel-filled breast implants.*

10. FDA Analysis of Implant Rupture

FDA's concern was reasonably estimating how the shape of the curve for the percentage of ruptured implants versus time changes over the expected lifetime of the device. For reasons described above, it is not known whether Inamed's extrapolation based on a constant percentage of ruptures per year is accurate. Therefore, for comparison purposes, FDA examined variations from this assumption, namely, models with linearly increasing, and quadratically increasing percentages of rupture per year.

In survival analysis, the probability of an event occurring by a given time, t, is a function of the rate at which events occur at times prior to time t. This occurrence rate is called the hazard rate. In this case, the hazard rate is the rate, or percentage, of ruptures expected to occur during a given year. Note that this percentage may depend on the year. For instance, the percentage of ruptures per year may be higher in year 6 than in year 1, due to fatigue failure of the implant. Thus, it may be possible to express the rate, or percentage, of ruptures per year as some simple function of the year. Different types of these functions, called hazard functions, correspond to different parametric survival models, which can then be used to calculate the probability of the event occurring by a given time. In this case, we would like to calculate the probability of a rupture occurring by year 10.

For the percentage of ruptures per year for symptomatic ruptures, we have 4 data points (derived from the probability of rupture by year 1, the probability of rupture by year 2, etc., through year 4) and for silent ruptures, we have two data points (from the MRI's at years 1 and 3). With this limited data, we must model the behavior of the percentage of ruptures per year through year 10.

We assumed three different ways for the percentage of ruptures per year to behave. One possibility is a constant percentage of ruptures per year for every year, which has already been assumed by Inamed. Another is a percentage of ruptures per year which increases linearly with time, so that the percentage of ruptures per year at year 10 is ten times as large as the percentage

of ruptures per year at year 1. For example, if the percentage of ruptures per year at year 1 is 0.3%, the projected percentage of ruptures per year at year 10 would be 3%. A final, and more extreme, way for the percentage of ruptures per year to behave would be for the rate to increase proportional to the square of time, or a quadratic model. In this case, the projected percentage of ruptures per year at year 10 would be 30%.

The model with constant percentage, or rate, of ruptures per year means that the age of the implant does not affect the occurrence of rupture. That is, the implant does not age. Failure is assumed to be caused by randomly occurring events, the frequency of which does not increase over time. Electronic equipment and computers are representative of devices with failure rates that are essentially constant.

The other two models postulate that the percentage, or rate, of ruptures per year increases as the implant ages. That is, failure is also due to the device "wearing out." In the linear model, the percentage of ruptures per year increases in a linear manner with time and in the quadratic model, the percentage of ruptures per year increases faster and faster with time. For example, the failure rates of equipment that are primarily mechanical in nature (e.g., valves and pumps in automobiles) increase, either linearly or quadratically, as these systems experience fatigue, corrosion, and other cumulative effects.

An important possibility for the behavior of a real-world hazard function is what is called a "bathtub" shaped hazard. That is, the rate of failure starts relatively high, decreases, and then levels out over time, and finally increases as the device ages. An example of such a failure pattern could be death rates over the human life-span in countries with high infant mortality. It is conceivable that a similar model could describe the percentage of rupture per year for breast implants. The percentage of ruptures per year could be initially elevated due to ruptures related to the implant procedure. The percentage of ruptures per year might then decrease and level out and finally begin to increase as the implants wear out. However, with complete data to year 3, it is impossible to fit such a model, which has three distinct stages over the lifetime of the device. For example, most of the percentages per year are not decreasing through year 3. It could be argued that we are still in the initial elevated part of the "bathtub." However, without additional data, it is impossible to know if this is correct. Because of the futility of fitting such a model, we will concentrate on the simpler models of constant percentage of ruptures per year, linearly increasing percentages of rupture per year, and quadratically increasing percentages of rupture per year.

The model arising from a constant percentage of ruptures per year is said to have a constant hazard, and gives rise to what is called the exponential survival model. If the constant hazard is λ, the probability of failure by time t is given by the exponential model as: $P(T \leq t) = 1 - \exp[-\lambda t]$.

The model with a linearly increasing percentage of ruptures per year is said to have a linearly increasing hazard and corresponds to one of the parameterizations of the Weibull survival model. For this model, if the hazard is given as the linear function λt, the probability of failure by time t is given by: $P(T \leq t) = 1 - \exp[-\lambda/2\ t^2]$.

Finally, the model with the quadratically increasing percentage of ruptures per year is said to have a quadratic hazard, and corresponds to another of the parameterizations of the Weibull model. For this model, if the hazard is given as the function λt^2, the probability of failure by time t is given by: $P(T \leq t) = 1 - \exp[-\lambda/3\ t^3]$.
We used these 3 parametric models to attempt to predict the probability that an implant will rupture by10 years. This exercise below will show that that the estimated probability that an implant will rupture by year 10 varies substantially depending on the model we choose for the percentage of ruptures per year. These types of engineering models are usually used to represent data already collected on systems in order to plan on scheduling replacing parts and service schedules. They are not intended to project future failure rates beyond known data. In order to truly make a statistical reliability model of the probability of implant rupture by year 10, it is necessary to collect data through year 10.

In all of our models, we used probabilities from the tables provided by Inamed. The 7 implants deemed confirmed by mammogram, ultrasound, or MRI (6 augmentation and 1 revision) as being intact, as well as the 2 retrieved implants reported by the physician as being intact but identified by the laboratory as being ruptured, are excluded from this analysis.

For symptomatic rupture, the percentages of ruptures per year were calculated by the difference in the probability of rupture from one year to the next. For example, the percentage of ruptures per year in year 3 would be given by the probability of rupture by year 3 minus the probability of rupture by year 2. It is necessary to subtract one year from another because the available probabilities are cumulative. In addition, these probabilities have associated uncertainty, in the form of a 95% confidence interval. We used these confidence limits to arrive at upper and lower bounds for the percentage of ruptures per year for each year. These confidence bounds in turn gave us a 95% confidence interval for the probability of rupture by year 10, but as will be seen, the confidence intervals depend critically upon the correctness of the assumed model (i.e., they vary substantially from on model to another).

For silent rupture, we assumed that the probability of silent rupture by year 2 represented the ruptures detected by the year-1 MRI. This probability was used as the percentage of silent ruptures per year for year 1. Similarly, we assumed the probability of silent rupture by year 4 actually represented ruptures detected by the year-3 MRI. The difference between the probability of silent rupture at year 2 and the probability of silent rupture at year 4 was taken as the percentage of silent ruptures over the two year period from year 1 to 3. Note that this is a 2-year percentage. To combine the silent and symptomatic percentages of rupture per year, we needed the 1-year percentages for silent rupture for each of the four years. We arrived at these 1-year percentages by fitting our various models to the year-1 and year-3 MRI data. For example, we fit a model assuming a constant percentage of ruptures per year to the data, and calculated the one-year rates from this model. Likewise, we assumed linearly increasing percentages of rupture per year and obtained the linearly increasing one-year percentages which best fit the data from the year-1 and year-3 MRI. The same was done for the quadratic model. Note that the procedure included projecting the year-4 percentage of silent rupture from the data through year 3.

Once the 1-year percentages of silent rupture were estimated, they were added to the 1-year percentages of symptomatic rupture to obtain the combined percentages of rupture per year for

years 1 through 4. We again fit our models to this data to find the best fitting constant percentage of ruptures per year, best fitting linearly increasing percentage of ruptures per year and best fitting quadratically increasing percentage of ruptures per year. To fit the model with a constant percentage of ruptures per year, we simply took the average of the percentage of ruptures per year for the four years of data. For the model with linearly increasing percentages of ruptures per year, we used SAS PROC REG to fit a line to the four data points consisting of the percentages of ruptures per year for years 1 through 4. Similarly, for the model with quadratically increasing percentage of ruptures per year, we used SAS PROC REG to fit a model proportional to the square of time. In both of the latter two models, the line and curve were forced to go through zero. This is equivalent to assuming there were no ruptures detected at the time of implant.

Graphs of the best fitting lines and curves for the percentages, or rates, of rupture per year are shown below for the augmentation cohort.

Figure 1a. Best fitting constant percentage for data through year 4.

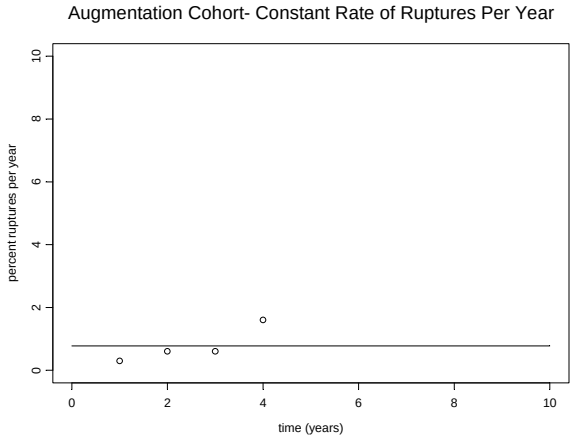


Figure 1b. Best fitting linearly increasing percentages for data through year 4.

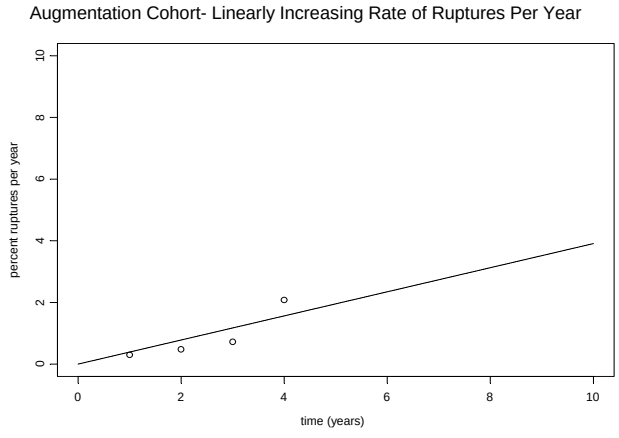
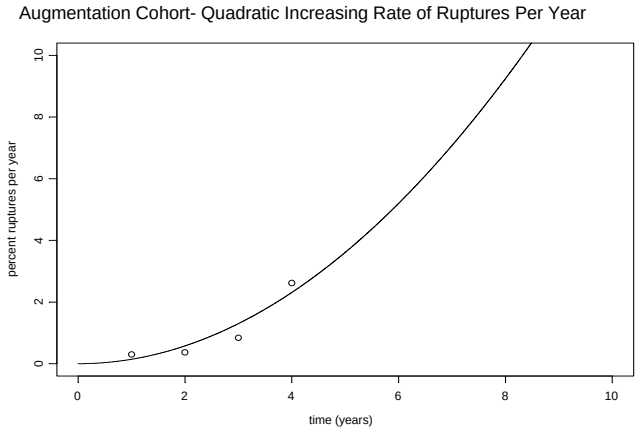


Figure 1c. Best fitting quadratically increasing percentages for data through year 4.



As can be seen from the graphs, the model with quadratically increasing hazard appears to have the best "fit." Note, however, that the percentage of symptomatic rupture for year 4 was influential, but was based on incomplete data (74 out of 331 implants). In addition, the year-4 data for silent ruptures was a projection of years 1-3 according to each of the models. The following three graphs show the best fitting models excluding the year 4 data.

Figure 2a. Best fitting constant percentage for data through year 3.

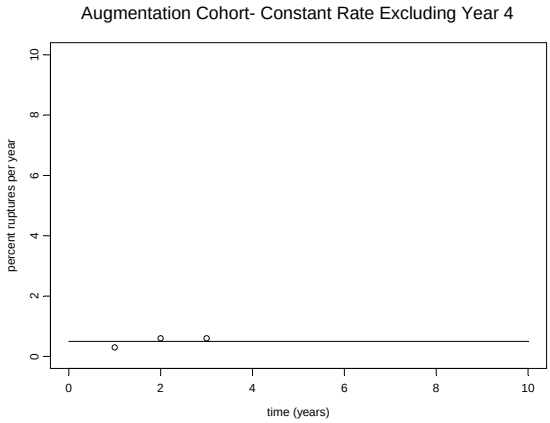


Figure 2b. Best fitting linearly increasing percentages for data through year 3.

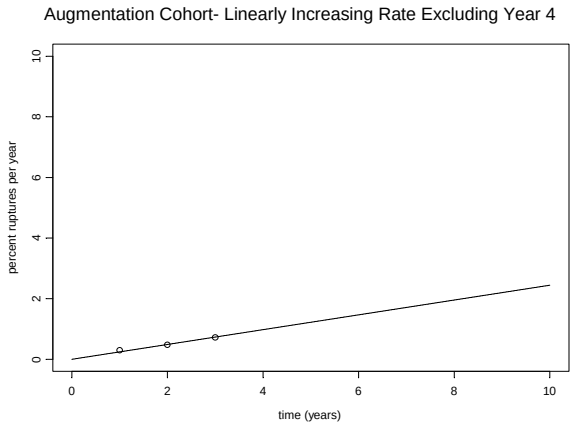
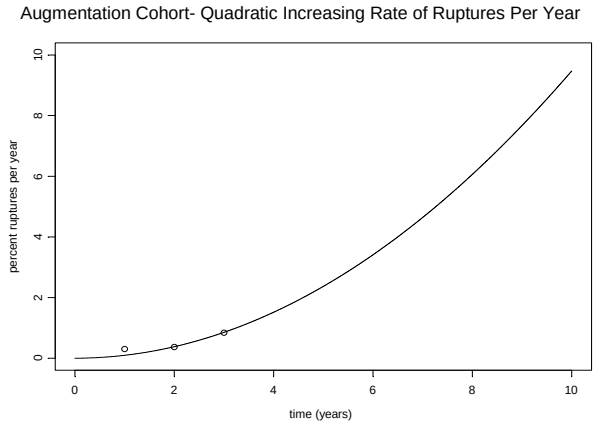


Figure 2c. Best fitting quadratically increasing percentages for data through year 3.



As can be seen from these latter graphs, it is difficult to tell which model is more appropriate. With three data points, each of the models appears to have a near perfect "fit." Note that the data points vary slightly from graph to graph. This is because we had to impute two 1-year percentages from the year 3 MRI data. That is, the 1-year percentages of rupture per year at years 2 and 3 were not known individually, and were calculated according to each of the models so that the total equaled the 2-year percentage observed with the year-3 MRI. This means we imputed different year-2 and year-3 percentages of silent rupture per year depending on whether we assumed constant, linearly increasing, or quadratically increasing percentages of silent rupture per year. All of this illustrates the difficulty of predicting the percentage of ruptures per year having silent rupture data from the year-1 and year-3 MRI. Moreover, the true long-term behavior of the percentage of ruptures per year is essentially unknown, and thus it is not possible to predict the probability of experiencing a rupture by year 10 with any certainty.

To illustrate the magnitude of the uncertainty in the long-term risk of rupture, we present the results in Table 10 below. As mentioned previously, the confidence intervals were derived from the 95% confidence intervals for the probability of rupture by a given year. That is, the upper and lower confidence limits for these probabilities were used to derive upper and lower confidence limits for the percentages of rupture per year. Constant, linearly increasing, and

quadratically increasing models were then fit to the upper and lower limits of the percentages of rupture per year to arrive at upper and lower limits for the probability of rupture by year 10.

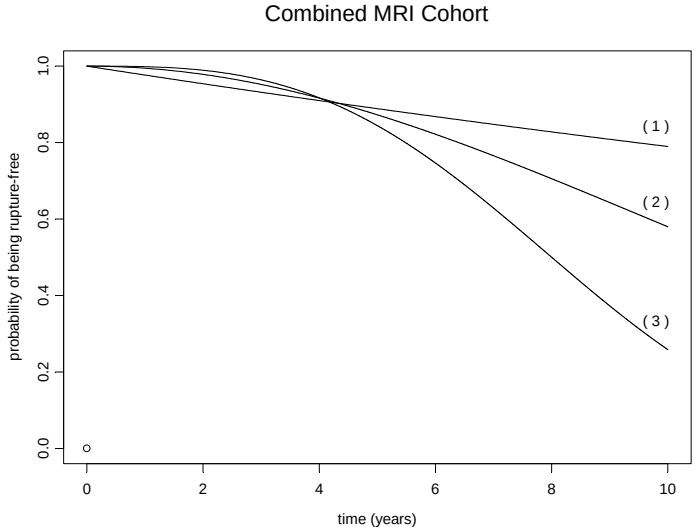
Table 10: Probability of Implant Rupture through 10 Years for MRI Cohort (Silent and Symptomatic) for 3 Models.

Model:	**Constant hazard**	**Linearly increasing Hazard**	**Quadratically increasing hazard**
Augmentation	7.5% (0.0, 16.3)	17.8% (0.0, 35.2)	38.2% (0.0, 64.4)
Reconstruction	38.9% (22.1, 52.9)	66.5% (45.7, 80.0)	93.0% (79.4, 97.7)
Revision	18.1% (6.1, 28.3)	35.9% (16.1, 49.7)	66.4% (38.2, 80.1)
Indications combined	21.0% (13.1, 28.8)	42.0% (29.1, 53.4)	74.2% (59.1, 84.3)

As can be seen from the table above, there is a dramatic difference in the estimated probability of rupture by 10 years depending on which model is assumed for the percentage of ruptures per year. Again, there is no purely statistical way of knowing which model fits better with the data provided.

Note that the spread of the estimates is extreme. For the combined MRI cohort, estimates of the probability of rupture by year 10 range from about 21% to 74%. Figure 3 below shows the survival curves for probability of rupture in the combined MRI cohort for the three different models we have examined.

Figure 3. Probability of being rupture-free for 3 different models of percentage of rupture per year.



(1) Constant percentage of ruptures per year
(2) Linearly increasing percentage of ruptures per year
(3) Quadratically increasing percentage of ruptures per year

Figure 3 shows the large difference in probability of experiencing a rupture given our three different models. Note that this figure does not include the confidence bounds.

Thus, the uncertainty is truly even larger. This uncertainty is the result of having 3-year and partial 4-year data for symptomatic rupture and data from years 1 and 3 for silent rupture. This is compounded by lack of retrieval study data regarding long-term failure modes and causes. It is difficult, therefore, to reasonably predict the probability of rupture through year 10 with the available data.

11. Summary

FDA conveyed three main issues with regard to rupture in the 1/7/04 not-approvable letter:

(1) What is the rupture rate over the lifetime of the device?

(2) When an implant does rupture, what is the incidence of intracapsular, extracapsular, and migrated gel, and what is the progression from intracapsular to extracapsular to migrated gel?

(3) What are the health consequences of implant rupture?

Inamed provided information primarily from their Core Study, their Adjunct Study, Danish literature data, and other literature to address these rupture issues.

Regarding the Inamed's Core Study data:

- The data consists of complete 3-year and partial 4-year data. For the reasons discussed above, it is difficult to reasonably predict the probability of rupture through year 10 with the available data.

- The data are of limited value to address the local health consequences of rupture due to the small number of patients with confirmed ruptures and because all patients had not yet had follow-up after rupture.

- The majority of silicone gel-filled breast implant ruptures are silent and detected only via MRI.

- Based on the MRI Cohort from the Inamed Core Study, the by-patient 4-year rupture rate is 3.4%, 20.5%, and 10.9%, respectively for augmentation, reconstruction, and revision patients. This rate is based on complete 3-year and partial 4-year data. This rate excludes ruptures which were noted on microscopic evaluation but not at the time of explant. This rate also excludes implants in which rupture was noted at the first but not the second MRI.

Regarding the Inamed's Adjunct Study data:

- Given the low follow-up rate in the Adjunct Study and the lack of screening for silent rupture, the Adjunct Study data are of limited value to characterize the rupture rate, rupture rate over time, and the health consequences of rupture because of the under-ascertainment of rupture and inadequate patient follow-up.

Regarding the Danish literature data:

- The Danish literature data are currently a major source of information to characterize the incidence of intracapsular rupture and extracapsular rupture, the progression of intracapsular

rupture to extracapsular rupture, and the local health consequences of implant rupture. However, it does not completely address all the health consequences of rupture.

- It includes data from several manufacturers and is not specific to Inamed implants.

- It provides information on the prevalence and incidence (over 2 years) of augmentation implant rupture; however, it is of limited value to characterize the rupture rate and rate over time of the Inamed implants because the data are not specific to the Inamed implants.

- For augmentation implants with a median duration of implantation of 12 years (range 3-25 years) which were not explanted in at least the first 3 years, the point prevalence of rupture is 36% if both definite and possibly ruptured implants are considered.

- The proportion of extracapsular ruptures of the total is approximately one-fourth.

- There is progression of silicone seepage in 11% of ruptured implants within 2 years, with some instances attributable to trauma while others seemed spontaneous.

- Approximately 10% of intracapsular ruptures progress to extracapsular rupture in 2 years.

- Women with evidence of extracapsular rupture on MRI were 6 times more likely to report breast hardness than women with intact implants (OR 6.3, 95% CI 1.7-23.5). Although not statistically significant, women with extracapsular rupture were 3 times more likely to report a connective tissue disease (OR 3.8, 95% CI 0.4-35.1), 2 times more likely to report pleuritis (OR 2.2 95% CI 0.1-39.4), and 1.7 times more likely to report fatigue (OR 1.7, 95% CI 0.5-5.9) than women with intact implants, when adjusted for age, placement, and type of implant.

- Women with ruptured implants were 2 times more likely to report non-serious pain to the affected breast (odds ratio 2.1; 95% CI 1.2 to 4.2) compared to women with intact implants.

- The Danish literature data describes a rupture incidence rate for definite or possible ruptures of 8.9 ruptures per 100 implants per year (95% confidence interval 6.6 – 11.3). Based on the ASPS website, there were about 250,000 augmentation patients voluntarily reported as having breast augmentation just in the year 2003, with an average increase of 10% per year since 2000. Assuming that augmentation patients have bilateral implants at the incidence reported in 2003, that would be 500,000 augmentation implants per year. If half of the augmentation mammoplasties reported in 2003 would be with gel-filled implants if approved (this is probably an underestimation), there would be 250,000 silicone gel-filled augmentation implants per year. Of these 250,000 silicone gel-filled implants per year, using the Danish literature data (i.e., 9 ruptures per 100 implants per year), one could expect at least 22,500 implant ruptures per year in augmentation patients.

Regarding other literature:

- In addition to the Danish literature data, there are case reports in other literature describing health consequences of rupture. However, this literature does not completely address all health consequences of rupture, and the literature is not specific to Inamed implants.

B. MODES AND CAUSES OF RUPTURE

In the original PMA presented to the October 2003 Panel, Inamed provided findings from an explanted device retrieval study. However, the October 2003 Panel and FDA found that the retrieval study was inadequate to characterize the modes and causes of rupture of their device.

In response to the 1/7/04 not-approvable letter, Inamed provided the following test results and information to address the modes and causes of rupture of their device:

(1) independent re-analysis of [redacted] retrieval data
(2) new retrieval report on Adjunct and Core Study devices
(3) Inamed's addendum to [redacted]
(4) analysis of in-vivo physical property data on subset of retrieved devices
(5) effect of autoclave disinfection on physical properties
(6) effect of bleach and autoclave disinfection on physical properties
(7) effect of cutting die size on physical properties
(8) effect of extraction on physical properties
(9) effect of surgical/manufacturing process on accelerated fatigue performance
(10) effect of pre-stress on tensile properties
(11) shelf life study showing effect on physical properties
(12) lipid effects on physical properties [redacted]
(13) assessment of manufacturing processes, including [redacted] Plan
(14) assessment of surgical techniques, including faculty questionnaire
(15) literature review.

This memo includes a detailed summary of only the first two test reports above, which are the ones that detail the failure modes of Inamed's retrieved explanted devices. However, the key outcomes from other tests and information provided in their August 2004 submission are briefly summarized as well.

As a note, in the original PMA submission, Inamed provided a retrieval study report ([redacted]. In their August 2004 submission, they provided an addendum to that report. The addendum to [redacted] did include failure mode data. Instead, it focused on the 113 devices with complaints, which is a subset of the data described in the independent report below. Thus, Inamed's addendum to [redacted] is not summarized in this review memo.

1. Independent Re-Analysis of the Inamed Explanted Device Retrieval Study Report [redacted]

Inamed contracted with [redacted], to perform an independent review of Inamed's retrieval report, [redacted] which was originally presented to the October 2003 Panel. The [redacted] study included 339 silicone gel breast implant devices retrieved between 7/31/00 and 10/1/02. This included 10 devices from the Core Study and 141 devices from the Adjunct Study, which comprised 45% of the 339 implants in the retrieval study. The remaining 188 (55%) devices were either implanted earlier, when the devices were legally marketed, were returned unused due to an intraoperative observation, or were of unknown origin (e.g., no serial number could be identified to link to a study).

The purpose of re-analysis was to determine if any new information regarding modes and causes of rupture could be determined from these explanted devices. was given copies of manufacturing documents, raw complaint data tables, the original micrographs obtained by optical microscopy that Inamed used to originally classify the modes of failure, and other documents necessary to re-analyze the original report . asked Inamed to generate schematics of the anterior and posterior sides of ruptured explanted shells from the original report. In addition, after review of micrographs, asked Inamed to repeat optical microscopy analysis for many failed shells. then re-analyzed the improved micrographs. This iteration process continued until was satisfied that he could determine the modes of failure from the available micrographs. He used the final set of micrographs, often in combination with the shell schematics, to determine the modes of failure for 55 shells. For the 72 devices for which micrographs were not obtained, the failure mode for most of these were determined by Inamed visual inspection in conjunction with review of the shell schematics. For some of these cases, optical microscopy was used in the analysis, but micrographs were not taken.

recommended that scanning electron microscopy (SEM) be used to confirm or refute questionable failure sites/modes determined by optical microscopy. SEM analysis was not performed for all failed devices. Instead, SEM was used for a selected number of failed devices that did not have extensive openings. (Extensive openings would take an inordinate length of time to analyze by SEM.) The SEM analysis was consistent with the optical microscopy findings.

There were 339 devices in the original report which were re-analyzed using optical microscopy, SEM, shell schematics, and/or information obtain during review. The 339 devices were re-classified as follows:

Re-classification of Retrieved Devices	**N=339**	**Device Status**
Functional[1]	158	Intact
Gel-related observation[2]	40	Intact
Surface-related observation[3]	9	Intact
Bladder separation only for Style 153	1	Intact
Posterior sharp edge opening for Style 153	39	Failed/ruptured
Surgical instrument damage	36	Failed/ruptured
Fold flaw failure	6	Failed/ruptured
Manufacturing	6	Failed/ruptured
Sharp edge opening *(cause unknown)*	24	Failed/ruptured
Style 82 which is not under PMA review	2	Excluded from analysis
Unable to locate device for re-analysis	2	Excluded from analysis
Unable to analyze[4]	16	Excluded from analysis

[1]Devices with intact shells and no gel or surface-related observations.
[2]Devices with intact shells but noted observations for gel, such as bubbles or particles.
[3]Devices with intact shells but noted observations for shell surface characteristics (e.g., scalloping around radius, dimpling of implant).
[4]Pieces of the failed shell were missing, the shell was fragmented into extremely small sizes, or the patient requested that the device not be altered.

As shown in the table above, there are 208 devices that are intact and 20 excluded for different reasons. This leaves a total of 111 failed/ruptured devices available for analysis. The table below summarizes the number and percentage of the different failure modes based on the 111 failed devices.

Failure Mode	N (% of 111)
Posterior sharp edge opening for Style 153	39 (35%)
Surgical instrument damage	36 (32%)
Fold flaw failure	6 (5%)
Manufacturing	6 (5%)
Sharp edge opening *(cause unknown)*	24 (22%)

Of the 111 failed devices, Inamed provided the following table summarizing the average (and range) of in-vivo years for each given failure mode (for those devices with a reported in-vivo time).

Failure Mode	N	Ave (Yrs)	Range (Yrs)
Posterior sharp edge opening for Style 153	36	4.23	0.19 - 9.47
Surgical instrument damage	30	2.35	0 - 10.48
Manufacturing	6	8.98	2.28 - 12.35
Fold flaw failure	3	14.00	9.65 - 18.73
Sharp edge opening *(cause unknown)*	24	7.15	0 – 19.55

Of the 111 failed devices examined by [redacted], Inamed clarified that one had multiple failure modes. One device had striations (indicative of surgical damage) and a manufacturing defect. [redacted] classified this as a manufacturing failure mode. In addition, no correlation to the location of a rupture was found for any other given failure mode (except for those specific to Style 153).

The following is a discussion of failure modes identified by [redacted]:

- **Posterior sharp edge opening for Style 153 failures** are sharp edge openings on the posterior side of the implant that originates near lower patch (typically above bladder/shell bond). This failure mode is unique to Style 153 because Style 153 has a specific patch design that bonds with the inner lumen.

- **Fold flaw failures** are creases or wrinkles in shell at opening with or without abrasion/flex fatigue on inside or outside surfaces. The morphology of fold flaw can appear in several forms. [redacted] stated that Inamed's re-analyzed devices showed 3 different fold flaw forms:

    - shell abrasion about a small pinhole
    - shell wear generated a small pinhole with surrounding wear abrasion, which is located on a very large tear
    - small hole developed into large crease due to flex fatigue but no interior/exterior shell abrasion.

- **Manufacturing failures** are defects created a local weakness that may have contributed to rupture. [redacted] stated that Inamed re-analyzed devices showed 3 different types of manufacturing defects:
    - Thin spot – untextured shell thickness is very thin locally and below manufacturing specifications.
    - Layer separation – 2 or more layers locally separated
    - Divot – small indent on inside of shell that appears as a shiny spot on a micrograph (shiny because parallel machining line [redacted] are not there) which progressed into a tear

- **Surgical failures** are opening caused by surgical technique, including shell damage by instrument or implantation procedure. Contact with the instrument can cause a tear through the entire shell thickness, or minor contact with the instrument can cause a microscopic flaw in the shell surface that eventually results in shell rupture in-vivo. The implanting technique of forcing an implant through a small opening into the breast pocket can result in similar damage to the shell. [redacted] found that the morphology and location of these failures varied considerably. For these devices, [redacted] believes that the devices were damaged during implantation but went unnoticed. The device was then subjected to in-vivo loading due to daily activities. The loading on the device in the vicinity of the flaw cause it to propagate into a tear. Although [redacted] discussed surgical damage during implantation (forcing the device into a small pocket), this type of damage was not identified in his re-analysis of the retrieval study data. Only surgical instrument damage was identified in his re-analysis.

- **Sharp edge opening failures** show no sign of fold, abrasion, flex fatigue, manufacturing defect, or surgical instrument damage at opening. The cause(s) of these sharp edge openings are unknown. [redacted] stated that it may be due to a microscopic flaw induced in the shell during implantation or produced in the shell during manufacturing. The flaw then develops into a tear after in-vivo loading.

The retrieval study, [redacted], also incorporated a materials property analysis of the explanted devices. The study included ultimate break force, ultimate elongation, patch joint, and bladder joint (Style 153 only) testing, stratified by smooth and textured styles. The original testing involved 32 smooth and 37 textured devices. The original data showed no difference in the mechanical properties of failed and non-failed devices for both smooth and textured devices.

[redacted] performed an independent review of the material property testing previously conducted by Inamed. [redacted] analyzed the mean and median ultimate break force, ultimate elongation, tensile strength, and 200% modulus data, as well as material property values at the shell radius. After review of the material property raw data, [redacted] excluded 1 smooth device because of its reliability due to slippage in the grips and excluded another 11 smooth and 12 textured devices for not having available in-vivo times. Therefore, [redacted] re-analysis involved 20 smooth and 25 textured devices, and, of these, 2 of the smooth devices and 7 of the textured devices were ruptured. The in-vivo implantation time for the majority of the samples was 0 to ≈3 years.

- For the smooth devices analyzed, [redacted] stated that there was no time-dependent degradation in average shell strength. It is important to note that the time period for

implantation for the majority of these devices in this analysis was only 0-3 years. In addition, the explant samples fell within the range of control (i.e., Final Product Release Testing) data, and all data met or exceeded ASTM standards. There was no difference in the properties of intact and failed shells. The properties were fairly uniform around the shell.

- For the textured devices, stated that the ultimate break force, elongation, and tensile strength tended to fall below the control data as a function of increased in-vivo time. However, the 200% modulus was within the control data range. therefore, concluded that only the upper portion of the stress-strain curve for the textured devices is affected by implantation (i.e., based on ultimate physical properties at lower or below control range), which indicates that neither swelling or in-vivo aging affects the lower portion (i.e., based on constant moduli results over time). explained this reduction in shell strength properties, but a constant modulus, as due to the diffusion of non-crosslinked silicone from the gel into the shell. Despite the effect of swelling, all of the shell strength property data are "essentially" above the ASTM standards.

In summary, identified the modes and causes of rupture for 87 (78%) of the 111 failed devices included in the original explanted device retrieval study. For an additional 24 (22%) devices, identified the mode of failure (i.e., sharp edge openings) but could not determine the cause of the opening. Along with other testing, recommended additional research to identify the failure mechanisms (i.e., cause of rupture) for the devices with sharp edge openings. re-analysis of the material property data also indicated that degradation of the in-vivo shell strength was not responsible for shell failure, at least through 3 years.

2. 2004 Retrieval Program Report

In response to the 1/7/04 not-approvable letter, Inamed also conducted a new retrieval study of explanted devices. The purpose of the retrieval study was to analyze returned devices to identify and investigate failure modes. This report presents the results from the retrieval program for all Core and Adjunct Study devices received in the laboratory through 3/31/04.

Of the >80,000 devices implanted in the Core and Adjunct Studies, 442 were returned to Inamed and analyzed prior to 3/31/04. Of these 442 devices analyzed in 402 were from the Adjunct Study and 40 were from the Core Study.

Inamed stated that the analyses in were performed following recommendations. The analyses included visual inspection, microscopic inspection, review of micrographs, review of schematics, and/or physical property testing. The table below provides the device classifications for the 442 devices.

Classification of Retrieved Core and Adjunct Study Devices	N=442	Device Status
Functional[1]	244	Intact
Gel-related observation[2]	35	Intact
Surface-related observation[3]	8	Intact
Surgical damage[4]	63	Failed/ruptured
Posterior sharp edge opening for Style 153[5]	48	Failed/ruptured
Surgical impact[7]	5	Failed/ruptured
Manufacturing[8]	4	Failed/ruptured
Bladder separation only (Style 153)[9]	2	Failed/intact
Fold flaw failure[10]	1	Failed/ruptured
Sharp edge opening *(unknown cause)*[6]	12	Failed/ruptured
Unable to analyze[11]	20	Excluded from analysis

[1]Devices with intact shells and no gel or surface-related observations.
[2]Devices with intact shells but noted observations for gel, such as bubbles or particles.
[3]Devices with intact shells but noted observations for shell surface characteristics (e.g., scalloping around radius, dimpling of implant).
[4]Devices with openings attributed to damage caused by surgical instruments.
[5]Devices with opening in vicinity of lower patch, specific to Style 153.
[6]Devices with sharp edge openings that are not associated with thinning of shell as a result of fold flaw or do not have characteristics consistent with surgical damage. In other words, the cause of the opening could not be determined.
[7] showed that physical properties can be affected by localized stresses induced by the implantation procedure. There were 5 that showed evidence of localized stressing based on the same shift in the stress-strain curve as found in
[8]Includes 1 device that was assembled using the incorrect shell causing a discrepancy in the product dimensions and 3 devices with divots inside shell
[9] Device with inner lumen detached. Although the outer shell was intact, the inner lumen was free-floating.
[10]Devices with openings where shell has been creased, which Inamed attributes to improper pocket size or improper position in the pocket. Results from thinning of the shell from the shell abrading on itself causing eventual rupture.
[11]Pieces of the failed shell were missing, the shell was fragmented into extremely small sizes, or the patient requested that the device not be altered.

The table below provides the failure modes for the 135 failed/ruptured devices, stratified by style:

Failure Modes	Styles							
	10	20	40	45	110	120	153	Total
Surgical damage (instrument)	1	3	10	10	14	7	18	63 (47%)
Posterior sharp edge - Style 153 only							48	48 (36%)
Surgical impact (localized stress)				1	4			5 (4%)
Manufacturing			1		1		2	4 (3%)
Bladder separation for Style 153 only							2	2 (1%)
Fold flaw failure			1					1 (1%)
Sharp edge opening *(unknown cause)*			3		5		4	12 (9%)
Total for style	1 (1%)	3 (2%)	15 (11%)	11 (8%)	24 (18%)	7 (5%)	74 (55%)	135 (100%)

For the ruptured devices for which in-vivo times were available, Inamed provided the following table summarizing the average and range of in-vivo years, stratified by failure mode:

Failure Mode	N	Avg (Yrs)	Range (Yrs)
Surgical damage	61	1.92	0 – 5.08
Posterior sharp edge for Style 153 only	46	2.55	0.09 – 5.13
Surgical impact	4	1.15	0.12 – 2.52
Manufacturing	4	2.03	0.44 – 3.02
Fold flaw failure	1	0.26	0.26
Sharp edge opening *(unknown cause)*	12	1.42	0.07 – 3.97

In summary, Inamed identified the modes and causes of rupture for 123 (91%) of the 135 failed devices. For the remaining 12 (9%), Inamed identified the mode of failure (i.e., sharp edge openings) but could not determine the cause of the opening.

Inamed stated that, although the location of failure is not part of their retrieval program, they examined this and found no correlation to the location of a rupture for any other given failure mode (except for those specific to Style 153). Therefore, no other correlation was discussed in this report.

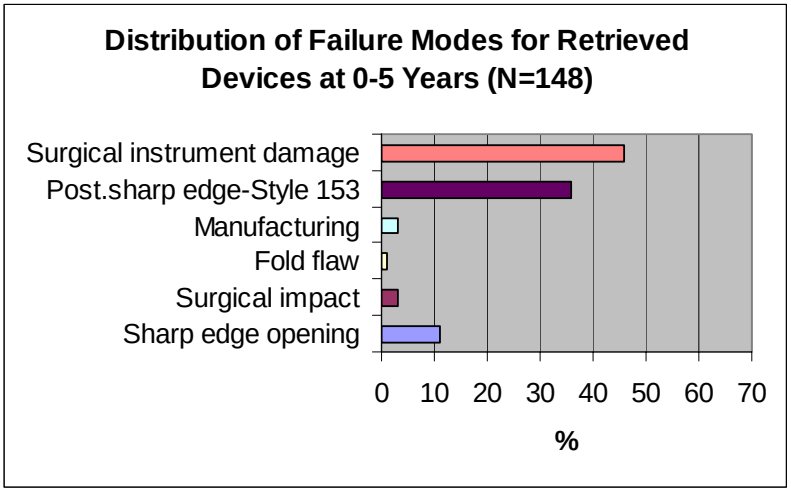
3. Supplemental Analysis of Two Reports

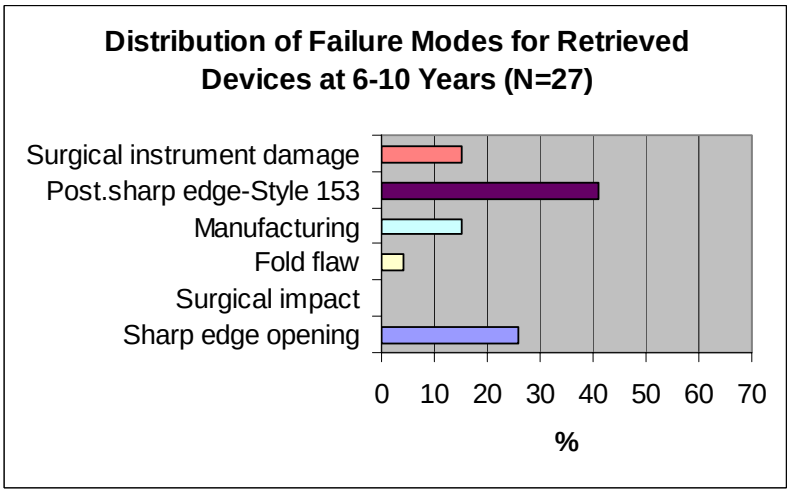
The data from the two reports above cannot determine the time at which a given failure mode will occur because the data are based on only a small collection of retrieved implants that were available for analysis. The data can, however, be used to present the distribution of device failure types observed in this sample at particular time frames. Accordingly, this section presents a different analysis of the retrieved ruptured devices from the two reports above, with duplicate devices removed. The analysis also focuses on only those ruptured devices with reported in-vivo times.

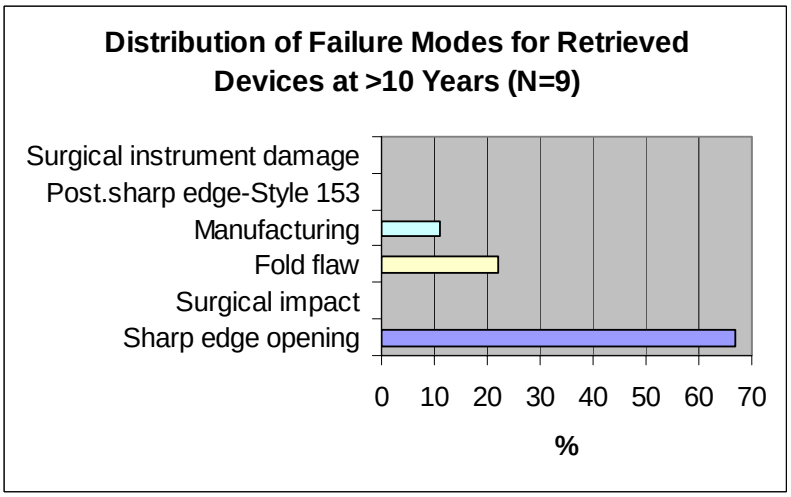
The table below summarizes the number and percentage of retrieved devices (n=184) from the two studies discussed above that were observed with the specified failure mode.

Failure Mode	# (%) of Retrieved Devices Ruptured During Specified In-vivo Time		
	0-5 years	6-10 years	>10 years
Surgical instrument damage	68 (46%)	4 (15%)	0 (0%)
Posterior sharp edge - Style 153 only	54 (36%)	11 (41%)	0 (0%)
Manufacturing	4 (3%)	4 (15%)	1 (11%)
Fold flaw failures	1 (1%)	1 (4%)	2 (22%)
Surgical impact	4 (3%)	0 (0%)	0 (0%)
Sharp edge opening *(unknown cause)*	17 (11%)	7 (26%)	6 (67%)
Total	148 (100%)	27 (100%)	9 (100%)

The following bar graphs reflect the percentage (or distribution) of the failures modes from the table above.







4. Other Testing and Information

Changes in crosslink density are used as a measure of assessing chemical degradation. Inamed assessed the crosslink density of several samples under various conditions, such as after pre-stressing, extraction/swelling, and/or mechanical testing. No significant changes were observed.

There was a significant reduction in fatigue device performance when devices were subjected to simulated surgical procedures (local stress and pin hole damage) followed by accelerated fatigue.

Inamed's testing showed that the effect of lipid infiltration or diffusion of non-crosslinked silicone did not adversely effect the finished sterile device testing.

The literature showed that a major factor impacting shell integrity was surgical damage, which is consistent with Inamed's testing. The literature discusses localized weakening of the implant caused by the surgeon's fingers placing pressure on a specific area of the device during implantation.[11,12] One of Inamed's report showed that stress at low elongations can permanently affect the shell's physical properties in the strained regions. The literature is conflicting with regard to whether or not mechanical strength of the shell decreases over time. Some investigators found a correlation[13,14,15], while others found no significant difference.[16,17] Inamed's testing showed that the physical properties do not change over the reported in-vivo times. In terms of chemical/physical composition of the shell, the literature showed that the in-vivo migration of lipids from surrounding tissues into the shell, with a lower rate of lipid infiltrations for 3rd generation and textured implants.[18,19] However, the literature showed no relationship between lipid infiltrations and decreased tensile strength of shells. In addition, literature studies also show that diffusion of non-crosslinked silicones from implant filler into shell impacts strength.[20,21] However, some investigators believe that there is an initial decrease in properties due to the diffusion of non-crosslinked silicone from the gel into the shell, followed by equilibrium with the first few years and that there is no change in shell chemistry or that this swelling is a risk factor for rupture.[11,17,22,23,24]

5. Inamed's Proposed Next Steps Based on Findings

This section summarizes Inamed's proposed changes to the design, manufacturing, or labeling, as well as any additional analyses that they intend to perform based on the findings of their modes and causes of rupture analysis.

- Inamed is investigating the samples with sharp edge openings to determine any commonality.
- To address the numerous posterior sharp edge openings of Style 153, Inamed is in the process of modifying the design of Style 153
- With regard to manufacturing-based failures, Inamed modified one manufacturing process

- Inamed is researching whether there is a correlation between surgical factors (e.g., incision size, incision location, and implant placement) and device rupture.

- Inamed stated that modes and causes of rupture findings will be incorporated into their physician education/training.

6. Summary

Through their explanted device retrieval studies, Inamed provided information regarding the modes and causes of rupture for devices implanted for a range of in-vivo times.

Failure modes associated with surgical technique include: (1) sharp instrument damage that causes immediate or subsequent rupture; (2) localized stress that causes weakening in shell; and (3) creation of fold during implantation that leads to abrasion and subsequent rupture.

The retrieval study data above show that the observed failures at the earlier timepoints were due to surgical instrument damage. Inamed stated that the longer-term failures attributed to surgical damage could have been due to a delayed intraoperative damage, explantation instruments, or instruments used during in-situ procedures (e.g., cyst biopsy). Inamed also clarified that, although a retrieval study analysis may be able to determine whether an implant was damaged by a surgical instrument, one cannot determine, with certainty, when it occurred. Therefore, it is possible that the failures due to surgical damage that were observed in devices implanted for longer time periods may have occurred at the time of implantation and were just not detected, or they may have occurred later, as a result of an invasive procedure that was performed after implantation surgery.

As noted above, numerous ruptures were observed in Style 153 implants. Inamed has proposed a device modification that they believe should reduce the ruptures due to this unique failure mode.

With regard to manufacturing failures, Inamed noted that 6 devices had failures attributed to manufacturing defects. Inamed stated that, in their opinion, manufacturing-based failures are rare and are not related to current quality control measures. Accordingly, Inamed did not test whether changes in the device manufacturing would have any effect on the failure modes.

With respect to fold flaw failures, the mechanism by which it occurs is described to be a crease or wrinkle in the shell that, under in-vivo cyclic loading, eventually leads to a shell opening. However, the data show scattered timepoints for development of the fold flaw failures. While literature reports that the surgical implantation procedure may induce a fold in the implant, it is not known for certain whether the reported fold flaw failures were originally caused by the surgical implantation procedure or some other unknown factors that lead to the development of the fold.

With respect to the failures due to sharp edge openings, Inamed stated that they do not know the cause of this failure mode and it is currently under investigation. They stated that it is possible that the sharp edge opening failures that occurred at later time periods may have been due to cyclic failures, such as fold flaw. Inamed stated that they were in the process of obtaining explanted devices with longer-term in-vivo dates and performing material and chemical property testing on them to evaluate this issue

The issue of when pure cyclic fatigue occurs remains unanswered. The current data do not show devices rupturing from pure cyclic fatigue. However, Inamed has not provided information to explain how they would be able to determine cyclic fatigue as a failure mode in a retrieval study. In addition, they have not provided physical or chemical property testing on materials from failure areas on devices that were subjected to fatigue testing. Therefore, it remains unknown whether or not there is physical or chemical property degradation that may lead to the cyclic fatigue and eventual rupture of the devices. Instead, Inamed states only that cyclic failure is due to mechanical stress leading to pinpoint failure. *Assuming that devices will eventually fail from cyclic fatigue, Inamed will need to determine how to characterize this failure mode and will need to estimate when failure due to cyclic fatigue may occur over the expected lifetime of the device. In addition, until retrieved devices are observed to be ruptured due to pure cyclic fatigue, the appropriateness of a fatigue test methodology cannot be assessed.*

FDA believes that Inamed provided adequate information to characterize the modes and causes of rupture of their device through ≈10 years. However, the modes and causes of rupture information cannot be correlated to the in-vivo lifetime of the device. The tests were set up to test hypotheses about failure modes, to force failures, and/or to perform device characterizations of a subset of explanted devices returned to Inamed for analyses. Continued retrieval studies and long-term clinical data will be necessary before a validated correlation could be made.

C. INAMED'S POSTAPPROVAL PLANS

At the October 2003 Panel meeting, Inamed's proposed Core postapproval study protocol was determined to be inadequate by the Panel. Inamed had proposed a 2-phase postapproval study. Phase I involved patients continuing with their evaluations as per the current protocol through their 5-year evaluation timepoint. Phase II involved a Post-Approval Survey Study for continued follow-up from 6-10 years using mail-in surveys reporting the status of the implants for selected critical safety outcomes, as well as patient satisfaction.

During the October 2003 Panel meeting, Inamed described additional postapproval plans that they propose to develop, should their device be approved. The Panel then discussed Inamed's proposal and made several recommendations, including a Core postapproval study that required physician follow-up through 10 years and a patient registry that collected data on CTD, rupture, the status of offspring of women implanted with the devices, and the status of women after explantation, as well as other clinical endpoints. The Panel also recommended that Inamed be required to develop a physician education and certification program. These issues were included in Inamed's 1/7/04 not-approvable letter. Below are Inamed's August 2004 responses to the 1/7/04 not-approvable letter requesting them to provide more detailed postapproval plans that address these cited issues.

1. Core Postapproval Study

Inamed's revised protocol, **Investigator Brochure Addendum: Postapproval Study**, is a modification of the existing IDE study protocol. As per the current IDE study protocol, the patients will continue to be evaluated by their physicians annually through 10 years. The MRI cohort will also continue to include evaluations at the remaining 5, 7, and 9-year timepoints, without enrolling additional patients into the MRI Cohort. While there were minor modifications made to the protocol and its attachments, the following are the primary differences between the IDE study protocol and the proposed postapproval study protocol:

- Patients who are explanted without receiving replacement implants will be followed via a telephone survey instead of being discontinued from the study.

- Inamed removed the requirement to complete the QoL questionnaire at years 6, 8, and 10. Inamed does not believe that this questionnaire provides useful data this far postoperatively because there are so many other factors that play into the patient's life. Instead, Inamed believes that the information on the postoperative case report form, which includes patient satisfaction with implant results and reasons for dissatisfaction, is more useful in judging the potential impact upon patients with breast implants.

Inamed described the measures that they plan to take to maintain study compliance. These include telephone calls and faxed reminders to clinical sites, monthly monitoring of the number of patients overdue for visits, utilizing a professional search company to locate patients who moved, and providing financial incentives to patients and investigators.

2. Patient Registry

Inamed's current breast implant registry does not collect prospective data, but, instead, collects device serial and catalog numbers, patient indication and date of implantation, physician contact information, and patient contact information at the time of surgery for patients who receive their silicone gel product.

Inamed presented their patient registry at the October 2003 Advisory Panel meeting. The Panel recommended several changes be made to the registry, including the collection of clinical data, such as clinical outcomes after device explantation, lactation and reproductive adverse events, and second-generation effects in children of women who receive their silicone gel breast implants.

In their August 2004 response, Inamed provided their rationale why they do not believe development of a comprehensive outcomes registry in the U.S. is feasible. Instead, Inamed proposes to address the issues raised by the Panel in the following ways:

- collect data on Core Study patients out to 10 years with the addition of telephone follow-up of explanted patients and removal of the QOL questionnaire after year 4

- obtain data from Danish Breast Implant Registry (see below for details)

- link Inamed's registry with its rupture warranty programs that provide financial incentives to report events, such as rupture. This will allow Inamed to "potentially" contact patients who reported a device rupture in order to collect additional clinical outcome data. The warranties supply between $1200-$2400 toward surgical costs and free replacement products

- modify their current Inamed registry form to request authorization from patients to forward information to 3rd party organizations for participation in large epidemiological studies. Inamed believes that large epidemiological studies, incorporating control groups, are the only means of obtaining conclusions regarding the clinical outcome data requested by the Advisory Panel. Thus, they believe that organizations, such as NIH, are better suited and have better resources and access to data for conducting such studies. *Inamed did not provide any specific arrangements or agreements that have been reached with organizations, like NIH, nor have they provided any plans or proposals for doing so.*

With respect to the Danish Breast Implant Registry, it is an established registry in Denmark that uses electronically-linked medical records. It is not run by Inamed but does contain data specific to Inamed's breast implants. It is important to note that the data in the registry are collected only when a patient makes a visit to a healthcare provider (i.e., there is no prospective collection of data and no required postoperative evaluation timepoints). The Danish Breast Implant Registry can be used to collect some preoperative and postoperative data, as well as data on any follow-up doctor visits or surgeries.

No CTD or other type of systemic information is collected postoperatively as part of the Danish Breast Implant Registry. Inamed stated that this information is potentially accessible via links from the Danish Breast Implant Registry to other National (Danish) registries (e.g., Cancer

Registry, Mortality Registry, Birth Outcomes Registry, Psychiatric Registry, Outpatient Registry and Hospital Discharge Registry). In particular, Inamed stated that the latter two registries are where CTD and other rheumatology information would be housed. The Mortality Registry may also include CTD and rheumatology information if the woman succumbed to one of these types of diseases. *However, Inamed did not provide any specific plans or proposals for sponsoring or conducting studies using the Danish Breast Implant registry data to evaluate the potential risk of CTD for women with breast implants.*

Inamed provides financial support to the Danish Breast Implant Registry, which gives them access to the data, including the ability to link the data from women with breast implant to Danish registries that track CTDs, cancer, and other conditions. *As noted above, although Inamed provided a description of what data are or are not collected in the Danish Breast Implant Registry, Inamed did not provide their plans for how they would analyze these data to address the questions raised by the Panel members.*

3. Physician Education/Training

In their August 2004 submission, Inamed described several educational initiatives. The most significant initiative is their ongoing training course entitled the "Inamed Academy." The Inamed Academy is a forum by which the following breast implant topics are discussed:

- local risks, such as rupture (both symptomatic and asymptomatic), leakage, gel bleed, gel migration, and capsular contracture, which are presented in the context of literature review and Inamed clinical study experience
- systemic effects with review of published literature and discussion of types of study that examine the association
- silicone technology
- medical-legal issues
- informed consent process and suggestions for getting patient informed consent (e.g., methods of dissemination)
- patient monitoring
- management of complications (e.g., suspected rupture).

Inamed also described other mechanisms for educating physicians, including continuing education publications that will be disseminated at professional society meetings and trade shows and through email and the internet. The specific educational materials were not provided. Inamed also referred to the package insert as part of physician education/training. Refer to Tab 3 of your Panel package for a copy of Inamed's draft package insert.

Some Advisory Panel members recommended that physicians be certified prior to receiving access to the device for implantation. Inamed does not agree with the Panel that certification of training should be a condition of access to their silicone gel product.

Inamed did not provide any educational materials with specific information with regard to the frequency and method of screening for rupture, nor did they address removal after confirmed intracapsular or extracapsular rupture. The FDA is seeking panel input on appropriate labeling for these devices, should an approvable recommendation be made. Refer to Tab 2 of your Panel package for a copy of the Panel questions.

4. Other Postapproval Plans

Other proposed postapproval activities include conducting a focus group study, which is designed to improve the patient labeling. The focus group study protocol is not described in this review memo because it was presented at the October 2003 Panel meeting.

In addition, at the October 2003 Panel meeting, Inamed proposed two postapproval plans - a model surgical informed consent form and a patient education booklet. In their August 2004 submission, Inamed clarified that there will not be a separate form or booklet and that all patient information relevant to making an informed decision will be included in their patient labeling brochure. Refer to Tab 3 of your Panel package for copies of Inamed's draft patient brochures.

D. CTD SIGNS AND SYMPTOMS

In the 1/7/04 non-approvable letter, FDA requested Inamed to provide additional information on the connective tissue disease (CTD) signs and symptoms (S/S) reported for the Core Study.

Inamed collected CTD signs and symptoms from the patients at baseline and at 1, 2, 4, 6, 8, and 10 years in the Activities and Lifestyle questionnaire to assist in determining CTD diagnoses, if present. This self-administered questionnaire includes a Modified Health Assessment Questionnaire (MHAQ), which assesses the ability to perform various physical functions of daily living, and it includes a variety of signs and symptoms related to rheumatic diseases and to general health. The intention of this questionnaire is to identify patients who warrant additional evaluation and referral to a rheumatologist.

Inamed performed several analyses of the Core Study data as well, as comparisons of the Core Study CTD S/S results with that from their saline-filled breast implant study, which used the same self-reported questionnaire.

General estimating equation (GEE) models, with age group as a covariate, were used to test the effects of Inamed's silicone-filled breast implants on CTD S/S for augmentation patients. Inamed stated that, because of violations to the missing completely at random (MCAR) rule, GEE analyses for CTD signs and symptoms in the reconstruction and revision indications were not performed. However, per FDA's request, in a 1/25/05 email, Inamed provided the p-values for the change from baseline, SAS code, and corresponding SAS output for each of the GEE models for all 3 indication groups (i.e., augmentation, reconstruction, and revision). These results showed significant differences in binary response, after adjusting for an age effect, for the following CTD categories:

- Other, Skin, General, Muscle, and Joint categories for augmentation patients
- Other, Skin, and General categories for reconstruction patients
- Other, Muscle and Joint categories for revision patients.

Inamed noted that the probability of experiencing multiple CTD S/S increased with age for augmentation patients in all major CTD categories. In fact, Inamed claimed that "in general, the increases in baseline for some CTD signs and symptoms in the Core Study augmentation patients were mainly a function of aging." Inamed's claim is incorrect. While it is true that age was a significant factor for the General, Joint, Neurological, and Skin categories for augmentation patients, they cannot claim that increases in CTD were mainly a function of aging. Other factors in addition to aging could also have been significant, and perhaps more important, than aging. As noted previously, the fact of having an implant was a significant factor for 5 out of the 8 CTD S/S categories for augmentation patients, even after adjusting for age.

Inamed evaluated the rate of fibromyalgia (FM) signs/symptoms (S/S) by including questions related to pain and fatigue and pain in the back or neck or chest that were self-reported by the patients. Using these questions, Inamed found that 3% of the patients in the Core Study reported FM S/S at the 2 and 3-year visits. Inamed also noted an increase in responses to fatigue questions of 3.2% from baseline. The prevalence of FM in the female population ranges from 2-5% depending on patient demographic factors, such as age.

To determine whether patients who were dissatisfied with their implants were more likely to report CTD S/S, Inamed used Pearson Correlation Coefficients. Although none of the CTD complaints were shown to impact patient dissatisfaction, Inamed acknowledged that the non-significant results do not prove that such a relationship does not exist, but that it cannot be demonstrated with the given sample size.

In evaluating rupture and CTD S/S, Inamed noted that 3 patients in the confirmed rupture and 3 patients in the confirmed non-rupture group had FM S/S (defined by positive responses to questions about fatigue greater than zero and unusual fatigue and pain in the back or neck or chest). There were no associations between rupture and reporting FM S/S. Recall that these data are based on patient self-reports and that physical findings on tenderness on examination, which is needed for a diagnosis of FM, were not performed on these patients.

The table below summarizes the presence of selected CTD S/S and the presence or absence of implant rupture in the Core Study.

Selected CTD S/S and Presence/Absence of Rupture		**Confirmed Non-rupture**	**Confirmed and Unconfirmed Rupture**
Joint Total	Yes	11	31
	No	12	21
Joint Pain	Yes	3	7
	No	20	35
Fatigue	Yes	14	25
	No	9	17
Pain	Yes	11	20
	No	12	22
Muscle Weakness	Yes	2	2
	No	21	40

Comparisons between the non-MRI and MRI subgroups found significant differences in time to rupture, possible FM, and many CTD categories, with significantly greater reporting of FM S/S and CTD S/S in the MRI group. Inamed attributed these findings to what they characterize as unnecessary explant surgery to rule out rupture, resulting in increased patient anxiety, which is causing this higher rate of reporting CTD S/S in general and FM S/S in specific.

Inamed also stated that there is an association between self-reporting 3 or more FM S/S (such as muscle weakness, back pain, neck pain, fatigue, chest pain, and aches) and having an unresolved complication from a secondary procedure. They stated that the majority of patients reporting CTD S/S had unresolved complications at some time; however, they did not provide statistical analyses to support this finding.

In evaluating whether the CTD S/S reporting differed between Inamed's saline-filled and gel-filled breast implant studies, Inamed found similar amounts of differences from baseline between the augmentation and reconstruction patients with saline-filled or gel-filled differences. Using both parametric and non-parametric tests, no statistically significant differences in the change

from baseline were noted for fatigue, hand swelling, muscle weakness, aches, back pain, and neck pain. However, for both saline and gel-filled breast implant patients in Inamed's studies, the following CTD S/S increased by more than 5% from baseline: back pain; neck pain; hand swelling; fatigue; and aches.

In summary:

- In evaluating the whether the increases in CTD S/S from baseline were related to age, the increases in the following CTD categories occurred despite age:
    - Augmentation: Other, Skin, General, Muscle, Joint
    - Reconstruction: Other, Skin, General
    - Revision: Other, Muscle, Joint.

- The responses to fatigue questions increased by 3% from baseline; however, the prevalence of FM S/S reporting was within the range reported for the U.S. population.

- No statistical associations were found for CTD S/S reporting and implant rupture or patient satisfaction; however, lack of statistical association could have been due to the sample size rather than the lack of a relationship.

- Patients in the MRI Cohort and patients with unresolved complications tended to report higher frequencies of CTD S/S and FM S/S.

- When compared to the patients having undergone saline-filled breast implants, the increase in CTD S/S were not significantly different for patients having silicone gel-filled breast implants.

- Without a control/comparison group of patients without implants followed for the same duration of follow-up and with similar demographic characteristics, the interpretation of these data is difficult.

E. PATIENT SATISFACTION

In the 1/7/04 not-approvable letter, FDA requested Inamed to provide additional information on patients who reported to be "definitely dissatisfied" and "somewhat dissatisfied" in the Core Study. FDA wanted to better understand the reasons for patient dissatisfaction.

Inamed reviewed complete 3-year data, extracted in May 2004. Data were reported by patient for all follow-up visits, and each unique dissatisfaction was only reported once per patient. For example, a specific reason for dissatisfaction reported bilaterally counts as one report. If a patient reported more than 1 reason for dissatisfaction, then each reason is reported separately. Therefore, the sum of the reasons is greater than the number of patients reporting dissatisfaction.

The table below summarizes the reasons for dissatisfaction for each of the indications through 3 years. For augmentation patients, the most common reasons for dissatisfaction reported were capsular contracture (56% of reasons), followed by asymmetry (17%), followed by ptosis and implant malposition (both at 11%). For reconstruction patients, the most common reasons were capsular contracture (28%), patient desire for style/size change (25%), and asymmetry (18%). For revision patients, the most common reasons were capsular contracture (50%), wrinkling (18%), and patient desire for style/size change and implant malposition (both at 16%).

Reasons for Dissatisfaction through 3 Years	Augmentation N=54 patients	Reconstruction N=40 patients	Revision N=50 patients
Asymmetry	9 (17%)	7 (18%)	3 (6%)
Breast firmness			1 (2%)
Breast lump, mass, cyst			1 (2%)
Breast pain	1 (2%)	3 (8%)	4 (8%)
Breast shape	1 (2%)	4 (10%)	4 (8%)
Breast tissue contour	2 (4%)		1 (2%)
CC I/II	11 (20%)		11 (22%)
CC III/IV, unknown	19 (35%)	11 (28%)	14 (28%)
Implant malposition	6 (11%)	6 (15%)	8 (16%)
Implant palpability			4 (8%)
Infection			1 (2%)
Insufficient/excess skin		2 (5%)	
Loss of skin sensation			1 (2%)
Nipple pain	1 (2%)		
Nipple/areola size/position	2 (4%)		1 (2%)
Other		3 (8%)[1]	1 (2%)[2]
Patient desire for size/style change	5 (9%)	10 (25%)	8 (16%)
Pregnancy related contracture??	1 (1%)		
Ptosis	6 (11%)	1 (3%)	1 (2%)
Scarring	4 (7%)	1 (3%)	2 (4%)
Seroma			1 (2%)
Wrinkling	1 (2%)	4 (10%)	9 (18%)
Total Reasons	69	52	76

[1]Includes "doesn't feel right," "Thinks they are causing shortness of breath/chest pain," and "feel foreign."
[2]Includes "not her breasts."

F. RETROSPECTIVE COLLECTION OF COMPLICATIONS

In the 1/7/04 not-approvable letter, FDA requested Inamed to provide additional information regarding their retrospective collection of immediately-postoperative local complications for some of the patients in the Core Study.

Inamed stated that retrospective data were collected for 717 patients (396 augmentation, 123 reconstruction, and 198 revision). Of the 717 patients, 100 patients were identified as having the local complications that required retrospective data collection. Retrospective data for these 100 patients were collected at the 0-4 week and 6-month timepoints only. An additional 150 complication reports were collected. Of the 150 additional complication reports, 133 had onset during the 0-4 week timepoint and 17 had onset during the 6-month timepoint.

FDA had concerns about the reliability of the retrospective data. Inamed believes that the retrospective data are reliable because the data were readily available in the patient charts via source documentation, such as patient progress notes. The same data collection rules, definitions, outcome measurements, and quality assurance processes were used across as used for the prospective data.

Based on the information provided, FDA agrees that under-reporting of local complications in the retrospective group was minimal and should not affect overall conclusions regarding the data set.

G. GEL BLEED

For the original PMA presented at the October 2003 Panel, Inamed provided gel bleed testing as described in the ASTM standard, F703. The ASTM F703 test method was not developed to mimic in-vivo conditions but, instead, to accelerate the bleed diffusion process to compare various smooth implant designs. The ASTM F703 test method involves the placement of implant samples on silicone disks, as well as silicone disks with no implants (controls). The testing is performed in air at 110°F for 8 weeks, with weekly weight measurements of the silicone disks. The weight gain and weight gain rates through 8 weeks are calculated, using the control disks values to account for factors such as humidity.

In the 1/7/04 not-approvable letter, FDA asked Inamed to provide new gel bleed testing that mimics the in-vivo environment in order to identity the gel bleed constituents (including the platinum species (or other catalysts)), the rate that the gel constituents bleed out, and how that rate changes over time. FDA believes that this information is needed to fully characterize the device and its interactions with the body over its expected lifetime. It is also needed so that women may be informed of the identity and quantity of chemical constituents that leak out of an intact implant.

In their August 2004 submission, Inamed provided new gel bleed testing, which is summarized below.

Test Method -

Results - After 8 weeks, 3 test and 3 control disks were sent for analysis of adsorbed silicones to a contract laboratory. After solvent extraction, silicones were identified and quantified by gas chromatography (flame ionization detection) and gas chromatography-mass spectrometry (GC/MS). In addition, 3 tests and 3 control disks were sent to a different contract laboratory for platinum and tin analysis

Inamed focused much of the comparison/analysis of the new test results to those of the original ASTM F703 testing. FDA does not believe that this comparison is useful or appropriate, because, as noted above, the ASTM F703 testing does not mimic in-vivo conditions. Therefore, FDA did not include those discussions in this summary.

Overall Gel Bleed Rate - After 8 weeks, Inamed used gravimetric analysis to determine an average normalized weight gain of the disks of 0.0021 g/cm^2, which gives a cumulative normalized average bleed rate of 0.0003 $gm/cm^2/wk$. The amount of silicone bleed leveled off at

8 weeks. Inamed believes that 8-week study duration is sufficient based on the gel bleed quantity essentially leveling off at 0.002 gm/cm^2 after 28 days of exposure.

The analysis was able to identify and quantity cyclic species D8 to D21 and linear specifics MD6M to MD18M. Only the total quantity (in ppm) was provided for the species, not the bleed rates over time.

Inamed stated that the gel bleed values for cyclic species <D8 and linear species <MD6M measured in this experiment were unreliable because the control disks were found to be "extremely efficient" in capturing volatilized, low molecular weight (LMW) silicones from the local environment. Inamed stated that the silicones found in the control disks are the result of contamination through contact with the incubator and silicones that existed in the disk at the time of purchase. According to Inamed, contamination by volatile silicones is easy for filters because of their high surface area which can becomes saturated with silicones adsorbed from the gas phase. *FDA believes that this "contamination" issue indicates a fundamental flaw with the test methodology that impacts the reliability of the test results for all silicone moieties, not just the LMW silicones.*

Inamed also analyzed the gel bleed to determine if there were metal constituents.

levels in both the test and control disks were below detection limits (<0.001µg/mL of aqueous sample and <0.04 ppm in the solid). Regarding tin, there was no identified level of tin above what was on the control disks (the detection limit for tin was reported 0.005µg/mL of aqueous sample and <0.18 ppm in the solid). Inamed stated that only Pt and tin were analyzed for because these are the only 2 metals used as catalysts. However, our breast implant guidance document recommends that all gel bleed constituents, not just catalysts, be analyzed. Although Inamed concluded from these results that Pt and tin were not detected in the gel bleed, FDA believes that based on the limitations of the test methodology that such a conclusion can be made.

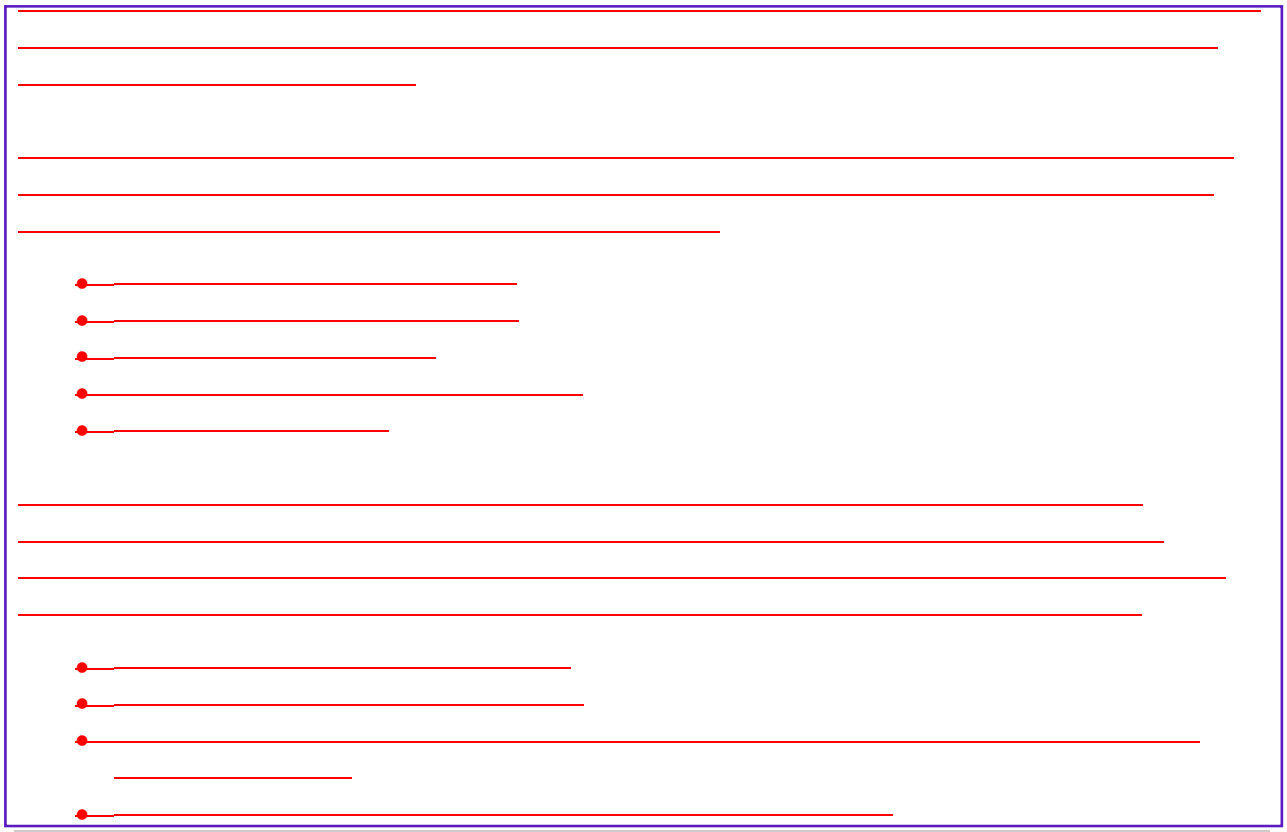
FDA considers Inamed's new testing to be of limited value based on the following outstanding issues:

- *The methodology used cannot be extrapolated to in-vivo conditions for the following reasons: (1) There is no evidence silica disk with octadecyl function groups mimic in-vivo conditions because the type of contact between the implant and the surface is not the same as the type of contact seen in-vivo. (2) The testing was performed at 110^{o}F (43°C), as specified in ASTM F703. Inamed stated that this serves to expose the breast implant to a worst case temperature condition that could occur after implantation. This worst case temperature was not intended to be indicative of the actual in-vivo situation because a patient would not survive such a consistently elevated temperature.*

(3) Inamed did not provide a rationale why the disk size can be extrapolated to in-vivo conditions. The human body is several hundred times larger than the [redacted] disk, and the test device is tens of times smaller than the largest implant. This leads to questions about how the amount of diffusion was impacted in the new in-vitro testing. (4) Inamed stated that equilibrium was reached at 8 weeks, but it is not known how this applies in-vivo.

- *Inamed did not provide the rate of diffusion for each gel bleed constituent.*
- *Inamed did not analyze for high MW silicone polymers in the gel bleed.*
- *Inamed did not discuss potential reasons why platinum or tin was not detected. Inamed should have determined the efficiency of platinum and tin binding by, and elution from, the [redacted] disks under the test conditions. Because these efficiencies were not determined, it is not possible to know if platinum (and tin) that might be present in the implants was not a constituent of the gel bleed or, if it was a constituent of the gel bleed, was not eluted from the disks. Also, Inamed did not provide information on the binding capacity of the [redacted] disks for representative silicones and platinum (or tin). Therefore, the maximum amount of these materials that can be bound by a disk is not known.*

H. DESIGN & MANUFACTURING CHANGES



I. SHELF LIFE DATA

In the 1/7/04 not-approvable letter, FDA requested Inamed to provide shelf life data to support their desired 5-year shelf life on their product labeling.

Inamed provided a combination of real-time and accelerated shelf life testing on their silicone gel product and approved saline breast implants. With their combination of data, Inamed was able to validate their accelerated test model out to 3 years, and accordingly, justify a 3-year shelf life on their silicone gel breast implant product labeling.

Inamed's goal is a 5-year shelf life. Thus, they plan to continue with their testing.

J. LABELING RECOMMENDATIONS

In the 1/7/04 not-approvable letter, FDA requested Inamed to provide recommended wording for their labeling on several different topics.

FDA acknowledges that some of the proposed wording will need to be modified to accurately reflect data/information from Inamed's PMA, the literature, or other sources, should the product be approved.

This section of the review memo focuses only on those topics for which FDA is seeking Panel input as outlined in the Panel questions provided in Tab 2 of your Panel package. These labeling topics include: (1) the recommended method and frequency for screening for silent rupture; (2) recommendations for clinical management of suspicious and confirmed, intracapsular and extracapsular rupture; and (3) information on potential health consequences of extracapsular and migrated gel. There are other labeling issues included in the 1/7/04 not-approvable letter; however, as noted above, FDA is not seeking specific Panel comment on the issues not specifically mentioned.

In Tab 3 of your Panel package, we provided copies of Inamed's draft package insert, augmentation patient brochure, reconstruction patient brochure, and revision patient brochure that contain the proposed wording for all topics in the 1/7/04 not-approvable letter.

Below are the three labeling topics for which FDA will seek your input as to the extent to which Inamed's recommendations are supported by the available data/information. After each topic is FDA's discussion of that topic.

1. Method and Frequency for Screening for Silent Rupture

Proposed Package Insert Wording:

> ***"Monitoring for Asymptomatic Implant Rupture*** - Patients should be informed that periodic evaluation of the integrity of their breast implants is required to determine whether the implant has ruptured in the absence of any clinical symptoms. While there are various diagnostic methods available to evaluate for possible implant rupture including physical examination, mammogram, and ultrasound, FDA believes the best method for detection of rupture is Magnetic Resonance Imaging (MRI). In most cases, an MRI diagnosis of rupture or possible rupture is consistent with a ruptured implant at explantation (Brown et al. 2000, Hölmich et al. 2004). INAMED's clinical study results and other published reports have found that in some cases MRI may falsely show a breast implant rupture when there is none. Scaranelo et al. (2004) found that the sensitivity and specificity of MRI to detect rupture in asymptomatic patients was 64% and 77%, respectively. Thus, MRI findings of rupture should not be considered definitive (Scaranelo et al. 2004). MRI screening should be performed every 1-2 years or at a frequency recommended by the patient's plastic surgeon."

Proposed Patient Brochure Wording:

> "A woman may not always notice if her implant has ruptured. Although there may be a change in the shape or size of the breast, as well as some physical symptoms, in some cases, there may be no detectable evidence of rupture. This is referred to as silent rupture.

As a result, women with breast implants should periodically have their breast implants evaluated to determine if the implants have ruptured.

While there are various diagnostic methods available to evaluate for possible implant rupture including physical examination, mammogram, and ultrasound, the U.S. Food and Drug Administration believes the best method for detection of rupture is Magnetic Resonance Imaging (MRI). MRI screening should be performed every 1-2 years or at a frequency recommended by your plastic surgeon. INAMED's clinical study results and other published reports have found that in some cases MRI may falsely show a breast implant rupture when there is none. The decision to remove a suspected ruptured implant should be undertaken following discussion between you and your surgeon."

Inamed recommends that MRI be performed every 1-2 years OR by a frequency recommended by the plastic surgeon. The basis for recommending this frequency is not clear. This frequency of screening is performed in the Core Study and in the Danish studies published in the literature, but no justification was given as to why it is appropriate. The proposed labeling does not explain that, in the Core Study data, most silicone gel-filled breast implant ruptures are silent. The labeling indicates that MRI may falsely indicate rupture when none exists; however, it does not acknowledge that this is less common if explant is used to determine rupture status, based on their study. The sensitivity and specificity that Inamed cited for MRI is significantly lower than other larger or more recent studies.

2. Clinical Management of Suspicious and Confirmed, Intracapsular and Extracapsular Rupture

Proposed Package Insert Wording:

*"**Clinical Management of Suspected and Confirmed Rupture*** - Patients should be informed that following a diagnosis of suspected or confirmed rupture that implant removal might be recommended by the surgeon, particularly in those instances where there may be evidence that silicone gel has moved beyond the confines of the fibrous capsule that typically forms around the device. Most surgeons in INAMED's clinical studies have chosen to remove implants suspected of rupture. The decision to remove an asymptomatic but ruptured implant should be undertaken following discussion between the patient and the surgeon.

Patients should be aware that, rarely, an intracapsular rupture may progress to an extracapsular rupture. Hölmich et al. (2004) conducted a study of whether ruptured breast implants are associated with changes over time according to MRI evaluations taken 2 years apart. They found that of 77 implants with MRI evidence of intracapsular rupture at baseline, MRI revealed that 7 (9%) had evidence of extracapsular silicone 2 years later. The decision to remove a ruptured implant with the presence of either intracapsular or extracapsular gel should be undertaken following review of all available clinical information and after careful consideration between the patient and the surgeon."

Proposed Patient Brochure wording:

"All implants, including breast implants, can fail over time and need to be removed or replaced. They are not to be considered life-time devices. Breast implants can rupture when the shell develops a hole or a tear. Some implants rupture in the first few months after being implanted and some rupture after several years. Rupture may be caused by damage to the

implant by surgical instruments or other trauma to the implant during surgery, capsular contracture, closed capsulotomy, stresses such as trauma or intense physical manipulation after surgery, excessive compression during mammographic imaging and unknown/unexplained reasons.

Sometimes when an implant ruptures, the silicone gel filler is released from the implant shell. If that happens, the silicone gel is typically contained within the scar capsule that has formed around the implant. Rarely, the silicone gel filler may move beyond the fibrous capsule and into the breast tissue or away from the breast, particularly if the scar capsule is ruptured.

If an implant ruptures, removal or replacement of the implant may be necessary. Along with the rupture, patients may experience local complications, such as hard knots in the breast, uneven appearance of the breasts, pain or tenderness, tingling, swelling, numbness, burning, or changes in breast sensation. These complications may also be experienced by patients with non-ruptured implants. There is no evidence that silicone gel that moves beyond the breast capsule causes any symptoms or disease elsewhere in the body. However, most surgeons in INAMED's clinical studies have chosen to remove implants suspected of rupture. The decision to remove a ruptured implant with the presence of gel within or outside of the scar capsule should be undertaken following review of all available clinical information and after careful consideration between you and your surgeon."

Inamed stated that the decision of whether or not an intracapsular ruptured implant should be removed is left to the patient and physician's choice. However, Inamed also stated that it is clinical practice in the U.S. to remove implants that are confirmed to be ruptured. In addition, Inamed stated that it is rare that the gel moves beyond the fibrous capsule (i.e., extracapsular or migrated gel) and, if it does, there is no evidence that it causes symptoms or disease elsewhere in the body. This is in contrast to the literature, which cites that silicone migration beyond the breast capsule associated with implant rupture does cause local complications such as pain and neuropathy.

3. Potential Health Consequences of Extracapsular and Migrated Gel

Proposed Package Insert Wording:

"Potential systemic health consequences of extracapsular or migrated gel following rupture - When breast implants rupture, in most cases, any silicone gel that is released from the device is contained in the fibrous capsule that develops around the device shortly after implantation. If there is a loss of integrity in the fibrous capsule, which most likely occurs as a result of closed capsulotomy, trauma, or compression mammography, silicone gel may migrate from the implant through the capsule and into the surrounding breast tissue. The medical literature suggests that approximately 25% of ruptured breast implants may have evidence of silicone gel in the breast tissue around the fibrous capsule (Hölmich et al. 2001, Berg et al. 2002, Herborn et al. 2002, Hölmich et al. 2003). There has been no clinical evaluation of the migration of silicone gel from a ruptured implant beyond breast tissue, but the medical literature contains a relatively small number of case reports of silicone gel detected distant from the implantation, primarily in women with ruptured implants. The frequency of this event is quite rare given the millions of breast implants that have been implanted.

Extracapsular gel or migration of gel may be accompanied by localized pain or discomfort. Hölmich et al. (2004) conducted MRI analysis of 64 Danish women (126 implants) who were found to have a ruptured implant in an earlier study (96/126 ruptured implants), where the implants were not removed. The authors obtained questionnaire data on symptoms that developed between the first and second MRI examinations. The results were compared to all women with intact implants at both MRI assessments (98 women with 193 intact implants) for self-reported breast symptoms. Compared to women with intact implants, women with ruptured implants reported a significantly increased frequency of non-specific breast changes, changes in breast shape, breast pain, and any breast change. There is no evidence that extracapsular gel or migrated gel pose a risk of systemic disease in breast implant patients."

Proposed Patient Brochure Wording:

"**Rupture -** ...There is no evidence that silicone gel that moves beyond the breast capsule causes any symptoms or disease elsewhere in the body.

LABORATORY AND ANIMAL TESTING - Laboratory and animal testing of INAMED's silicone-filled breast implants revealed that the materials of which the implants are manufactured are safe, the silicone elastomer shell is durable, and there is a low potential for the implant to leak or rupture. Testing conducted by INAMED also revealed that only minimal amounts of the silicone gel filler bleed across an intact silicone elastomer shell over time and that the constituents (components) of this gel do not pose a health concern."

FDA believes that the patient brochure does not adequately describe the reported consequences of ruptured implants, as detailed in the package insert. FDA believes that unless surveillance is actively performed for migrated gel (i.e. either with MRI, mass spectroscopy, or biopsy), it is incorrect to assume that this is a rare occurrence. Additionally, the paragraph describing the laboratory and animal testing in the patient labeling relates to gel bleed, which is a separate issue from extracapsular or migrated gel. However, gel bleed should be addressed in the package insert as well.

K. DEVICE EFFECTIVENESS

Effectiveness issues were not included in Inamed's 1/7/04 not-approval letter. The information below is that taken from FDA's clinical memo provided in Tab 5 of your Panel package. For convenience sake, FDA is providing this information as part of this review memo because you will need to consider the risks and benefits, as a whole, for Inamed's product when providing your final recommendation for this PMA (approvable, approvable with conditions, or not approvable).

1. Effectiveness Data for Augmentation

With respect to **breast size**, most patients increased by 1or 2 cup sizes. Approximately 6% of patients experienced no change or decreased breast size due to correction of congenital asymmetry or change in shape without change in size.

Inamed collected both patient and physician satisfaction. Because the patient satisfaction is more relevant, physician satisfaction information was omitted. Inamed collected both general patient satisfaction and satisfaction based on pre-operative expectation of satisfaction. With respect to **general patient satisfaction**, of the 425 patients (of 494) who completed this questionnaire at 2 years, there was a small decline in mean satisfaction from the 0-4 week follow-up timepoint (on a 1-5 point scale) of 4.9 (SD 0.3) to 4.8 (SD 0.7) at 2 years. With respect to patient satisfaction compared to pre-operative expectation of satisfaction, of the 351 (of 494 patients) who responded to these questions, most patients reported being satisfied or very satisfied with their implants at 1 and 2 years post-implant. Approximately 2.6% of these patients were very dissatisfied or dissatisfied, and another 2.6% were neutral regarding their satisfaction at 2 years compared to their pre-operative expectation. There were small but statistically significant declines in mean patient satisfaction at both 1 and 2 years compared to pre-operative expectations of satisfaction. The mean pre-operative expectation value of 4.9 (SD 0.4) was compared to 4.6 (SD 0.7) at 2 years.

With respect to the **Health Status Questionnaire (SF-36 and MOS-20),** the core augmentation cohort reported statistically significantly higher levels for all measures at baseline compared to normative values for the general female population. There were small, statistically significant declines in some subscales of these measures in breast implant recipients over time. However, the 2-year values for the augmentation cohort were generally numerically higher than normative values for the general female population (statistical comparison of 2-year augmentation to normative scores was not performed by Inamed). The results of selected health status measures are summarized in the table below. Note that most of the changes, even those that are worse, are small.

Assessment method	Statistically significant change in pre- to 2-year post-implant score	Direction of change
SF-36 Role Emotional	Yes	Worse
SF-36 Role Physical	Yes	Worse
SF-36 General Health	Yes	Worse
SF-36 Pain	No	Worse
SF-36 Social	Yes	Worse
SF-36 Physical	No	Worse

Assessment method	Statistically significant change in pre- to 2-year post-implant score	Direction of change
SF-36 Vitality	Yes	Worse
SF-36 Mental Health	Yes	Worse
MOS-20 Health Perceptions	Yes	Worse
MOS-20 Physical Functioning	No	Worse
MOS-20 Social Functioning	No	Worse
MOS-20 Mental Health	Yes	Worse
TSCS Physical Self	Yes	Better
Rosenberg Self Esteem	No	Worse
Semantic Differential	No	Same
Body Esteem-Total Score	Yes	Better
Body Esteem-Sexual Attractiveness	Yes	Better
Body Esteem-Weight Concern	No	Better
Body Esteem-Physical Condition	Yes	Worse

2. Effectiveness Data for Reconstruction

Inamed did not collect **breast size** information for the reconstruction patients.

Inamed collected both patient and physician satisfaction. Because the patient satisfaction is more relevant, physician satisfaction information was omitted. Inamed collected both **general patient satisfaction** and satisfaction based on pre-operative expectation. With respect to general patient satisfaction, of the 177 patients (of 221) who completed this questionnaire at 2 years, there was a small decline in mean satisfaction from the 0-4 week follow-up timepoint of 4.8 (SD 0.6) to 4.5 (SD 0.9) at 2 years. With respect to **patient satisfaction compared to pre-operative expectation** of satisfaction, of the 166 patients (of 221) who responded to these patient satisfaction questions, the majority of patients reported being satisfied or very satisfied with their implants at both 1 and 2 years post-implant. Approximately 9.0% of these patients reported being dissatisfied or very dissatisfied, and another 6.0% were neutral regarding their satisfaction at 2 years compared to their pre-operative expectations. There were small but statistically significant declines in patient satisfaction at both 1 and 2 years compared to their pre-operative expectations of satisfaction. The mean pre-operative expectation value of 4.6 (SD 0.5) was compared to 4.2 (SD 1.0) at 2 years.

With respect to the **Health Status Questionnaire (SF-36 and MOS-20),** the core reconstruction cohort reported statistically significant higher levels at baseline compared to normative values for most subscales of the SF-36: general health; social functioning; physical functioning; vitality; and mental health. At 2 years, all subscales were generally higher than at baseline for the breast reconstruction cohort, with statistically significant improvement noted in role limitations due to physical health problems. The 2-year scores for the breast reconstruction cohort are numerically higher than the normative values, although statistical comparisons were not made. The table below summarizes the results of selected health status measures. Note that most of the changes, even those that are worse, are small.

Assessment method	Statistically significant change in pre- to 2-year post-implant score	Direction of change
SF-36 Role Emotional	No	Better
SF-36 Role Physical	Yes	Better
SF-36 General Health	No	Worse
SF-36 Pain	No	Better
SF-36 Social	No	Better
SF-36 Vitality	No	Better
SF-36 Physical	No	Better
SF-36 Mental Health	No	Better
MOS-20 Health Perceptions	No	Worse
MOS-20 Physical Functioning	Yes	Better
MOS-20 Social Functioning	No	Better
MOS-20 Mental Health	No	Better
TSCS Physical Self	No	Worse
Rosenberg Self Esteem	No	Worse
Semantic Differential	No	Better
Body Esteem-Total Score	No	Worse
Body Esteem-Sexual Attractiveness	No	Better
Body Esteem-Weight Concern	No	Worse
Body Esteem-Physical Condition	No	Worse

3. Effectiveness Data for Revision

Inamed did not collect **breast size** information for the revision patients.

Inamed collected both patient and physician **satisfaction**. Because the patient satisfaction is more relevant, physician satisfaction information was omitted. Inamed collected both general patient satisfaction and satisfaction based on pre-operative expectation of satisfaction. With respect to **general patient satisfaction**, of the 173 patient (of 225) who completed this questionnaire at years, there was a small decline in mean satisfaction from the 0-4 week timepoint of 4.4 (SD 0.8) to 4.4 (SD 1.1) at 2 years. With respect to **patient satisfaction compared to pre-operative expectation** of satisfaction, of the 129 of 225 patients (58.4%) who responded to these patient satisfaction questions, the majority of patients reported being satisfied or very satisfied with their implants at both 1 and 2 years post-implant. At 2 years, ≈10.1% of these patients reported being dissatisfied or very dissatisfied, with 9.3% reporting being neutral regarding their satisfaction compared to their pre-operative expectations. There were small but statistically significant declines in mean patient satisfaction at both 1 and 2 years compared to pre-operative expectations of satisfaction. The mean pre-operative expectation of satisfaction value of 4.7 (SD 0.5) was compared to 4.2 (SD 1.1) at 2 years.

With respect to **Health Status Questionnaire (SF-36 and MOS-20)**, the core revision cohort reported statistically significantly higher levels at baseline compared to normative population data for all subscales of the SF-36. At 2 years, all subscales declined for the revision cohort, but were still either higher or comparable to normative population values. The table below summarizes the results of selected health status measures. Note that most of the changes, even those that are worse, are small.

Assessment Method	Statistically significant change in pre- to 2-year post-implant score	Direction of Change
SF-36 Role Emotional	Yes	Worse
SF-36 Role Physical	No	Worse
SF-36 General Health	Yes	Worse
SF-36 Pain	No	Worse
SF-36 Social	Yes	Worse
SF-36 Physical	No	Worse
Vitality	No	Worse
Mental Health	Yes	Worse
MOS-20 Health Perceptions	Yes	Worse
MOS-20 Physical Functioning	No	Worse
MOS-20 Role Functioning	No	Worse
MOS-20 Social Functioning	No	Worse
MOS-20 Mental Health	Yes	Worse
TSCS Physical Self	Yes	Worse
Rosenberg Self Esteem	Yes	Worse
Semantic Differential	No	No Change
Body Esteem-Total Score	No	Worse
Body Esteem-Sexual Attractiveness	No	Better
Body Esteem-Weight Concern	No	Worse
Body Esteem-Physical Condition	Yes	Worse

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