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RESPONSE TO DEFICIENCY 1

A. MRI COHORT ENROLLMENT

The FDA requested that Inamed increase enrollment in the MRI cohort; however, the number of implants enrolled and analyzed in the MRI cohort is already larger than the sample size proposed in the study's protocol, which was designed to provide adequate precision. A total of 663 implants was enrolled instead of 525 implants, due to enrollment of additional patients and a larger than estimated number of Reconstruction and Revision patients undergoing bilateral implantation, rather than unilateral implantation. As stated in the protocol:

"Determination of the appropriate sample size for the serial MRI portion of this study was based on obtaining a precision of approximately $\pm 2.5\%$ for estimating a by-device rate of 5% at 9 years. To obtain the desired precision level, a total of 525 devices must be enrolled in the study (assuming a 60% 9-year drop-out rate)."

Although the asymptomatic by-device rupture rate may be higher than 5% at 9 years, the sample size remains adequate because (1) the 60% estimate for the 9-year drop-out rate was over-estimated, (2) a total of 663 devices was enrolled instead of 525, and (3) FDA's guidance document indicates that a 4% precision level is acceptable.

FDA has asked Inamed to increase the MRI sample size to identify more ruptured implants and, in turn, give Inamed the ability to provide more information regarding consequences following rupture and other issues surrounding rupture outlined in this deficiency. However, this information is already available without increasing the size of the MRI cohort, as a greater number of rupture patients and new information to characterize rupture are now available. In Amendment 3 (submitted June 12, 2003), Inamed provided information on 24 patients who had experienced rupture. Subsequent to submitting Amendment 3, additional ruptures have been reported for Core Study patients. Furthermore, additional data is now available for those rupture patients originally reported in the PMA. Finally, not only does this response contain additional information on new ruptures and longer term data on existing ruptures, but it also provides more details for all of the ruptured patients, as requested by the FDA.

Inamed believes that the additional patients and the additional analyses provided in this deficiency sufficiently characterize the clinical consequences of rupture and the other rupture issues for which FDA requested information. These issues are thoroughly addressed in the responses to Deficiencies 1b-f and 2b and elsewhere throughout this amendment. Therefore, Inamed believes it is not necessary to enroll

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more patients in the MRI cohort in order to provide sufficient information to the Agency.

The Core Clinical Study data used to construct various responses to this deficiency was extracted on May 19th, 2004. Current study follow-up (i.e., compliance adjusted for deaths and explantations) at 3 years and partial 4 years is 86% and 80%, respectively, for the augmentation cohort, 94% and 89% for the reconstruction cohort, and 87% and 81% for the revision cohort, respectively. Furthermore, 81% of the eligible patients in the MRI cohort have obtained their 2nd Serial MRI. Patient accounting is further detailed in Attachment 1-1.

To further address why it is not necessary to enroll additional women into the MRI cohort, additional analyses were conducted. One of the additional analyses was performed to redesign the method of estimating the rupture risk in order to resolve the following FDA criticism:

The risk of overall rupture was underestimated because it was calculated using the entire cohort while only 30% of the population was screened with MRIs.

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

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

Enrollment Indication	MRI Cohort Actual Silent Rupture Results			NON-MRI Cohort Results	
	# of Implants Enrolled	# of Silent Ruptures*	% Silent Ruptures	# of Implants Enrolled	Expected # of Silent Ruptures
Augmentation	331	5	1.5%	656	10
Reconstruction	182	17	9.3%	179	17
Revision	150	8	5.3%	284	16
TOTAL					

* Current results through partial 4 year data.

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After determining the expected number of implants with silent rupture in each cohort, the distribution of failure times for the expected silent ruptures in the non-MRI cohort was determined by using the distribution of failure times seen in the MRI cohort. For example, in the augmentation MRI cohort there were 5 silent rupture failures on the following days post enrollment: 80, 766, 960, 1137, and 1483. In order to obtain the same distribution in the non-MRI cohort the following failure time points were prescribed: 2 patients were assumed to fail at 80 days, 2 patients at 766 days, 2 patients at 960, etc. The result in the non-MRI cohort for augmentation was 2 patients at each of the 5 failure time points. The result in the non-MRI cohort for reconstruction and revision was 1 and 2 patients, respectively, at each of the failure time points identified from the MRI cohort.

Out of the 43 expected silent ruptures in the non-MRI cohort, 7 were identified via explantation for a non-rupture reason (e.g., exchange to increase size) and, therefore, only 36 implants needed to be weighted with a silent rupture status (43 expected silent ruptures minus 7 identified silent ruptures = 36 silent ruptures to be weighted). In order to retain a similar failure time point distribution (described above) and include the actual failure time points of the 7 implants, the distribution was adjusted. For example, in the non-MRI augmentation cohort there were 2 silent ruptures with actual failure time points of 220 and 596; these two time points are closest to the prescribed 80 and 766 time points. Therefore, the distribution of silent rupture failure time points in the augmentation non-MRI cohort was adjusted as follows:

- 1 implant at 80 days (expected) & 1 implant at 220 days (actual)
- 1 implants at 766 days (expected) & 1 implant at 596 days (actual)
- 2 implants at 960 days (expected)
- 2 implants at 1137 days (expected)
- 2 implants at 1483 days (expected)

The distribution of each cohort was adjusted as described above related to the known time points for the 7 non-MRI cohort silent ruptures (i.e., 2 augmentation adjustments (as illustrated above), 4 reconstruction adjustments, and 1 revision adjustment). For each of the 36 "expected" silent ruptures in the distribution, a failure-free implant in the non-MRI cohort was identified. Implants with the longest failure free time were identified and coded as failures according to the expected time point distribution. Choosing the longest survivors to be coded as failures created a worst-case estimate in the Kaplan-Meier calculation.

After identifying the total number (and failure time points) of the weighted silent ruptures, all ruptures were combined and a Kaplan-Meier analysis was performed.

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The analysis contained 36 weighted silent ruptures in addition to the reported ruptures described in the table below (37 silent ruptures and 6 symptomatic ruptures).

Core Study Reported Ruptures: 4 Years

Cohort (MRI/Non- MRI)	Population	Type (Silent/ Symptomatic)	Number of Implants	
MRI	Augmentation	Silent	5	
		Symptomatic	1	
	Reconstruction	Silent	17	
		Symptomatic	1	
	Revision	Silent	8	
		Symptomatic	0	
	Total MRI		Silent	30
			Symptomatic	2
	Non-MRI	Augmentation	Silent	2
			Symptomatic	3
Reconstruction		Silent	4	
		Symptomatic	0	
Revision		Silent	1	
		Symptomatic	1	
Total Non-MRI		Silent	7	
		Symptomatic	4	

Estimates of rupture risk obtained from the analysis are presented in Attachment 1-2, Tables 1-12 and summarized below:

¹ Only confirmed and unconfirmed ruptures were included in the analysis. All suspected ruptures later found to be non-ruptures are not included. A more detailed table containing confirmation status of each patient/device is located in Attachment 1-6. Tables describing the rupture rates are located in Attachment 1-2.

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Core Study Preliminary Risk of Rupture Overall (Silent & Symptomatic)

Statistic/Population	Risk of Rupture at 4 Years
Risk of Rupture (Overall)	
Combined	5.5%
Augmentation	1.7%
Reconstruction	15.1%
Revision	7.7%
Risk of Silent Rupture	
Combined	5.2%
Augmentation	1.4%
Reconstruction	14.7%
Revision	7.5%
Risk of Symptomatic Rupture	
Combined	0.3%
Augmentation	0.3%
Reconstruction	0.4%
Revision	0.3%

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

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

Population	Range Obtained from Combinations
Combined	5.1% - 5.2%
Augmentation	1.6% - 1.7%
Reconstruction	12.3% - 15.1%
Revision	6.0% - 7.7%

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

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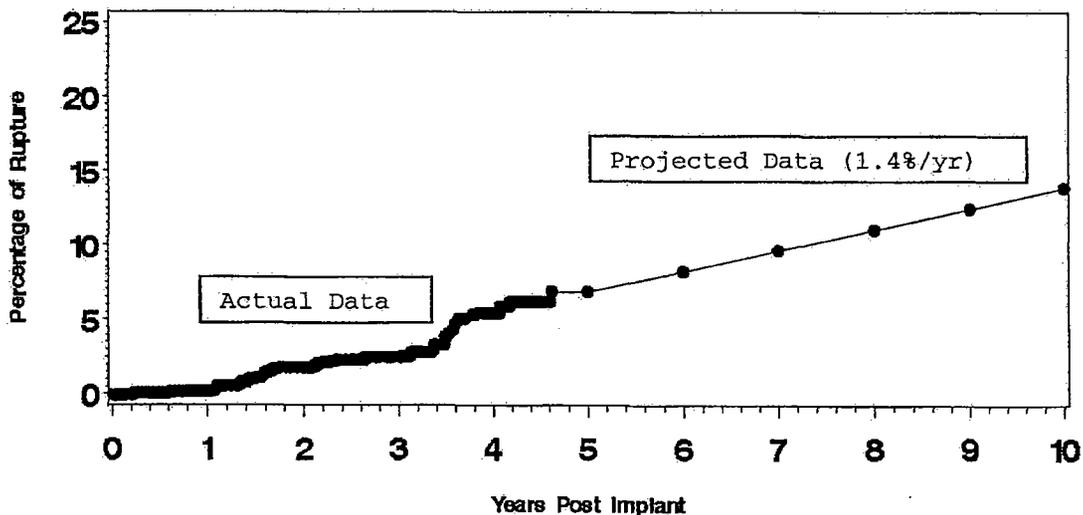
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Although the rupture rate in the reconstruction cohort appears higher than the rupture rates in the other 2 cohorts, Inamed believes this is primarily based on the increased use of Style 153 implants in this cohort. In the reconstruction cohort, 64% of the devices used were Style 153, whereas patients in the augmentation and revision cohorts were not as likely to receive Style 153 devices (8% of augmentation devices and 30% of revision devices). Since use of Style 153 devices was higher in the reconstruction cohort and 70% of the ruptures (confirmed and unconfirmed) were reported with Style 153 devices, the reconstruction rupture rate is higher than the other cohorts. Rupture related to the Style 153 device is further discussed in the response to Deficiency 3.

In response to FDA's issue concerning "the shape of the curve for the percentage of ruptured implants versus time changes over the expected lifetime of the device", Inamed constructed a curve indicating a 13.9% overall rupture risk at 10 years. The 10-year risk was derived by considering the following:

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

Percentage of Rupture Over Time (by Implant)



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Inamed believes the estimate of 1.4% annual increase in ruptures is conservative and probably will prove to be lower as the Core Study progresses. The 1.4% is overestimated due to the 3.0% increase seen between the 3 and 4-year time points. Because 4-year data is incomplete, Inamed expects that the 5.5% 4-year risk will decrease upon analysis of complete 4-year data, just as the 3-year silent rupture rate of 2.7% based on partial 3-year data, submitted to FDA as part of the pending PMA P020056, has decreased to 2.4% with complete 3 year data, as reported in Table 5 of Attachment 1-2 in this response.

Another confirmation of the appropriateness of Inamed's estimated 10 year rupture rate for the silicone-filled implants subject to this PMA, is the comparability to the long term rupture rate in Inamed's 1995 saline study, in which the implant shells are essentially the same as the shells for Inamed's gel implants. As discussed in detail in Deficiency 2, the 4-year rupture rate for the Core augmentation cohort is similar to the 4-year deflation rate for the saline augmentation cohort. At 8 years the augmentation deflation rate is 7.3%, leading to the conclusion that the rupture rate for augmentation patients would be similar at 8 years with a progression at 10 years in line with the 10 year estimate described above. Thus, Inamed's estimate of a 13.9% rupture rate at ten years appears to be an appropriate, and quite possibly conservative, estimate.

B. TISSUE SAMPLING ANALYSIS

Human Tissue Collection and Analysis

The FDA requested results of tissue sampling of the surrounding breast tissue and capsule for ruptured implants to determine whether the rupture led to extracapsular gel or gel migration. This request presupposes the existence of such tissue samples and the ability to accurately test the samples for gel constituents.

Unfortunately, standard medical practice does not involve the removal of tissue samples during breast explantation surgeries, so tissue samples are not available for the Core Study patients who have previously experienced a rupture. Prospectively collecting tissue samples for future implant ruptures would be hindered by the following:

- Lack of willingness of patients to consent to tissue sampling, especially due to ethical and privacy concerns over tissue research, with privacy concerns likely increasing next year with the implementation of federal legislation requiring HIV tests for all subjects contributing tissue for research
- Insufficient sample size due to the low overall number of ruptures, the necessity for "no mastectomy" to permit ample tissue for collection and the necessity of

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subglandular implant placement, so that the implant is in close proximity to the breast tissue

- Lack of validated standardized methods for tissue specimen collection and handling
- Lack of validated test methodologies for analyses of different silicone species or levels in human tissues
- Potential for contamination of tissue samples by silicone in or on surgical instruments and laboratory equipment
- Difficulty in collecting control samples due to unwillingness of control patients to consent to tissue sampling
- Confounding factor of patient exposure to environmental sources of the same silicone constituents found in silicone implants (See detailed explanation below.)

To expand on the above points, further clarification is warranted. Regarding tissue collection, surgeons attempt to conserve as much surrounding tissue as possible when removing a ruptured breast implant. In standard medical practice surgeons typically only remove tissue and forward it for laboratory evaluation if they suspect some type of pathology. Any quantity of tissue removed would be excised with the objective of minimal patient disfigurement. Furthermore, for patients undergoing reconstruction surgery there is typically little, if any, surrounding breast tissue available for harvesting adjacent to the ruptured implant.

As will be discussed in detail in Deficiency 1c, only 25 ruptured implants have been explanted from Core Study patients over a four year period, and only 3 of those devices were from non-mastectomy breasts with a subglandular placement. Considering the *potential* sample size was only 3 implants in a four year period, there is then the issue of patients granting consent for tissue samples to be used for research purposes. Furthermore, with so few potential tissues it would not be possible to develop an appropriate sample size from which to collect meaningful data. Even if an appropriate sample size of tissues could be procured, multiple hurdles exist for the successful collection and analyzing of the tissues for gel constituents.

Further complicating the execution of tissue sampling is the lack of standardized procedures for tissue specimen collection, handling and storage. In the absence of standardized procedures, tremendous variability in the processes used could occur, which in turn, could adversely affect the integrity of the samples and the subsequent analytical results. Numerous opportunities to introduce bias into the study are present, from tissue collection throughout the chain of custody that could allow for cross-contamination of the tissue by surgical or laboratory equipment. Supposing that standardized procedures were developed, the logistics would be daunting to train all

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of the involved medical personnel and laboratory staff to ensure their compliance with the applicable procedures for tissue collection, handling and processing.

Assuming that all of the above obstacles could be overcome, validated standardized methodologies for the analyses of different gel constituents or silicone species or levels in human tissues currently do not exist. Multiple analytical techniques may be required depending on the molecular weight siloxane being evaluated. The hurdles include a lack of standardized siloxane assays and the lack of reliable/reproducible laboratory procedures to ensure that the tissues are not compromised and that all hazardous/infectious materials regulations are met.

To establish procedural methodologies and provide appropriate baseline and controls, known samples with specific standards must be used. Therefore, only prominent silicone species with commercially available standards can be considered for testing. FDA's newly released 2004 Breast Implant Update² recognizes that "Currently, there are no FDA-approved tests to detect silicone in the body". Without such analytical capabilities available, collection and testing of breast tissue may be inaccurate at best and quite possibly meaningless or misleading, especially without well-defined control tissues. Therefore, one cannot determine accurate and precise measurements of different silicone species levels. Because of the same clinical and practical issues addressed above, it would also make the collection, processing and analysis of control samples, e.g., surrounding tissue of saline implants, not feasible.

To summarize, tissue samples that could yield meaningful data for analysis cannot be obtained in the majority of patients, so there is limited opportunity to collect samples. Similar obstacles impede the collection of control samples. In addition, any samples collected would be tainted by the patient's exposure to environmental sources of silicone, as well as possible silicone contamination from surgical or laboratory instruments and equipment. Therefore, analyses would be unable to determine the source of silicone constituents found in the tissues. And, even if silicone constituents could be identified, there would be no way to determine a temporal relationship with the time and source of silicone exposure.

Siloxanes in Tissue

Gel implant constituents do not occur in patient tissues only as a result of extracapsular gel or migrated gel from breast implants. A close examination of human exposure to siloxanes provides a more complete picture. Siloxanes are ubiquitous in a multitude of products and devices and, as a result, many compounds may reside in human tissues. Indeed, the same silicone constituents described in gel

² "FDA Breast Implant Consumer Handbook – 2004."
<http://www.fda.gov/cdrh/breastimplants/indexbip.PDF>

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breast implant constituents are also found in personal health products, food, oral medication, syringe lubrication and injection needles. So, basically, tissue analyses would not be helpful in differentiating silicone species from breast implant ruptures versus silicone species from environmental exposure.

This issue of silicone in tissues has been addressed in animals. A pharmacokinetics study (previously submitted in PMA P020056) was initiated by Inamed to directly examine the subsequent mobility of Inamed silicone gel in tissue following direct placement of silicone into a soft tissue compartment. Three (3) female rats were subcutaneously implanted with 3.4 grams of carbon-¹⁴ radiolabeled silicone gel as a bolus for 30 days. Upon harvest of the surrounding tissues, 99.49% of the introduced radioactive silicone remained at the implantation site. This directly demonstrated that there is minimal movement of silicone gel from the implantation site. Biocompatibility evaluations of silicone gel presented in P020056, confirm the lack of interaction of gel with tissue. For instance, exposure of gel to a cell monolayer in cytotoxicity testing is not observed to induce cellular distress. Additionally, exposure of gel to paravertebral muscle in the rabbit for 90 days resulted in histological observations considered by the pathologist to demonstrate the non-toxicity of gel implants in rabbit tissue.

Furthermore, documentation was provided [REDACTED] regarding the pharmacokinetics of silicone elastomers, gel, fluids and low molecular weight compounds. This comprehensive literature review included published journal articles and publicly available Dow Corning studies that in summary indicated that silicone materials appear to have low mobility, typically remain where implanted, and elicit only a local response.

These data support the pharmacokinetic studies of silicone that were reviewed as part of the evaluation performed by the Committee on the Safety of Silicone Breast Implants, Institute of Medicine (IOM). Based on their findings, the IOM stated, *Studies using whole fluids, gels, elastomers, or experimental implant models injected or implanted in ways that are directly relevant to the human experience with implants are also reassuring. These studies show that depots of gel, whether free or in implants, remain almost entirely where injected or implanted. Even low molecular weight cyclic and linear silicone fluids appear to have low mobility* (Institute of Medicine, 2000)³.

This conclusion is consistent with the findings of the Independent Review Group (IRG), which determined *that the relevant studies have shown only local reactions to*

³ Institute of Medicine, Committee on the Safety of Silicone Breast Implants. 2000. *Safety of Silicone Breast Implants*. Bondurant, S., V. Ernster, and R. Herdman, editors. National Academy Press, Washington, D.C. 560 pgs. [<http://books.nap.edu/books/0309065321/html/index.html>]

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silicones. Systemic damage and dispersal of silicone polymers throughout the body has not been well demonstrated, despite various claims, even after rupture of gel-filled implants (Independent Review Group, 1998)⁴. Furthermore as noted in Deficiency 1f, patients with ruptured implants are no more likely to experience local complications than patients with non-ruptured implants.

Due to the infeasibility of collecting tissue samples from patients during explantation of ruptured implants and successfully analyzing these tissues for silicone species, Inamed considers Deficiency 1b to be best answered via scientific computer modeling rather than human tissue sampling. Furthermore, with so many siloxanes in the environment, tissue sampling would yield data that would be of little to no clinical value because any silicone constituents found in the tissue samples could be attributed to the environment rather than exposure to silicone gel via ruptured breast implants.

Physiologically Based Pharmacokinetic (PBPK) Model

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

PBPK modeling represents the current state-of-the-art tool for integrating and describing pharmacokinetic data. The resulting PBPK model can therefore be used to make informed decisions about the disposition of silicones that may migrate from intact or ruptured gel implants. Because of its underlying biological basis, PBPK models are also a method of choice for decreasing the uncertainties associated with extrapolating across species, routes of exposure and dose in human health risk assessments (Luu et al., 1998). This capability is especially important for situations where it is neither ethical nor technically or statistically feasible to obtain the necessary data in humans.

Inamed's initial PBPK model is based on published PBPK modeling developed for D₄, octamethylcyclotetrasiloxane, to describe possible silicone movement from a breast implant depot. Additional animal tissues (blood and fat) and human tissues (blood and breast) partition coefficients data are being determined to describe an

⁴ Independent Review Group (IRG). 1998. *Silicone Gel Breast Implants. The Report of the Independent Review Group*. Jill Rogers Associates, Cambridge, UK. 38pgs. [http://www.silicone-review.gov.uk/silicone_implants.pdf]

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implant based exposure PBPK compartment. An interim report of the preliminary D₄ model and the supporting data is provided in Attachment 1-3. PBPK modeling can express the absorption, tissue distribution, metabolism and elimination of a compound, as well as the biological interaction of a compound with tissues and systems of the body, especially for situations where it is not ethical or possible to obtain necessary data in humans. Compared to time and research efforts associated with generating meaningful data without the assistance of PBPK modeling, use of PBPK simulations allow the data associated with a smaller sample size to be accurately extrapolated and become predictive of the movement of silicone species into and out of the human body.

Specific PBPK modeling for octamethylcyclotetrasiloxane (D₄) is described in the literature (Luu and Hutter, 2001; Andersen et al., 2001; Sarangapani et al., 2002 and 2003; and Reddy et al., 2003). As FDA scientists have stated "PBPK models will reduce the uncertainties in the human risk assessment process ... [and] will provide a much needed scientific basis to the traditional human risk assessment for medical devices" (Luu *et al.*, 1998). Copies of these cited articles are provided in Attachment 1-4.

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

"The resulting implant site simulations were based on both a young adult (pre-menopausal) woman and a matured (post-menopausal) woman using worst-case exposure conditions (i.e., no shell to stimulate complete rupture of the largest available implants; maximum levels of D₄ in silicone; and a range of assumed breast tissue fat contents from very low to virtually all fat). The resulting simulations indicate that D₄ is cleared primarily by exhalation with highest concentrations achieved briefly in breast tissues of a post-menopausal woman due to the very high assumed fat content. D₄ is predicted to be cleared to levels below 1 ppm within ~30 days. Thus, it is unlikely that D₄ would be detected in any tissue of the body within a few weeks of receiving an implant, even if immediately ruptured, under the assumptions used in this initial PBPK model."

In addition to the D₄ modeling, Inamed's intent is to continue development of the PBPK model to incorporate mid- and large-molecular weight silicone constituents into a final model providing a range of silicone gel species.

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SUMMARY

As noted above, the potential sample size for tissue sampling from appropriate Core Study patients was only 3 implants within 4 years. Even if there were an adequate pool of rupture patients available, patients may be unwilling to consent to the tissue sampling for a myriad of reasons. Given the low probability of sufficient samples, the absence of validated methods for collecting and analyzing the tissues and the prevalence of daily exposure to siloxanes in the environment, the impracticality of human tissue sampling is apparent. In addition, no evidence of gel migration was found in the Core Study or in animal pharmacokinetics studies. This demonstrates that a woman's exposure to silicone gel from a ruptured implant is likely limited to the breast area. Furthermore, toxicological studies show the non-toxicity of gel, which is supported by Core Study data showing that patients with ruptured implants are no more likely to experience local complications than patients with non-ruptured implants.

Considering the constraints associated with patient tissue testing and the lack of valid scientific methodologies for determining silicone from breast implant tissue analysis, Inamed believes that the PBPK methodology is the appropriate approach to address FDA's concern regarding the identification of gel implant constituents in surrounding breast tissue exposed to a ruptured silicone-filled implant.

Based on preliminary PBPK data on D₄, we are confident that this scientific method is a viable alternative to the problem-fraught human tissue sampling analysis proposed by FDA. Inamed intends to continue the program to test low, mid- and high molecular weight species and proposes that these analyses be provided to FDA on a post-approval basis, since toxicological and other studies demonstrate that the issue of human exposure to silicone gel breast implant constituents is not a significant safety issue for women.

C. FREQUENCY OF OBSERVED INTRACAPSULAR, EXTRACAPSULAR, AND MIGRATED GEL

Out of 1,782 implants (940 patients) enrolled in the Core Study, there has been only one case of extracapsular gel reported and no cases of migrated gel. The instance of extracapsular gel occurred following an incision made during an exploratory surgery to check the implant status. The physician created an incision large enough to insert his finger through to feel the implant surface for signs of rupture or free gel. At the time of the exploratory surgery, free gel was found only on the implant surface, and the physician noted the absence of extracapsular gel. Replacement surgery was scheduled for a later date. Before the replacement surgery could occur, extracapsular gel was found oozing through the incision site, and the physician believe this was a result of his opening the capsule during the digital exploration.

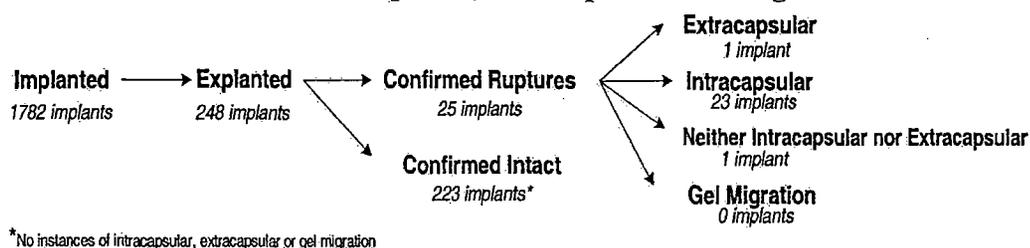
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The following details the findings of intracapsular and extracapsular gel at the time of implant removal for Core Study patients:

- Augmentation: 96 explanted devices with 5 occurrences of intracapsular gel and 1 occurrence of extracapsular gel. Refer to Attachment 1-5 for further details of the patient's clinical course (Patient ID C0010-A025) before and after the extracapsular gel finding
- Reconstruction: 81 explanted devices with 13 occurrences of intracapsular gel and 0 occurrences of extracapsular gel
- Revision: 71 explanted devices with 5 occurrences of intracapsular gel and 0 occurrences of extracapsular gel

Figure 1-1
Breakdown of Extracapsular, Intracapsular and Migrated Gel



In conclusion, the occurrence of extracapsular or migrated gel has proven to be extremely rare in the Core Study. There were no cases of gel migration, and the one case of extracapsular gel was most likely procedure-induced during a secondary surgical procedure. These results are consistent with the findings in the Adjunct Study as delineated in Deficiency 2a, which showed just four extracapsular ruptures and two instances of gel migration out of 99 confirmed ruptures. Core Study patients will continue to be monitored for circumstances surrounding rupture throughout the remainder of the study.

D. POTENTIAL LOCAL HEALTH CONSEQUENCES OF RUPTURE

In the Core Clinical Study, 43 confirmed and unconfirmed ruptured implants have been identified in 42 patients. The clinical course for each of these patients is detailed in patient summaries in Attachment 1-5. A table describing these patients/implants by rupture classification (i.e., silent versus symptomatic) and sub-cohort (MRI versus Non-MRI), and a figure showing the breakdown for the combined cohorts are located in Attachment 1-6.

Overall, the information presented in the patient summaries does not show any unexpected adverse events or consequences (i.e. local complications). The

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complications experienced most frequently after confirmed rupture were redness (23.5%), infection (17.6%) and swelling (17.6%). All of these are common complications following surgery. No patterns developed, and no complications appeared with an alarming frequency to suggest a relationship with rupture. This is consistent with the published literature findings and Adjunct Study results described in Deficiency 2, which show that the local complications experienced by women with ruptured implants were not significantly different from the local complications experienced by women with intact implants.

A comparison of the complications experienced by patients with confirmed ruptured implants with those patients with confirmed intact implants is further discussed in Deficiency 1f. Tables 1-5 of Attachment 1-8 present the number and types of complications experienced by patients, and Figure 1-3 in Deficiency 1f provides an overview depicting the number of complications experienced.

E. PROSPECTIVE CLINICAL FOLLOW-UP FOR EXPLANTED PATIENTS WITHOUT REPLACEMENTS

Although FDA requested prospective data on patients explanted without replacement implants, Inamed also gathered retrospective data in order to obtain information from as many patients as possible. For the Core Study patients meeting this criteria to date, retrospective data is presented below.

Retrospective Data

Inamed examined the existing data available on current patients retrospectively. There were a total of 25 patients who were explanted and not re-implanted at the time of discontinuation from the Core Study. Of the 25 patients, 11 were from the Augmentation cohort, 11 from the Reconstruction cohort and 3 were from the Revision cohort.

Each study site was asked to contact the respective patients and ask them a set of questions. The questions are as follows:

- *Has the patient experienced any complications since her last follow-up?*
- *Has the patient had any breast surgery since her last follow-up?*
- *Has the patient had a non-study breast implant device(s) placed since her last follow-up?*
- *Has the patient developed new or recurrent breast cancer since her last follow-up?*
- *Has the patient reported a CTD or Autoimmune Disease since her last follow-up?*

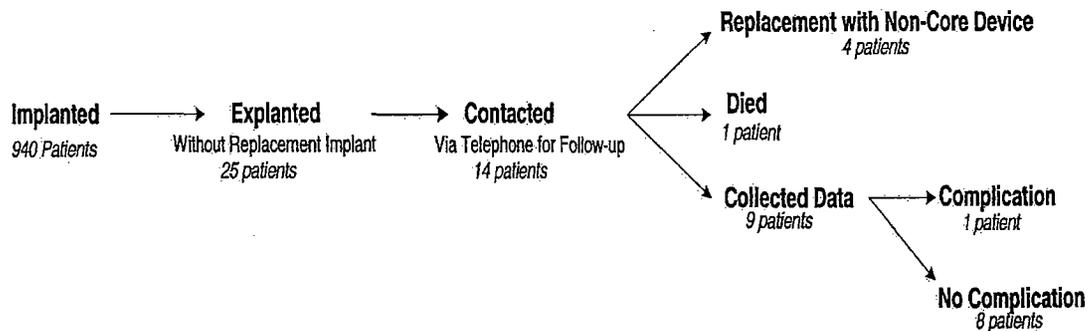
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Out of the 25 available patients, sites were able to make contact with 14 patients. Of the remaining 11 patients, 6 were unable to be contacted (4 for whom the site and sponsor were unable to obtain current contact information and 2 patients who did not respond to contact attempts). Three (3) patients have not yet been contacted by the site and 2 patients refused to communicate with the site any further regarding study data.

Of the 14 patients on whom data was gathered, 4 had been reimplanted with new non-study implants and 1 died due to metastatic brain cancer. Hence 9 patients remain for whom data was gathered. Figure 1-2 below illustrates the status of these 14 patients.

**Figure 1-2
Retrospective Data Gathered on Core Explanted Patients
with No Replacement Implants**



Complications

Of the 9 patients for whom data was gathered, only 1 experienced complications after the removal of her implants. This patient reported mild soreness from the explant surgery.

Breast Surgery

Of the 14 patients who were contacted, 5 had undergone additional breast surgery, 4 with placement of nonstudy implants since their discontinuation from the Core Study. The patient and corresponding procedures are listed below:

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New or Recurrent Breast Cancer

None of the contacted patients experienced new or recurrent breast cancer.

CTD or Autoimmune Disease

None of the contacted patients had developed a CTD or an autoimmune disease.

Summary

None of the patients discontinued from the Core Study due to explant evidenced local or systemic complications different in nature or frequency than those patients still implanted with Core Study devices. This provides reassurance that the Core Study results are indicative of all patient experiences with Inamed's silicone-filled breast implants and that negative results have not been masked by patients being explanted and discontinued from the study.

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F. PATIENTS WITH RUPTURES VERSUS PATIENTS WITHOUT RUPTURES

Underlying the analysis for comparison of consequences for patients with ruptured implants versus patients with non-ruptured implants is the fact that all patients who have a confirmed rupture have also undergone implant removal. Therefore, many of the outcomes (e.g., swelling, scarring, low patient satisfaction) seen after confirmed rupture may be due to the implant removal procedure itself. In order to evaluate the role of rupture in causing future outcomes (i.e., consequences), it is most useful to compare explants that have been confirmed ruptured to those that have been confirmed intact. In preparation for this analysis, the Core Study patient population was stratified by rupture status, and the following groups were defined:

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- Confirmed Rupture – includes implants that have been explanted and have been confirmed to be ruptured
- Unconfirmed Rupture – includes implants that are suspected of being ruptured, but have not yet been explanted to obtain confirmation
- Rupture – includes implants that have either a confirmed or unconfirmed rupture (i.e., a combination of the above 2 categories)
- Confirmed Intact – includes implants that have been explanted and have been confirmed to be intact
- Intact – includes all implants except those that have been confirmed to be ruptured or are currently classified as an “unconfirmed rupture”

Group	Number of Patients	Number of Implants
Confirmed Rupture	25	25
Unconfirmed Rupture	17	18
Confirmed & Unconfirmed Rupture	42	43
Confirmed Intact	131	208
Intact	935	1739

Patient Satisfaction

Patient satisfaction at each follow-up interval was calculated for each of the 5 patient groupings described above. Tables 1-5 in Attachment 1-7 present satisfaction by follow-up interval. In the Confirmed Rupture group, satisfaction is calculated after the explantation confirming rupture. In the Unconfirmed Rupture group, satisfaction is calculated after the estimated date of rupture. In the Confirmed Intact group, satisfaction is calculated after the explantation confirming non-rupture. In the Intact group, all satisfaction since enrollment is included in the calculation. The comparison is presented below between the Confirmed Rupture group and the Confirmed Intact group:

- Confirmed Rupture group: At 3 years, 100% of patients were satisfied.
- Confirmed Intact group: At 3 years, 84% of patients were satisfied.

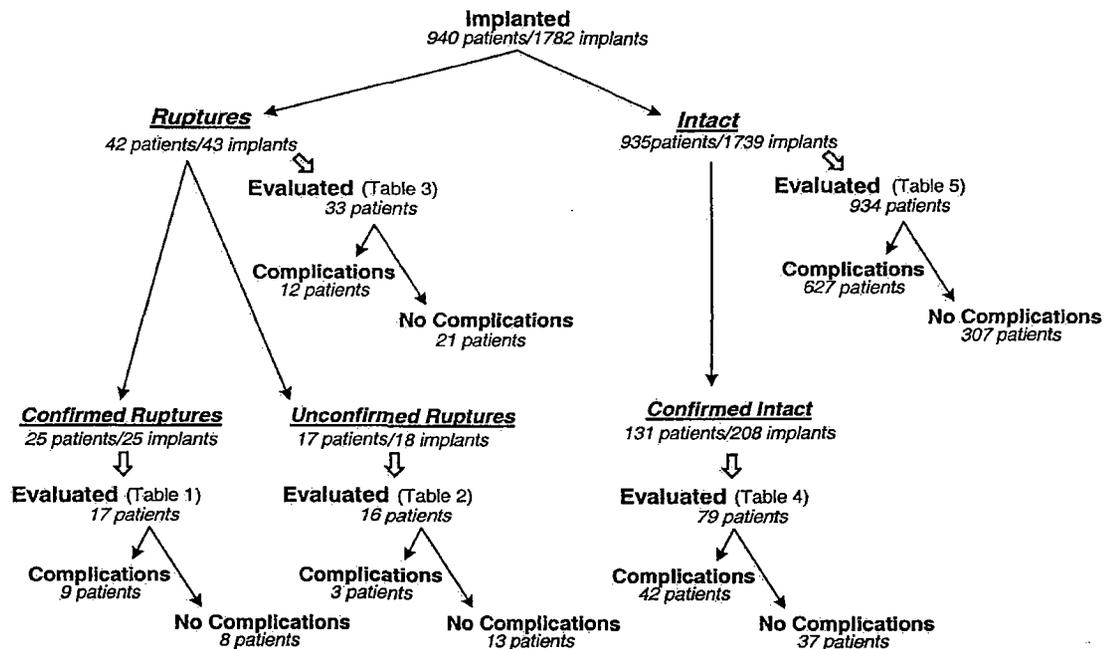
As indicated above, satisfaction is high in both groups. This is consistent with the Adjunct Study findings noted in Deficiency 2b, which revealed that very few patients expressed dissatisfaction with their breast implants even following a confirmed rupture.

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Local Complications

The percentage of patients and implants with local complications was calculated for each of the 5 groups described above (Tables 1-5 in Attachment 1-8). As evidenced by Figure 1-3 below, the percentage of patients who experienced complications is virtually identical for those patients with confirmed ruptures (52.9% = 9/17) versus those with confirmed intact implants (53.1% = 42/79).

Figure 1-3
Local Complications Flow Diagram



That is, breakdown of complications amongst the five groups showed:

- **Confirmed Rupture:** Local complications occurring after the explantation confirming rupture were examined and presented in Table 1 of Attachment 1-8. Twenty-five (25) patients experienced a confirmed rupture; however, only 17 patients were included in the analysis because 8 patients have not yet had any follow-up after the explantation. The patients included had an average follow-up of 1.3 years after the explantation.
- **Unconfirmed Rupture:** Local complications occurring after the estimated date of rupture were examined and presented in Table 2. Seventeen (17) patients are classified as having an unconfirmed rupture; however, only 16 patients were

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included in the analysis because 1 patient has not yet had any follow-up after the estimated date of rupture. The patients included had an average follow-up of 1.2 years after the estimated date of rupture.

- **Confirmed and Unconfirmed Rupture:** Local complications occurring for two groups above were examined as a single group and presented in Table 3. Forty-two (42) patients were classified as having either a confirmed or unconfirmed rupture; however, only 33 patients were included in the analysis because 9 patients had not yet had any follow-up after explant or estimated date of rupture. The patients included had an average follow-up of 1.2 years after the explant or estimated rupture date.
- **Confirmed Intact:** Local complications occurring after the explantation confirming non-rupture were examined and presented in Table 4. One hundred thirty-one (131) patients underwent explant confirming non-rupture; however, only 79 patients were included in the analysis because 52 patients have not yet had any follow-up after the explantation. The patients included had an average follow-up of 2.5 years after the explantation.
- **Intact group:** All local complications occurring since enrollment were examined and presented in the table. Nine hundred thirty-five (935) patients are currently assumed to have intact implants; however, only 934 patients were included in the analysis because 1 patient has not yet had any follow-up. The patients included had an average follow-up of 3.6 years after the implantation.

The comparison is presented below between the Confirmed Rupture group and the Confirmed Intact group:

- **Confirmed Rupture:** Seventeen (17) patients have been followed after confirmation (i.e., removal) of a ruptured implant for an average of 1.3 years. The most common local complications experienced after removal of confirmed ruptured implants are: redness (24%, n=4), swelling (18%, n=3) and infection (18%, n=3).
- **Confirmed Intact:** Seventy-nine (79) patients have been followed after confirmation (i.e., removal) of an intact implant for an average of 2.5 years. The most common local complications experienced after removal of confirmed non-ruptured implants are: capsular contracture (14%, n=11), breast pain (14%, n=11) and swelling (13%, n=10).

In addition to the frequency analysis (above), a Cox proportional hazard regression analysis was conducted to examine whether implant rupture is a risk factor for any of the local complications. A multivariate model was derived using rupture as the potential risk factor and adjusting for cohort (augmentation, reconstruction and revision). Since all patients in the Confirmed Rupture group had undergone implant removal, the Confirmed Intact group was chosen as the index comparison group to

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create the regression model and calculate the risk ratios. Each model proved to be unreliable due to the small sample size, and, therefore, no conclusions can be drawn from these results.

Connective Tissue Disease Signs/Symptoms

The percentage of patients with connective tissue disease (CTD) signs/symptoms was calculated for each of the 5 groups described above (Tables 1-5 in Attachment 1-9). In the Confirmed Rupture group, new signs/symptoms occurring after the explantation confirming rupture were examined and presented in Table 1. In the Unconfirmed Rupture group, new signs/symptoms occurring after the estimated date of rupture were examined and presented in Table 2. In the Confirmed Intact group, new signs/symptoms occurring after the explantation confirming non-rupture were examined and presented in Table 4. In the Intact group, all signs/symptoms occurring since enrollment were examined and presented in Table 5. The comparison is presented below between the Confirmed Rupture group and the Confirmed Intact group:

- **Confirmed Rupture:** Eleven (11) patients have completed at least one CTD questionnaire after confirmation (i.e., removal) of a ruptured implant. Over 20% of this group experienced the following CTD signs/symptoms for the first time following ruptured implant removal: skin (27%), gastrointestinal problems (27%) and muscle (46%).
- **Confirmed Intact:** Seventy-two (72) patients have completed at least one CTD questionnaire after confirmation (i.e., removal) of an intact implant. Over 20% of this group experienced the following CTD signs/symptoms for the first time following intact implant removal: gastrointestinal problems (24%) and neurological (21%).

In comparing the frequencies between the two groups, the following signs/symptoms categories had frequency differences of at least 5% indicating that more women with confirmed rupture experience the sign/symptom than in women with confirmed intact implants: muscle (46% versus 16.7%) and skin (27.3% versus 18.1%). Many of these increases may be due to patient aging and other variables, which are investigated further in the response to Deficiency 4.

Summary

In conclusion, Inamed successfully estimated a 10 year overall rupture rate of 13.9%, which does not suffer from underestimation of silent ruptures. Based on Core Study results, virtually all of these ruptures will be intracapsular, with occurrence of gel migration extremely rare. For those patients who experience a rupture, Core Study

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findings show no difference in local complications or patient satisfaction as compared to patients with confirmed intact implants. With a greater number of ruptures examined in the Adjunct Study, results also indicated that extracapsular gel and gel migration were infrequent occurrences and that there was no difference in the complications experienced between patients who experience rupture and those who do not experience rupture. Any increases in CTD signs and symptoms for Core Study rupture patients are thought to be a factor of aging and other variables as discussed in Deficiency 4. Therefore, a risk of rupture does not appear to be a factor that should deter women from seeking silicone-filled breast implantation.

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CORE STUDY - AUGMENTATION

Table 1: Patient Compliance

	1 Year	2 Years	3 Years	4 Years
Theoretically Due	494	494	494	427
Deaths*	0	0	1	1
Explant-Related Discontinuations*	3	5	14	12
Without Replacement	0	2	7	6
Replacement with Non-Study Device	3	3	7	6
Unknown Replacement Status	0	0	0	0
Expected	491	489	479	414
Actual Evaluated	425	439	410	333
Lost-to-Follow-Up	66	50	69	81
% Follow-Up	86.6%	89.8%	85.6%	80.4%

* Deaths and Explant-Related Discontinuations are reported cumulatively.

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CORE STUDY - RECONSTRUCTION

Table 2: Patient Compliance

	1 Year	2 Years	3 Years	4 Years
Theoretically Due	221	221	221	147
Deaths*	1	5	9	11
Explant-Related Discontinuations*	5	11	14	18
Without Replacement	4	6	6	5
Replacement with Non-Study Device	1	4	6	11
Unknown Replacement Status	0	1	2	2
Expected	215	205	198	118
Actual Evaluated	205	194	186	105
Lost-to-Follow-Up	10	11	12	13
% Follow-Up	95.3%	94.6%	93.9%	89.0%

* Deaths and Explant-Related Discontinuations are reported cumulatively.

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CORE STUDY - REVISION

Table 3: Patient Compliance

	1 Year	2 Years	3 Years	4 Years
Theoretically Due	225	225	225	218
Deaths*	0	2	4	6
Explant-Related Discontinuations*	4	7	10	12
Without Replacement	1	2	3	2
Replacement with Non-Study Device	3	5	7	10
Unknown Replacement Status	0	0	0	0
Expected	221	216	211	200
Actual Evaluated	177	188	183	162
Lost-to-Follow-Up	44	28	28	38
% Follow-Up	80.1%	87.0%	86.7%	81.0%

* Deaths and Explant-Related Discontinuations are reported cumulatively.

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CORE STUDY - SERIAL MRI

Table 4: Patient Compliance for the MRI-Cohort

	Total	Augmentation	Reconstruction	Revision
1st Serial MRI				
Theoretically Due	351	166	107	78
Deaths	0	0	0	0
Explant-Related Discontinuations	7	7	0	0
Expected	344	159	107	78
Actual Evaluated	309	136	101	72
Lost-to-Follow-Up	35	23	6	6
% Follow-Up	89.8%	85.5%	94.4%	92.3%
2nd Serial MRI				
Theoretically Due	297	166	61	70
Deaths	0	0	0	0
Discontinued Due to Claustrophobia/ Metal-Implanted Devices	4	4	0	0
Explant-Related Discontinuations	7	7	0	0
Expected	286	155	61	70
Actual Evaluated	232	131	44	57
Lost-to-Follow-Up	54	24	17	13
% Follow-Up	81.1%	84.5%	72.1%	81.4%

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CORE STUDY - All Implants

Table 1: Risk of First Occurrence of Overall Rupture

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	0	922	0.0%	0	1744	0.0%
6 Months	2	894	0.2% (0.0%, 0.5%)	2	1691	0.1% (0.0%, 0.3%)
1 Year	3	867	0.3% (0.0%, 0.7%)	3	1638	0.2% (0.0%, 0.4%)
2 Years	30	799	3.5% (2.3%, 4.8%)	30	1531	1.9% (1.2%, 2.5%)
3 Years	39	734	4.7% (3.2%, 6.1%)	40	1408	2.5% (1.8%, 3.3%)
4 Years	72	518	10.1% (7.8%, 12.3%)	74	1032	5.5% (4.3%, 6.7%)

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CORE STUDY - AUGMENTATION

Table 2: Risk of First Occurrence of Overall Rupture

Time	By Patient				By Implant			
	Number Affected		Number Remaining		Number Affected		Number Remaining	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
4 Weeks	0	0.0%	486	0.0%	0	0.0%	971	0.0%
6 Months	2	0.4%	481	0.4%	2	0.2%	961	0.2%
1 Year	3	0.6%	468	0.6%	3	0.3%	935	0.3%
2 Years	4	0.8%	446	0.8%	4	0.4%	892	0.4%
3 Years	9	2.0%	409	2.0%	9	1.0%	822	1.0%
4 Years	14	3.4%	314	3.4%	14	1.7%	634	1.7%

* 5 implants failed after the 4 year time point.

CORE STUDY - RECONSTRUCTION

Table 3: Risk of First Occurrence of Overall Rupture

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	0	220	0.0%	0	359	0.0%
6 Months	0	205	0.0%	0	332	0.0%
1 Year	0	197	0.0%	0	317	0.0%
2 Years	16	172	8.4% (4.4%,12.3%)	16	286	5.2% (2.7%, 7.7%)
3 Years	20	156	10.6% (6.2%,15.0%)	21	257	6.9% (4.1%, 9.8%)
4 Years	33	76	22.9% (15.6%,30.2%)	35	137	15.1% (10.2%,19.9%)

CORE STUDY - REVISION

Table 4: Risk of First Occurrence of Overall Rupture

Time	By Patient				By Implant			
	Number Affected		Number Remaining		Number Affected		Number Remaining	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
4 Weeks	0	--	216	0.0%	0	0.0%	414	0.0%
6 Months	0	--	208	0.0%	0	0.0%	398	0.0%
1 Year	0	--	202	0.0%	0	0.0%	386	0.0%
2 Years	10	(2.0%, 8.2%)	181	5.1%	10	(2.0%, 8.2%)	353	2.7% (1.0%, 4.3%)
3 Years	10	(2.0%, 8.2%)	169	5.1%	10	(2.0%, 8.2%)	329	2.7% (1.0%, 4.3%)
4 Years	25	(9.3%,20.0%)	128	14.6%	25	(9.3%,20.0%)	261	7.7% (4.8%,10.7%)

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CORE STUDY - ALL IMPLANTS (Aug, Recon, & Revis)

Table 5: Risk of First Occurrence of Silent Rupture

Time	By Patient				By Implant				
	Number Affected		Number Remaining		Number Affected		Number Remaining		Cumulative Risk (95% CI)
	n	%	n	%	n	%	n	%	
4 Weeks	0	0.0%	922	0.0%	0	0.0%	1744	0.0%	--
6 Months	2	0.2%	894	0.2%	2	(0.0%, 0.5%)	1691	0.1%	(0.0%, 0.3%)
1 Year	3	0.3%	867	0.3%	3	(0.0%, 0.7%)	1638	0.2%	(0.0%, 0.4%)
2 Years	29	3.4%	799	3.4%	29	(2.2%, 4.6%)	1531	1.8%	(1.2%, 2.5%)
3 Years	37	4.4%	735	4.4%	38	(3.0%, 5.8%)	1409	2.4%	(1.7%, 3.2%)
4 Years	68	9.6%	519	9.6%	70	(7.4%, 11.8%)	1033	5.2%	(4.0%, 6.4%)

* 3 implants failed past the 4 year time point

CORE STUDY - AUGMENTATION

Table 6: Risk of First Occurrence of Silent Rupture

Time	By Patient				By Implant				
	Number Affected		Number Remaining		Number Affected		Number Remaining		Cumulative Risk
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	
4 Weeks	0	0.0%	486	0.0%	0	0.0%	971	0.0%	--
6 Months	2	0.4%	481	0.4%	2	0.2%	961	0.2%	(0.0%, 0.5%)
1 Year	3	0.6%	468	0.6%	3	0.3%	935	0.3%	(0.0%, 0.7%)
2 Years	4	0.8%	446	0.8%	4	0.4%	892	0.4%	(0.0%, 0.8%)
3 Years	9	2.0%	409	2.0%	9	1.0%	822	1.0%	(0.4%, 1.7%)
4 Years	12	2.8%	314	2.8%	12	1.4%	634	1.4%	(0.6%, 2.2%)

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CORE STUDY - RECONSTRUCTION

Table 7: Risk of First Occurrence of Silent Rupture

Time	By Patient				By Implant			
	Number Affected		Number Remaining		Number Affected		Number Remaining	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
4 Weeks	0	0.0%	220	0.0%	0	0.0%	359	0.0%
6 Months	0	--	205	0.0%	0	0.0%	332	0.0%
1 Year	0	--	197	0.0%	0	0.0%	317	0.0%
2 Years	16	(4.4%, 12.3%)	172	8.4%	16	(2.7%, 7.7%)	286	5.2%
3 Years	19	(5.7%, 14.3%)	157	10.0%	20	(3.8%, 9.4%)	258	6.6%
4 Years	32	(15.1%, 29.5%)	77	22.3%	34	(9.9%, 19.5%)	138	14.7%

CORE STUDY - REVISION

Table 8: Risk of First Occurrence of Silent Rupture

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	0	216	0.0%	0	414	0.0%
6 Months	0	208	0.0%	0	398	0.0%
1 Year	0	202	0.0%	0	386	0.0%
2 Years	9	181	4.6% (1.7%, 7.5%)	9	353	2.4% (0.9%, 4.0%)
3 Years	9	169	4.6% (1.7%, 7.5%)	9	329	2.4% (0.9%, 4.0%)
4 Years	24	128	14.2% (8.9%, 19.5%)	24	261	7.5% (4.6%, 10.4%)

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CORE STUDY - ALL IMPLANTS (Aug, Recon, & Revis)

Table 9: Risk of First Occurrence of Symptomatic Rupture

Time	By Patient				By Implant			
	Number Affected		Number Remaining		Number Affected		Number Remaining	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
4 Weeks	0	0.0%	922	0.0%	0	0.0%	1744	0.0%
6 Months	0	0.0%	895	0.0%	0	0.0%	1692	0.0%
1 Year	0	0.0%	869	0.0%	0	0.0%	1640	0.0%
2 Years	1	0.1% (0.0%, 0.4%)	826	0.1% (0.0%, 0.4%)	1	0.1% (0.0%, 0.2%)	1558	0.1% (0.0%, 0.2%)
3 Years	2	0.3% (0.0%, 0.6%)	761	0.3% (0.0%, 0.6%)	2	0.1% (0.0%, 0.3%)	1436	0.1% (0.0%, 0.3%)
4 Years	4	0.6% (0.0%, 1.1%)	568	0.6% (0.0%, 1.1%)	4	0.3% (0.0%, 0.6%)	1084	0.3% (0.0%, 0.6%)

CORE STUDY - AUGMENTATION

Table 10: Risk of First Occurrence of Symptomatic Rupture

Time	By Patient				By Implant				
	Number Affected		Number Remaining		Number Affected		Number Remaining		Cumulative Risk
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	
4 Weeks	0	0.0%	486	0.0%	0	0.0%	971	0.0%	--
6 Months	0	0.0%	482	0.0%	0	0.0%	962	0.0%	--
1 Year	0	0.0%	470	0.0%	0	0.0%	937	0.0%	--
2 Years	0	0.0%	448	0.0%	0	0.0%	894	0.0%	--
3 Years	0	0.0%	416	0.0%	0	0.0%	829	0.0%	--
4 Years	2	0.6% (0.0%, 1.3%)	321	0.6% (0.0%, 1.3%)	2	0.3% (0.0%, 0.7%)	641	0.3% (0.0%, 0.7%)	--

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CORE STUDY - RECONSTRUCTION

Table 11: Risk of First Occurrence of Symptomatic Rupture

Time	By Patient				By Implant			
	Number		Cumulative Risk		Number		Cumulative Risk	
	Affected	Remaining	n	% (95% CI)	Affected	Remaining	n	% (95% CI)
4 Weeks	0	220	0.0%	--	0	359	0.0%	--
6 Months	0	205	0.0%	--	0	332	0.0%	--
1 Year	0	197	0.0%	--	0	317	0.0%	--
2 Years	0	188	0.0%	--	0	302	0.0%	--
3 Years	1	168	0.6%	(0.0%, 1.6%)	1	270	0.4%	(0.0%, 1.0%)
4 Years	1	99	0.6%	(0.0%, 1.6%)	1	162	0.4%	(0.0%, 1.0%)

CORE STUDY - REVISION

Table 12: Risk of First Occurrence of Symptomatic Rupture

Time	By Patient				By Implant			
	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)
	n	n	% (95% CI)		n	n	% (95% CI)	
4 Weeks	0	216	0.0%	--	0	414	0.0%	--
6 Months	0	208	0.0%	--	0	398	0.0%	--
1 Year	0	202	0.0%	--	0	386	0.0%	--
2 Years	1	190	0.5%	(0.0%, 1.5%)	1	362	0.3%	(0.0%, 0.8%)
3 Years	1	177	0.5%	(0.0%, 1.5%)	1	337	0.3%	(0.0%, 0.8%)
4 Years	1	148	0.5%	(0.0%, 1.5%)	1	281	0.3%	(0.0%, 0.8%)

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Note: 18 pages were deleted

INTERIM PROGRESS REPORT

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**Development of Initial Physiologically Based Pharmacokinetic (PBPK)
Model to Describe the Disposition of D₄ Migration from Implants**

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SUMMARY

This interim report describes the work completed to date on behalf of Inamed to develop a physiologically based pharmacokinetic (PBPK) model for potentially relevant silicone constituents that may migrate from intact or ruptured silicone breast implants into surrounding tissues. While the choice of appropriate silicone constituents will ultimately be driven by results from ongoing gel migration studies, the initial PBPK model was based upon the extensive toxicological and PBPK modeling database on octamethylcyclotetrasiloxane (D₄). After the introduction section, which provides a brief explanation of D₄ PBPK models available in the peer-reviewed literature, the 3-tiered work scope of Inamed's approach is described. Subsequently, the initial methods and results generated to date are summarized. The resulting implant site simulations were based on both a young adult (pre-menopausal) woman and a matured (post-menopausal) woman using worst-case exposure conditions (i.e. no shell to simulate complete rupture of the largest available implants; maximum levels of D₄ in silicone; and a range of assumed breast tissue fat contents from very low to virtually all fat). The resulting simulations indicate that D₄ is cleared primarily by exhalation with highest concentrations achieved briefly in breast tissues of a post-menopausal woman due to the very high assumed fat content. D₄ is predicted to be cleared to levels below 1 ppm within ~30 days. Thus, it is unlikely that D₄ would be detected any tissue of the body within a few weeks of receiving an implant, even if immediately ruptured, under the assumptions used in this initial PBPK model. As the additional data on diffusion rates, partition coefficients, etc., are collected, the model will continue to be refined to complete the tasks associated with this project.

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Attachment 1-6 Table

CORE STUDY - RUPTURE STATUS (I.E., SILENT VS. SYMPTOMATIC) BY CONFIRMATION STATUS

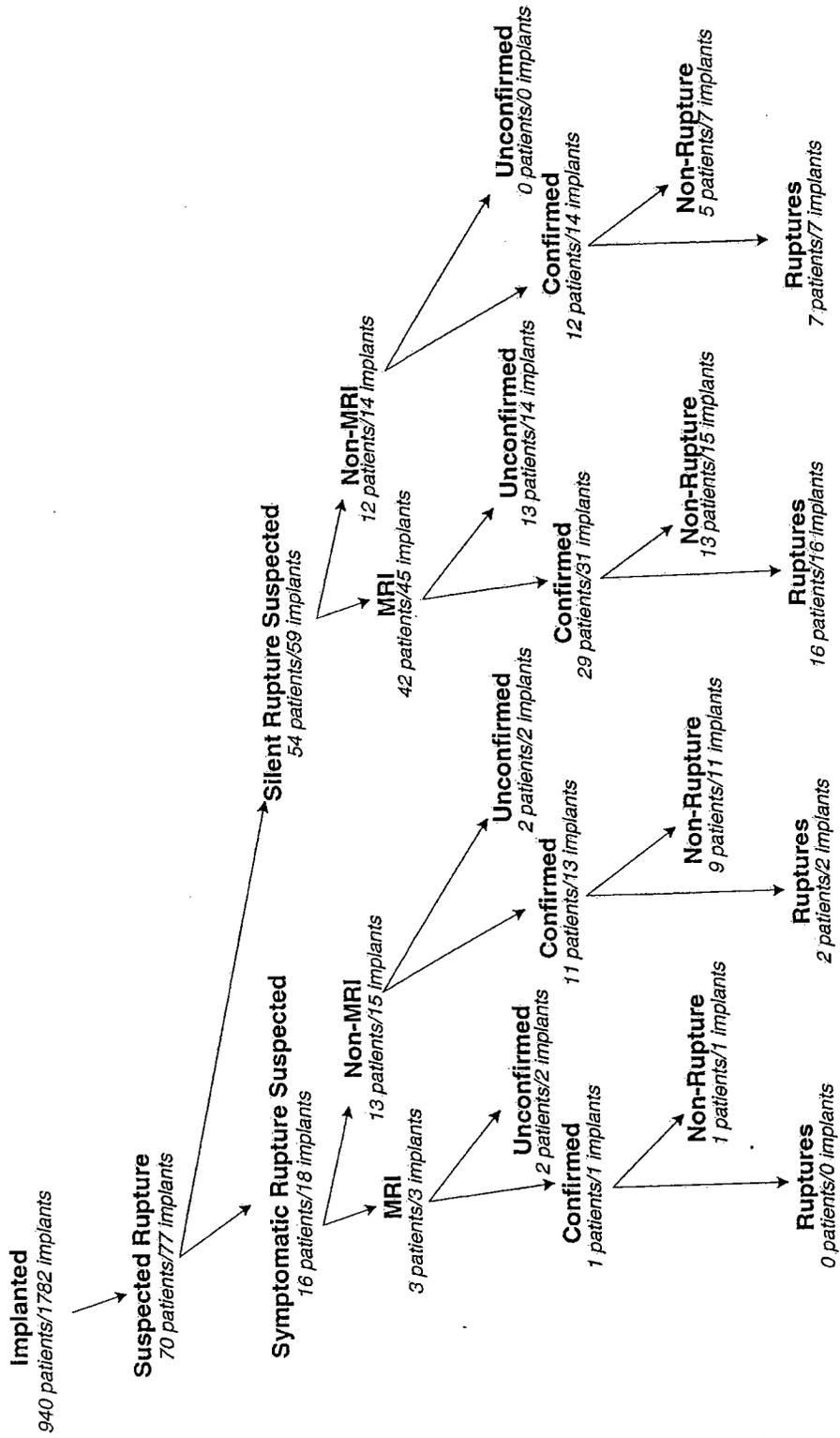
Population	Type (Silent/ Symptomatic)	Confirmation Status	Cohort MRI/ Non-MRI	Number of Patients	Number of Implants
Augmentation	Silent	Confirmed Non-Rupture	MRI	8	9
Augmentation	Silent	Confirmed Non-Rupture	Non-MRI	2	4
Augmentation	Silent	Confirmed Rupture	MRI	3	3
Augmentation	Silent	Confirmed Rupture	Non-MRI	2	2
Augmentation	Silent	Unconfirmed Rupture	MRI	2	2
Augmentation	Silent	Unconfirmed Rupture	Non-MRI	0	0
Augmentation	Symptomatic	Confirmed Non-Rupture	MRI	0	0
Augmentation	Symptomatic	Confirmed Non-Rupture	Non-MRI	4	5
Augmentation	Symptomatic	Confirmed Rupture	MRI	0	0
Augmentation	Symptomatic	Confirmed Rupture	Non-MRI	1	1
Augmentation	Symptomatic	Unconfirmed Rupture	MRI	1	1
Augmentation	Symptomatic	Unconfirmed Rupture	Non-MRI	2	2
Reconstruction	Silent	Confirmed Non-Rupture	MRI	3	3
Reconstruction	Silent	Confirmed Non-Rupture	Non-MRI	1	1
Reconstruction	Silent	Confirmed Rupture	MRI	10	10
Reconstruction	Silent	Confirmed Rupture	Non-MRI	4	4
Reconstruction	Silent	Unconfirmed Rupture	MRI	6	7
Reconstruction	Silent	Unconfirmed Rupture	Non-MRI	0	0
Reconstruction	Symptomatic	Confirmed Non-Rupture	MRI	0	0
Reconstruction	Symptomatic	Confirmed Non-Rupture	Non-MRI	1	1
Reconstruction	Symptomatic	Confirmed Rupture	MRI	0	0
Reconstruction	Symptomatic	Confirmed Rupture	Non-MRI	0	0
Reconstruction	Symptomatic	Unconfirmed Rupture	MRI	1	1
Reconstruction	Symptomatic	Unconfirmed Rupture	Non-MRI	0	0
Revision	Silent	Confirmed Non-Rupture	MRI	2	3
Revision	Silent	Confirmed Non-Rupture	Non-MRI	2	2
Revision	Silent	Confirmed Rupture	MRI	3	3
Revision	Silent	Confirmed Rupture	Non-MRI	1	1
Revision	Silent	Unconfirmed Rupture	MRI	5	5
Revision	Silent	Unconfirmed Rupture	Non-MRI	0	0
Revision	Symptomatic	Confirmed Non-Rupture	MRI	1	1
Revision	Symptomatic	Confirmed Non-Rupture	Non-MRI	4	5
Revision	Symptomatic	Confirmed Rupture	MRI	0	0
Revision	Symptomatic	Confirmed Rupture	Non-MRI	1	1
Revision	Symptomatic	Unconfirmed Rupture	MRI	0	0
Revision	Symptomatic	Unconfirmed Rupture	Non-MRI	0	0
TOTAL				70	77

*Ruptures determined to be false reports based upon additional Investigator follow-up are not included in the analyses for implant rupture.

** 5 patients are double counted in this column because they had a different rupture status on the right and left. [REDACTED] (MRI) has one side with Silent Confirmed Non-Rupture and the other side with Silent Confirmed Rupture; [REDACTED] (Non-MRI) has one side with Silent Confirmed Non-Rupture and the other side with Silent Confirmed Rupture.

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Attachment 1-6 Figure: Rupture Classification Flow Diagram



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CORE STUDY - ALL COHORTS - Confirmed Ruptures

Table 1: Patient Assessment of Implants, with Both Primary and Secondary Study Devices Included

Time	Patients	Satisfaction Level*					Mean	SD
		Definitely Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Definitely Satisfied	Descriptive Statistics		
0-4 Weeks	0	0.0%	0.0%	0.0%	0.0%	0.0%	N/A	N/A
6 Months	0	0.0%	0.0%	0.0%	0.0%	0.0%	N/A	N/A
1 Year	0	0.0%	0.0%	0.0%	0.0%	0.0%	N/A	N/A
2 Years	3	0.0%	0.0%	0.0%	100%	5.0	5.0	0.0
3 Years	9	0.0%	22.2%	44.4%	33.3%	4.1	4.1	0.8
4 Years	11	0.0%	9.1%	36.4%	45.5%	4.2	4.2	1.0

* Satisfaction level could range from 1 (definitely dissatisfied) to 5 (definitely satisfied).

CORE STUDY - ALL COHORTS - Unconfirmed Ruptures

Table 2: Patient Assessment of Implants, with Both Primary and Secondary Study Devices Included

Time	N	Satisfaction Level*					Mean	SD
		(Allowable Range 1 - 5)						
		Definitely Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Definitely Satisfied	Descriptive Statistics		
0-4 Weeks	0	0.0%	0.0%	0.0%	0.0%	0.0%	N/A	N/A
6 Months	0	0.0%	0.0%	0.0%	0.0%	0.0%	N/A	N/A
1 Year	0	0.0%	0.0%	0.0%	0.0%	0.0%	N/A	N/A
2 Years	2	0.0%	0.0%	0.0%	50.0%	50.0%	4.5	0.7
3 Years	4	0.0%	0.0%	25.0%	25.0%	50.0%	4.3	1.0
4 Years	14	7.1%	14.3%	7.1%	14.3%	57.1%	4.0	1.4

* Satisfaction level could range from 1 (definitely dissatisfied) to 5 (definitely satisfied).

CORE STUDY - ALL COHORTS - Confirmed and Unconfirmed Ruptures

Table 3: Patient Assessment of Implants, with Both Primary and Secondary Study Devices Included

Time	Satisfaction Level* (Allowable Range 1 - 5)								Mean	SD
	Patients	Definitely Somewhat		Somewhat		Definitely		Descriptive Statistics		
		Dissatisfied	Satisfied	Dissatisfied	Satisfied	Dissatisfied	Satisfied			
	N	%	%	%	%	%	%			
0-4 Weeks	0	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	N/A	N/A	
6 Months	0	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	N/A	N/A	
1 Year	0	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	N/A	N/A	
2 Years	5	0.0%	0.0%	0.0%	0.0%	20.0%	80.0%	4.8	0.4	
3 Years	13	0.0%	0.0%	23.1%	38.5%	38.5%	38.5%	4.2	0.8	
4 Years	25	4.0%	12.0%	8.0%	24.0%	24.0%	52.0%	4.1	1.2	

* Satisfaction level could range from 1 (definitely dissatisfied) to 5 (definitely satisfied).

CORE STUDY - ALL COHORTS - Assumed Intact

Table 4: Patient Assessment of Implants, with Both Primary and Secondary Study Devices Included

Time	N	Satisfaction Level*					Descriptive Statistics	
		Definitely Satisfied		Somewhat Satisfied		Mean	SD	
		%	%	%	%			
0-4 Weeks	921	0.2%	1.0%	0.8%	8.8%	89.3%	4.9	0.5
6 Months	792	1.1%	3.2%	0.9%	14.5%	80.3%	4.7	0.7
1 Year	801	1.6%	4.1%	0.9%	16.9%	76.5%	4.6	0.8
2 Years	814	2.0%	4.5%	1.7%	14.6%	77.1%	4.6	0.9
3 Years	773	2.1%	4.7%	1.9%	14.6%	76.7%	4.6	0.9
4 Years	612	2.1%	4.6%	2.9%	16.5%	73.9%	4.6	0.9

* Satisfaction level could range from 1 (definitely dissatisfied) to 5 (definitely satisfied).

CORE STUDY - ALL COHORTS - Confirmed Intact

Table 5: Patient Assessment of Implants, with Both Primary and Secondary Study Devices Included

Time	N	Satisfaction Level* (Allowable Range 1 - 5)					Descriptive Statistics	
		Definitely Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Definitely Satisfied	%	Mean	SD
0-4 Weeks	0	0.0%	0.0%	0.0%	0.0%	0.0%	N/A	N/A
6 Months	27	0.0%	11.1%	0.0%	29.6%	59.3%	4.4	1.0
1 Year	40	2.5%	5.0%	5.0%	45.0%	42.5%	4.2	0.9
2 Years	54	5.6%	3.7%	3.7%	20.4%	66.7%	4.4	1.1
3 Years	57	7.0%	8.8%	3.5%	17.5%	63.2%	4.2	1.3
4 Years	54	3.7%	9.3%	9.3%	14.8%	63.0%	4.2	1.2

* Satisfaction level could range from 1 (definitely dissatisfied) to 5 (definitely satisfied).

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CORE STUDY

Table 1: Complications Experienced After Confirmed Ruptures Only

Complication	Patients (N = 17)		Implants (N = 17)	
	n	%	n	%
Complications				
Breast Pain	2	11.8%	2	11.8%
Bruising	1	5.9%	1	5.9%
Capsular Contracture	2	11.8%	2	11.8%
Infection	3	17.6%	3	17.6%
Lymphadenopathy	1	5.9%	1	5.9%
Redness	4	23.5%	4	23.5%
Seroma	2	11.8%	2	11.8%
Skin Rash	1	5.9%	1	5.9%
Swelling	3	17.6%	3	17.6%

NOTE: The patients included have an average follow-up after the event of 1.3 years, ranging from 14 days to 4.6 years. 41.2% of patients have at least 1 year of follow-up after the event. 52.9% (n=9) of the 17 patients experienced at least 1 complication.

000282

CORE STUDY

Table 2: Complications Experienced After Unconfirmed Ruptures Only

Complication	Patients (N =16)		Implants (N =17)	
	n	%	n	%
Complications				
Asymmetry	1	6.3%	1	5.9%
Redness	1	6.3%	1	5.9%
Tightness	1	6.3%	1	5.9%

NOTE: The patients included have an average follow-up after the event of 1.2 years, ranging from 155 days to 3.5 years. 25.0% of patients have at least 1 year of follow-up after the event. 18.8% (n=3) of the 16 patients experienced at least 1 complication.

000283

CORE STUDY

Table 3: Complications Experienced After Rupture (Confirmed and Unconfirmed)

Complication	Patients (N =33)		Implants (N =34)	
	n	%	n	%
Complications				
Asymmetry	1	3.0%	1	2.9%
Breast Pain	2	6.1%	2	5.9%
Bruising	1	3.0%	1	2.9%
Capsular Contracture	2	6.1%	2	5.9%
Infection	3	9.1%	3	8.8%
Lymphadenopathy	1	3.0%	1	2.9%
Redness	5	15.2%	5	14.7%
Seroma	2	6.1%	2	5.9%
Skin Rash	1	3.0%	1	2.9%
Swelling	3	9.1%	3	8.8%
Tightness	1	3.0%	1	2.9%

NOTE: The patients included have an average follow-up after the event of 1.2 years, ranging from 14 days to 4.6 years. 33.3% of patients have at least 1 year of follow-up after the event. 36.4% (n=12) of the 33 patients experienced at least 1 complication.

CORE STUDY

Table 4: Complications Experienced After Confirmed Non-Rupture at Explant

Complication	Patients (N =79)		Implants (N =122)	
	n	%	n	%
Complications				
Asymmetry	7	8.9%	8	6.6%
Breast Cancer	2	2.5%	2	1.6%
Breast Mass Cyst Lump	5	6.3%	5	4.1%
Breast Pain	11	13.9%	14	11.5%
Bruising	6	7.6%	7	5.7%
Capsular Contracture	11	13.9%	14	11.5%
Delayed Healing	3	3.8%	3	2.5%
Extrusion	2	2.5%	2	1.6%
Hypertrophic Scarring	1	1.3%	1	0.8%
Implant Visibility	1	1.3%	2	1.6%
Infection	2	2.5%	2	1.6%
Irritation	1	1.3%	1	0.8%
Lymphadenopathy	2	2.5%	2	1.6%
Malposition	5	6.3%	5	4.1%
Nipple Complication	1	1.3%	2	1.6%
Other Abnormal Scarring	3	3.8%	4	3.3%
Other Complication Specified**	1	1.3%	1	0.8%
Redness	8	10.1%	8	6.6%
Seroma	4	5.1%	4	3.3%
Skin Rash	1	1.3%	1	0.8%
Swelling	10	12.7%	12	9.8%
Tightness	5	6.3%	5	4.1%
Tissue/Skin Necrosis	1	1.3%	1	0.8%
Wrinkling	6	7.6%	8	6.6%

NOTE: The patients included have an average follow-up after the event of 2.5 years, ranging from 5 days to 4.9 years. 82.3% of patients have at least 1 year of follow-up after the event. 53.2% (n= 42) of the 79 patients experienced at least 1 complication.

**Other Complication was specified as: CONTOUR DEFECT

CORE STUDY

Table 5: Complications Experienced in the Intact Group after Implantation

Complication	Patients (N =934)		Implants (N =1737)	
	n	%	n	%
Complications				
Asymmetry	142	15.2%	171	9.8%
Breast Cancer	8	0.9%	8	0.5%
Breast Mass Cyst Lump	59	6.3%	66	3.8%
Breast Pain	133	14.2%	182	10.5%
Bruising	79	8.5%	137	7.9%
Capsular Contracture	160	17.1%	222	12.8%
Delayed Healing	33	3.5%	42	2.4%
Extrusion	7	0.7%	7	0.4%
Fibrocystic Disease	5	0.5%	6	0.3%
Fluid Accumulation	7	0.7%	7	0.4%
Hematoma	18	1.9%	20	1.2%
Hypertrophic Scarring	45	4.8%	73	4.2%
Implant Visibility	3	0.3%	5	0.3%
Infection	19	2.0%	23	1.3%
Irritation	6	0.6%	7	0.4%
Loss of Nipple Sensation	24	2.6%	38	2.2%
Loss of Skin Sensation	11	1.2%	17	1.0%
Lymphadenopathy	5	0.5%	6	0.3%
Lymphedema	3	0.3%	3	0.2%
Malposition	73	7.8%	101	5.8%
Nipple Complication	21	2.2%	34	2.0%
Other Abnormal Scarring	41	4.4%	60	3.5%
Other Complication Specified**	14	1.5%	15	0.9%
Palpability	30	3.2%	40	2.3%
Pneumothorax	2	0.2%	2	0.1%
Ptosis	33	3.5%	57	3.3%
Redness	50	5.4%	62	3.6%
Seroma	40	4.3%	50	2.9%
Skin Hypersensitivity	6	0.6%	8	0.5%
Skin Paresthesia	4	0.4%	6	0.3%
Skin Rash	23	2.5%	37	2.1%
Swelling	180	19.3%	302	17.4%
Tightness	50	5.4%	62	3.6%
Tissue/Skin Necrosis	19	2.0%	20	1.2%
Wrinkling	79	8.5%	118	6.8%

NOTE: The patients included have an average follow-up after the event of 3.6 years, ranging from 1 day to 5.3 years. 95.5% of patients have at least 1 year of follow-up after the event. 67.1% (n=627) of the 934 patients experienced at least 1 complication.

000286

Table 5 (cont.)

**Other Complications were specified as:

- (1) THINNESS, (2) THICKENED AREA OF SOFT TISSUE,
- (3) SKIN LAXITY, (4) CONTOUR DEFECT,
- (5) MEDIAL PUCKERING, (6) ALLERGIC REACTION TO COMPAZINE,
- (7) ALLERGIC REACTION TO COMPAZINE.NO SIDE INDICATED, (8) TRAUMA,
- (9) BREAST PAIN DUE TO FALL, (10) MILD TO MODERATE VENOUS CONGESTION
- (11) MONDOR'S SYNDROME (R) BREAST ONLY, (12) LUMPINESS,
- (13) HERNIATION POST AUTO ACCIDENT, (14) DIMPLE,
- (15) SOFT TISSUE FULLNESS

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CORE STUDY

Table 5: CTD Signs/Symptoms Experienced After Intact

CTD Category	Patients (N =879)	
	n	%
Gastrointestinal	283	32.2%
General	261	29.7%
Joint	263	29.9%
Muscle	273	31.1%
Neurological	262	29.8%
Other	225	25.6%
Skin	237	27.0%
Urinary	91	10.4%

NOTE: Of the 935 patients, only 879 patients are included in the above table because 56 patients did not complete any CTD sign/symptoms questionnaires after the event. The patients included completed their last questionnaire an average of 3.5 years after the event, ranging from 1 days to 5.2 years. 82.0% (n=721) of the 879 patients experienced at least 1 CTD sign/symptom.

000289

CORE STUDY

Table 4: CTD Signs/Symptoms Experienced After Confirmed Non-Rupture at Explant

CTD Category	Patients (N =72)	
	n	%
Gastrointestinal	17	23.6%
General	10	13.9%
Joint	14	19.4%
Muscle	12	16.7%
Neurological	15	20.8%
Other	14	19.4%
Skin	13	18.1%
Urinary	5	6.9%

NOTE: Of the 131 patients, only 72 patients are included in the above table because 59 patients did not complete any CTD sign/symptoms questionnaires after the event. The patients included completed their last questionnaire an average of 2.4 years after the event, ranging from 19 days to 4.3 years. 66.7% (n=48) of the 72 patients experienced at least 1 CTD sign/symptom.

000290

CORE STUDY

Table 3: CTD Signs/Symptoms Experienced After Rupture (Confirmed and Unconfirmed)

CTD Category	Patients (N =25)	
	n	%
Gastrointestinal	5	20.0%
General	6	24.0%
Joint	2	8.0%
Muscle	7	28.0%
Neurological	2	8.0%
Other	5	20.0%
Skin	3	12.0%

NOTE: Of the 42 patients, only 25 patients are included in the above table because 17 patients did not complete any CTD sign/symptoms questionnaires after the event. The patients included completed their last questionnaire an average of 1.2 years after the event, ranging from 9 days to 3.7 years. 60.0% (n=15) of the 25 patients experienced at least 1 CTD sign/symptom.

000291

CORE STUDY

Table 2: CTD Signs/Symptoms Experienced After Unconfirmed Ruptures Only

CTD Category	Patients (N =14)	
	n	%
Gastrointestinal	2	14.3%
General	4	28.6%
Joint	2	14.3%
Muscle	2	14.3%
Neurological	1	7.1%
Other	3	21.4%

NOTE: Of the 17 patients, only 14 patients are included in the above table because 3 patients did not complete any CTD sign/symptoms questionnaires after the event. The patients included completed their last questionnaire an average of 1.0 year after the event, ranging from 9 days to 2.4 years. 50.0% (n=7) of the 14 patients experienced at least 1 CTD sign/symptom.

000292

CORE STUDY

Table 1: CTD Signs/Symptoms Experienced After Confirmed Ruptures Only

CTD Category	Patients (N =11)	
	n	%
Gastrointestinal	3	27.3%
General	2	18.2%
Muscle	5	45.5%
Neurological	1	9.1%
Other	2	18.2%
Skin	3	27.3%

NOTE: Of the 25 patients, only 11 patients are included in the above table because 14 patients did not complete any CTD sign/symptoms questionnaires after the event. The patients included completed their last questionnaire an average of 1.6 years after the event, ranging from 173 days to 3.7 years. 72.7% (n=8) of the 11 patients experienced at least one CTD sign/symptom.

000293

Email Subject: P020056 (Deficiency 1)

Sent to FDA: Wednesday, October 05, 2004

Attached are the additional tables you requested during our September 29th TC. Tables 1-12 in the first attachment include the following Kaplan Meier risk rates by cohort, (i.e. augmentation, reconstruction and revision) and by combined (overall) study population:

- Risk of Silent Rupture for the MRI Cohort;
- Risk of Symptomatic Rupture for the MRI Cohort; and
- Risk of Symptomatic Rupture for the Non-MRI Cohort

Please keep in mind that these rates include unconfirmed as well as confirmed ruptures. Also attached are MRI compliance tables representing "by-patient" and "by-implant" compliance for the first and second serial MRIs. The "by-implant" compliance is being presented per your request. The "by-patient" compliance table is a revised table from what we submitted in Amendment 8. When calculating the "by-implant" compliance rates we realized there was a programming error relative to the second MRI numbers that caused the previous "by-patient" table to be inaccurate. We highlighted the new numbers in the revised "by-patient" table, so that you can easily see the changes. The corrected "by-patient" MRI compliance is actually slightly to moderately higher than the rates we previously submitted in Amendment 8.

KM ANALYSIS - MRI COHORT - AUGMENTATION

Table 1: Risk of First Occurrence of Silent Rupture

Time	By Patient				By Implant			
	Number Affected		Number Remaining		Number Affected*		Number Remaining	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
4 Weeks	0	0.0%	161	0.0%	0	0.0%	320	0.0%
6 Months	1	0.6% (0.0%, 1.8%)	160	0.6% (0.0%, 1.8%)	1	0.3%	317	0.3% (0.0%, 0.9%)
1 Year	1	0.6% (0.0%, 1.8%)	159	0.6% (0.0%, 1.8%)	1	0.3%	315	0.3% (0.0%, 0.9%)
2 Years	1	0.6% (0.0%, 1.8%)	155	0.6% (0.0%, 1.8%)	1	0.3%	308	0.3% (0.0%, 0.9%)
3 Years	3	2.0% (0.0%, 4.2%)	137	2.0% (0.0%, 4.2%)	3	1.0%	274	1.0% (0.0%, 2.1%)
4 Years	4	3.0% (0.0%, 5.9%)	31	3.0% (0.0%, 5.9%)	4	1.5%	61	1.5% (0.0%, 3.0%)

* 1 implant with rupture after 4 years does not appear in the "number affected" above

KM ANALYSIS - MRI COHORT - AUGMENTATION

Table 2: Risk of First Occurrence of Symptomatic Rupture

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	0	164	0.0%	0	327	0.0%
6 Months	0	162	0.0%	0	322	0.0%
1 Year	0	160	0.0%	0	318	0.0%
2 Years	0	158	0.0%	0	315	0.0%
3 Years	0	140	0.0%	0	277	0.0%
4 Years	1	38	2.1% (0.0%, 6.1%)	1	74	1.1% (0.0%, 3.1%)

KM ANALYSIS - NON-MRI COHORT - AUGMENTATION

Table 3: Risk of First Occurrence of Symptomatic Rupture

Time	By Patient				By Implant			
	Number Affected		Cumulative Risk		Number Affected*		Cumulative Risk	
	n	n	% (95% CI)		n	n	% (95% CI)	
4 Weeks	0	200	0.0%	--	0	400	0.0%	--
6 Months	0	172	0.0%	--	0	344	0.0%	--
1 Year	0	135	0.0%	--	0	269	0.0%	--
2 Years	0	97	0.0%	--	0	192	0.0%	--
3 Years	0	68	0.0%	--	0	133	0.0%	--
4 Years	1	39	1.6% (0.0%, 4.7%)		1	77	0.8% (0.0%, 2.4%)	

* 2 implants with rupture after 4 years do not appear in the "number affected" above

KM ANALYSIS - MRI COHORT - RECONSTRUCTION

Table 4: Risk of First Occurrence of Silent Rupture

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	0	103	0.0%	0	175	0.0%
6 Months	0	103	0.0%	0	171	0.0%
1 Year	0	103	0.0%	0	170	0.0%
2 Years	8	93	7.8% (2.6%,12.9%)	8	159	4.7% (1.5%, 7.9%)
3 Years	10	50	10.2% (4.2%,16.3%)	10	90	6.2% (2.4%, 9.9%)
4 Years	16	36	22.3% (11.9%,32.7%)	17	70	14.2% (7.5%,20.8%)

KM ANALYSIS - MRI COHORT - RECONSTRUCTION

Table 5: Risk of First Occurrence of Symptomatic Rupture

Time	By Patient				By Implant			
	Number Affected		Cumulative Risk		Number Affected		Cumulative Risk	
	n	Number Remaining	n	% (95% CI)	n	Number Remaining	n	% (95% CI)
4 Weeks	0	106	0	0.0%	0	180	0	0.0%
6 Months	0	106	0	0.0%	0	176	0	0.0%
1 Year	0	106	0	0.0%	0	175	0	0.0%
2 Years	0	102	0	0.0%	0	164	0	0.0%
3 Years	1	64	1	1.3% (0.0%, 3.9%)	1	105	1	0.8% (0.0%, 2.4%)
4 Years	1	49	1	1.3% (0.0%, 3.9%)	1	77	1	0.8% (0.0%, 2.4%)

KM ANALYSIS - NON-MRI COHORT - RECONSTRUCTION

Table 6: Risk of First Occurrence of Symptomatic Rupture

Time	By Patient				By Implant			
	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)
	n	n			n	n		
4 Weeks	0	91	0.0%	--	0	142	0.0%	--
6 Months	0	69	0.0%	--	0	108	0.0%	--
1 Year	0	53	0.0%	--	0	82	0.0%	--
2 Years	0	40	0.0%	--	0	61	0.0%	--
3 Years	0	28	0.0%	--	0	42	0.0%	--
4 Years	0	10	0.0%	--	0	16	0.0%	--

KM ANALYSIS - MRI COHORT - REVISION

Table 7: Risk of First Occurrence of Silent Rupture

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	0	77	0.0%	0	148	0.0%
6 Months	0	77	0.0%	0	148	0.0%
1 Year	0	77	0.0%	0	148	0.0%
2 Years	3	74	3.9% (0.0%, 8.2%)	3	144	2.0% (0.0%, 4.3%)
3 Years	3	68	3.9% (0.0%, 8.2%)	3	130	2.0% (0.0%, 4.3%)
4 Years	8	58	11.3% (3.9%, 18.7%)	8	116	6.0% (1.9%, 10.0%)

KM ANALYSIS - MRI COHORT - REVISION

Table 8: Risk of First Occurrence of Symptomatic Rupture

Time	By Patient				By Implant			
	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)
	n	n	% (95% CI)	n	n	% (95% CI)		
4 Weeks	0	78	0.0%	--	0	150	0.0%	--
6 Months	0	78	0.0%	--	0	150	0.0%	--
1 Year	0	78	0.0%	--	0	150	0.0%	--
2 Years	0	78	0.0%	--	0	146	0.0%	--
3 Years	0	72	0.0%	--	0	135	0.0%	--
4 Years	0	66	0.0%	--	0	118	0.0%	--

KM ANALYSIS - NON-MRI COHORT - REVISION

Table 9: Risk of First Occurrence of Symptomatic Rupture

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	0	110	0.0%	0	210	0.0%
6 Months	0	93	0.0%	0	177	0.0%
1 Year	0	82	0.0%	0	155	0.0%
2 Years	1	62	1.4% (0.0%, 4.1%)	1	114	0.8% (0.0%, 2.2%)
3 Years	1	48	1.4% (0.0%, 4.1%)	1	89	0.8% (0.0%, 2.2%)
4 Years	1	29	1.4% (0.0%, 4.1%)	1	54	0.8% (0.0%, 2.2%)

KM ANALYSIS - MRI COHORT - COMBINED

Table 10: Risk of First Occurrence of Silent Rupture

Time	By Patient				By Implant			
	Number Affected	Number Remaining	Cumulative Risk		Number Affected*	Number Remaining	Cumulative Risk	
	n	n	% (95% CI)		n	n	% (95% CI)	
4 Weeks	0	341	0.0%	--	0	643	0.0%	--
6 Months	1	340	0.3% (0.0%, 0.9%)		1	636	0.2% (0.0%, 0.5%)	
1 Year	1	339	0.3% (0.0%, 0.9%)		1	633	0.2% (0.0%, 0.5%)	
2 Years	12	322	3.6% (1.6%, 5.5%)		12	611	1.9% (0.8%, 3.0%)	
3 Years	16	255	4.9% (2.5%, 7.2%)		16	494	2.6% (1.3%, 3.9%)	
4 Years	28	125	11.9% (7.5%, 16.2%)		29	247	6.7% (4.2%, 9.2%)	

* 1 augmentation implant with rupture after 4 years does not appear in the "number affected" above

KM ANALYSIS - MRI COHORT - COMBINED

Table 11: Risk of First Occurrence of Symptomatic Rupture

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	0	348	0.0%	0	657	0.0%
6 Months	0	346	0.0%	0	648	0.0%
1 Year	0	344	0.0%	0	643	0.0%
2 Years	0	338	0.0%	0	625	0.0%
3 Years	1	276	0.3% (0.0%, 1.0%)	1	517	0.2% (0.0%, 0.5%)
4 Years	2	153	0.9% (0.0%, 2.3%)	2	269	0.5% (0.0%, 1.3%)

KM ANALYSIS - NON-MRI COHORT - COMBINED

Table 12: Risk of First Occurrence of Symptomatic Rupture

Time	By Patient				By Implant			
	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)	Number Affected*	Number Remaining	Cumulative Risk	% (95% CI)
	n	n			n	n		
4 Weeks	0	401	0.0%	--	0	752	0.0%	--
6 Months	0	334	0.0%	--	0	629	0.0%	--
1 Year	0	270	0.0%	--	0	506	0.0%	--
2 Years	1	199	0.5%	(0.0%, 1.3%)	1	367	0.2%	(0.0%, 0.7%)
3 Years	1	144	0.5%	(0.0%, 1.3%)	1	264	0.2%	(0.0%, 0.7%)
4 Years	2	78	1.2%	(0.0%, 2.9%)	2	147	0.7%	(0.0%, 1.6%)

* 2 augmentation implants with rupture after 4 years do not appear in the "number affected" above

CORE STUDY - SERIAL MRI

Table 1: Compliance for the MRI Cohort (calculated by-implant)

	Total	Augmentation	Reconstruction	Revision
1st Serial MRI				
Theoretically Due	663	331	182	150
Deaths	0	0	0	0
Explant-Related Discontinuations Expected	12	12	0	0
Actual Evaluated	651	319	182	150
Lost-to-Follow-Up	589	277	170	142
% Follow-Up	62	42	12	8
	90.5%	86.8%	93.4%	94.7%
2nd Serial MRI				
Theoretically Due	574	331	109	134
Deaths	1	0	1	0
Discontinued Due to Claustrophobia/ Metal-Implanted Devices	12	10	2	0
Explant-Related Discontinuations Expected	31	22	9	0
Actual Evaluated	530	299	97	134
Lost-to-Follow-Up	450	263	79	108
% Follow-Up	80	36	18	26
	84.9%	88.0%	81.4%	80.6%

CORE STUDY - SERIAL MRI

Table 1: Patient Compliance for the MRI Cohort (calculated by-patient)

	Total	Augmentation	Reconstruction	Revision
1st Serial MRI				
Theoretically Due	351	166	107	78
Deaths	0	0	0	0
Explant-Related Discontinuations	6	6	0	0
Expected	345	160	107	78
Actual Evaluated	314	139	101	74
Lost-to-Follow-Up	31	21	6	4
% Follow-Up	91.0%	86.9%	94.4%	94.9%
2nd Serial MRI				
Theoretically Due	297	166	61	70
Deaths	1	0	1	0
Discontinued Due to Claustrophobia/ Metal-Implanted Devices	6	5	1	0
Explant-Related Discontinuations	17	11	6	0
Expected	273	150	53	70
Actual Evaluated	232	131	44	57
Lost-to-Follow-Up	41	19	9	13
% Follow-Up	85.0%	87.3%	83.0%	81.4%

Email Subject: P020056 (Deficiency 1)

REDACTED

The patient you're referring to below (no intracapsular or extracapsular gel) received bilateral Style 153 implants and is in the Reconstruction Cohort. She was also enrolled in the Serial MRI Cohort. Her ID [REDACTED] and the patient summary is included in Attachment 1-5 of Amendment 8. This patient had suspected bilateral ruptures via the second serial MRI, but both implants were found to be intact upon explantation. The right implant had a detached inner lumen/bladder, but to reiterate, the outer lumen, i.e. shell was found to be intact upon explantation. The left implant had no breach in integrity of either the inner or outer lumen/bladder, and therefore was found to be intact upon explantation..

The information below is a follow up to the other questions you raised today during your two telephone calls:

- This confirms our conversation earlier today during which time I told you that the reason the Recon and Revision "Theoretically Due" numbers for the second serial MRI are lower than you expected, is because these two cohorts did not begin enrollment into the Serial MRI portion of the study until approximately a year after the Augmentation serial MRI portion began. Therefore, not all Serial MRI Recon and Revision patients are "due" for their second MRI yet.
- The average duration of implantation for the implants reported in the Serial MRI Cohort compliance table for "2nd Serial MRI" by indication is:
 - Augmentation 2.5 years
 - Reconstruction 4.1 years
 - Revision 4.2 years
- This confirms our conversation from earlier today whereby we explained that the "Number of Patients" in the table on page 25 add up to more than the total number of patients enrolled into the study because many patients received bilateral implants. Therefore, some patients were counted twice for the purposes of this table if both of their implants were involved. We also confirmed that the "Number of Implants" in this same table equals 1,782, as is also identified on page 8.

Email Subject: P020056 (Deficiency 1)

Sent to FDA: Wednesday, October 20, 2004

Attached is the response to your questions below. Please note that Reconstruction Patient [REDACTED] in the "Confirmed Rupture at Explant" category was actually determined to have a ruptured inner bladder of our double lumen/bladder device, the Style 153. The outer lumen/bladder, i.e. shell, was found to be intact. However, at the time of database extraction for Amendment 8, she was still included in the "rupture" category. For consistency sake, we have included her in the same category in this table.

Also, you may note a discrepancy with the patient summary for Augmentation Patient [REDACTED]. The patient summary identifies her rupture category as "unconfirmed", when in fact the second MRI demonstrated that her implant was indeed not ruptured.

REDACTED

RESPONSE TO ISSUES

1. The attached table provides the patient IDs, by indication, for the 38 implants with evidence of rupture on MRI.
2. The attached table also provides a breakdown of the 38 implants by “rupture confirmation status”. The patient IDs for the implants that were explanted are listed in the first two rows of the table (i.e., “Confirmed Rupture at Explant” and “Confirmed Non-Rupture at Explant”).
3. Please see the row titled “Confirmed Non-Rupture at Explant” on the attached table.
4. Please see the row titled “Confirmed Rupture at Explant” on the attached table.

Note: The false positive percent was calculated as: $9/24 = 37.5\%$

$$2+2+1+4 = 9$$

$$2+2+1+4+15=24$$

Rupture Confirmation Status	Number of Implants
Confirmed Rupture at Explant	15
Confirmed Non-Rupture at Explant	2
Confirmed Non-Rupture with follow-up Mammogram	2
Confirmed Non-Rupture with follow-up Ultrasound	1
Confirmed Non-Rupture with follow-up MRI	4
Unconfirmed	14

REDACTED

Email Subject: P020056 (Deficiency 1)

Sent to FDA: Friday, January 21, 2005

As requested below (Items 1-3) and per our telephone conversation on January 7th, the attached tables include the KM risk rates for rupture calculated WITHOUT the non-MRI cohort estimate of silent ruptures. The patient ID numbers for those patients classified into the "silent" vs. "symptomatic" rupture categories as per your second set of requests in the January 14th email (Items 1-4 below), are included as footnotes on the applicable attached tables.

The second attachment to this email includes identification of the Style 153 devices per your request in a January 7th email (copied below). Patient ID numbers were asterisked if the identified implant is a Style 153 device.

REDACTED

CORE STUDY - AUGMENTATION

Table 1: Risk of First Occurrence of "Observed" Rupture Among MRI Cohort Patients

Time	By Patient				By Implant				
	Number Affected		Number Remaining		Number Affected		Number Remaining		Cumulative Risk % (95% CI)
	n	%	n	% (95% CI)	n	%	n	% (95% CI)	
4 Weeks	0	0.0%	166	0.0%	0	0.0%	331	0.0%	--
6 Months	1	0.6%	165	0.6% (0.0%, 1.8%)	1	0.3%	328	0.3% (0.0%, 0.9%)	--
1 Year	1	0.6%	163	0.6% (0.0%, 1.8%)	1	0.3%	324	0.3% (0.0%, 0.9%)	--
2 Years	1	0.6%	160	0.6% (0.0%, 1.8%)	1	0.3%	318	0.3% (0.0%, 0.9%)	--
3 Years	3	1.9%	147	1.9% (0.0%, 4.1%)	3	1.0%	294	1.0% (0.0%, 2.0%)	--
4 Years	5	3.4%	125	3.4% (0.5%, 6.3%)	5*	1.7%	250	1.7% (0.2%, 3.2%)	--

* Includes the following patients:

SILENT rupture: [REDACTED]

SYMPTOMATIC rupture: [REDACTED]

Note: Patient [REDACTED] (silent rupture) is not included in the "Number Affected" at 4 years because her rupture occurred after the 4-year time point.

CORE STUDY - RECONSTRUCTION

Table 2: Risk of First Occurrence of "Observed" Rupture Among MRI Cohort Patients

Time	By Patient				By Implant			
	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)
	n	n	%	(95% CI)	n	n	%	(95% CI)
4 Weeks	0	107	0.0%	--	0	182	0.0%	--
6 Months	0	107	0.0%	--	0	178	0.0%	--
1 Year	0	107	0.0%	--	0	177	0.0%	--
2 Years	8	99	7.5%	(2.5%,12.5%)	8	168	4.5%	(1.5%, 7.6%)
3 Years	11	92	10.4%	(4.6%,16.1%)	11	157	6.3%	(2.7%, 9.8%)
4 Years	17	45	20.5%	(11.3%,29.7%)	18*	85	13.1%	(7.2%,19.0%)

* Includes the following patients:

SILENT rupture: [REDACTED]

SYMPTOMATIC rupture: [REDACTED]

CORE STUDY - REVISION

Table 3: Risk of First Occurrence of "Observed" Rupture Among MRI Cohort Patients

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	0	78	0.0% --	0	150	0.0% --
6 Months	0	78	0.0% --	0	150	0.0% --
1 Year	0	78	0.0% --	0	150	0.0% --
2 Years	3	75	3.9% (0.0%, 8.1%)	3	146	2.0% (0.0%, 4.2%)
3 Years	3	73	3.9% (0.0%, 8.1%)	3	142	2.0% (0.0%, 4.2%)
4 Years	8	62	10.9% (3.8%, 18.1%)	8*	123	5.7% (1.9%, 9.6%)

* Includes the following patients:

SILENT rupture: [REDACTED]

SYMPTOMATIC rupture: None

CORE STUDY - ALL PATIENTS (A and R and V)

Table 4: Risk of First Occurrence of "Observed" Rupture Among MRI Cohort Patients

Time	By Patient				By Implant			
	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)
	n	n	% (95% CI)		n	n	% (95% CI)	
4 Weeks	0	351	0.0%	--	0	663	0.0%	--
6 Months	1	350	0.3%	(0.0%, 0.8%)	1	656	0.2%	(0.0%, 0.4%)
1 Year	1	348	0.3%	(0.0%, 0.8%)	1	651	0.2%	(0.0%, 0.4%)
2 Years	12	334	3.5%	(1.5%, 5.4%)	12	632	1.9%	(0.8%, 2.9%)
3 Years	17	312	5.0%	(2.7%, 7.2%)	17	593	2.7%	(1.4%, 3.9%)
4 Years	30	232	9.8%	(6.5%, 13.2%)	31	458	5.4%	(3.6%, 7.3%)

CORE STUDY - AUGMENTATION

Table 5: Risk of First Occurrence of "Observed" Rupture Among NON MRI Cohort Patients

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	0	320	0.0%	0	640	0.0%
6 Months	0	317	0.0%	0	634	0.0%
1 Year	1	306	0.3% (0.0%, 0.9%)	1	612	0.2% (0.0%, 0.5%)
2 Years	2	287	0.7% (0.0%, 1.6%)	2	575	0.3% (0.0%, 0.8%)
3 Years	2	266	0.7% (0.0%, 1.6%)	2	532	0.3% (0.0%, 0.8%)
4 Years	3	195	1.1% (0.0%, 2.2%)	3*	390	0.5% (0.0%, 1.1%)

* Includes the following patients:

SILENT rupture: [REDACTED]

SYMPTOMATIC rupture: [REDACTED]

Note: Patients [REDACTED] and [REDACTED] (symptomatic ruptures) are not included in the "Number Affected" at 4 years because their ruptures occurred after the 4-year time point.

CORE STUDY - RECONSTRUCTION

Table 6: Risk of First Occurrence of "Observed" Rupture Among NON MRI Cohort Patients

Time	By Patient				By Implant			
	Number Affected		Number Remaining		Number Affected		Number Remaining	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
4 Weeks	0	0.0%	113	0.0%	0	0.0%	177	0.0%
6 Months	0	0.0%	98	0.0%	0	0.0%	154	0.0%
1 Year	0	0.0%	90	0.0%	0	0.0%	140	0.0%
2 Years	3	3.6% (0.0%, 7.6%)	78	3.6% (0.0%, 7.6%)	3	2.3% (0.0%, 4.9%)	123	2.3% (0.0%, 4.9%)
3 Years	4	4.9% (0.2%, 9.6%)	69	4.9% (0.2%, 9.6%)	4	3.2% (0.1%, 6.2%)	106	3.2% (0.1%, 6.2%)
4 Years	4	4.9% (0.2%, 9.6%)	43	4.9% (0.2%, 9.6%)	4*	3.2% (0.1%, 6.2%)	65	3.2% (0.1%, 6.2%)

* Includes the following patients:

SILENT rupture: [REDACTED]

SYMPTOMATIC rupture: None

CORE STUDY - REVISION

Table 7: Risk of First Occurrence of "Observed" Rupture Among NON MRI Cohort Patients

Time	By Patient				By Implant			
	Number Affected		Number Remaining		Number Affected		Number Remaining	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
4 Weeks	0	0.0%	138	0.0%	0	0.0%	264	0.0%
6 Months	0	--	130	0.0%	0	--	248	0.0%
1 Year	0	--	124	0.0%	0	--	236	0.0%
2 Years	2	(0.0%, 4.1%)	111	1.7%	2	(0.0%, 2.1%)	212	0.9%
3 Years	2	(0.0%, 4.1%)	101	1.7%	2	(0.0%, 2.1%)	192	0.9%
4 Years	2	(0.0%, 4.1%)	81	1.7%	2*	(0.0%, 2.1%)	153	0.9%

* Includes the following patients:

SILENT rupture: [REDACTED]

SYMPTOMATIC rupture: [REDACTED]

CORE STUDY - ALL PATIENTS (A and R and V)

Table 8: Risk of First Occurrence of "Observed" Rupture Among NON MRI Cohort Patients

Time	By Patient				By Implant			
	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)
	n	n	% (95% CI)	n	n	% (95% CI)		
4 Weeks	0	571	0.0%	--	0	1081	0.0%	--
6 Months	0	545	0.0%	--	0	1036	0.0%	--
1 Year	1	520	0.2% (0.0%, 0.5%)		1	988	0.1% (0.0%, 0.3%)	
2 Years	7	476	1.4% (0.4%, 2.4%)		7	910	0.7% (0.2%, 1.3%)	
3 Years	8	436	1.6% (0.5%, 2.7%)		8	830	0.9% (0.3%, 1.4%)	
4 Years	9	319	1.9% (0.7%, 3.1%)		9	608	1.0% (0.3%, 1.6%)	

CORE STUDY - AUGMENTATION

Table 9: Risk of First Occurrence of "Observed" Rupture (MRI + NON-MRI Patients Combined)

Time	By Patient				By Implant			
	Number Affected		Number Remaining		Number Affected		Number Remaining	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
4 Weeks	0	0.0%	486	0.0%	0	0.0%	971	0.0%
6 Months	1	0.2% (0.0%, 0.6%)	482	0.2% (0.0%, 0.6%)	1	0.1% (0.0%, 0.3%)	962	0.1% (0.0%, 0.3%)
1 Year	2	0.4% (0.0%, 1.0%)	469	0.4% (0.0%, 1.0%)	2	0.2% (0.0%, 0.5%)	936	0.2% (0.0%, 0.5%)
2 Years	3	0.6% (0.0%, 1.4%)	447	0.6% (0.0%, 1.4%)	3	0.3% (0.0%, 0.7%)	893	0.3% (0.0%, 0.7%)
3 Years	5	1.1% (0.1%, 2.1%)	413	1.1% (0.1%, 2.1%)	5	0.6% (0.1%, 1.0%)	826	0.6% (0.1%, 1.0%)
4 Years	8	1.9% (0.6%, 3.3%)	320	1.9% (0.6%, 3.3%)	8*	1.0% (0.3%, 1.6%)	640	1.0% (0.3%, 1.6%)

*A total of 11 unconfirmed and confirmed ruptured implants have been identified in the augmentation cohort; only 8 are reported in the "Number Affected" because 3 occurred after the 4-year time point (See Tables 1 and 5).

CORE STUDY - RECONSTRUCTION

Table 10: Risk of First Occurrence of "Observed" Rupture (MRI + NON-MRI Patients Combined)

Time	By Patient				By Implant			
	Number Affected		Cumulative Risk		Number Affected		Cumulative Risk	
	n	% (95% CI)	Number Remaining	% (95% CI)	n	% (95% CI)	Number Remaining	% (95% CI)
4 Weeks	0	0.0%	220	0.0%	0	0.0%	359	0.0%
6 Months	0	0.0%	205	0.0%	0	0.0%	332	0.0%
1 Year	0	0.0%	197	0.0%	0	0.0%	317	0.0%
2 Years	11	5.8% (2.5%, 9.1%)	177	5.8% (2.5%, 9.1%)	11	3.6% (1.5%, 5.7%)	291	3.6% (1.5%, 5.7%)
3 Years	15	8.0% (4.1%, 11.8%)	161	8.0% (4.1%, 11.8%)	15	5.0% (2.5%, 7.4%)	263	5.0% (2.5%, 7.4%)
4 Years	21	13.5% (7.9%, 19.2%)	88	13.5% (7.9%, 19.2%)	22	9.0% (5.2%, 12.7%)	150	9.0% (5.2%, 12.7%)

CORE STUDY - REVISION

Table 11: Risk of First Occurrence of "Observed" Rupture (MRI + NON-MRI Patients Combined)

Time	By Patient				By Implant			
	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)	Number Affected	Number Remaining	Cumulative Risk	% (95% CI)
	n	n	%	(95% CI)	n	n	%	(95% CI)
4 Weeks	0	216	0.0%	--	0	414	0.0%	--
6 Months	0	208	0.0%	--	0	398	0.0%	--
1 Year	0	202	0.0%	--	0	386	0.0%	--
2 Years	5	186	2.6%	(0.3%, 4.8%)	5	358	1.3%	(0.2%, 2.5%)
3 Years	5	174	2.6%	(0.3%, 4.8%)	5	334	1.3%	(0.2%, 2.5%)
4 Years	10	143	5.7%	(2.3%, 9.2%)	10	276	3.0%	(1.2%, 4.9%)

CORE STUDY - ALL PATIENTS (A and R and V)

Table 12: Risk of First Occurrence of "Observed" Rupture (MRI + NON-MRI Patients Combined)

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	0	922	0.0%	0	1744	0.0%
6 Months	1	895	0.1% (0.0%, 0.3%)	1	1692	0.1% (0.0%, 0.2%)
1 Year	2	868	0.2% (0.0%, 0.5%)	2	1639	0.1% (0.0%, 0.3%)
2 Years	19	810	2.2% (1.2%, 3.2%)	19	1542	1.2% (0.7%, 1.7%)
3 Years	25	748	3.0% (1.8%, 4.1%)	25	1423	1.6% (1.0%, 2.2%)
4 Years	39	551	5.3% (3.6%, 6.9%)	40*	1066	2.9% (2.0%, 3.8%)

*A total of 43 unconfirmed and confirmed ruptured implants have been identified in the Core Study; only 40 are reported in the "Number Affected" because 3 occurred after the 4-year time point (See Tables 1 and 5).

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Rupture Confirmation Status	Number of Implants
Confirmed Rupture at Explant	15
Confirmed Non-Rupture at Explant	2
Confirmed Non-Rupture with follow-up Mammogram	2
Confirmed Non-Rupture with follow-up Ultrasound	1
Confirmed Non-Rupture with follow-up MRI	4
Unconfirmed	14

* Style 153 Device

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RESPONSE TO DEFICIENCY 2

To more fully address the question of rupture, Inamed examined this issue using several different approaches. The first approach is to quantify long-term rupture rates by presenting data from Inamed's complaint database, as well as by providing an analysis of Inamed's silicone gel-filled vs. saline-filled breast implants. Subsequent to this discussion Inamed will address items a-d above with data from the Adjunct Study and the published literature. In addition, while no ruptures have been reported for Inamed's silicone-filled implants that are tracked as part of the Danish Breast Implant Registry, Inamed will continue to monitor this database for pertinent information.

LONG-TERM RUPTURE RATE

Based on analysis of complaints received by Inamed, the Kaplan-Meier rupture rate at 10.4 years (3,785 days) is 4.11% for the silicone breast implant styles presented in PMA P020056. This represents 491 ruptures out of 95,339 devices manufactured and implanted in United States women between 1993-2003 (Attachment 2-1). While Inamed recognizes that this data relies upon voluntary reporting of device failures and theoretically could be subject to underreporting, the company's warranty program provides financial incentives for reporting failed devices. Inamed believes these financial incentives provide for reporting that is not grossly misrepresentative of actual device failures in the field.

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RESPONSE TO DEFICIENCY 2

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Another representation of long-term rupture rates for Inamed's silicone-filled breast implants is predicated on Inamed's saline-filled breast implant deflation rates. Because the shells of Inamed's saline-filled implants are essentially the same as the shells of Inamed's silicone-filled implants, long term saline deflation (loss of shell integrity) rates can be used to estimate the rate of loss of shell integrity (rupture) for silicone-filled devices. This comparability is demonstrated by the 4-year rupture rate of 1.7% in the Core Augmentation cohort versus the 4-year deflation rate of 3.1% in Inamed's 1995 Saline Augmentation Clinical Study. Saline deflation should be considered the worst case failure rate for Inamed's implant shells because saline deflation rates include valve failures that do not occur in gel-filled devices. Furthermore, failures in the shells of saline-filled devices result in deflation, which would be easily noticed by the patient and physician, while failures in the shells of silicone-filled devices may be subject to silent rupture. Whereas a ruptured silicone-filled implant may maintain its size and shape with the gel retained inside the breast capsule, a deflated saline-filled implant loses its size and shape as the saline leaves the shell and is absorbed into the body. Thus, it is expected that the deflation rate for Inamed's saline-filled implants will be slightly higher than the rupture rate for Inamed's silicone-filled implants, as is supported by a comparison of the 4 year data for both types of implants. This comparison was based on data from the augmentation cohorts of both studies (1995 Saline Study [A95] and the Core Study) because all of Inamed's saline-filled shells are single lumen, and the Core augmentation cohort is not heavily weighted with double lumen gel-filled implants. At 8 years post implantation, the saline-filled implant deflation rate was 7.3%, suggesting that the 8-year rupture rate for Inamed's silicone-filled breast implants with comparable shell characteristics would be less than 7.3%.

For the silicone-filled implants in the Adjunct Study, Kaplan-Meier 5-year rupture rate by-patient was 3.0% in the Reconstruction cohort and 2.7% in the Revision cohort (Attachment 2-2), including both confirmed and unconfirmed ruptures. The Adjunct Study by-implant rupture rate at 5 years was 2.3% in the Reconstruction cohort and 1.9% in the Revision cohort. As of June, 2004 the Danish Breast Implant Registry had no reports of ruptures for Inamed's PMA devices; therefore, no Kaplan-Meier risk rates for rupture have been calculated from that database.

In the published literature, implant age was noted as a factor in rupture. One retrospective study of 180 women noted that the average age at which silicone gel implants tend to rupture was 13.4 years (Rohrich et al. 1998). Implant generation is also a factor in rupture as noted by Holmich et al. (2001), with third generation implants (such as the subject of Inamed's PMA) showing a lower prevalence of rupture than second generation implants. Holmich et al. (2003a) estimated a 10-year rupture-free implant survival of 83%-85% for third generation implants intact at 3 years.

In summary, Inamed quantified long-term rupture rates based on the data from the Adjunct Study, comparison of saline-filled implant shells to silicone-filled implant shells

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and complaint database reports of rupture. A reasonable annual progression in the rupture rate is demonstrated by the Adjunct Study's rate of ~2% at 5 years after implantation (reconstruction and revision patients) and the saline-filled shell to silicone-filled shell comparison rate of ~7% at 8 years (augmentation patients) after implantation. This progression is in line with the Core Study estimate of a 13.9% overall rupture rate at 10 years for Inamed's silicone-filled breast implants.

The following presents additional clinical data on Inamed's silicone-filled breast implants from the Adjunct Study, as well as relevant information from the published literature (Attachment 2-3) to address implant rupture (Items 2a-d). Copies of all articles cited in this response are included in Attachment 2-6.

A. INTRACAPSULAR GEL, EXTRACAPSULAR GEL AND MIGRATED GEL

Of the 105 patients who experienced rupture in the Adjunct Study (N = 46,314) as of the data extraction on July 2, 2004, 99 of the ruptures were confirmed at explant. Six (6) patients have not yet undergone surgery to confirm the status of the suspected rupture. Ninety-five (95) of the 99 confirmed ruptures were intracapsular, and one was extracapsular [REDACTED]. Of the remaining three confirmed ruptures, two reconstruction patients (Patient [REDACTED]) had delayed wound healing and implant extrusion with silicone gel leaking from the wound. One reconstruction patient ([REDACTED]) had silicone gel leaking from her nipple reconstruction incision after the physician nicked the capsule and possibly the implant during a secondary procedure. The revision patient with an extracapsular rupture ([REDACTED]) and one reconstruction patient with an intracapsular rupture ([REDACTED]) had gel migration to the left axilla; however, the physician believes that the gel migration for the intracapsular rupture was caused by multiple needle procedures on the left breast.

Inamed's Adjunct Study findings are consistent with the published literature (Attachment 2C), which shows that the majority of ruptured implants are accompanied by intracapsular versus extracapsular gel. One large European study, Holmich et al. (2001), examined 271 Danish women via MRI and found 26.5% of their implants to be ruptured, with 78% of the ruptures intracapsular and 22% extracapsular. Eighty-eight percent (88%) of these devices were implanted for 6 or more years, and 56% were implanted for over 10 years. Adjunct Study results are also consistent with published literature findings showing that migration of silicone gel beyond the breast tissue is infrequently reported.

Adjunct Study reports of extracapsular gel are substantially lower than the rates of 22-31% seen in the literature for ruptured implants (Brown et al. 2000, 2001 and 2002; Holmich et al. 2001; Middleton 1998); however, most large published studies rely on MRI to identify extracapsular gel whereas the Adjunct Study reports of extracapsular gel are based on confirmation at explant. MRI is subject to false positives as noted in the Adjunct Study where three patients ([REDACTED]) were identified by MRI as having extracapsular ruptures, which were refuted at explant surgery. Scaranelo et al. (2004) examined asymptomatic patients via MRI and correlated the MRI diagnosis with

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surgical findings to determine that MRI had a false positive rate of 43%. This is consistent with the Core Study findings of ~36% false positives with MRI diagnoses of rupture. Some small studies (Netscher et al. 1996; Quinn et al. 1996) that employed surgery to confirm an extracapsular diagnosis identified extracapsular rates of 3-5%, consistent with the Adjunct Study findings. The Danish Breast Implant Registry shows no reports to date of gel migration for Inamed's PMA devices.

In addition, as previously presented in response to Item 1b, PBPK modeling can express the absorption, tissue distribution, metabolism and elimination of a compound, as well as the biological interaction of a compound with tissues and systems of the body. Therefore, Inamed developed a PBPK computer model for D₄ (based on published PBPK D₄ modeling) to describe possible silicone movement from a breast implant depot. The initial PBPK model indicates that implant site simulations based on both a young adult woman and a post-menopausal woman with a simulated double rupture of the largest available implants would result in D₄ being cleared to levels below 1 ppm within 30 days. Therefore, it is unlikely that D₄ would be detected in any tissues of the body within a few weeks of receiving an implant, even if immediately ruptured, under the assumptions used in Inamed's PBPK model.

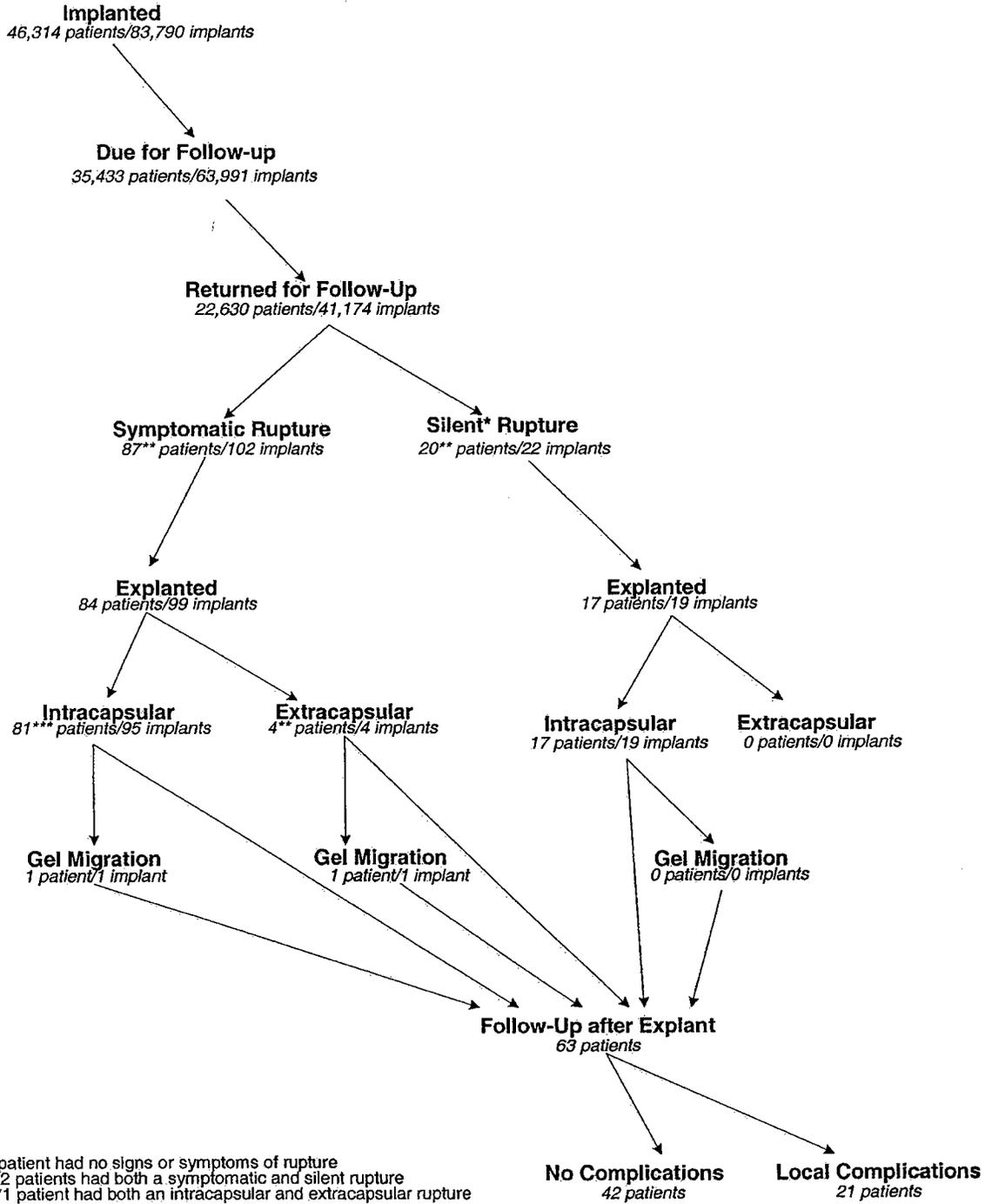
In conclusion, there were very few occurrences of extracapsular gel or gel migration out of the 99 confirmed ruptures in the Adjunct Study. This is consistent with the Core Study findings, which showed no gel migration and only one instance of extracapsular gel, most likely attributable to a secondary surgical procedure. Therefore, both of Inamed's clinical studies are in accordance in determining a very small risk of gel moving out of the breast capsule after an implant rupture.

B. LOCAL HEALTH CONSEQUENCES OF RUPTURES

Figure 2A provides an overview of the clinical course for women in the Adjunct Study who have experienced ruptured implants. As illustrated in the diagram, 46,314 patients were implanted in the Adjunct Study as of the data extraction on July 2, 2004. Of those 46,314 patients, 105 patients reported experiencing an implant rupture (4 of which were extracapsular) and 21 of those rupture patients experienced local complications after the ruptured implant was removed.

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Figure 2A
Adjunct: Overview of Rupture Progression



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A detailed description of the clinical course for each Adjunct patient who experienced rupture, by cohort, is included in a table format in Attachment 2-4 and narrative format in Attachment 2-5.

To examine possible patterns in complications during the course of a rupture, the complications are reported separately based on whether they occurred concomitant with the rupture diagnosis or after the ruptured implant was removed. Table 2-1 summarizes complications occurring concomitant with implant rupture in the Adjunct Study, and Table 2-2 summarizes complications occurring after confirmed implant rupture (i.e., after explantation).

As noted in Table 2-1, almost one-third of Adjunct Study patients (31.3%) exhibited no complications along with the rupture. For the remaining patients, the most frequent complications experienced with rupture were capsular contracture (35.4%), asymmetry (20.2%), breast pain (14.1%), implant palpability (14.1%), implant malposition (12.1%), wrinkling (10.1%), implant visibility (8.1%) and swelling (5.1%). All other complications occurred at a rate of less than 4%.

Table 2-1
Adjunct: Concomitant Complications Experienced With Confirmed Rupture

Complication	Patients (N=99)	
	n	%
No Complications	31	31.3%
Complications		
Asymmetry	20	20.2%
Breast Pain	14	14.1%
Capsular Contracture	35	35.4%
Delayed Wound Healing	1	1.0%
Implant Extrusion	1	1.0%
Implant Malposition	12	12.1%
Implant Palpability	14	14.1%
Implant Visibility	8	8.1%
Irritation	3	3.0%
Loss of Nipple Sensation	2	2.0%
Lymphadenopathy	2	2.0%
Nipple Hypersensitivity/Paresthesia	2	2.0%
Skin Hypersensitivity/Paresthesia	2	2.0%
Skin Rash	1	1.0%
Swelling	5	5.1%
Tissue/Skin Necrosis	1	1.0%
Wrinkling	10	10.1%

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The Adjunct Study complications concomitant with rupture are the same types of complications that women with non-ruptured implants experienced in the Adjunct Study. Likewise, Holmich et al. (2003b), in a follow up to the study of Danish women, found no significant differences in self-reported symptoms among the women with ruptured implants versus the women with intact implants, except for a higher rate of capsular contracture in women with extracapsular ruptures. Average length of time implanted was 14 years.

As noted in Table 2-2, two-thirds of Adjunct Study patients (66.7%) experienced no complications after rupture and underwent no additional surgeries after the ruptured implant was removed. Only 6 patients specified dissatisfaction with their implants at follow up visits after the ruptured implant was removed.

The most frequent post-rupture complications were asymmetry (15.9%), implant palpability (15.9%), capsular contracture (11.1%), implant malposition (11.1%), wrinkling (11.1%), implant visibility (7.9%) and breast pain (6.3%). All other complications occurred at a rate of less than 4%. The most frequent reoperations after removal of the ruptured implant were additional implant removal with replacement (15.9%), "other" procedure, e.g., implant placement (15.9%) and capsulectomy (4.8%). All other reoperations occurred at a rate of less than 4%.

Table 2-2
Adjunct: Complications Experienced After Confirmed Rupture

Complication	Patients (N=63*)	
	n	%
No Complications	42	66.7%
Complications		
Asymmetry	10	15.9%
Breast Pain	4	6.3%
Capsular Contracture	7	11.1%
Implant Malposition	7	11.1%
Implant Palpability	10	15.9%
Implant Visibility	5	7.9%
Irritation	2	3.2%
Loss of Nipple Sensation	2	3.2%
Lymphadenopathy	1	1.6%
Nipple Hypersensitivity/Paresthesia	1	1.6%
Skin Hypersensitivity/Paresthesia	1	1.6%
Suspected Rupture	2	3.2%
Tissue/Skin Necrosis	1	1.6%
Wrinkling	7	11.1%
Reoperations		
Capsulectomy	3	4.8%

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Capsulorraphy	2	3.2%
Capsulotomy	2	3.2%
Implant Removal with No Replacement	1	1.6%
Implant Removal with Replacement	10	15.9%
Other Procedure**	10	15.9%

*Of the 99 patients with confirmed ruptures, only 63 patients are included in this table because 22 patients were discontinued due to explantation of all study devices and 14 patients have not yet had any follow-up after the rupture confirmation. Average follow up is 1.8 years, ranging from 14 days to 4.7 years.

**Other procedures include implant placement, breast biopsy, repair wound dehiscence, pocket revision and nipple reconstruction

As with complications concomitant to rupture, the types of local complications observed after rupture in Inamed's silicone-filled implants from the Adjunct Study occur in women with breast implants, regardless of whether or not they have experienced ruptured implants. This similarity of reported complications between patients with and without ruptures is also supported in the published scientific literature (Attachment 2-3), as well as in the Core Study results described in Deficiency 1. Since there have been no ruptures reported to date for Inamed's PMA devices in the Danish Breast Implant Registry, consequently there are no complications associated with rupture to report.

C. SILENT RUPTURE PROGRESSION TO SYMPTOMATIC RUPTURE

In the Adjunct Study all but one patient who was diagnosed with a silent rupture underwent surgery soon after identification to confirm the status of the suspected rupture and remove the implant if it was not intact. However, there was one reconstruction patient (██████████) whose asymptomatic rupture was identified on 9/5/02 by a CT scan ordered by her oncologist. At follow up visits with her plastic surgeon on 3/19/03 and 3/17/04 the patient presented with moderate right asymmetry. This suspected rupture has not yet been confirmed because the patient has lymphoma and does not wish to undergo surgery at this time.

As seen in both the Adjunct Study and the published literature (Attachment 2-3), standard clinical practice is to explant a device when rupture is identified, resulting in little data on silent ruptures that progress to symptomatic ruptures. The Danish Breast Implant Registry has reported no ruptures for Inamed's PMA devices; therefore, no data exists in that database on silent ruptures progressing to symptomatic ruptures.

D. INTRACAPSULAR RUPTURE PROGRESSION TO EXTRACAPSULAR RUPTURE

In the Adjunct Study no cases were noted of intracapsular ruptures that progressed to extracapsular ruptures. Indeed, of the four extracapsular ruptures reported, two were due to wound dehiscence and implant extrusion with the silicone gel leaking out of the incision site, and a third was due to the physician nicking the capsule and possibly the implant during a nipple reconstruction procedure.

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As noted above in Item 2c, standard clinical practice is to explant a device when rupture is identified, resulting in little data regarding intracapsular ruptures that progress to extracapsular ruptures. Literature shows that extracapsular rupture is generally caused by a trauma to the breast and not a progression from an intracapsular rupture. However, a recent prospective follow up study on the Danish cohort, Holmich et al. (2004), performed a second MRI two years after the first screening MRI to assess the changes over time in untreated ruptures. Results showed that 9% of intracapsular ruptures progressed to extracapsular ruptures over a 2 year period, although the progression was minor in most cases. For the intracapsular ruptures that developed into extracapsular ruptures, 3 of the 7 women reported trauma to the affected breast between the first and second MRI, and an additional woman underwent a mammogram during that time period (Attachment 2-3). In the Danish Breast Implant Registry there have been no reports of ruptures for Inamed's PMA devices, so no data is available on intracapsular ruptures progressing to extracapsular ruptures for that population.

SUMMARY

In conclusion, Inamed demonstrates a rupture rate for its silicone-filled breast implants, which progresses from ~2% at 5 years after implantation to an estimated ~7% at 8 years after implantation and ~14% at 10 years, based on data from clinical trials and Inamed's saline-filled to silicone-filled shell comparison. Based on Inamed's Core and Adjunct Clinical Studies and the published literature, the vast majority of these ruptures are expected to be intracapsular, with a small percentage of extracapsular ruptures and an even smaller percentage evidencing migrated gel. Inamed's Core and Adjunct Clinical Studies, as well as the literature also show that patients with ruptured implants experience the same types of complications experienced by women with non-ruptured implants. While the Danish Breast Implant Registry has not yet reported any ruptures for Inamed's PMA devices, Inamed will continue to collect this data and provide it to FDA in postapproval reports should this PMA be approved, along with the long-term postapproval follow-up data for the Core Study.

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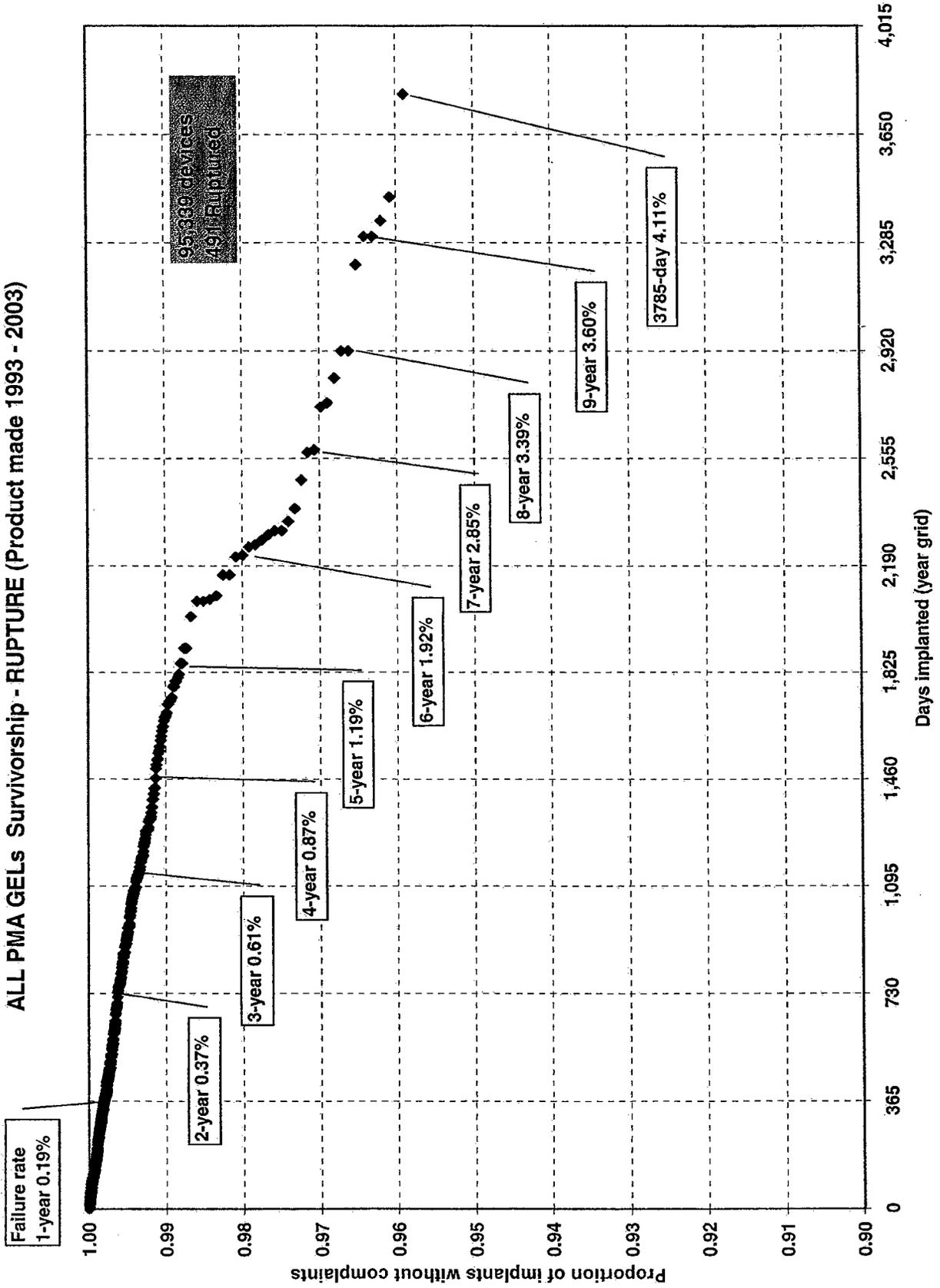
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ALL PMA GELS Survivorship - RUPTURE (Product made 1993 - 2003)



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ADJUNCT CLINICAL STUDY: RECONSTRUCTION

Table 1: Risk of First Occurrence of Implant Rupture

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	1	10722	0.0% (0.0%, 0.0%)	1	18441	0.0% (0.0%, 0.0%)
6 Months	4	10488	0.0% (0.0%, 0.1%)	4	18004	0.0% (0.0%, 0.0%)
1 Year	9	8429	0.1% (0.0%, 0.1%)	9	14393	0.1% (0.0%, 0.1%)
2 Years	21	3265	0.4% (0.2%, 0.6%)	21	5368	0.2% (0.1%, 0.4%)
3 Years	32	2379	0.8% (0.5%, 1.1%)	34	3902	0.5% (0.3%, 0.7%)
4 Years	39	516	1.6% (0.9%, 2.3%)	43	838	1.1% (0.7%, 1.6%)
5 Years	45	310	3.0% (1.7%, 4.3%)	51	492	2.3% (1.4%, 3.2%)

ADJUNCT CLINICAL STUDY: REVISION

Table 2: Risk of First Occurrence of Implant Rupture

Time	By Patient			By Implant		
	Number Affected	Number Remaining	Cumulative Risk	Number Affected	Number Remaining	Cumulative Risk
	n	n	% (95% CI)	n	n	% (95% CI)
4 Weeks	0	10898	0.0% --	0	20293	0.0% --
6 Months	7	10598	0.1% (0.0%, 0.1%)	8	19704	0.0% (0.0%, 0.1%)
1 Year	15	8557	0.1% (0.1%, 0.2%)	18	15878	0.1% (0.0%, 0.1%)
2 Years	31	3712	0.5% (0.3%, 0.7%)	39	6775	0.4% (0.2%, 0.5%)
3 Years	45	2686	0.9% (0.6%, 1.2%)	55	4889	0.6% (0.4%, 0.8%)
4 Years	54	740	1.7% (1.1%, 2.3%)	64	1339	1.0% (0.7%, 1.4%)
5 Years	60	408	2.7% (1.7%, 3.7%)	73	724	1.9% (1.2%, 2.5%)

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LITERATURE REVIEW SURROUNDING BREAST IMPLANT RUPTURE

A search of the published scientific literature from 1966 to the present on silicone gel-filled breast implants was undertaken to identify clinical studies and case series that provided information in response to FDA's request for additional rupture information. This review includes literature previously provided to FDA as part of P020056, as well as new literature search results. Furthermore, detailed data from clinical studies on intracapsular rupture, extracapsular rupture, "silent" rupture, gel migration, and timing of certain events are provided in Appendix 1.

FREQUENCY OF INTRACAPSULAR GEL

Intracapsular rupture has been described by Ahn and Shaw (1994) as "rupture of the implant shell in which silicone-gel leakage is contained within an intact fibrous capsule." According to the Institute of Medicine's report on the safety of silicone breast implants (IOM 1999), rupture is considered to be a loss of integrity of the implant shell and is diagnosed only when silicone gel is present outside the implant. When the fibrous capsule that surrounds a ruptured implant remains intact and contains the silicone, this is an intracapsular rupture. Using these definitions, we identified published literature that provided information on the frequency of or clinical evidence of intracapsular silicone gel in breast implant patients.

For the majority of the publications reviewed, the frequency of rupture and the detection of intracapsular or extracapsular silicone were not the primary objectives of the study. Therefore, we relied on the investigators' own descriptions of intracapsular or extracapsular ruptures, rather than assuming ruptures to be of any specific type. In addition, as the sensitivity and specificity of imaging techniques can vary in their ability to detect rupture, and no imaging technology is 100% accurate, rupture details provided by surgical explantations rather than from imaging results were reported whenever available.

There are clinical studies and case series that provide information on intracapsular silicone gel in breast implant patients. In most cases, the devices were found to be ruptured and were of a design available before 1990, which were silicone elastomer shells filled with a noncohesive (softer, semi-liquid) silicone gel. The study data from general populations of women with breast implants suggest that less than 20% of women with breast implants are found to have evidence of rupture with intracapsular gel. Approximately 20% of implants and 31-78% of ruptured implants have evidence of intracapsular rupture or silicone.

Clinical Studies

The prevalence of intracapsular gel or intracapsular rupture has been investigated in several clinical studies. Some of the studies involved a general population of women with breast implants, some involved women in whom rupture was suspected, and some

involved women who underwent explantation or revision surgery for a variety of reasons. The details of these studies are presented in Appendix 1.

Studies of general populations of women with breast implants. Destouet et al. (1992) conducted a retrospective study of 350 asymptomatic women with silicone gel-filled or saline-filled implants who underwent screening mammograms. Eighteen implants in 16 patients were found to be ruptured. Extravasation of silicone gel within the fibrous capsule was surgically confirmed in 16 of the 350 women (5%). DeAngelis et al. (1994) examined 32 women (57 implants, both silicone gel and saline) who underwent imaging studies; surgery was performed on 19 implants in 11 patients. Among patients who underwent surgery, 15 of 19 implants (79%) were found to be ruptured; 6 silicone gel-filled implants were found to have evidence of intracapsular rupture. Holmich et al. (2001) examined a cohort of 271 Danish women (533 implants) for evidence of rupture using magnetic resonance imaging (MRI). One-hundred-forty-one implants (27%) were found to be ruptured; 110 of the ruptured implants (78%) had evidence of intracapsular gel.

Studies of women in whom breast implant rupture is known. Sanger et al. (1995) examined a cohort of 31 women undergoing explantation of their silicone gel-filled implants or removal of silicone gel-associated granulomas. Among the 41 implants with capsule biopsies, 9 implants (22%) were found to have ruptured with gel contained in or adjacent to the fibrous capsule.

Studies of women who underwent breast implant explantation or revision surgery. Everson et al. (1994) examined a cohort of 32 women (63 implants) who underwent imaging studies prior to explantation surgery for a variety of reasons. There were 22 ruptures overall (35%) and 21 of the implants (33%) (95% of the ruptures) were intracapsular. Malata et al. (1994) conducted a prospective cohort study of 51 women (83 implants) with silicone gel-filled implants who underwent explantation or revision breast surgery. Fourteen of the 51 women (27%) experienced an implant rupture. Ten of the women (14%) (71% of women with ruptured breast implants) were found to have intracapsular ruptures. Ahn et al. (1995) conducted a prospective clinical study of 139 implants explanted from 72 symptomatic patients. Of the 139 implants removed, 31% were found to be ruptured. Twenty-one of the 139 implants (15%) had evidence of intracapsular fluid. Beekman et al. (1997) conducted a prospective study of 40 breast implant patients (71 implants) who underwent explantation for a variety of reasons. Fifty-eight of 71 (82%) implants were found to have failed. In 26 of the 71 capsules (37%), silicone particles were found in the inner half of the capsule thickness; in 24 of the capsules (34%), silicone particles were present in the outer half of the capsule thickness. Beekman et al. (1999) reported that of 18 women (35 single-lumen silicone gel-filled breast implants) who had explantation surgery for various reasons, 45.7% of the implants (16 of 35) were found to be ruptured; all were intracapsular ruptures. Ikeda et al. (1999) examined a cohort of 30 symptomatic patients (59 implants) evaluated with MRI, ultrasound, and mammography. Thirty-one implants in 16 patients had surgical correlation. Thirteen of 31 implants (42%) were found to be ruptured; 9 of 31 implants (29%) and 9 of 13 ruptures (69%) demonstrated evidence of intracapsular rupture.

Herborn et al. (2002) examined a cohort of 25 women (41 implants) who had undergone MRI. Fifteen of the 41 implants (37%) were found to be ruptured. Ten of the 41 implants (24%) (67% of ruptured implants) demonstrated intracapsular gel.

Case Series

One case series was identified in the scientific literature describing silicone gel found outside of a ruptured implant but within the intact fibrous capsule. Conant et al. (1995) conducted intraoperative sonography on nine patients (16 implants) and one patient with painful breast nodules after previous explantation of a ruptured implant to localize any free silicone. Nine of the 17 breasts (52%) with ruptured implants had silicone contained within the fibrous capsule. Given the millions of silicone gel-filled breast implants that have been implanted since 1960, the number of published reports describing silicone gel from a ruptured implant contained in an intact fibrous capsule is very, very small. This likely suggests that fibrous capsule containment of gel is a common clinical finding with ruptured implants, especially for implants with less cohesive silicone gel, and is generally not sufficiently notable to report as a case study.

Summary

In summary, intracapsular gel (evidence of silicone gel within an intact fibrous capsule) has been reported to be observed in less than 20% of women with breast implants (20% of implants). It is not an uncommon finding in women with ruptured implants; as many as 78% of ruptured implants have been reported to be accompanied by the presence of gel within the capsule.

FREQUENCY OF EXTRACAPSULAR GEL

Extracapsular rupture has been described by Ahn and Shaw (1994) as “rupture of the implant shell in which silicone leakage extends behind the confines of the fibrous capsule into the surrounding tissues.” The Institute of Medicine’s 1999 report on silicone breast implants defines rupture as a loss of integrity of the implant shell and is diagnosed only when silicone gel is present outside the implant (IOM 1999). If the fibrous capsule loses its integrity and silicone gel escapes into the surrounding breast tissue or migrates further, it is considered to be an extracapsular rupture. Using these definitions, we identified published literature that clearly reported on the frequency of or clinical evidence of extracapsular silicone gel in breast implant patients. Among the locations considered to be “surrounding tissues” were breast parenchyma, ducts, and breast musculature.

For the majority of the publications reviewed, the frequency of rupture and the detection of intracapsular or extracapsular silicone were not the primary objectives of the study. Therefore, we relied on the investigators’ own descriptions of intracapsular or extracapsular ruptures, rather than assuming ruptures to be of any specific type. In addition, as the sensitivity and specificity of imaging techniques can vary in their ability to detect rupture, and no imaging technology is 100% accurate, rupture details provided

by surgical explantations rather than from imaging results were reported whenever available.

There are clinical studies and case series that provide information on extracapsular silicone gel in breast implant patients. In all cases, the devices were ruptured, and in most cases, the devices were of a design available before 1990, which were silicone elastomer shells filled with a noncohesive (softer, semi-liquid) silicone gel. The study data from general populations of women with breast implants suggest that approximately 20% or fewer women are found to have implants ruptured with evidence of extracapsular silicone. Approximately 12% of implants and 25% or fewer ruptured implants have evidence of extracapsular rupture or gel.

Clinical Studies

The prevalence of extracapsular gel or extracapsular rupture has been examined in a number of clinical studies. The details of these studies are presented in Appendix 1. Some of the studies involved a general population of women with breast implants, some involved women for whom rupture was suspected, and some involved women who underwent explantation or revision surgery.

Studies of general populations of women with breast implants. DeAngelis et al. (1994) examined 32 women (57 implants, both silicone gel and saline) who underwent imaging studies; surgery was performed on 19 implants in 11 patients. Among patients who underwent surgery, 15 of 19 implants (79%) were found to be ruptured; 3 silicone gel-filled implants were found to have evidence of extracapsular rupture. Berg et al. (1995) examined a cohort of 282 women (534 implants) using MRI and ultrasound to reveal implant status. Extracapsular spread of gel was noted in 4 of 282 women (1.2%) at surgery; only two of the implants were found to be grossly ruptured. Middleton (1998) examined 1,626 single-lumen silicone-gel filled implants using MRI and found that 27% were definitely ruptured; of those that were ruptured, 26% had silicone outside as well as inside the fibrous capsule. Brown et al. (2000, 2001, and 2002) examined a cohort of 344 women with breast implants who had an MRI to reveal implant status. The study population was chosen without regard to patient symptoms, and rupture results were presented by consensus interpretation of MRI by two or more radiologists. The overall rupture rate was 69% of women (55% of implants). Extracapsular silicone was identified in 21% of women, and among women with ruptured implants, 31% experienced an extracapsular rupture. Prevalence of extracapsular silicone by implant was found to be 12%, and prevalence of extracapsular silicone in ruptured implants was 22%. Holmich et al. (2001) examined a cohort of 271 Danish women (533 implants) for evidence of rupture using MRI. One-hundred-forty-one implants were found to be ruptured (26%) upon MRI; 31 of the ruptured implants had extracapsular gel (22%). Twenty-three of the 271 women in this study (8%) had extracapsular implant ruptures. Berg et al. (2002) conducted a study in which 359 women were imaged using MRI to determine the prevalence of rupture in 687 implants. In 12% of implants, extracapsular silicone was identified by MRI. Holmich et al. (2003a) again examined the cohort of 271 Danish women with silicone gel-filled cosmetic implants (533 implants) and performed a second

MRI to determine the incidence of rupture in patients who were free from rupture at baseline. Of 26 incident implant ruptures diagnosed at MRI, 6 (23%) were found to have evidence of extracapsular gel.

Studies of women in whom breast implant rupture is known. Andersen et al. (1989) conducted a retrospective analysis of 18 women with ruptured implants; 10 patients (56%) had evidence of silicone migration outside of the implant capsule. Conant et al. (1995) conducted intraoperative sonography on nine patients (16 implants) and one additional patient with painful breast nodules after previous explantation of a ruptured implant to localize any free silicone. Eight of 17 breasts (47%) had free silicone extravasation, and in two breasts with ruptured implants, silicone gel was found in the pectoralis major muscle and the fascia. Soo et al. (1997) examined a cohort of 44 women (86 implants) who underwent MR imaging prior to explantation surgery for a ruptured implant. Two implants (2%) had evidence of extracapsular rupture.

Studies of women who underwent breast implant explantation or revision surgery. Netscher et al. (1996) examined a cohort of 81 patients (160 implants) and found 42 ruptured implants (26%); 2 of the implants (1% of implants, 5% of ruptures) were found to have extracapsular ruptures. Quinn et al. (1996) examined a cohort of 54 women (108 implants) who underwent MRI to assess implant status; implant rupture was identified at the time of explantation surgery. Thirty of 108 implants (28%) were found to be ruptured; 1 of 108 implants (1%) was an extracapsular rupture (3% of ruptured implants). Beekman et al. (1997) conducted a prospective study of 40 patients with 71 implants; in 17 capsules, silicone particles were found outside of the capsule (24%) but only nine implants were found ruptured. Peters et al. (1997) examined a cohort of 100 women with silicone gel-filled implants who requested explantation; six of the capsules (3%) from a total of five of the patients (5%) demonstrated extracapsular silicone. Ikeda et al. (1999) examined a cohort of 30 symptomatic patients (59 implants) evaluated with MRI, ultrasound, and mammography; 31 implants in 16 patients had surgical correlation. Thirteen of 31 implants (42%) were found to be ruptured at explantation; 4 of 31 implants (13%) and 4 of 13 ruptured implants (31%) demonstrated evidence of extracapsular rupture. Herborn et al. (2002) examined a cohort of 25 women (41 implants) who had undergone MRI; 15 of the 41 implants (37%) were found to be ruptured; 5 of the 41 implants (12%) demonstrated extracapsular gel.

Summary

In summary, extracapsular gel (evidence of silicone gel outside of the fibrous capsule but within breast tissue) has been reported to be observed in approximately 20% of women with breast implants (12% of implants). It is, as expected, almost always observed in association with ruptured implants.

FREQUENCY OF MIGRATED GEL AND DESTINATION OF MIGRATED GEL

Migrated gel is defined here as silicone gel that has moved from inside an intact or ruptured breast implant beyond the breast tissue and local musculature. Using this

definition, we identified published literature that clearly reported on clinical evidence of silicone gel migration in breast implant patients.

All of the evidence of migration of silicone gel from the breast implant site is available from case reports or case series describing silicone gel found distant from a breast implant location. In virtually all cases, the implants are ruptured as a result of closed capsulotomies to treat capsular contracture, trauma, or compression mammography. Closed capsulotomy is no longer the treatment of choice for women with capsular contracture. In all but one case, the devices were of a design available before 1990, which were silicone elastomer shells filled with a noncohesive (softer, semi-liquid) silicone gel. Given the millions of silicone gel-filled breast implants that have been implanted since 1960, the number of case reports describing silicone gel from a ruptured breast implant found distant from the breast area is extremely small. Even with under-reporting, there does not appear to be a great prevalence of silicone gel migration distant from the breast as the result of a ruptured implant.

The most commonly reported sites of silicone gel migration are the axilla, regional lymph nodes, and upper arm. Goin (1978) described a woman with bilateral breast implants whose right implant ruptured as a result of closed capsulotomy and the silicone gel migrated into the right axilla. Huang et al. (1978) described a woman who had closed capsulotomy that resulted in a ruptured implant and migration of silicone to the arm. Wintsch et al. (1978) described silicone gel in the axillary and regional lymph nodes of a woman following implant rupture. Foster et al. (1983) described two cases in which women who had had closed capsulotomies were found to have silicone material in the subcutaneous tissue of the arm. Truong et al. (1988) described silicone lymphadenopathy in four women with five breast implants. Four of the five implants were grossly intact and one had a tear with silicone in surrounding breast tissue despite an intact capsule. Persellin et al. (1992) reported on a patient who had closed capsulotomy of her left breast and was found to have a ruptured implant and gel extrusion along fascial planes into the axilla where a silicone pseudotumor developed. Sanger et al. (1992) described a case in which rupture of a subpectoral implant released silicone gel that migrated to a patient's arm and resulted in nerve impairment.

Ahn and Shaw (1994) reported on four clinical cases of silicone-gel found in breast tissue and muscle of women with ruptured silicone gel-filled implants. Each of these women had had closed capsulotomies. In one patient, silicone gel was found to have migrated from the left implant to the axilla and medial upper arm, and silicone gel was also removed from her bicep muscle. Conant et al. (1995) conducted intraoperative sonography on nine patients (16 implants) and one patient with painful breast nodules after previous explantation of a ruptured implant to localize any free silicone. In one breast with a ruptured implant, silicone lymphadenopathy was localized.

Kulber et al. (1995) conducted a retrospective study of 23 patients with silicone breast implants who had axillary lymph node biopsies for palpable masses. Mammography was conducted on 12 of 15 augmentation patients, and rupture was found in two patients and a breast mass was found in three patients with palpable masses in both the breast and axilla.

Five of eight reconstruction patients had mammography and all were normal. Five augmentation and two reconstruction patients had ultrasound, and all demonstrated material suggestive of silicone in the axilla. MRI was performed on four augmentation patients, and silicone was identified in three. Axillary node biopsies of all patients revealed that ten augmentation patients had axillary masses consistent with siliconosis, and silicone granulomas were identified in the axilla of five patients. Six reconstruction patients had pathology consistent with axillary siliconosis, and two patients had silicone in the axilla.

Teuber et al. (1995) reported on a patient whose right silicone gel-filled implant ruptured, probably as a result of a blunt trauma she sustained to the chest, and silicone was reported to have migrated down the soft tissues of her right arm from her axilla to her wrist. Teuber et al. (1999) reported on three cases in which women with ruptured breast implants experienced migration of silicone gel (one of the patients was described in the Teuber et al. 1995 article). Of the other two women, one had closed capsulotomy to treat capsular contracture. Her implant ruptured and was removed. Shortly thereafter, she was found to have silicone granulomas in her right upper arm and chest. The third patient was found to have free silicone within her biceps along the musculocutaneous nerve and the brachial artery/median nerve area 3 years after implantation of double-lumen implants. Shaaban et al. (2003) reported a case in which a woman with bilateral cohesive breast implants was found to have a ruptured left implant and a silicone lymphadenopathy in her left axilla.

In some cases, silicone gel from a ruptured implant was found some distance from the upper chest and arm. Capozzi et al. (1978) described a woman with a possible history of a chest trauma whose left implant had ruptured and silicone gel and fibrous nodules were found extended from her rib cage and abdomen almost down to her inguinal area, demonstrating migration of free gel along the subcutaneous tissue plane. Hirmand et al. (1994) reported on a woman who had bilateral silicone gel-filled breast implants for 20 years with multiple closed capsulotomies for capsular contracture during that time. After 20 years, she complained of pain in the upper back, and mammography revealed a ruptured left implant with a firm mass just below the left axilla on the chest wall; this was found to be a siliconoma. A year later, she returned with upper left back pain and was found to have a left pleural effusion. Analysis of the pleural effusion fluid by scanning electron microscopy revealed material with "the electron energy pattern of silicone" consisting of particles measuring about 5 μm . One year later, residual silicone was identified and removed from her chest.

Silicone gel has also been found in the back and as far away as the groin. Meyer et al. (1998) reported on an unusual case of silicone granulomas with inflammation in the upper eyelids of a woman 10 years after breast reconstruction with silicone gel-filled breast implants. Baack and Wagner (2003) described a patient who had had reconstruction surgery with latissimus dorsi flaps and silicone gel implants. Twelve years after surgery, she was found to have a ruptured left implant with silicone gel present in the capsule; she was also found to have a pseudosynovial-lined cavity with free-flowing silicone gel in her lower back. Topping et al. (2003) described a woman

with silicone gel-filled breast implant reconstruction of the left breast who developed left side chest pain several years after implantation. MRI revealed a ruptured implant with free silicone extending as far posteriorly as the erector spinae muscle.

Silicone gel migration has also been reported in women with intact (nonruptured) breast implants. Hausner et al. (1978) described a woman with bilateral augmentation mammoplasty who, during biopsy for suspected cancer, was found to have refractile material in her axillary lymph nodes. Her devices were found to be intact. Pflleiderer and Garrido (1995) and Garrido et al. (1994) identified silicone using ^1H -localized spectroscopy in the livers of women with intact silicone gel-filled breast implants.

One somewhat unique clinical study compared the tissue distribution of silicone (organosilicon polymers) in 15 women with breast implants (14 silicone gel-filled and 1 saline-filled) and 14 age- and sex-matched controls (Barnard et al. 1997). None of the women with implants had a history of trauma to the breast area. Only one woman was found to have a ruptured implant. Twelve of the women had devices implanted before 1990, involving implant designs that were filled with a noncohesive silicone gel (year of implantation was unknown for 3 cases). Capsule, breast, axillary lymph nodes, abdominal fat, liver, lung, and spleen were examined using atomic absorption spectrometry (AAS) and light microscopy. Silicone was found microscopically in at least one capsule section from all implant cases and in at least one lymph node in 8 of 15 implant cases but not in lymph nodes from controls. AAS revealed silicon in all capsules and in the axillary lymph nodes, breast, and abdominal fat from implant cases when compared with controls, although measurable amounts of organosilicon polymers were also found in tissues from the control group.

Summary

In summary, migration of silicone gel beyond the breast tissue is very, very rarely observed. When it is observed, it is generally found in association with a ruptured implant caused by closed capsulotomy (no longer the treatment of choice), trauma, or compression mammography.

The Frequencies of Intracapsular and Extracapsular Gel and Gel Migration Beyond Breast Tissue

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. The medical literature suggests that 78% of ruptured devices may result in the collection of silicone gel in the fibrous capsule. 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. There has been no clinical evaluation of the migration of silicone gel from a ruptured implant beyond breast tissue. However, 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.

LOCAL COMPLICATIONS

The 1999 Institute of Medicine's report on the safety of silicone breast implants (IOM 1999) describes a number of local and perioperative complications seen with breast implants. Of these, several have been reported in the medical literature in women with ruptured silicone gel-filled breast implants, notably:

- Silicone granuloma
- Axillary adenopathy
- Acute and chronic breast and chest wall pain
- Changes in the shape and/or size of the breast
- Swelling of the breast (unrelated to gel migration)
- Silicone exudation through skin or nipple
- Axillary pain
- Operative wound infection
- Peri-implant hematoma or seroma
- Skin blistering, cysts, and necrosis
- Loss or change in sensation of the breast or nipple
- Others

The published medical literature was reviewed for information on these local health consequences experienced by patients with ruptured implants, and the findings are described in some detail below.

Clinical Studies

While there are numerous clinical studies that discuss local and systemic complications associated with breast implants, many of these studies were conducted on a general population of women with breast implants or women with either intact or ruptured implants and not populations of women with ruptured implants alone. Because the local consequences of rupture reported in clinical studies are quite varied, and measures of statistical association are rare, general conclusions about local complications found with implant rupture cannot be drawn. The following paragraphs detail clinical studies providing information on local health consequences of ruptured implants.

Andersen et al. (1989) conducted a retrospective review of 18 patients, 14 of whom experienced implant rupture. Ten patients presented with an axillary, breast, or chest wall nodule; six complained of a change in breast size; five noticed the breast became softer; four complained of pain and/or tenderness, three had a change in the shape or symmetry of the breast, and three had no signs or symptoms.

Roscullet et al. (1992) analyzed sonographic findings in 16 women with 19 ruptured implants. Patients presented with the following clinical symptoms leading to imaging studies and eventual diagnosis of rupture: palpable masses (seven breasts), mass and pain (one patient, both breasts), mass and breast deformity (one breast), change in breast shape (three patients, four breasts), and pain (1 breast). In two women (two breasts), biopsy showed a silicone granuloma.

In a retrospective study to evaluate aging and rupture of breast implants, deCamara et al. (1993) provided some clinical details on patients who had experienced rupture. In the ruptured group, four patients had severe pain in the breast, complained of injury to the breast, and had formed palpable masses adjacent to the ruptured implants. None of the women in the study had axillary lymphadenopathy. Surgical treatment of these patients involved removing the implants and the silicone gel. The postoperative course on all the patients was uneventful. There were no postoperative infections or inflammation of the breasts despite extensive silicone extravasation in some of the cases.

In a study of the sensitivity and specificity of imaging techniques, Everson et al. (1994) studied a group of 32 women (63 implants) who underwent imaging studies prior to explantation surgery for various reasons. There were 22 ruptures overall (35%). All but one of these patients had signs and symptoms suggestive of rupture, including pain and itching in the breast and joint swelling.

Malata et al. (1994) reported on a cohort of 51 patients (83 implants) who underwent revisional breast surgery for a variety of reasons. Fourteen of the 51 women (27%) experienced an implant rupture. Postoperative courses were uneventful except for one patient who developed a late hematoma.

Berg et al. (1995) conducted a study in a cohort of 282 women (534 implants, single- and double-lumen) who received an MRI and ultrasound to reveal implant status. Among 40 patients with implant rupture (14% of implants), 26 patients reported breast pain (65% of ruptures), 15 patients reported contracture (37.5%), 6 patients reported flattening (15%), 1 patient reported enlargement (2.5%), 5 patients reported migration (12.5%), 4 patients reported change in shape (10%), 7 patients reported a mass (17.5%), 5 patients reported myalgia (12.5%), 10 patients reported arm and/or neck pain (25%), and 2 were asymptomatic (5%).

In a study of a group of 300 women (592 implants) who had elected implant removal for a variety of reasons, Robinson et al. (1995) found that among symptomatic women, 102/142 (71.8%) were found to have ruptured or bleeding implants. However, this was not significantly different from the percentage of ruptures found in asymptomatic women (70.9%).

In a cohort of 31 women undergoing explantation of silicone gel breast implants or removal of silicone gel-associated granulomas, Sanger et al. (1995) conducted biopsies of fibrous capsules and granulomas to test for tissue humoral response. In three patients,

previously ruptured implants resulted in silicone granulomas in the arm (two) and chest/axilla (one).

In a retrospective study of 350 silicone breast implants in 159 patients, Cohen et al. (1997) found that 41% of patients who described their breasts as being distorted were found to have ruptured implants. Change in the shape of the patients' breasts was significantly correlated with implant failure ($p=0.014$).

Thomas et al. (1997) conducted a study among 25 patients referred for explantation of bilateral silicone gel-filled implants to assess patient-reported symptoms. Ruptured implants were observed in 11 of the 25 patients (44%). Patients in whom rupture was found reported signs and symptoms of fatigue, leg pains, chest pain, hip and shoulder pain, aches, and joint pain.

In a cross sectional study of 317 women with silicone breast implants compared to 317 matched nonimplant controls, Park et al. (1998) reported that ten patients required replacement of their implants following rupture. In one case, rupture followed a closed capsulotomy, and one developed a silicone granuloma. The remainder had no problems.

Brown et al. (2002) found that 8.2% of women with extracapsular rupture reported rash on the breast or chest compared to 6.3% of women with no extracapsular silicone. This finding was not statistically significant (OR 1.3; 95% CI 0.4, 3.7).

Holmich et al. (2003b) conducted a clinical follow-up study in a subgroup of 238 women who had completed a survey on diseases and symptoms after being randomly selected to participate in a study to determine the prevalence of implant rupture by MRI. Local symptoms reported among women with implant rupture ($n=92$) and extracapsular rupture ($n=23$), respectively, were breast pain (23%, 26%), breast hardness (43%, 76%), and unspecified neck, shoulder, or back pain (47%, 48%). None of these findings demonstrated a statistically significant increase in symptoms compared to women with intact implants. Two years later, Holmich et al. conducted MRI analysis of 64 of the Danish women (126 implants) who were found to have a ruptured implant in the earlier study (96/126 ruptured implants), but whose implants were not removed (Holmich et al. 2004). They also 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 (29%, OR 2.1, 95% CI 1.2, 3.8), changes in breast shape (25%, OR 2.5, 95% CI 1.3, 4.8), breast pain (23%, OR 2.2, 95% CI 1.2, 4.2), and any breast change (53%, OR 1.9, 95% CI 1.2, 3.1).

Case Series

Information is available from case series on local complications reported with ruptured breast implants. The most commonly reported symptoms and local complications include

silicone granuloma, axillary adenopathy, acute and chronic breast and chest wall pain, and changes in the size and/or shape of the breast. In addition, there are infrequent reports of silicone exudation through the skin or nipple, peri-implant hematoma or seroma, skin blistering, breast swelling, loss or change in sensation of the breast or nipple, and axillary pain.

Truong et al. (1988) described silicone lymphadenopathy in four women with five breast implants. Four of the five implants were grossly intact and one had a tear with silicone in the surrounding breast tissue despite an intact capsule. Clinical presentations included erythematous, scaly lesion of the nipple, a 2-cm mass in the breast with dimpling of the overlying skin, pain in the axilla and lateral portion of the breast, and nontender 1-cm nodules in the breast.

Ahn and Shaw (1994) described four women who experienced local health consequences associated with ruptured implants. The first woman presented with symptoms of bilateral breast pain, and changes in the shape and size of her left breast implant 6 years after augmentation mammoplasty. Upon surgery for bilateral implant removal and capsulectomy, the right implant was intact, but the left was ruptured with extracapsular silicone found in the surrounding muscle tissue and axilla. This patient had an uncomplicated postoperative course and there was complete resolution of local symptoms after 2 years, with the exception of palpable firmness in the left axilla and moderate paresthesia in the upper left arm.

The second patient described by Ahn and Shaw (1994) complained of bilateral breast pain, bilateral chest wall tightness and axillary pain one year following the replacement of her right breast implant, which had ruptured following bilateral augmentation mammoplasty 15 years earlier. Upon examination, the patient was also found to have palpable masses in the axilla and lateral pectoralis major muscle, thinning of the skin of the left breast, and decreased sensation of the nipple-areola complex. An MRI revealed evidence of silicone-gel extravasation into the pectoralis major muscle and axilla. The patient had an uneventful postoperative course with resolution of breast pain and improvement of all pre-existing symptoms by 20 months.

In a third case reported by Ahn and Shaw (1994), a patient presented with bilateral breast pain, change in the shape and size of the right breast, recurrent bilateral capsular contractures, and bilateral ptosis 11 years after bilateral augmentation mammoplasty. Upon implant removal, capsulectomy and mastopexy, it was confirmed that extracapsular rupture of the right implant and intracapsular rupture of the left implant had occurred. Multiple silicone granulomas in the right pericapsular tissue, parenchyma, and right pectoralis major muscle were found. The patient had an uneventful postoperative course and all local and systemic symptoms had completely resolved by 18 months.

The fourth patient described by Ahn and Shaw (1994) was a woman who developed a palpable mass in her left breast following a closed capsulotomy 3 years after bilateral augmentation mammoplasty. Over the next 6 years, this mass and the patient's breast size both increased, and she also noticed smaller lumps develop in her left breast and left

elbow. Further signs and symptoms included breast pain, axillary pain, upper extremity paresthesia, lower back pain, neck pain, and diffuse paresthesia. Surgery to remove her implants revealed an intact right implant and a ruptured left implant with extravasation of silicone beyond the capsule and into her bicep muscle. The patient initially had an uneventful postoperative course, but after 5 months, experienced a recurrent palpable mass in her upper arm. After this silicone granuloma was removed, moderate systemic symptoms persisted, and her left axilla and upper arm had increased firmness and scarring. The patient required long term physical therapy of the left shoulder, elbow, and hand, but was satisfied with her outcome.

Teuber et al. (1999) reported on three cases in which women with ruptured breast implants experienced migration of silicone gel. One woman had closed capsulotomy to treat capsular contracture and immediately experienced persistent pain in the right breast. Her implant ruptured and was removed. Shortly thereafter, she was found to have silicone granulomas in her right upper arm and chest. She underwent a second surgery, but continued to experience small, painful nodules along the surgical scar, with pain and paresthesia radiating down the right arm. Later, painful granulomas appeared over the right upper arm and chest. Another patient was found to have free silicone within her biceps along the musculocutaneous nerve and the brachial artery/median nerve area three years after implantation of double-lumen implants. She initially presented with left shoulder pain and paresthesia and underwent surgeries to remove the ruptured implants as well as the nodules of free silicone. She continued to have pain in the left arm and intermittent swelling of the elbow.

Summary

In summary, patients with ruptured breast implants may report local health consequences, most commonly pain, change in breast shape, breast hardness, and neck or shoulder pain. In some studies, as many as 50% of women with ruptured implants reported one or more local health concern(s) and in some women, the device was explanted as a result. The local complications experienced by women with ruptured implants were not significantly different from the local complications experienced by women with intact implants.

PROGRESSION OF SILENT TO SYMPTOMATIC RUPTURES

A "silent" breast implant rupture is defined as the undetected loss of integrity of the silicone elastomer envelope (Cook et al. 2002). It may be considered to be synonymous with an asymptomatic rupture. Intracapsular rupture of silicone gel breast implants in particular, can go unrecognized as there may be no change in the configuration of the breast, no patient complaints, and no physical diagnostic finding (IOM 1999). Data from the scientific literature on silent rupture are limited, as clinical studies investigating breast implant rupture in a population specifically defined as asymptomatic are rare. However, the available data suggest that 5% of women or fewer (less than 1% of implants) have silent breast implant ruptures.

Destouet et al. (1992) conducted a retrospective examination of screening mammograms from 350 asymptomatic women with breast implants and found that 5% of women had ruptured implants. Berg et al. (1995) identified two cases of asymptomatic rupture in their study of 282 women (1% of women, 0.4% of implants), where overall there were 40 ruptured implants (7% of implants). In a screening study using ultrasound to detect potential implant rupture in 307 asymptomatic women with 385 implants, Park et al. (1996) found only three patients with ruptured implants (1%) and one of these was a saline implant.

Brown et al. (2000) provided some of the only data available about the timing of "silent" rupture, as they reported a median implant age at rupture of 10.8 years in an "unreferred" population of women with breast implants. However, this study's definition of "silent rupture" is somewhat imprecise. Brown et al. (2000) noted that their study population is "unreferred" and draw conclusions about silent rupture rates, however this "unreferred" population is not strictly asymptomatic, but instead as the authors stated, patients were included "without regard for any local or systemic symptoms." In this study, 344 women (687 implants) with silicone gel breast implants underwent MR imaging and 265 (77%) of the women were found to have at least one breast implant that was rated by radiologists as being ruptured or indeterminate (55% of implants were ruptured affecting 69% of women). Only 31 (9%) of the study participants reported prior to the MRI that they thought their implants might be ruptured.

Little information was found in the scientific literature relating the incidence, prevalence, and timing of silent ruptures that progressed to symptomatic ruptures, although this is not an unexpected finding. Breast implant ruptures are reported in the scientific literature when a population of women with breast implants is examined for evidence of implant rupture or when a case is reported because of an unusual circumstance associated with the rupture (e.g., the rupture results in the migration of silicone gel outside the fibrous capsule.) When a ruptured implant is identified, either upon imaging or because the patient is symptomatic, standard clinical practice is to explant the ruptured device and replace it, if it is clinically safe to do so, and the patient desires a replacement. As noted in the 2004 FDA information update on breast implant risks, plastic surgeons commonly recommend removal of the implant if it has ruptured, even if the silicone is still enclosed within the scar tissue capsule (FDA 2004). Clinical studies and case reports of rupture almost always capture data at only one time point, either through imaging of the breast implant or through surgery for explantation or revision.

Furthermore, as noted by the Institute of Medicine's report on the safety of silicone gel implants (1999) "Careful explantation and direct visual examination are the standard for diagnosis of silicone gel-filled implant rupture, both unsuspected or silent, and for confirmation of rupture. Explantation allows only a retrospective or confirmatory diagnosis. It is not a prospective means of resolving the question of presence or timing of rupture in an individual patient."

Summary

In summary, silent ruptures are breast implant ruptures not accompanied by physical symptoms. That is, the patient is unaware that her implant has ruptured. The available medical literature suggests that silent rupture is rare, occurring in less than 5% of women with breast implants (less than 1% of implants). It is extremely difficult to identify women for whom silent ruptures become symptomatic, since without information about the timing of the rupture, it is difficult to determine whether an observed adverse event predated or postdated implant rupture (Cook et al. 2002).

PROGRESSION OF INTRACAPSULAR TO EXTRACAPSULAR RUPTURES

According to the Institute of Medicine's 1999 report of silicone breast implants (IOM 1999), rupture is a loss of integrity of the implant shell and is diagnosed only when silicone gel is present outside the implant. When the fibrous capsule that surrounds a ruptured implant remains intact and contains the silicone, this is considered an intracapsular rupture. If the fibrous capsule loses its integrity and silicone gel escapes into the surrounding breast tissue or migrates further, this is considered to be an extracapsular rupture.

Using these definitions, the published literature was reviewed for information on the frequency, incidence, prevalence, clinical evidence and timing of intracapsular ruptures that progressed to extracapsular ruptures.

Information available from the published literature on intracapsular rupture in general populations of women with breast implants suggest that approximately 20% of implants examined and between 31% and 78% of implants found to be ruptured, released silicone gel that remained within the confines of the fibrous capsule (Destouet et al. 1992, DeAngelis et al. 1994, Holmich et al. 2001). The overall findings from the literature on extracapsular rupture in general populations of women with breast implants suggest that approximately 12% of implants and 25% or fewer ruptured implants demonstrated evidence of extracapsular rupture or presence of extracapsular gel (DeAngelis et al. 1994, Berg et al. 1995, Middleton 1998, Brown et al. 2000, Brown et al. 2001, Holmich et al. 2001, Berg et al. 2002, Brown et al. 2002, Holmich et al. 2003a).

Breast implant ruptures are reported in the scientific literature when a population of women with breast implants is examined for evidence of implant rupture or when a case is reported because of an unusual circumstance associated with the rupture (e.g., the rupture results in the migration of silicone gel outside the fibrous capsule). When a ruptured implant is identified, either upon imaging or because the patient is symptomatic, standard clinical practice is to explant the ruptured device and replace it if it is clinically safe to do so and the patient desires a replacement. As noted in the 2004 FDA information update on breast implant risks, plastic surgeons commonly recommend removal of the implant if it has ruptured, even if the silicone is still enclosed within the scar tissue capsule (FDA 2004). As a result, implants with diagnosed intracapsular

rupture are not left in place to progress to extracapsular rupture, even if this was a common event.

Only one study was identified in the scientific literature that examined the outcomes of ruptured implants that are not explanted (Holmich et al. 2004). This study prospectively assessed whether ruptured implants are associated with changes over time according to MRI evaluations taken 2 years apart. At the baseline MRI, there were 64 women (126 implants) who had at least one ruptured implant. Among the 126 implants, 96 were ruptured at baseline, and 77 of these were intracapsular ruptures. Of the 77 implants with intracapsular rupture at baseline MRI, 69 (90%) showed no changes at the follow-up MRI 2 years later. In 7 implants (9%) extracapsular silicone was present at the follow-up MRI, and in one implant initially thought to show extracapsular silicone, no silicone was found outside the capsule upon operation.

Typically, extracapsular ruptures result from closed capsulotomy to treat capsular contracture, a blunt trauma, or compression mammography. Closed capsulotomy is no longer the treatment of choice for capsular contracture. Extracapsular ruptures occur when the fibrous capsule is broken and silicone gel is forcibly ejected from the capsule, which generally occurs as an acute event and typically not as a progression from an intracapsular rupture. However, Holmich et al. (2004) identified a few cases in which intracapsular rupture progressed spontaneously to extracapsular rupture, as well as a few cases of further progression of extracapsular silicone deposition. In 11% of the intracapsular ruptures Holmich et al. noted 2 years prior, there appeared to be a progression of silicone seepage, although it was minor in most cases. The authors interpret these findings to mean that the fibrous capsule surrounding an implant is not impermeable to silicone and that an intracapsular rupture may not be a permanent condition. The authors concluded, however, that in most cases, implant rupture is a "harmless event."

Summary

In summary, there is little scientific or medical information on the progression of intracapsular ruptures to extracapsular ruptures. Extracapsular ruptures are most likely to result from closed capsulotomy (a treatment no longer recommended), trauma, or compression mammography than to occur spontaneously. Only one study, Holmich et al. (2004) provided information on the progression from intracapsular rupture to extracapsular rupture. In her population of Danish women with breast implants, 9% of implants examined using MRI demonstrated evidence of extracapsular silicone 2 years after diagnosis of intracapsular rupture.

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Appendix 1

Table of Clinical Studies that Provide Details Surrounding Breast Implant Rupture

Citation	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture and signs Rupture	Gel migration	Timing of rupture progression	Local complications with rupture and clinical course
Ahn et al. 1995	Silicone gel Augmentation, reconstruction	Prospective clinical study of 139 implants explanted from 72 symptomatic patients to examine the possible effects of microbial colonization on implant integrity.	Of the 139 implants removed, 31% were found to be ruptured. Twenty-one of the 139 implants (15%) had evidence of intracapsular fluid.	No data	No data	No data
Andersen et al. 1989	Silicone gel in all but 1 patient Augmentation, reconstruction	Retrospective analysis of 32 patients with ruptured implants: 18 patients treated by the authors and 14 patients from previous case reports.	Three (3) patients in this analysis (17%) presented with no symptoms of rupture (i.e., "silent" rupture). Among the 24 patients who underwent mammography, 10 patients (41.7%) had silicone migration outside the implant capsule (extracapsular rupture). Among 8 mammograms that were falsely negative for rupture, 7 of these were found to have silicone contained within the fibrous capsule.	No data	No data	Ten (10) patients presented with an axillary, breast, or chest wall nodule; 6 complained of a change in breast size; 5 noticed the breast became softer; 4 complained of pain and/or tenderness, 3 had a change in the shape or symmetry of the breast, 3 had no signs or symptoms.

Citation	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture and silent rupture	Gel migration	Timing of rupture progression	Local complications with rupture and clinical course
Barnard et al. 1997	Silicone gel, 1 saline	Autopsy comparison of tissue distribution of organosilicon polymers between 15 women with breast implants and 14 controls frequency matched for sex and age.	In only one case (1/15, 6.7%), the implant had ruptured and dissected beyond the capsule with prominent fibrotic encirclement of silicone and numerous surrounding multinucleated giant cells.	Statistically significant increases of organosilicon polymers were found in the axillary lymph nodes, breast, and abdominal fat of women with breast implants compared to the nonimplant group. No difference was found in the concentration of organosilicon polymer in the liver, lung, or spleen.	There was no apparent relationship between the concentration of organosilicon polymers and years after implant or type of implant.	No data
Beekman et al. 1997	Silicone gel Augmentation	Cohort of 40 women with 71 breast prostheses that had been explained for various reasons (primarily capsule formation) and had the fibrous capsules histologically tested for degree of silicone gel migration.	Intracapsular rupture was found in 30 implants (42.3% of implants); no extracapsular ruptures were found.	4/71 capsules (5.6%) showed no signs of extracapsular migration; 26/71 (36.6%) showed migration to inner half of capsule thickness; 24/71 (33.8%) showed migration to outer half of capsule thickness; 17/71 (23.9%) showed extracapsular migration.	No data	No data

Citation	Implant type and reason	Study description	Intracapsular implants, extracapsular rupture, and silent ruptures	Gel migration	Timing of rupture progression	Local complications with rupture and clinical course																														
Beekman et al. 1999	Silicone gel Augmentation and reconstruction	Cohort of 18 women with 35 single-lumen silicone gel breast implants who underwent imaging studies prior to explantation surgery for various reasons.	Overall, 45.7% of implants were found to be ruptured at surgery (16/35 implants). No extracapsular ruptures were encountered.	No data	No data	No data																														
Berg et al. 1995	Silicone gel Single and double-lumen implants	Cohort of 282 women with 534 silicone-containing breast implants (single- and double-lumen) who received an MRI and ultrasound to reveal implant status; accuracy of imaging techniques were assessed.	Extracapsular spread of gel was noted in only 4 cases at surgery (4/282 women, 1.2%); 2 with leakage and 2 gross ruptures. Asymptomatic or "silent" rupture was noted in 2 implants in this study.	No data	No data	<p>Symptom</p> <table border="1"> <tr> <td>Breast pain</td> <td>26</td> <td>17</td> </tr> <tr> <td>Contracture</td> <td>15</td> <td>15</td> </tr> <tr> <td>Flattening</td> <td>6</td> <td>1</td> </tr> <tr> <td>Enlargement</td> <td>1</td> <td>1</td> </tr> <tr> <td>Migration</td> <td>5</td> <td>2</td> </tr> <tr> <td>Shape change</td> <td>4</td> <td>0</td> </tr> <tr> <td>Mass</td> <td>7</td> <td>7</td> </tr> <tr> <td>Myalgias</td> <td>5</td> <td>2</td> </tr> <tr> <td>Arm and/or neck pain</td> <td>10</td> <td>3</td> </tr> <tr> <td>Asymptomatic</td> <td>2</td> <td>2</td> </tr> </table> <p>Rupture (n=40)</p> <p>Leakage (n=28)</p>	Breast pain	26	17	Contracture	15	15	Flattening	6	1	Enlargement	1	1	Migration	5	2	Shape change	4	0	Mass	7	7	Myalgias	5	2	Arm and/or neck pain	10	3	Asymptomatic	2	2
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Asymptomatic	2	2																																		

Citation	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture, and silent rupture	Evaluation	Timing of rupture progression	Local complications with rupture and clinical course
Berg et al. 2002	Silicone gel Augmentation, other	Cohort of 359 women with 687 silicone gel implants and 28 saline implants who received an MRI to reveal implant status; accuracy of imaging techniques were assessed.	By consensus interpretation (2 or more radiologists) of MRI, extracapsular silicone was identified in 12.4% of implants (85/687).	No data	No data	No data on local complications
Brown et al. 2000	Single-lumen silicone gel (50%), double-lumen silicone gel (50%) Augmentation, other	Cohort of 344 "unreferred" women with 687 implants who received an MRI to reveal implant status.	In this "unreferred" population of women chosen to participate without regard to presence of symptoms, rupture rates were 236/344 women (68.6%) or 378/687 implants (55%). The authors consider rupture in an unreferred population to be indicative of "silent" rupture.	No data	No data	No data

Citation	Implant type and reason	Study description	Intracapsular rupture, Extracapsular rupture and silent rupture	Generalization	Timing of rupture progression	Local complications with rupture and clinical course														
Brown et al. 2001 and Brown et al. 2002	Silicone gel (single-lumen or double-lumen) Augmentation	Cohort of 344 women with 687 breast implants who responded to a questionnaire that included questions of health status.	<p>Rupture results were presented by consensus interpretation of MRI by 2 or more radiologists. Overall rupture rates were 236/344 women (68.6%) or 378/687 implants (55%).</p> <p>Extracapsular silicone was identified in 73/344 women (21.2%). Among women with ruptured implants, 73/236 (30.9%) experienced an extracapsular rupture. Prevalence of extracapsular silicone by implant was found to be 12.4% (85/687 implants), and prevalence of extracapsular silicone in ruptured implants was 85/378 (22.4%).</p>	No data	<table border="1"> <thead> <tr> <th>Implant age (yrs)</th> <th>% Extracapsular silicone</th> </tr> </thead> <tbody> <tr> <td>6-10</td> <td>0.9%</td> </tr> <tr> <td>11-15</td> <td>8.1%</td> </tr> <tr> <td>16-20</td> <td>11.6%</td> </tr> <tr> <td>21-25</td> <td>0.6%</td> </tr> <tr> <td>26+</td> <td>0%</td> </tr> <tr> <td>All</td> <td>21.2%</td> </tr> </tbody> </table>	Implant age (yrs)	% Extracapsular silicone	6-10	0.9%	11-15	8.1%	16-20	11.6%	21-25	0.6%	26+	0%	All	21.2%	No data on local complications
Implant age (yrs)	% Extracapsular silicone																			
6-10	0.9%																			
11-15	8.1%																			
16-20	11.6%																			
21-25	0.6%																			
26+	0%																			
All	21.2%																			

Author	Implant type and reason	Study description	Implant capsule rupture, extracapsular rupture and silent rupture	Examination	Timing of rupture progression	Local embolizations with rupture and clinical course
Brown et al. 2002	Silicone gel	Further reporting of results from Brown et al. 2001: Cohort of 344 women with 687 breast implants who responded to a questionnaire that included questions of health status	No data	No data	No data	8.2% of women with extracapsular rupture reported rash on the breast or chest compared to 6.3% of women with no extracapsular silicone. This finding was not statistically significant. (OR: 1.3, 95% CI: 0.4, 3.7)
Cohen et al. 1997	Silicone gel Augmentation, reconstruction	Retrospective study of 350 breast implants to investigate factors related to failure.	No data	No data	No data	A significant correlation was found between implant failure and patients reporting a change in the shape of their breast (p=0.014). In 41% of patients' breasts that were described as being distorted, the implants had failed.

000337

CONFIDENTIAL
-28-

Citation	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture, and silent rupture	Gel migration	Timing of rupture progression	Local complications with rupture and clinical course
Conant et al. 1995	Silicone gel	Cohort of 9 women with 16 silicone breast implants and 1 additional patient with a prior implant removal, all who underwent intraoperative sonography for localization of free silicone for suspected rupture.	Intracapsular rupture was found in 9/17 breasts (53%); 8/17 breasts (47%) had free silicone extravasation (extracapsular gel).	In 2 breasts, silicone had infiltrated the pectoralis major muscle and fascia.	No data	No data
DeAngelis et al. 1994	Silicone gel, single- and double-lumen, saline single-lumen Augmentation and reconstruction	Cohort of 32 women with 57 breast implants who underwent imaging studies; surgery was performed on 19 implants in 11 patients within 2 months of the imaging studies.	Among the 11 patients (with 19 implants) who underwent surgery, there were 15 ruptures (79%). Intracapsular rupture was noted in 6 single-lumen silicone gel implants and extracapsular rupture in 3 silicone gel single-lumen implants. The remaining ruptures included 1 saline implant, and 5 double-lumen implants where only the outer (saline) lumen had ruptured. Two of the intracapsular ruptures were not detected through imaging, and were only found upon surgery.	In 6 patients with ruptured implants seen at surgery, globules of silicone were seen either in the breast parenchyma distant from the implant or close to the shell. In 2 patients there was evidence of migration of an implant; 1 inferiorly and 1 laterally.	Implantation of the prostheses had been performed an average of 10 years (range, 2-19 yrs) prior to the first MR imaging.	No data

Citation	Implant type and reason	Study description	Intra capsular rupture, extracapsular rupture and silent rupture	Germiation	Timing of rupture progression	Local complications with rupture and clinical course
De Camara et al. 1993	Silicone gel Reasons not specified	Retrospective study evaluating aging and rupture of implants in 31 women with 51 implants who underwent explantation surgery.	In one case silicone gel was found external to the ruptured, contracted shell.	No data	No data	<p>In the ruptured group, 4 patients had severe pain in the breast and complained of injury to the breast.</p> <p>None of the women in the study had axillary lymphadenopathy.</p> <p>Firm masses were palpable adjacent to the implants in 4 patients with ruptured implants.</p> <p>Surgical treatment of these patients involved removing the implants and the silicone gel.</p> <p>The postoperative course on all the patients was uneventful. There were no postoperative infections or inflammation of the breasts despite extensive silicone extravasation in some of the cases.</p>

Citation	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture and silent rupture	Calibration	Timing of rupture progression	Local complications with rupture and clinical course
Destouet et al. 1992	Silicone gel filled (92%) (including 15 women with polyurethane-covered implants), double-lumen (5%), saline (3%) Reason not specified	Retrospective cohort study of 350 asymptomatic women who underwent screening mammograms.	Implant failure evidenced by extravasation of silicone was found in 18 implants in 16 of 350 women (5%). Ten (10) of the ruptures were classified as large silicone gel leaks, 3 were moderate, and 5 were small. Of the 2 patients with bilateral ruptured implants, 1 had large leaks bilaterally and the other patient had 1 small and 1 large leak.	No data	No data	No data
Everson et al. 1994	Silicone gel	Cohort of 32 women with 63 breast implants who underwent imaging studies prior to explantation surgery for various reasons.	There were 22 ruptures overall (22/63, 34.9%) and 21 were intracapsular ruptures (33.3%).	No data	No data	All but one of these patients had signs and symptoms suggestive of rupture, including pain and itching in the breast and joint swelling. Ten patients had biochemical evidence of autoimmune abnormalities.

Citation	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture, and Silent Rupture	Cell migration	Timing of rupture progression	Local complications with rupture and clinical course
Herborn et al. 2002	Silicone gel (implied), single-lumen Augmentation, reconstruction, other	Cohort of 25 patients with 41 implants who received an MRI to reveal implant status prior to explantation surgery; accuracy of imaging techniques were assessed.	Evaluation of 41 explants at surgery found: ruptures: 24.4% (15/41), intracapsular ruptures: 36.6% (10/41), extracapsular ruptures 12.2% (5/41)	No data	No data	No data
Holmich et al. 2003a	Silicone gel filled, single- and double-lumen Augmentation	Cohort of 186 women with 317 implants who had baseline and follow-up MRIs to determine an estimate of the incidence of implant rupture.	There were 33 "definite" ruptures determined by MRI or surgery of the 317 implants (10%) in this study. Of these 33 ruptured implants, 26 were diagnosed at MRI and 7 at surgery. Of the 26 diagnosed at MRI, 6 (23%) were extracapsular ruptures. The authors fail to discuss extracapsular silicone in the ruptured implants found at surgery.	No data	No data	No data

Citation	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture, and silent rupture	Calcification	Timing of rupture progression	Local complications with rupture and clinical course
Holmich et al. 2003b	Silicone gel Augmentation	Clinical follow-up of 238 of the 271 women from Holmich et al. 2001 who had completed a survey on diseases and symptoms.	Reported rates are redundant with Holmich et al. 2001 as this population is a subset.	No data	No data	Local symptoms reported among women with implant rupture (n=92) and extracapsular rupture (n=23), respectively were: breast pain (23%, 26%), breast hardness (43%, 76%), and unspecified neck, shoulder, or back pain (47%, 48%). None of these findings demonstrated a statistically significant increase in symptoms compared to women with intact implants.
Holmich et al. 2001	Silicone gel Augmentation	Cohort of 271 women with 533 implants randomly selected to determine the prevalence of implant rupture by MRI.	Overall, there were 141 implants found to be ruptured (26.5%) upon MRI. Of the ruptured implants, 110/141 (78%) were intracapsular and 31/141 (22%) were extracapsular. There were 23/271 women (8.5%) with extracapsular implant ruptures.	No data	No data	No data

000342

Citation	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture, and silent rupture	Chemigation	Timing of rupture progression	Local complications with rupture and clinical course	
Holmich et al. 2004	Silicone gel Augmentation	Cohort of 162 women with 319 implants who had undergone a baseline MRI in 1999 and follow-up MRI in 2001. Women with at least 1 ruptured implant at baseline (64 women with 96/126 implants ruptured) were compared to all women with intact implants at both assessments (98 women with 193 intact implants) for self-reported breast symptoms, changes in serum antibodies, and progression of rupture.	Among the 96 implants found to be ruptured at the baseline MRI, 77 were intracapsular (80.2% of ruptured implants) and 19 were extracapsular (19.8% of ruptured implants). These results are a subset of those reported by Holmich et al. 2001.	No data	Of the 77 implants with intracapsular rupture at baseline MRI, 69 (90%) showed no changes at the follow-up MRI approximately 2 years later, 7 implants (9%) showed extracapsular silicone, and 1 (1%) thought to show extracapsular silicone was found at operation to have an intact capsule with no silicone outside the capsule. Among the 19 implants in 14 women with extracapsular rupture noted on baseline MRI, in 16 implants (84%) the silicone remained stationary, and in 3 implants (16%), the effusion of extracapsular silicone was found to have increased at follow-up MRI approximately 2 years later.	Self-reported breast symptoms among patients with ruptured implants (n=96 implants)	
						No. Ruptured Implants (%)	OR (95% CI)*
						Symptom	
						Change in implant	28 (29%) 2.1 (1.2-3.8)
						Breast has become harder	7 (7%) 0.9 (0.3-2.1)
						Breast has become softer	20 (21%) 1.7 (0.9-3.2)
						Change in breast shape	24 (25%) 2.5 (1.3-4.8)
						Change in breast size	20 (21%) 1.9 (1.0-3.7)
						Pain in breast	22 (23%) 2.2 (1.2-4.2)
						Any breast change	51 (53%) 1.9 (1.2-3.1)
						Pain in relevant shoulder/arm	8 (9%) 1.2 (0.5-2.9)

Gibson	Implant type and reason	Seeds resumption	Large ipsilateral or contralateral rupture and silent rupture	Cell migration	Timing of rupture progression	Local complications with rupture and fibrotic scars
						* OR compared to women with intact implants, n=193 implants

000344

CONFIDENTIAL
-35-

Author	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture, and silent rupture	Gel migration	Timing of rupture progression	Local complications such as rupture and clinical course
Ikeda et al. 1999	Silicone gel Single-lumen, double-lumen, triple-lumen.	Cohort of 30 symptomatic patients with 59 implants prospectively evaluated via MRI, ultrasound and mammography.	Among the 31 implants in 16 patients where surgical confirmation occurred, there were 13/31 ruptures (42% of implants). Intracapsular rupture accounted for 9/31 implants (29%) and 9/13 ruptured implants (69.2%). Evidence of extracapsular silicone was found in 4/31 implants (13%) and 4/13 ruptured implants (30.7%). No data	No data	No data	No data
Kulber et al. 1995	Silicone gel Augmentation, reconstruction	Cohort of 23 women who had axillary biopsies after silicone breast implantation had their medical records reviewed to reveal timing of axillary mass detection.	No data	By design, all patients in this study had palpable axillary masses; 16 patients had pathology consistent with axillary siliconosis.	Among the 16 patients with pathology consistent with axillary siliconosis, 10 patients had implants an average of 6 years (range, 1-12 yrs) for augmentation, and 6 patients had implants an average of 5 years (range 1-22 yrs) for reconstruction.	No data

000345

CONFIDENTIAL

-36-

Author	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture, and silicone leakage	Cellularization	Timing of rupture progression	Local complications with rupture and clinical course
Malata et al. 1994	Silicone gel Augmentation, reconstruction	Prospective cohort study of 51 patients with 83 implants who underwent revisional breast surgery for significant capsular contracture, suspected implant rupture, or anxiety regarding their implants.	Fourteen of the 51 women (27%) experienced an implant rupture, and ten of these were found to be intracapsular ruptures (10/14, 71%). The overall rate of intracapsular rupture was 12% (10/51).	No data	No data	Postoperative courses were uneventful except for one patient who developed a late hematoma. There were no systemic complications from implant rupture and the mean blood silicone level was normal. The average crude index of disease activity in systemic autoimmune disease was found to be normal. One patient with pre-existing pernicious anemia had elevated autoantibodies. The authors conclude that in this study, implant gel leakage was not associated with serious systemic effects.
Middleton 1998	Silicone gel Augmentation, reconstruction	Clinical follow up study of 1,626 single-lumen silicone-gel filled implants using MRI to detect possible rupture.	Among the 1,626 implants, 27.2% were "definitely ruptured"; of those that were ruptured, 26.2% had silicone outside, as well as inside the fibrous capsule.	No data	No data	No data

Citation	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture and silent rupture	Calcification	Timing of rupture progression	Focal complications with rupture and clinical course
Netscher et al. 1996	Silicone gel (94%) and saline (6%) Augmentation (60.5%) and reconstruction (39.5%)	Cohort of 81 patients with 160 implants who underwent imaging studies to assess the accuracy of rupture detection prior to surgery for implant removal. Cross-sectional study of 317 women with silicone breast implants compared to 317 matched nonimplant controls to examine the potential relationship between silicone gel breast implants and connective tissue diseases.	There were 2 extracapsular ruptures found in this study (2/160 breasts, 1.3%) and 42 implant ruptures overall (26%).	No data	No data	No data
Park et al. 1998	Silicone gel Augmentation, reconstruction	Cross-sectional study of 317 women with silicone breast implants compared to 317 matched nonimplant controls to examine the potential relationship between silicone gel breast implants and connective tissue diseases.	Ten patients had required replacement of their implants following rupture.	In one case, rupture followed a closed capsulotomy and one developed a silicone granuloma.	No data	In one case, rupture followed a closed capsulotomy and one developed a silicone granuloma. The remainder had no problems and none had positive antibodies in their blood.

Citation	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture, and silent rupture	Gel migration	Timing of rupture/progression	Local complications with rupture and clinical course
Park et al. 1996	Silicone gel, Saline Augmentation, reconstruction	Prospective cohort study of 307 asymptomatic women with 385 implants who underwent ultrasound to detect implant rupture.	There were 3 women in this study with an ultrasound scan suggestive of rupture who went on to have the implant removed surgically. Thus, there were 3/307 women (1%) who experienced "silent rupture" (asymptomatic) in this study (2 silicone gel, 1 saline)	No data	No data	No data
Peters et al. 1997	Silicone gel Augmentation, reconstruction	Cohort of 100 patients with 186 implants who had requested explanation for various reasons.	Only 6 of the capsules (6/186, 3.2%) from a total of 5 of the patients demonstrated extracapsular silicone. In 1 patient, the extravasation appeared to be related to a previous surgical biopsy.	No data	No data	No data
Quinn et al. 1996	Silicone gel	Cohort of 54 women with 108 implants who underwent MR imaging (prior to explantation surgery) to assess implant status and inter-observer reliability.	Implant rupture was identified at the time of explantation surgery. There were 30/108 (27.8%) implant ruptures; of which 1 was an extracapsular rupture (0.9%).	No data	No data	No data

Citation	Implant type and reason	Study description	Intra-capsular rupture, extracapsular rupture, and "silent rupture"	Gel migration	Timing of rupture progression	Local complications with rupture and clinical course
Robinson et al. 1995	Bi-lumen (n=47) and single-lumen gel-filled (n=253) Augmentation, reconstruction	Cohort of 300 women with 592 implants who had elected implant removal for various reasons.	Implant status was determined upon surgical explantation. Among symptomatic women, 102/142 (71.8%) were found to have ruptured or bleeding implants; among asymptomatic women, 112/158 (70.9%) were found to have ruptured or bleeding implants (i.e., "silent rupture").	No data	No data	Among "symptomatic" patients reporting a variety of complaints, 102 of 142 (71.8%) were found to have ruptured implants. This is not significantly different from the percentage of ruptures found in asymptomatic women (70.9%).
Roscullet et al. 1992	Silicone gel Augmentation, reconstruction	Sonographic findings in 16 women with 19 ruptured implants.	In 2 ruptured implants, sonography showed masses corresponding to extruded silicone gel masses. In one case, surgery confirmed that the mass contained silicone gel within a fibrous wall adherent to the implant capsule, with a communication between the mass of silicone gel and the implant.	No data	No data	Patients presented with the following clinical symptoms leading to imaging studies: palpable masses (7 breasts), mass and pain (1 patient, both breasts), mass and breast deformity (1 breast), change in breast shape (3 patients, 4 breasts), and pain (1 breast). In 2 women (2 breasts), biopsy showed a silicone granuloma.

Citation	Implant type and reason	Study description	Intracapsular rupture and "silent rupture"	Gel migration	Timing of rupture and progression	Local complications with rupture and clinical course
Sanger et al. 1995	Silicone gel	Cohort of 31 women undergoing explantation of silicone gel breast implants or removal of, silicone gel-associated granulomas, had biopsies of fibrous capsules and granulomas to test for tissue humoral response.	There were 9 intracapsular ruptures ("implants found to be ruptured with the gel contained within the fibrous capsule or immediately adjacent to it") found among the 41 implants undergoing capsule biopsies (22%).	In 3 patients, previously ruptured implants resulted in silicone granulomas in "distant sites."	No data	In 3 patients, previously ruptured implants resulted in silicone granulomas in the arm (2) and chest/axilla (1).

Citation	Implant type and reason	Study description	Intracapsular rupture, extracapsular rupture and silent rupture	Calcification	Timing of rupture progression	Local complications with rupture and clinical course
Soo et al. 1997	Silicone gel	Cohort of 44 women with 86 breast implants who underwent imaging studies prior to explanation surgery for suspected implant rupture.	There were 2 implants showing MR evidence of extracapsular rupture. At surgery, 48 of the 86 implants were found to be ruptured (55.8%).	One patient had MR evidence of a large protrusion of silicone into the axilla, and one patient had MR evidence of a small silicone nodule in the breast parenchyma.	No data	No data
Thomas et al. 1997	Silicone gel Augmentation, reconstruction	Cohort of 25 patients referred for explanation of silicone gel-filled breast implants at one institution.	Rupture was found in 44% (11/25) of these referred patients.	No data	No data	Patients in whom rupture was found reported signs and symptoms of: fatigue, leg pains, chest pain, hip and shoulder pain, aches, and joint pain. In 2 patients with rupture, a positive ANA was found.

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RESPONSE TO DEFICIENCY 3

To fully examine the issue of rupture, it is critical to understand how ruptures occur *in vivo* and the role played by various contributing factors. Based on feedback from noted expert materials scientist [REDACTED] and leading plastic surgeons, Inamed instituted a myriad of improvements in the methods of analysis for the Retrieval Study. Subsequently, Inamed analyzed 442 PMA devices and successfully identified the modes and causes of rupture for 91.1% of the silicone-filled breast implants evidencing rupture. In addition to increasing the level of understanding regarding why and how ruptures occur, Inamed also assessed the durability of the PMA devices and determined that durability is not a significant concern for these implants. Additionally, Inamed not only assessed the manufacturing processes related to release specifications as requested by FDA, but we also conducted a comprehensive evaluation of every aspect of our silicone-filled breast implant manufacturing processes in concert with our Hazard Analysis Critical Control Point (HACCP) program.

Following the discussion below regarding the evaluation of modes and causes of rupture, Inamed will address items a-e above with summaries of the new technical reports and literature review findings.

EVALUATING THE MODES AND CAUSES OF RUPTURE

As part of Inamed's Quality System and Corrective and Preventative Action (CAPA) process and in response to the above deficiency, several actions were initiated by Inamed. The actions included a re-evaluation of returned failed devices, as addressed in our response to Deficiencies 3a and 3b; an assessment of manufacturing processes related to release specifications that may relate to the risk of rupture, as addressed in our response to Deficiency 3c; an assessment of the surgical techniques that could increase the risk of

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rupture, as addressed in our response to Deficiency 3d; and a comprehensive literature review of durability/explant studies, as addressed in our response to Deficiency 3e.

Highlights of Inamed's manufacturing quality control factors related to the risk of rupture are as follows:

- All identified defects from failed devices (see the response to Deficiency 3a) are currently included in quality inspections and, in all cases, the acceptance criteria for these defects are zero (0).
- Each manufactured device shell is inspected for these defects, i.e. no sampling plans are used, and 100% inspection is used at several stages of the manufacturing process.
- Based on the last 12 month period, the level of occurrence of identified defects from rejected devices is very low (e.g. .001 or .0001 for all defects).
- In the case of one defect associated with 2 failures, [REDACTED]
[REDACTED]
[REDACTED] This change was made prior to initiation of the Core Clinical Study; only one patient was enrolled in the Adjunct Study prior to implementation of the change.
- [REDACTED]
[REDACTED]
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[REDACTED] s.

As part of Inamed's Quality System process, Inamed will continue to review its manufacturing processes with particular attention to defect awareness, acknowledging the impact that manufacturing defects have on device performance and, ultimately, on the patients, the end users.

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A. INDEPENDENT RE-ANALYSIS OF CURRENT RETRIEVAL DATA

An independent re-analysis of Inamed's original Retrieval Study, TR-409, *Technical Report on Gel Retrieval Program for Styles 10, 20, 40, 45, 110, 120 and 153*, was conducted by [REDACTED]. [REDACTED] evaluation is provided in Attachment 3-2, and Inamed's original report is provided in Appendix 1 of Attachment 3-2.

One of the main objectives of the re-analysis was to determine the exact failure modes for the retrieved devices, and the study was successful in doing so. The devices included in this re-analysis are a subset of those analyzed in the new Retrieval Study discussed in Deficiency 3b; therefore, a comprehensive analysis of the findings for all analyzed devices is provided in Deficiency 3b. Similar classifications of failure modes were identified in both [REDACTED] re-analysis and Inamed's new Retrieval Study, which encompassed additional devices returned subsequent to the retrieval report previously included in PMA P020056.

Inamed reviewed [REDACTED] findings and prepared a written response (Attachment 3-3) to his recommendations. Inamed's response document primarily serves to identify how Inamed is addressing [REDACTED] recommendations for conducting retrieval study testing. Some of the activities Inamed initiated in response to [REDACTED] recommendations include implementation of the new tests noted below, revised test methodology and continued efforts to develop new laboratory tests. Based on the conclusions and recommendations in [REDACTED] report, the following testing was conducted:

1. [REDACTED], *Study of Effect of Autoclave Disinfection on Physical Properties of Silicone-Filled Breast Implants* (Attachment 3-4)
2. [REDACTED], *Study of Effect of Bleach and Autoclave Disinfection on Physical Properties of Silicone-Filled Breast Implants* (Attachment 3-5)
3. [REDACTED], *Study of Effects of Cutting Die Size on Measure Results for Tensile Properties of Silicone-Filled Breast Implant Shells* (Attachment 3-6)
4. [REDACTED], *Crosslink Density Study of Effects of Extraction of Mechanical Properties of Silicone-Filled Breast Implants* (Attachment 3-7)
5. [REDACTED], *Assessment of Surgical and Manufacturing Process Impact to Gel Implant Shell Integrity* (Attachment 3-8)
6. [REDACTED], *Study of Tensile Properties of Pre-Stress Gel Shells* (Attachment 3-9)
7. [REDACTED], *Analysis of in-vivo Physical Property Data for Silicone-Filled Breast Implants* (Attachment 3-10)

In general, these tests showed that stressing the device during implantation surgery may decrease shell integrity, the disinfection methods for retrieved devices do not affect the implant's physical properties, and no correlation was noted between swelling and cross-link density for pre-stressed shells versus non-stressed shells.

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Inamed will continue exploring a number of [REDACTED] recommendations as part of our ongoing research into failure modes.

B. NEW RETRIEVAL STUDY

During [REDACTED] independent analysis of the original retrieval report, Inamed performed additional retrieval activities based upon his recommendations, utilizing increased and improved analytical tools for the identification of failure modes. This resulted in the following:

- A re-analysis of Inamed's existing silicone-filled breast implant Retrieval Study was conducted and reported as an addendum to the original report, [REDACTED], *Gel Retrieval Program for Styles 10, 20, 40, 45, 110, 120 and 153*. The report addendum presents the results of a re-analysis of the 339 devices originally included in the retrieval report provided to PMA P020056. The [REDACTED], *Addendum to Technical Report on Gel Retrieval Program for Styles 10, 20, 40, 45, 110, 120 and 153* is provided in Attachment 3-11; and
- A new retrieval report, which included all explanted Core and Adjunct devices returned before March 31, 2004, was prepared. [REDACTED], *2004 Technical Report on the Retrieval Program for Styles 10, 20, 40, 45, 110, 120 and 153*, is provided in Attachment 3-12.

The re-analysis findings were essentially the same as the new Retrieval Study findings, except the re-analysis findings were based on a smaller pool of devices, i.e. the original 339 devices. Therefore, the results reported below focus on the findings from the new retrieval study, which reports on an expanded number of devices.

Results for the new Retrieval Study show that 155 implants (35%) of the Core and Adjunct Clinical devices returned to the Device Analysis Laboratory were found to be ruptured. Of the ruptured devices returned for analysis, 87.1% of the devices were analyzed; 12.9% of the devices could not be analyzed either due to patient refusal to allow destructive testing of the implant or the complete device shell was not returned to the lab. Modes of failure were identified for 91.1% of the ruptured devices that could be analyzed; Inamed was unable to determine the mode of failure for only 8.9% of analyzed devices.

Significantly, surgical damage has been found to be the leading cause of failure in Inamed's silicone-filled breast implants returned for analysis. Table 3-1 below summarizes the modes of failure identified in the new Retrieval Study.

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Table 3-1
Modes of Failure for Ruptured Implants

Failure Mode	Implants (N=135)*	
	n	%
Surgical Damage	63	46.7%
Posterior Opening (Style 153 implant)**	48	35.6%
Surgical Impact***	5	3.7%
Manufacturing Defect	4	3.0%
Bladder Separation without Rupture (Style 153 implant)	2	1.5%
Fold Flaw Failure	1	0.7%
Unknown (openings where the failure mode could not be identified)	12	8.9%

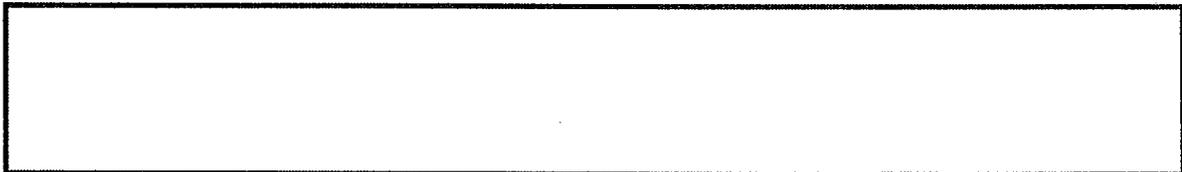
*does not include the 20 implants classified as "unable to analyze"

** [REDACTED]

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

Inamed revised its retrieval program to add a specific component for ongoing investigations into failure modes. This underscores Inamed's commitment to continue working on the development of new laboratory tests and implementing additional tools and techniques to evaluate the mechanics of implant rupture and associated factors.

Since the most prevalent mode of device failure related to ruptures is a direct result of surgeon actions during implantation, theoretically the failure rate, which is already low, could be reduced through surgeon education. Inamed's plans for surgeon education are delineated in Deficiency 12 and include the dissemination of retrieval results to physicians as part of the INAMED Academy. The plans encompass education on rupture prevention as well as revised device labeling, included in Deficiency 9, to incorporate warnings on surgical practices that may lead to rupture.



To further address other device failure modes, ongoing research activities related to silicone-filled breast implant failure modes have been initiated. These studies include:

- Evaluation of damage caused by stresses induced on the devices during implantation and explantation;
- Development of a laboratory test method to accurately and consistently simulate fold flaw failure;
- Evaluation of the change in extraction and crosslink density over time in-vivo;

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- Evaluation of the effect of shell damage on enhanced swelling and subsequent potential shell weakening;
- Determination of new failure modes using Scanning Electron Microscope (SEM); and
- Correlating clinical data to device analysis results to identify possible outside influences on implant durability.

C. ASSESSMENT OF MANUFACTURING PROCESSES RELATED TO RELEASE SPECIFICATIONS

As discussed in our above response to Deficiencies 3a and 3b, explanted devices were re-evaluated to determine cause of failure. Based on the re-evaluation of the devices included in Inamed's [REDACTED], *Addendum to Technical Report on Gel Retrieval Program for Styles 10, 20, 40, 45, 110, 120 and 153*, six of the 339 devices (1.8%) had failures that were attributed to manufacturing defects:

- Two (2) textured devices had a shell thickness of the non-textured portion of the shell at or below 0.005" [REDACTED].
- Three (3) devices had a concave area or "divots" on the inside of the shell resulting in thinning of the non-textured portion of the shell.
- One (1) device had an area where there was separation of the shell layers.

While it is recognized that the manufacturing process, inspection criteria and release specifications have established criteria and limits for imperfections, such as bubbles and contaminants, the allowed imperfections have **not** been related to device rupture based on analysis of returned devices in both the independent re-analysis conducted by [REDACTED] and in Inamed's new Retrieval Study. In fact, [REDACTED] stated in his report that very few of Inamed's implant failures were due to manufacturing defects.

As part of the device analysis, any opening in the implant is inspected under microscopes. Any defect such as a bubble or an imbedded particle would be identified in the lab and noted in the analysis results for that device. For the devices analyzed as part of the original and new retrieval reports, no imperfections were identified along the openings. Observed failures were **not** the result of inadequate specifications.

As discussed above related to Inamed's HACCP plan, in an effort to determine if any other allowable imperfections were related to device rupture, Inamed completed a detailed and in-depth assessment of our manufacturing processes, including manufacturing controls, inspection standards and release specifications. The outcome of the re-evaluation was:

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- All identified defects from failed devices are currently included in the inspection process and, in all cases, the acceptance criteria for these defects are zero; and
- Each manufactured device shell is 100% inspected for these defects at several stages of the manufacturing process.

Based on the re-evaluation conducted by Inamed and as part of our ongoing CAPA process, device failure due to manufacturing defects is an infrequent occurrence. Adequate and appropriate manufacturing and quality control measures are in place and functioning well, as witnessed by FDA's recent facility inspections, as well as the context of such a small number of device failures for over 80,000 devices implanted in the Core and Adjunct Studies. As noted in the responses to Deficiencies 1 and 2, there were less than 200 implant ruptures experienced by these clinical study patients.

D. ASSESSMENT OF SURGICAL TECHNIQUES RELATED TO RISK OF RUPTURE

Based on direct analysis of explanted ruptured silicone-filled breast implants, observation of implantation surgeries and the published literature^{1,2}, the surgical techniques associated with device rupture are:

- Use of sharp instruments, such as scalpels, suture needles, forceps etc. in close proximity to the device. This can result in unintentional damage to the device and immediate or subsequent device rupture, i.e. surgical damage.
- Creation of a fold in the surface of the device during implantation, which allows the surface of the device to abrade against itself and result in the creation of a hole in the device shell. While the occurrence of fold flaw failure is low for silicone-filled breast implants (0.6%), surgical technique is suspected as a contributing factor.
- Straining the shell by forcing the implant through a small opening. Surgical technique is suspected to be a cause of localized weakening of the shell, which could make the device more subject to rupture.

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

Inamed has not identified surgical techniques other than those noted above that would have an adverse impact on the durability of the device or which would increase the risk of device rupture over time. This is consistent with the information provided in the 2004 FDA Breast Implant Consumer Handbook³, which states that possible surgical causes of rupture are damage by surgical instruments and too much handling during surgery.

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While Inamed has experience analyzing and testing returned devices, comprehensive assessment of surgical techniques in relation to the risk of rupture, would not be considered complete without feedback from surgeons familiar with the use of these devices. Therefore, Inamed approached 5 leading plastic surgeons for their assessments of the impact of surgical technique on risk of device rupture. The plastic surgeons queried are acknowledged experts in the field who serve as faculty and directors for INAMED Academy, an educational program that provides a forum for the exchange of information and best practice ideas among plastic surgeons. A list of the surgeons surveyed and the results of their feedback are provided in Attachment 3-13.

Survey results showed that the surgeons ranked incision size as having the highest impact on implant survivability, with size of dissected pocket and transaxillary approach both ranked as having a moderate impact. With one exception, the surgeons were unaware that the majority of implant ruptures analyzed by Inamed had evidence of surgical damage. In order to promote improved implantation techniques, Inamed will apprise the faculty of the Retrieval Study findings and introduce an element concerning iatrogenic damage into the curriculum of INAMED Academy.

E. COMPREHENSIVE LITERATURE REVIEW: DURABILITY/EXPLANT STUDIES

A review of relevant published literature examining the effect of shell integrity, chemical/physical composition and shell strength on durability of silicone-filled breast implants is included in Attachment 3-14.

The literature review showed that the primary factor impacting shell integrity is surgical damage during implantation. This is consistent with both the findings from Inamed's Retrieval Study and the re-analysis by [REDACTED], which showed that the failure mode for almost half of the ruptured implants returned for analysis could be attributed to surgical damage.

In terms of the chemical/physical composition of the shell, studies have shown the *in vivo* migration of lipids from surrounding tissues into the implant shell, with a lower rate of lipid infiltration noted for third generation implants and textured implants^{4,5}. No relationship has been established between lipid infiltration and decreased tensile strength of implant shells. Studies have also shown the diffusion of non-crosslinked silicones from the implant filler into the implant shell^{6,7}. While this causes swelling of the implant shell, the studies note that it does not appear to change the chemical nature of the implant shell or to be a primary risk factor for implant rupture^{8,9}.

Inamed found that the effect of lipid or the diffusion of non-cross linked silicone did not adversely affect the finished sterile device for Inamed's silicone-filled breast implant shell material. Studies performed by Inamed show no significant decrease in physical properties *in vivo* or during shelf life studies. There was also no statistically

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significant difference between the physical properties of ruptured shells as compared to nonruptured shells. These studies are included in the following attachments:

- [REDACTED], *Shelf Life Study* (Attachment 3-15)
- [REDACTED] *The Preliminary Study of Lipid effects on Silicone Shell Physical Properties* (Attachment 3-16)
- [REDACTED], *Analysis of In-vivo Physical Properties for Silicone-Filled Breast Implants* (Attachment 3-10)
- [REDACTED], *2004 Technical Report on the Retrieval Program for Styles 10, 20, 40, 45, 110, 120 and 153* (Attachment 3-12)

The published literature contains references to localized weakening of the implant shell being caused by the surgeon's fingers placing pressure on a specific area of the device during implantation^{10,11}. This mirrors the findings of Inamed's Retrieval Study. Furthermore, Inamed's Pre-Stress Gel Shell Study demonstrated that stress at low elongations can permanently affect a shell's physical property in the strained regions. Testing showed that the effect of straining the shell is a change in the physical property of the material and is detectable on the shell's stress/strain curve response. Shells were tested after straining at 200-400%, which is similar to what a device may experience during implantation. Reference [REDACTED], *Study of Tensile Properties of Pre-Stress Gel Shells* (Attachment 3-9).

The literature is contradictory on the question of shell strength being reduced with long term implantation, with some researchers finding a correlation between length of implantation and shell strength and elasticity^{12, 13, 14}, while others found no significant difference in these conditions as a function of implantation time^{15, 16}. Analysis of the data from Inamed's Gel Retrieval Study and its Study of *In vivo* Physical Properties for Silicone-Filled Breast Implants shows that mechanical properties do not change over time. These studies provide information about Inamed's implant shell's integrity, physical composition and strength. Reference [REDACTED], *2004 Technical Report on the Retrieval Program for Styles 10, 20, 40, 45, 110, 120 and 153* (Attachment 3-12) and [REDACTED], *Analysis of in-vivo Physical Property Data for Silicone-Filled Breast Implants* (Attachment 3-10).

Inamed has performed extensive mechanical testing per ASTM guidelines on finished product via release testing (FPRT), on product returned as part of the retrieval program, and as part of shelf life studies. Finished product release testing provides a baseline for physical properties. Compared with baseline data, mechanical data from returned gel-filled implants demonstrate that there is no significant decrease in shell physical properties when compared to time *in vivo*. This finding is supported by [REDACTED] independent review of Inamed's Retrieval Program. In his report, he concludes that "large scale shell material degradation *in vivo* is not responsible for implant failure." Therefore, based on [REDACTED] analysis as well as literature reports, there is no convincing data to support a concern that implants will "wear out"

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over time, with rupture rates increasing with the duration of implantation. [REDACTED]
[REDACTED] report and Inamed's mechanical testing studies are included in the following attachments:

- *An Independent Re-Analysis of the Inamed Technical Report [REDACTED] on Gel Retrieval Program for Styles 10, 20, 40, 45, 110, 120 and 153* (Attachment 3-2)
- [REDACTED], *Addendum to Technical Report on Gel Retrieval Program for Styles 10, 20, 40, 45, 110, 120 and 153* (Attachment 3-11)
- [REDACTED], *Shelf Life Study* (Attachment 3-15)
- [REDACTED], *Analysis of In-vivo Physical Properties for Silicone-Filled Breast Implants* (Attachment 3-10)

FATIGUE TESTING

Based on the information gleaned from evaluating explanted devices regarding characteristic modes of failure for Inamed's silicone-filled breast implants and reviews of literature, standards and guidance documents, new fatigue testing simulating *in-vivo* durability has not been identified. While device failure modes, including iatrogenic damage, have been further clarified as a result of retrieval analyses, Inamed did not identify any reproducible fatigue test method more representative of *in-vivo* experience that could be simulated at this time. Inamed continues to test hypotheses regarding failure modes by conducting accelerated fatigue testing, which simulates extreme conditions that may impact implant durability (e.g., experimentally skipping manufacturing steps to simulate stressing the shell). Our fatigue testing program will evolve as necessary to incorporate relevant findings from additional hypothesis testing.

SUMMARY

In conclusion, based on input from [REDACTED] and the addition of improved analytical tools, Inamed has developed a more robust retrieval program, which has been successful in identifying rupture failure modes for more than 90% of analyzed devices. The retrieval analyses conducted by both Inamed and [REDACTED] show that the primary cause of implant rupture in retrieved devices is surgical damage.

With surgical damage identified as a chief cause of implant rupture, the key to reducing implant ruptures is physician education in the avoidance of iatrogenic damage. Educating plastic surgeons to the importance of protecting implants from sharp-edged instruments during surgery and exploring methods of implantation to minimize the localized strain on the implant shell could mitigate the risk of rupture.

As a result of Inamed's critical assessment of our silicone-filled breast implant manufacturing processes, Inamed demonstrated that device failures due to manufacturing defects are minimal, implant durability is not a significant concern, and adequate quality control measures are in place. In addition, Inamed continues to review its manufacturing processes for possible improvements in prevention or identification of product defects.

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As noted in Deficiencies 1 and 2, the rupture rate is quite low in Inamed's Core and Adjunct clinical studies, which speaks to the overall durability of the devices. Correlating clinical data with device analysis results is another avenue Inamed is pursuing in an attempt to identify surgical influences on implant durability. Any new findings will be incorporated into Inamed's surgeon education program to enhance their knowledge of preventing future implant ruptures.

In an effort to identify additional failure modes that could lead to improvements in product design, Inamed's Gel Retrieval Program continues to test the performance of each returned explanted device by visibly examining the silicone elastomer shell (using optical microscopy) and conducting tests of shell integrity (elongation, tensile set, strength of joints, seams and seals). Inamed's ongoing research on failure modes includes evaluating the impact of localized stressing of the device during surgery, change in crosslink density over time and effect of shell damage on enhanced swelling, as well as work on developing a test to simulate fold flaw failure. These endeavors are aimed at identifying any possible manufacturing changes or recommendations regarding surgical practices in the field, which may further reduce the occurrence of rupture.

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Note: 10 pages were deleted

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Note: 346 pages were deleted

An Independent Re-Analysis of the Inamed
Technical Report [] on Gel Retrieval Program
for Styles 10, 20, 40, 45, 110, 120 and 153

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1.0 Summary

An independent re-analysis of the current Inamed retrieval data has been conducted. The data were contained in the Inamed Technical Report [REDACTED] on Gel Retrieval Program for Styles 10, 20, 40, 45, 110, 120 and 153 which was submitted to the FDA as part of the Inamed gel PMA application. The retrieval data pertained to devices that were associated with a complaint from the Inamed IDE Core and Adjunct Studies. There were many aspects associated with the re-analysis of the Inamed retrieval data. These included a review and evaluation of data collection and analysis techniques, test protocols, laboratory reports, laboratory equipment, finished devices, failed shell specimens, raw data, plus the guidance document and ASTM standards that Inamed used in preparing their original gel retrieval report. Inamed provided all information, data, documents, and materials that were requested. The comprehensive review of the entire Inamed gel retrieval program was necessary in order to determine if any new information regarding the modes of failure could be gained and to provide recommendations for improving the technology base used by Inamed to assess the performance and failure mechanisms of their devices.

Specification of the failure modes in the Inamed original retrieval and analysis study was vague. Hence, one of the main objectives of the re-analysis study was to specify the exact failure modes for the retrieved devices. The technical approach used to accomplish that goal included the application of optical microscopy, schematics of failed shells, field emission scanning electron microscopy, visual inspection, upgraded laboratory techniques developed by Inamed subsequent to the original retrieval study, and the evaluation of shell mechanical properties. All of the data contained in the original Inamed analysis was re-analyzed. Of the 339 devices considered, 46% were fully functional, 39% had failed shells, and 15% had intact

shells but were retrieved primarily due to surface or gel related observations. The focus of this study was on failed shells.

The re-analysis of the retrieval data resulted in a significant improvement in understanding the failure modes of retrieved devices. The re-analysis study demonstrated that degradation of the shell strength in vivo was not responsible for shell failure. It also demonstrated that the failure modes could be classified into five separate categories. The approximate percent of failed devices for each failure mode was:

Posterior Sharp Edge Opening for Style 153	31%
Surgical	28%
Sharp Edge Opening (Unknown)	19%
Fold Flaw	5%
Manufacturing	5%
	<u>88%</u>

In addition, approximately 12% of the devices were unable to be analyzed because pieces of the failed shell were missing, the shell was fragmented into extremely small pieces that were not amenable to analysis, or the patient requested that the device not be altered. Only 19% of the failed devices re-analyzed were classified with an unknown failure mode. One of the recommendations of this study is to establish a research project to identify the failure mechanisms for sharp edge openings. Possible causes of the unknown failure mode are listed in this report.

This study has provided new information regarding the modes of failure. It has also resulted in a series of recommendations for Inamed to improve their device retrieval and analysis program. Details for both aspects of the re-analysis study are presented in this report. Last, it should be noted that the total percent of failed devices was found to be very small. For the Core Study the percent of failed devices was conservatively calculated at 1.12%. Based

on the implantation time of the Core devices, the percent of failed devices is an order of magnitude less than published predictions.

Note: 8 pages were deleted

REDACTED

Effect of Autoclave Disinfection on Physical Properties
of Silicone-Filled Breast Implants

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The autoclave process, required as part of the retrieval program return process and retrieval analysis process, does not affect the physical properties of the smooth and Biocell® silicone-filled breast implants.

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Physical Properties Evaluation of Silicone-filled Breast
Implants After Bleach & Autoclave Disinfections

Note: 21 pages were deleted

The combination of bleaching and autoclave disinfection processes, required as part of the retrieval program return process and retrieval analysis process, does not affect the physical properties of the smooth and Biocell® silicone-filled breast implants.

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**EFFECT OF CUTTING DIE SIZE
ON MEASUREMENT RESULTS FOR TENSILE PROPERTIES
OF GEL-FILLED BREAST IMPLANT SHELLS**

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Based on two tailed pair sample t-test results, there is no statistically significant difference in the tensile property test results of gel filled breast implant shells when the specimens were prepared using different die sizes as long as the strain rate is kept the same.

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Note: 25 pages were deleted.

Title

Crosslink Density Study of Effect of Extraction on Mechanical Properties of Silicone-Filled Breast Implants

Summary

The purpose of this study was to determine the crosslink density of silicone-filled breast implant shells with the following conditions:

- Prior to assembly (i.e. no gel-exposure / no gel cure / no sterilization),
- After assembly (patched, gel filled and sterilized), and
- After subjecting the finished device shell to pre-straining.

The study also evaluates the mechanical properties of finished devices (ultimate break force, ultimate elongation and modulus at 200%) before and after the shell has been extracted in hexane solution.

Results of the study indicate that the assembly process increases the percent weight extracted increased by approximately 80% and the crosslink density decreased approximately 12%. The results of testing for finished products, which had been subjected to a pre-strain, demonstrated a non-statistically significant decrease in crosslink density as compared to non-strained finished product.

Test results of extracted shell samples demonstrated a 50% increase in ultimate break force, a 38% increase in ultimate elongation and a 6% decrease in the 200% modulus when compared to non-extracted samples.

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Note: 16 pages were deleted

Research Title: Assessment of Surgical and Manufacturing Process Impact to
Gel Implant Shell Integrity

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7. DISCUSSION

7.1. Local Stress Test

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7.1.1. Local stress caused by surgical tools or surgeon's fingers would have increase the possibility of fatigue failure on thin areas of textured surfaced implants compared to smooth implants. Shell thickness of implant prior to local stress and fatigue tests was not determined for this evaluation. The thickness of failure areas may have been thicker than local stressed areas.

7.2. Salt-residual Test

7.2.1. Samples failed in areas other than regions with salt crystal residue. Thickness of failure area appeared thinner than in salt residue areas in some samples.

7.3. Scalpel Test

7.3.1. This test has shown the damages caused by surgical scalpel nicks or scalpel scratches during the fatigue testing.

7.4. Pin Hole Test

7.4.1. While gel implant did not demonstrated failure or gel protrusion at 10 lb fatigue testing, gel has protruded from implant at accelerated test.

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Note: 13 pages were deleted

Research Title: Tensile properties of pre-stress gel shell

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9. CONCLUSION

- 9.1. The effect of stressing implant shell specimens even as low as 100% elongation was detectable in the low ranges of the shell's stress/strain curves. The loss of low strain shell physical strength while not statistically significant in the shell's ultimate physical properties was permanent in the low strain regions. The impact of stressing device shells similar to what the device may experience in surgical implantation procedures and resultant loss of strength potentially may have an effect on long-term shell integrity.

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Note: 14 pages were deleted

REPORT TITLE: Analysis of In-vivo Physical Property Data for Silicone-Filled Breast Implants

REDACTED

REPORT SUMMARY: This report presents the mechanical property data from the silicone-filled breast implant retrieval study report, [REDACTED], as a function of in-vivo time. It also compares this data to the results of Final Product Release Testing which serves as a baseline, or control, for shell mechanical properties.

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Note: 8 pages were deleted.

REPORT TITLE: Technical Report on Gel Retrieval Program for Styles 10, 20, 40, 45,
110, 120 & 153

REDACTED

REPORT SUMMARY: This report addendum presents the results of the re-analysis of the 339
devices originally included in the retrieval report submitted with the Gel
PMA application.

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Note: 8 pages were deleted.

REPORT TITLE: 2004 Technical Report on the Retrieval Program for Styles 10, 20, 40, 45, 110, 120 & 153 Silicone-Filled Breast Implants

REDACTED

REPORT SUMMARY: This report presents the results of the Retrieval Program for Silicone-Filled Breast Implants for all Core and Adjunct clinical study devices received in the Device Analysis laboratory on or before March 31, 2004.

The results of the retrieval program show that the primary reasons for device retrieval are not related to failure of the device. Surgical damage is the leading cause of silicone-filled breast implant failure.

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Assessment of Surgical Techniques Related to Risk of Rupture

Summary of Results of Surgeon Feedback

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Questionnaire Topics	Dr. # 1	Dr. # 2	Dr. # 3	Dr. # 4	Dr. # 5	Average Rating
1. Type of surgery						
a. Reconstruction	6	1	2	1	1	2
b. Revision	4	1	10	1	1	3
c. Augmentation	4	1	3	1	1	2
2. Implant placement						
a. Subcutaneous	1	1	3	1	1	1
b. Sub glandular	1	1	3	1	1	1
c. Sub muscular	1	1	3	1	1	1
3. The size of the incision used to implant the implant.						
a. 1-3 cm	10	7	10	8	10	9
b. 3-5 cm	5	4	5	5	5	5
c. >5 cm	5	1	2	1	1	2
4. Location of incision.						
a. Inframammary	10	1	3	1	1	3
b. Periareolar	5	2	3	1	5	3
c. Transaxillary	5	3	5		8	5
d. other						
5. The size of the incision relative to implant size	10	8	10	8	7	9
6. Size of pocket dissected for the implant relative to implant size.	10	6	4	5	6	6
7. Use of betadine on the implant.	1	1	1	1	1	1
8. Use of betadine in the pocket.	1	1	1	1	1	1
9. Use of surgical lubricants to place the implant.	1	1	2	1	3	2
10. Use of surgical sleeves to place the implant.	1	1	2	1	3	2
11. Post implantation patient care, such as wrapping/massage/other	1	1	3	1	5	2
12. Use of surgical tools						
a. Scalpel						
i. Thermal	4	1	9	1	2	3
ii. Mechanical	4	1	10	1	2	4
b. Retractors	4	1	8	2	5	4
c. Sutures	4	1	10	1	3	4
d. Forceps	3	1	8	1	3	3
13. Repositioning of implant during surgery.	3	1		1	6	3
14. Removal and re-implantation of same implant.	3	3	8	1	7	4
15. Use of Tissue expander.	3	1	2	1	2	2
16. Differences between use of smooth versus textured implants.	5	2	3	1	4	3
17. Difference based on the size of implant used.	6	2	5	1	4	4
18. Method of wound closure.	8	1	10	1	2	4
19. Use of post operative medicines.						
a. Antibiotics	1	1	2	1	2	1
b. Anti-inflammatory	1	1	2	1	2	1
c. Steroids	1	1	2	1	2	1

Note: 590 pages were deleted

LITERATURE REVIEW SURROUNDING BREAST IMPLANT DURABILITY

INTRODUCTION AND METHODOLOGY

The following is a review of the relevant published literature on silicone breast implant durability. This review relies upon the available medical and scientific literature to address the following questions:

- What is known about breast implant durability from explantation studies of breast implants?
- Why do silicone breast implants fail?
- Are there mechanical testing techniques that are able to predict implant failure after implantation?

Dialog and Medline searches were conducted combining the terms "breast implant" or "mammary prostheses" with the following key words: aging, biodurability, durability, explant, failure, integrity, life span, longevity, mechanical, properties, removal, retrieval, rupture, strength, survival, and testing. Several publications were retrieved in which ruptures were determined using diagnostic means; however, the primary source of information for this review is explantation studies in which breast implants were removed and examined or tested by clinicians or investigators.

In order to meet the request for a comprehensive literature review, all breast implant designs with silicone elastomer shells were included, regardless of filler type, and included silicone gel-, saline-, and alternate material-filled implants, as well as early- and current-generation implant designs. Relevant literature was retrieved, and bibliographic citations were reviewed to identify additional literature for consideration. Articles in the English language and those with English abstracts published between 1966 and May 2004 were considered for inclusion in this review.

In order to be comprehensive, this literature review includes information about gel implants that is not strictly relevant to Inamed's current silicone-filled products, which are the subject of the PMA this review supports. Whenever possible, the relevance of the data obtained from the scientific literature to currently produced Inamed products is addressed. Some literature in this review based findings on only a few devices, and likewise those references are identified, since the findings could be considered anecdotal.

WHAT TYPE OF INFORMATION IS AVAILABLE FROM EXPLANTATION STUDIES?

Breast implants may be surgically removed (explanted) for a number of reasons including capsular contracture, distortion of breast shape, local or systemic complaints, silicone phobia, suspected rupture, or request for a larger size implant. In some cases, patients undergo a capsulectomy (removal of the fibrous capsule shell) at the same time as the device explantation. When implants and capsules are explanted, the surgeon makes every effort to remove the implant and the capsule intact. Once removed, the implant may be visually inspected for evidence of changes in the integrity of the silicone elastomer shell. The implant

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is often then discarded. In many instances, however, implants are returned to the manufacturer where they may be made available for examination and physical testing of the implant shell to assess the effects of implantation on implant durability. Researchers use a variety of testing techniques to investigate breast implant durability including visual and microscopic analysis, chemical analysis, and mechanical testing of explanted silicone elastomer shells.

VISUAL AND MICROSCOPIC ANALYSIS

The cause of an implant failure is typically determined by visual and microscopic analysis. Brandon et al.¹ defined procedures for collecting and analyzing retrieved silicone elastomer breast implant shells for cause of failure. Failure sites are examined using optical and scanning electron microscopy (SEM) to identify holes, tears, abrasions, deposits of physiological origin, deformations, and irregularities (pitting or wear). They found that "SEM is the best method of identifying defects that have been surgically induced with instruments, either during implantation or explantation, and therefore, distinguishes between *in vivo* and induced failure." By comparing the SEM observations of explanted devices to SEM observations of implant shells for which the cause of damage is known, the investigators can often determine the immediate cause of the rupture.

Raman microprobe (LRM) spectroscopy, which identifies material on the basis of the molecule's characteristic spectrum of vibrational frequencies, can also be used to examine small regions of implant shells for evidence of failure or for the presence of foreign material in breast implant capsule tissue².

CHEMICAL ANALYSIS

Chemical analysis is used to determine if implantation causes any change in the chemical nature of the silicone elastomer shell and can be achieved by examining the elastomer's crosslink density. A large increase in crosslink density can make a silicone elastomer more brittle, potentially leading to decreased elongation and possibly failure¹. Crosslink density can be calculated from swelling measurements from hexane-extracted silicone elastomer specimens¹. Gas chromatography-mass spectrometry (GC/MS) can also be used to identify low-molecular-weight silicones, and Fourier-transform infrared spectroscopic analysis may be used to detect higher molecular weight materials and lipids in the shell¹. Matrix-assisted laser desorption ionization (MALDI) mass spectrometry has also been used to analyze silicone elastomer for the presence of high-molecular-weight polymers in the shell³. Differential scanning calorimetry (DSC) has been recently used to examine physical properties of silicone elastomer shells⁴.

High-resolution nuclear magnetic resonance (NMR) has been used to detect low molecular weight silicone oligomer species (octamethylcyclotetrasiloxane, D₄ and decamethylcyclopentasiloxane, D₅) in explanted shells^{4,5}.

MECHANICAL TESTING

Mechanical testing examines the strength of an explanted shell in an effort to determine whether mechanical properties have been affected by implantation. Mechanical testing can be conducted on samples obtained from explanted silicone elastomer shells using ASTM protocols¹. Specimens may be cut from failed and non-failed regions of the shell. Specimens

are tested for tensile strength and percent of elongation (to determine how much stress and stretching deformation the elastomer can withstand before breaking) and tear resistance using an Instron testing machine. When sufficient shell material is available, specimens may also be tested for strength properties following extraction with hexane to remove non-crosslinked low molecular weight silicones from the elastomer. If there is evidence of a fold flaw rupture, every effort is made to obtain specimens from this area to determine if there is any weakening of the shell at the fold location¹. Sealing patch bond strength may also be tested according to an ASTM protocol.

WHAT IS KNOWN ABOUT BREAST IMPLANT DURABILITY FROM EXPLANTATION STUDIES OF BREAST IMPLANTS?

The ability of a breast implant shell to contain the filler and maintain its shape for extended periods of time is challenged by several factors: the potential for shell damage during implantation, the inherent strength of the silicone elastomer, the integrity of the patch or valve (if relevant), the effect of implant filler on shell strength and composition, and the effect of the local biological environment on shell chemistry. Silicone elastomer materials may age with time, and because breast implants remain in place for several years, there is a question of whether the chemical composition and/or physical strength (durability) of the silicone elastomer may be compromised over time thus reducing implant lifespan. The integrity of the patch or valve is critical as these aspects of device design must be able to withstand both insertion of the implant through a narrow opening and long-term implantation. The filler material can also affect a shell's chemical composition and/or physical strength because filler or its components may migrate into the silicone elastomer and alter its chemical or physical properties. Finally, breast implants are placed either subglandularly or submuscularly and as a result, the breast implant shell is exposed to the local environment, which is at a higher temperature and humidity than externally. An implanted shell is also exposed to lipids and cellular constituents in the body, which have the potential to alter the silicone elastomer composition.

The scientific literature includes several investigations of explanted breast implants in an effort to examine the effect of implantation on implant durability. Explantation studies can provide information about an implant shell's integrity, chemical and physical composition, and strength.

SHELL INTEGRITY

Visual and microscopic examinations are the primary means by which the integrity of a breast implant shell is assessed. The published scientific literature provides information on the integrity of silicone gel- and saline-filled implants retrieved after explantation.

Silicone-Gel Filled Implants

Among the conditions reported to affect silicone gel-filled implant shell integrity are damage during implantation and potential calcification.

Damage during implantation Silicone gel-filled breast implants are prone to unintended instrument trauma during implantation⁶ or during explantation⁷. Failure can result from

damage by scalpels, suture needles, hypodermic needles, hemostats, and Adson forceps and is observable in explanted device shells using scanning electron microscopy⁷. Research conducted at Washington University⁴² revealed characteristic patterns of damage introduced by surgical instruments, and this information revealed that it is difficult to differentiate a pinhole caused by abrasion from one caused by instrument injury. In addition to the damage described above, damage to breast implant shells can result from breast biopsies, needle localization procedures, and cyst aspirations⁴².

Calcification Data on capsular calcification of silicone gel-filled implants is available from examination of explanted implants. Capsular calcification occurs in 16-33% of breast implants^{6,8,9} and has been suggested as a cause of implant shell failure because the roughened surface and sharp edges of the calcium plaque could puncture the implant. Calcification is found to be associated with implants containing fixation patches used to anchor the implants to the chest wall^{6,8}, and the frequency of calcification and the extent of calcification appear to be related to the duration of implantation^{8,9}. An effect of calcification on implant integrity, however, has not been established. Brandon et al.¹⁰ examined two intact Dow Corning Silastic 0 implants with heavy calcification that were removed after 28 years; they found no evidence of wear or abrasion on the outer surface of the shells.

Saline-Filled Implants

Among the conditions reported to affect saline-filled implant shell integrity are fold flaw leaks, patch or valve delamination, damage during implantation, and potential calcification.

Fold flaw leaks Explanted devices can provide information on fold flaw leaks in saline-filled implants. Fold flaw leaks, also referred to as crease fold failures, occur in saline-filled implants when the silicone shell folds back upon itself and over time generates a concentrated stress that can result in a fatigue crack or generation of a pinhole^{6,11,12}. Implant rupture and fold flaw leaks are more likely to occur when the implant is underfilled^{13,14}, but it can also occur as a result of capsular contracture or intermittent overpressure within the shell by either movement of the chest or muscular contractions¹². In an effort to better understand fold flaw leaks, Richardson et al.¹² compared time interval until failure between specimens of folded versus unfolded silicone elastomer shells obtained from unfilled devices. The measured outcome was a change in behavior of an alternating current signal, which reflected a change in the sample's physical characteristics that preceded catastrophic failure, and visual evidence of failure. Folded and creased samples had statistically significantly shorter fatigue lifetimes than unfolded samples. Cracks on the deeper folds began earlier than cracks on shallower folds suggesting that the greater a fold's depth, the greater the rate of crack propagation. The investigators concluded that "an in-folding of implant shell material will shorten the time to crack initiation in an *in vitro* setting" and that the data support the concept that "shell integrity breach begins from a microscopic defect, progresses through a growing length of crack, and if deflation goes unnoticed, may ultimately end with a complete, circumferential crack or tear." Investigators can often determine whether fold flaw is one cause of an implant's rupture by examining the explanted shell using SEM and comparing the observations with examples of SEMs obtained from devices known to rupture as a result of fold flaw failure¹. Lockwood³³ examined the strength of explanted saline- and silicone gel-filled breast implant shells, some of

which had evidence of fold flaws. She found that the specimens with fold flaws appeared to have the same tensile strength of specimens without fold flaws, suggesting that a reduction in shell strength does not contribute to shell failure at fold flaw sites.

Patch or valve delamination Explanted devices can also provide information on patch or valve detachment. Patch and valve detachment occurs as a result of delamination (failure of the chemical vulcanization process). Investigators can often determine whether delamination or detachment is a cause of an implant's rupture by examining the explanted shell using SEM.

Damage during implantation Visual and microscopic examination can be used to determine whether a breast implant shell sustained damage during implantation. All breast implants are prone to unintended instrument trauma during implantation⁶ or during explantation⁷. Failure can result from damage by scalpels, suture needles, hypodermic needles, hemostats, and Adson forceps, and is observable in explanted device shells using scanning electron microscopy⁷. Wound closure can also result in damage to the implant resulting in deflation. Rapaport et al.¹⁵ found that 7% of 2,844 deflated saline-filled implants voluntarily returned to Mentor within six months of surgery deflated from sharp instrument damage to the device shell, and most of these were probably caused by suture needle punctures during wound closure.

Calcification Explants can provide information on the presence of calcification on a breast implant shell. Capsular calcification has been suggested as a cause of implant shell failure because the roughened surface and sharp edges of the calcium plaque could puncture the implant⁶. Explanted saline implants have been found with areas of calcification attached to the shell, patch, or valve^{6, 8}, although no information was uncovered to assess whether the presence of capsular calcification is a cause of shell failure.

SHELL CHEMICAL/PHYSICAL COMPOSITION

The chemical and physical composition of a silicone elastomer shell may be altered in all implants with silicone elastomer shells by the migration of lipids from surrounding tissue into the shell and in silicone gel-filled implants from the diffusion of non-crosslinked silicones into the shell from the filler.

Lipid Infiltration

Some investigators reported finding evidence of lipid absorption into silicone elastomer breast implant shells. Adams et al.¹⁶ analyzed the lipid infiltration of 33 ruptured silicone gel implants (type or manufacturer not specified) with a mean implantation time of 13.1 years. The neutral lipid and phospholipid levels of the shell and gel were assayed by thin layer chromatography and were compared with control assays from two nonimplanted silicone gel implants. Positive assays for neutral lipids were found in 97% (32/33) of the implant shells, whereas no evidence of neutral lipids was found in the control group shells; 54% of the shells (18/33) were positive for phospholipids compared with no evidence in the control group shells. Birkefeld et al.⁵ also found evidence of lipid infiltration into silicone-gel-filled implants in their study of a virgin implant and two 3-year-old third-generation implants (both from one patient) manufactured in the mid-1980's. C¹³ liquid state NMR of a sample of the shell from the intact 3-year-old implant indicated the presence of phospholipids, as evidenced by resonances, which compared to the C¹³ NMR spectrum of a control phospholipid mixture. Birkefeld et al.⁴

examined NMR relaxation times in 26 explanted Dow Corning silicone breast implants and found higher values in second-generation than third-generation implants, which they suggest may be a result of the presence of lipids or low molecular weight silicones in the elastomer. They found that second-generation implants exhibit a higher lipid infiltration into the shell than third-generation designs. Textured implants appear to reduce the adsorption of lipids onto the shell⁴. Picard et al.¹⁷ detected lipids via ¹H NMR analysis at a level of approximately 0.2% in the silicone elastomer envelopes of an explanted Dow Corning implant (unidentified model with Dacron patches) and a Heyer Schulte (model 2000) implant with 17 years *in vivo*. No lipids were detected in the virgin "control" envelopes, a Dow Corning Silastic II envelope, and a Heyer Schulte model 2000 envelope.

Lipid infiltration has been suggested to decrease the tensile strength of the shells over time; however, this has not been scientifically established. Despite the evidence of lipid migration into silicone elastomer shells, the resulting effect on implant strength is not known.

Low-Molecular-Weight Silicone Diffusion Silicone gel filler can affect shell integrity by the diffusion of non-crosslinked silicones from gel into the silicone elastomer shell⁶. Low molecular weight silicones have been detected in explanted silicone elastomer shells. Wolf et al.³ examined specimens from five explanted shells implanted from 0 to 21 years and reported movement of low-molecular-weight cyclic silicone (octamethylcyclotetrasiloxane, D₄) into the silicone elastomer shell. Marotta et al.¹⁸ examined 51 explanted shells from four different manufacturers; the mean implant ages ranged from 5 to 18 years. Explanted Dow Corning, McGhan double-lumen, Meme-MP, Replicon, Sugitek SCL, Surgitek standard, and Surgitek double-lumen implant shells were found to be swollen with 20%, 19-20%, 32%, 24%, 16%, 22%, and 22%, respectively, extractable silicone oil. Birkefeld et al.⁵ used high-resolution nuclear magnetic resonance (NMR) to examine the aging of silicone elastomer breast implant shells and detected D₄ and dedamethylcyclopentasiloxane (D₅) in two 3-year-old third-generation explanted shells. Birkefeld et al.⁴ examined NMR relaxation times in 26 explanted Dow Corning silicone breast implants and found higher values in second-generation than third-generation implants, which they suggest may reflect the presence of lipids or low-molecular-weight silicones in the elastomer.

Swelling, which results from the diffusion of low-molecular-weight compounds from the gel into the shell, does not appear to be a primary risk factor for implant rupture nor does it seem to change the chemical nature of the silicone elastomer shell. Brandon et al.¹⁹ studied 42 single-lumen silicone gel implants manufactured by Dow Corning (2 Cronin, 18 Silastic 0 and Silastic I, and 22 Silastic II) and found that the seven implants with the longest implantation times (from 13 to 32 years) remained intact even with evidence of swelling (18.7-39.5%). In a rebuttal to Marotta et al.¹⁸, Brandon et al.²⁰ noted that "various types of silicone gel breast implants have remained intact with a large degree of shell swelling (20-40%) for implantation times ranging from 13 to 32 years." Wolf et al.²¹ also showed that the "mechanical forces involved in the swelling process do not degrade the silicone shell, even when the elastomer is cycled through five swelling-extraction cycles with an aggressive swelling agent." This is supported by data from Brandon et al.^{10, 22, 23, 24} showing relatively similar ultimate property values for the extracted Silastic 0, I, and II shells and their controls.

SHELL STRENGTH

Mechanical testing is the primary means by which the ultimate strength (tensile strength, elongation, stress, etc.) of a breast implant shell is assessed. The published scientific literature provides information on the strength of silicone gel- and saline-filled implants retrieved after explantation. Mechanical testing is the primary means by which the ultimate strength (tensile strength, elongation, stress, etc.) of a breast implant shell is assessed.

There are a number of explantation and MRI studies that found that length of implantation of silicone gel-filled breast implants is directly related to frequency of rupture^{18, 25, 26, 27, 28, 29}.

This prompted investigators to examine whether changes in the physical strength of the silicone elastomer shell may explain this observation. Investigators have reported that shell material may become weakened at the time of implantation and as a result of long-term implantation, and that migration of non-crosslinked silicones can affect shell strength.

The frequency of implant rupture over time differs between manufacturers and the era of manufacture. Surgical techniques may also influence the long-term durability of the implant, where newer techniques and medical practices may contribute to less stress and damage occurring during implantation or subsequent procedures. In general, silicone-filled breast implants may rupture over time. However, the frequency of rupture over time differs between manufacturers and implant generation. The information below indicates that earlier generation breast implants tend to fail at higher rates than later generation devices.

Effect of implantation process on shell strength There is some evidence of possible local weakening of an implant shell during implantation. During the implantation process, the shell may be stressed and deformed, and the surgeon's fingers may place pressure on a specific site of the implant causing local weakening of the shell^{22, 31}. In a somewhat unusual study design, Brandon et al.^{22, 30} implanted 14 Silastic II silicone gel-filled implants, all the same size and from the same manufacturing lot, into the breast tissue of a cadaver and immediately removed them to investigate the effect of the implantation process on shell strength. Twenty devices were not implanted and served as controls. SEM and mechanical testing were used to examine the implant shells. Average tensile strength of the explants was reduced 5% and breaking energy was reduced 8% compared with controls; average moduli values were decreased by a similar magnitude, but elongation and tear were relatively unchanged by brief implantation. The investigators also examined opaque regions on some of the shells where the surgeon's fingers forced the implant through the incision and believed them to be the result of delamination between the barrier coating layer and the base silicone elastomer of the shell. Mechanical analysis of these regions revealed decreased strength and elongation, which reflected the degree and length of time the local strain was applied to the shell. Brandon et al.²² noted that the small reduction in shell strength as a result of the implantation process was unlikely to be a major factor in implant durability.

Effect of long-term implantation on shell strength Some investigators compared mechanical properties of explanted breast implant shells (e.g., tensile strength, elongation, tear resistance, compression strength, and abrasion resistance) to nonimplanted (control) shells and found that the strength of a shell is compromised by implantation. Peters³² examined the compression strength of explanted implants and found that their compression breaking strength (0.62-10.8

psi) was lower than breaking strength pressures that had been recorded during closed compression capsulotomy (10-15 psi) putting these implants at risk for rupture during closed capsulotomy. Lockwood³³ examined 57 used saline- and silicone gel-filled shells (27 intact, 7 leaking, and 23 ruptured) that were implanted for 1-20 years. Samples from 40 used shells as well as 5 unused shells were tested according to ASTM standards. The shells represented several manufacturers and designs, including single- and double-lumen designs. They found that maximum stress was negatively correlated strongly with implantation time and negatively correlated weakly with shell condition. Maximum strain (a measure of extensibility) correlated strongly with both condition and implantation time. In addition, material strength and maximum strength of used Dow Corning shells were significantly less than unused shells of the same type. Greenwald et al.^{34, 35} mechanically tested specimens from 25 silicone gel-filled breast implant shells explanted from 15 women. They found a significant negative correlation between length of implantation and shell strength (mean peak strength), shell toughness (energy absorbed before puncture), and shell elasticity (elastic modulus). There was no effect of implant age on strain at rupture. Phillips et al.³⁶ examined 198 specimens from 29 explanted implant shells from silicone gel-filled implants (several manufacturers and designs) and compared strength parameters to 9 specimens from unused Dow Silastic II devices. They observed a decrease in implant strength (maximum force that a 6.35-mm wide strip of implant could withstand in tension and in terms of the maximum stress characteristic of the material itself) with implantation time. By comparison with the Dow standard implants, explanted shell specimens demonstrated a lower breaking force and the average breaking force of ruptured shell material was less than that of intact shells. Marotta et al.³⁷ examined the mechanical properties of shells from 22 explanted and 4 unused control breast implants. The devices included 10 Dow Corning single-lumen explants (average implantation time 9 years) and 12 McGhan style 76 double-lumen gel/saline implants (average implantation time 13 years); the unused devices included one Dow Corning single-lumen, two Dow Corning double-lumen, and one McGhan double-lumen. Samples from each shell were examined for tensile strength, tear strength, and % elongation at break. They reported that explant tensile strength and tear strength were severely degraded and that % elongation (strain to break) was also decreased in explant samples compared to control samples.

Marotta et al.¹⁸ examined the mechanical strength of silicone elastomer shell specimens obtained from 52 explanted devices (Dow Corning, McGhan, Surgitek and other, both single and double-lumen) and compared the results with reported properties of unimplanted devices. They found that tensile and tear strength were decreased (generally on the order of 26-45%) in the explanted shells in comparison to published values for unimplanted devices of the same make, and all were below the manufacturers' values for silicone gel-filled shells. In an invited discussion of the publication, Brandon et al.²⁰ made the following comments regarding Marotta et al.'s conclusions: (1) the explants in the Marotta study were not compared with the proper nonimplanted controls; (2) Marotta selectively presented published data supporting their conclusions; (3) Marotta et al. did not acknowledge published reports noting that tensile strength of explanted devices are within the data range for control implants; (4) the Marotta et al. analysis does not address failure in relation to manufacturer, model, or generation of breast implants; and (5) the meta-analysis is not representative of all breast implants or all implanted women.

Some, but not all, investigators also reported a relationship between length of implantation and reduced shell strength. Phillips et al.³⁶ examined 198 specimens from 29 explanted implant shells from silicone gel-filled implants (several manufacturers and designs) and observed a decrease in implant strength with implantation time. Wolf et al.³ examined specimens from five explanted shells implanted from 0 to 21 years; some implants demonstrated little change in tensile strength, whereas others showed an appreciable change, with ultimate elongation, breaking energy, and tear resistance decreasing over time. Marotta et al.¹⁸ examined the mechanical strength of silicone elastomer shell specimens obtained from 52 explanted devices (Dow Corning, McGhan, Surgitek and other, both single and double-lumen) and found no correlation between implant duration and decreased mechanical properties of the shells in these implants. In a response to the Marotta et al.¹⁸ publication, Brandon et al.¹⁹ confirmed that "We know of no scientific evidence supporting the contention that silicone gel implant shell strength declines throughout the life span of implants." In addition, Brandon et al. concluded that "... once an equilibrium swelling has been achieved, the mechanical properties of shells without a barrier coating remain relatively constant over time, no matter where the implants are (sitting on a shelf or implanted in a patient). Shells without a barrier coating ... also achieve equilibrium swelling when they are stored. However, once implanted, additional swelling occurs in barrier-coated shells, and it may take a few years before equilibrium is reached."

A number of investigations by Brandon and associates did not consistently find an effect of implantation on shell strength. Brandon et al.¹⁰ examined two intact but heavily calcified Dow Corning Cronin style Silastic 0 implants removed after 28 years. Mechanical analysis of specimens cut from the two shells revealed no statistically significant difference in mean tensile strength, elongation, moduli, and thickness between shells, but tear resistance was statistically significantly decreased compared to control samples. Silastic 0 control implants were not available for testing but because the Silastic I implant shell is identical, the mechanical analysis results for the explanted Silastic 0 devices were compared to Silastic I control devices. The examination revealed no decrease in tensile strength, elongation, tear resistance, 200% modulus, 400% modulus, and crosslink density between explanted and control devices suggesting that "long-term *in vivo* aging has not severely degraded the structural integrity of the explant shells, even after 28 years of implantation."

Brandon et al.²³ examined the ultimate mechanical properties of 18 shells from single-lumen Silastic 0 and Silastic I explants implanted from 6 to 28 years, compared with the corresponding properties of 7 unimplanted Silastic 0 and Silastic I control single-lumen implants. Data on ultimate mechanical properties (tensile strength, elongation percentage, and tear strength) were presented on the analyzed Silastic 0/I explants together with all of the data available to date on Silastic 0 and Silastic I explants (five other studies). The tensile strength data included 60 explants and 15 controls, elongation-to-failure data represented 50 explants and 15 control samples, and tear strength data represented 17 explants and 7 controls. Two types of regression analyses (on the data and on the ranked data) were performed on the ultimate stress, elongation, and tear strength and did not show a significant relationship between implantation time and mechanical properties of the silicone elastomer shell. Both regression analyses showed no statistically significant difference in ultimate strength, elongation, and tear strength as a function of implantation time through 28 years of implantation.

Brandon et al.²⁴ examined the ultimate mechanical properties of 22 single-lumen Silastic II implants (implantation time 0.3-13.2 years) and 43 controls implants. The average mechanical properties data were presented together with the data from 12 other explants and 10 controls from 5 other studies presented in the literature. Tensile strength and elongation to failure decreased initially following implantation but then reached equilibrium. Regression analyses of the data did not show a statistically significant difference in the tensile strength, elongation to failure, or tear resistance as a function of implantation time. The investigators believe that the initial decrease in properties followed by equilibrium can be explained by diffusion of non-crosslinked silicone from the gel into the shell.

Brandon et al.¹ analyzed explanted Cronin seamed (available 1964-1968), Silastic 0 (available 1969-1974), Silastic I (available 1975-1986), and Silastic II (available 1981-1992) devices implanted from 3 months to 32 years for tensile strength, elongation, tear resistance, and moduli (stress for a given strain) of the shell. They observed "no catastrophic decrease in the ultimate properties with implantation times of up to 32 years." For Silastic 0 and I implants, the ultimate mechanical properties were not found to degrade with implantation. For Silastic II implants, the ultimate strength properties initially decreased after implantation then reached equilibrium. Modulus values, which measure bulk material stability, were found to be independent of length of implantation suggesting long-term stability.

Effect of low-molecular-weight silicones Diffusion of low-molecular-weight silicones into the silicone elastomer shell during implantation has been reported, albeit not universally, to affect shell strength *in vivo*. The presence of non-crosslinked silicones in the shell, resulting in a swollen shell, has been reported to decrease tensile strength, elongation, and tear resistance. This was determined by comparing the strength of explanted shells examined as received to the same shells extracted to remove non-crosslinked silicones or to nonimplanted devices. The available information generally suggests that the decrease in shell strength *in vivo* occurs soon after implantation and reaches equilibrium; however, it does not appear to compromise the shell's integrity, as implants have remained intact with shell swelling of 20-40% for 13 to 32 years¹⁹. It should be noted that manufacturers use different shell formulations, which could impact the reported findings and make for questionable shell strength correlations between manufacturers.

Marotta et al.¹⁸ examined 51 explanted shells from four different manufactures; the mean implant ages ranged from 5 to 18 years. Explanted Dow Corning, McGhan double-lumen, Meme-MP, Replicon, Sugitek SCL, Surgitek standard, and Surgitek double-lumen implant shells were found to be swollen with 20%, 19-20%, 32%, 24%, 16%, 22%, and 22%, respectively, extractable silicone oil. They found that this swelling contributed to a loss of shell strength over time. In an invited discussion of the publication, Brandon et al.²⁰ noted that weakening of the shell as a result of swelling is not universally observed and Brandon's extraction studies indicate that elastomer shells are not degraded by the swelling process.

Brandon et al.¹⁰ examined two intact but heavily calcified Dow Corning Silastic 0 implants removed after 28 years. Samples obtained from the shells were treated with hexane to extract non-crosslinked polydimethylsiloxanes. The investigators found that diffusion of non-

crosslinked silicone from the gel into the shell resulted in a 40% reduction in tensile strength and a 20% reduction in elongation between unextracted and extracted specimens, although the elongation values were above ASTM-recommended values for silicone gel breast implants.

Brandon et al.²⁴ examined the mechanical properties of 18 Silastic II explants and 41 Silastic II controls (implanted for 0.3 to 13.2 years) before and after extraction of the noncrosslinked silicones with hexane. They reported that the elongation to failure and tensile strength were significantly reduced by this "swelling" effect (5% and 15% less, respectively, than controls). This decrease in ultimate properties of the explants compared to the controls resulted from the higher average percent extracted from the explants shells (23.4%) compared to that of the controls (9.8%). Equilibrium in the swelling appeared to be achieved within the first few years of implantation. Once the noncrosslinked silicones were removed, the strength properties returned to values similar to the original control values.

Wolf et al.²¹ examined the strength properties of silicone elastomer shells from one explanted Silastic I and one Silastic II elastomer shell (approximate implantation times 10 and 6 years, respectively). The investigators examined the failure properties of the shells as received and following extraction of the noncrosslinked material removed by extraction with hexane. In addition, the failure properties of the shells following as many as five cycles of swelling with D₄ and subsequent extraction were determined. For both the Silastic I and Silastic II shells, swelling of the explanted elastomer shell resulted in reduced strength compared to extracted shells. For the Silastic I implant, swollen approximately 20 wt%, the strain-to-fail and stress-to-fail values of the as received shell was 70% of the extracted shell. For the Silastic II implant, swollen approximately 27%, the as received strain-to-failure and stress-to-failure were 51% and 57%, respectively, of the extracted shell. For the Silastic I implant, saturating to 205 wt %, D₄ reduced the stress-to-fail and strain-to-fail to 13% and 28%, respectively, of the extracted shell. For the Silastic II implant, saturating to 218 wt% D₄, the stress-to-failure and strain-to-failure were reduced to 15% and 17%, respectively, of the extracted shell. For both the Silastic I and Silastic II implants, the overall mechanical properties of the shells were restored following extraction.

Brandon et al.¹⁹ analyzed the mechanical properties of 16 as received and extracted Silastic II gel-filled explants (implanted 0.3 to 13 years) to lot-matched controls. Samples from explanted devices had swelling levels twice that of their lot matched controls. For the 16 explants, the ratios of the explant value to the lot-matched control value were calculated for tensile strength, elongation, tear resistance, and 200% and 400% moduli. The tensile strength, elongation, and tear resistance of the samples as received were on average 75%, 82%, and 73% of the controls, respectively. However, the explant 200% and 400% moduli values were essentially unchanged compared to the controls. Despite the decrease in elongation, the values for each of the implants were still above the minimum acceptable value of 350 percent per ASTM standard F703. After extraction with hexane to remove noncrosslinked silicones, the ultimate properties returned to values similar to the controls (tensile strength and elongation values for the extracted shells were within 5-7% of controls and cross-link density, 200% modulus, and 400% modulus values were within 2% of controls).

Brandon et al.³¹ discussed the biodurability of four Cronin explants, two with implantation times of 32 years, one for 4.3 years, and one for 0.6 years, along with one Cronin control (32-year implantation). They concluded that no "catastrophic" decrease in the ultimate properties of the four shells was shown, with implantation times up to 32 years. The largest decrease in tensile strength, relative to the control, for an explanted shell, and the extracted shell were 35% and 24%. Elongation analysis of shells compared with the control showed reductions of 24% and 14% for shells and extracted shells, respectively.

Relationship Between Reduced Shell Strength and Rupture The scientific literature tends to support the observation that implantation can negatively affect the strength properties of silicone gel-filled breast implant shells. However, there is insufficient information about the magnitude of the reduction in strength associated with implant compromise (rupture). Phillips et al.³⁶ found that most implants older than 10 years (those at greatest risk for rupture) had material strengths no higher than 4 MPa, but that most implants at 5 years or less after implantation have material strengths between 5 and 10 MPa; 8-year-old implants experienced a strain of 300% before rupture, but unused implants may experience maximum strains of 1,000% or more before rupture.

Surprisingly, in some instances, implants with the greatest longevity were found to have the greatest reduction in shell strength. Brandon et al.²³ found that of the 50 Silastic 0 and Silastic I implants they analyzed, the four explants with the lowest elongation-to-failure values (273%, 288%, 312%, and 315%) were intact after implantation times of 8 to 12 years, despite having elongation-to-failure values below the ASTM-recommended value of 350%. In addition, of the 17 Silastic 0 and Silastic I explants studied, those with the lowest tear resistance values were intact. The investigators reported that tensile strength data from 60 Silastic 0 and Silastic I explants showed the average tensile strength of the ruptured and intact explants to be almost equivalent (738 psi versus 763 psi). Brandon et al.²⁴ reported that in 31 Silastic II explants, the implants with the lowest elongation-to-failure results (413% and 440%) were intact after 8 and 10 years implantation. The average tear resistance data of 22 Silastic II explants showed that the two explants with the lowest tear resistance values were both intact after 10 years *in vivo*. Brandon et al.³¹ reported that among four Cronin explants, the implant with the lowest elongation result (approximately 71% of the Cronin control) was still intact at the time of explantation (4.3 years), as was the explant with the lowest strength result (approximately 65% of the Cronin control) after 32 years *in vivo*. These findings strongly suggest that a decrease in implant mechanical properties is not a primary reason for implant failure.

WHY DO SILICONE BREAST IMPLANTS FAIL?

A number of external events can contribute to the risk of breast implant failure (rupture), including damage by surgical instruments during surgery; overfilling or underfilling of saline (only) implant; manually squeezing the breast to break a hardened capsule; trauma, injury, or intense physical manipulation; excessive compression during mammography; or unknown/unexplained reasons. Implant aging (decreased durability of the silicone elastomer shell with time in the body) has also been investigated as a risk factor in implant rupture. The factors associated with decreased life span of silicone gel-, saline-, and alternate material-filled implants differ.

Silicone Gel-Filled Implants

A number of techniques, mammography, ultrasonography, computerized tomography, and magnetic resonance imaging (MRI) have been used to diagnose implant rupture in women with breast implants. Scaranelo et al.⁵⁵ examined the sensitivity and specificity of some of these techniques in assessing rupture in 44 asymptomatic patients with silicone gel-filled implants. Results showed a false positive rate of 43% for MRI and 12% for ultrasonography. A false positive is a person who tests positive for rupture via a diagnostic test, but does not actually have a ruptured implant. These false positives could result in overestimating rupture rates for the studies relying on these screening tools for rupture diagnosis.

Several investigators examined the lifespan of silicone gel-filled breast implants in different patient populations and reported their results^{25, 38, 39, 40, 41, 42, 43}. Most found that failure rates for silicone gel-filled breast implants increase after 10 years and that the number of intact implants decreases with length of implantation. Beekman et al.³⁹ examined the status of 426 silicone gel-filled breast implants implanted between 22 days and 24 years (mean age 9.7 years). A Kaplan-Meier survival analysis revealed a progression of failure between 10 and 15 years of implant age. Benadiba et al.⁴³ examined 949 implants (saline- and silicone gel-filled) from a number of manufacturers implanted between 1984 and 1996 and reported that the global median lifespan of a breast implant is 127 months (10.6 years). Second-generation implants, subpectoral implant placement, and surface texturing, have all been found to be associated with decreased implant lifespan⁴¹.

Data from explantation and magnetic resonance imaging (MRI) studies suggest that certain device designs are associated with an increased risk of implant shell failure. For example, second-generation breast implants (manufactured 1972-1981; thin elastomer shell and less viscous gel than first generation implants; silicone patches, several manufacturers) are more likely to rupture than first-generation implants (made 1963-1972 primarily by Dow Corning with woven Dacron fixation patches on the posterior surface to anchor them to the chest wall) or third-generation devices (manufactured 1981 to present; stronger thicker shell, more cohesive gel, barrier layer in shell, several manufacturers)^{11, 41}. For second-generation implants, duration of implantation and subglandular placement are also related to failure rate⁴⁴. First-generation implants have been found to rupture at the site of the attachment of the Dacron patch, although this is considered to be a result of the explantation procedure¹¹. However, Young et al.⁴² argued against the use of the "generational classification scheme," which suggests that second-generation implants are more prone to rupture than first-generation implants. They note that it is impossible to discern the generation of an implant by implantation date and that an investigator really needs to understand the designs and formulations offered by each manufacturer in order to accurately categorize an implant.

The literature suggests that physical trauma or damage during implantation is the most frequently observed causes of failure of silicone gel-filled implants. In terms of implant aging, explantation studies revealed that during implantation, the silicone elastomer shell can absorb low-molecular-weight silicones from the gel filler and lipids from the surrounding tissue. Absorption of these materials can cause shell swelling that may result in a decrease in mechanical properties of the shell. Some investigators report that this effect is related to length

of implantation. Despite evidence that the mechanical strength of the shell can be impacted, insufficient information is available to determine whether a decrease in shell strength is a significant cause of implant failure (rupture) or to determine how much shell strength can be compromised before failure occurs.

While silicone-filled breast implants may rupture over time, the frequency of rupture differs between manufacturers and implant generation. The information above indicates that an earlier generation of breast implants tends to fail at higher rates than other generations. Based upon these conclusions, it cannot be assumed that similar failure rates for earlier generation devices will occur with Inamed's current product.

Saline-Filled Implants

Saline-filled breast implants are available worldwide since 1965 and have been the only device design commercially marketed in the U.S. since 1992⁴⁵. Saline-filled implants have a silicone elastomer shell and are generally filled with saline prior to and at the time of implantation through a valve. Rupture of saline-filled breast implants is generally obvious to the patient because the implant empties quickly and there is a commensurate change in breast shape or fullness.

The lifespan of a saline-filled breast implant is the time from implantation to implant failure (rupture). Benadiba et al.⁴³ examined 949 implants (saline- and silicone gel-filled) from a number of manufacturers implanted between 1984 and 1996 and reported that the global median lifespan of a breast implant is 127 months (10.6 years); the median global lifespan for saline implants was 108 months (9 years). Saline-filled implant shells typically fail for a number of reasons, including shell elastomer fatigue, fold flaw cracking, faulty valve mechanisms, and patch delamination^{6, 12, 15}.

There is some evidence that implant manufacturer or style plays a role in the rupture of saline-filled breast implants⁶. Lantieri et al.¹⁴ conducted a study of 709 saline breast implants and found that the deflation rate of textured saline-filled implants was 7% lower than that of smooth membrane implants; percent implant fill was lower in deflated implants than in intact implants (suggesting fold flaw) and lower in smooth implants than textured. Cunningham et al.⁴⁵ conducted a multicenter retrospective study of 450 patients (882 saline-filled implants) and found that the risk of deflation was higher for Surgitek and Heyer Schulte/Mentor model 1800 than other implant designs. Heat-cured platinum-catalyzed shells have been found to have high deflation rates when they are filled with saline than room-temperature cured shells⁶.

The literature suggests that the most frequently observed causes of failure of saline-filled implants are physical trauma, damage during implantation, and fold flaw resulting in pinhole leaks or crack propagation. Fold flaw is most often minimized by adequate or overfilling of implants at the time of implantation. There is no information from explantation studies to suggest that the chemical or physical composition of the silicone elastomer shells of saline-filled implants is compromised with implantation.

Alternative-Fill Implants

There are two major types of alternate fill breast implant designs that have been clinically tested and marketed—soybean oil-filled implants and hydrogel-filled implants.

Soybean Oil-Filled Breast Implants Trilucent™ breast implants consist of a silicone elastomer shell filled with USP medical-grade soybean oil. The implants were clinically tested in Europe and in the U.S. and Canada, and marketed in Europe. During the years 1995 through March 1999, at least 9,000 Trilucent™ implants were implanted in 5,000 women in the U.K., and 3,500 were implanted in Germany, and the implant was widely available throughout Europe. The manufacturer withdrew the product from the market in mid-1999 following an announcement by U.K. Medical Device Agency (MDA) advising that because insufficient information was available on the safety of the product, no further devices should be implanted. In June 2000, the MDA issued a Hazard Notice recommending that all women with Trilucent™ breast implants consider having their implants removed. As a result of that announcement, a large number of women in Europe sought explantation of their devices and clinicians were able to provide some information on the physical state of the explanted devices.

Among the observations made of explanted Trilucent™ shells were that they were sometimes found to be discolored and friable with yellowish-brown granules^{46, 47, 48, 49}, and the shell was sometimes easily detached from the anterior patch and posterior transducer patch^{47, 48, 49, 50}. There was also reported to be evidence of lipid infiltration into the silicone elastomer, likely to be the soybean oil filler^{46, 47, 49, 50}. Some investigators reported that the elasticity and tensile strength of the shells was reduced compared to their original state^{50, 51}; however, none of the investigators provided any testing data to support this. One possible cause of shell failure in Trilucent™ breast implants is related to the potential effect of the filler on the strength of the silicone elastomer shell, particularly in the region of the patch.

The literature suggests that for Trilucent™ implants, the potential exists for lipids from the soybean oil filler to move into the silicone elastomer shell. However, there is no information from explantation studies to support a measurable effect of lipid absorption on shell strength.

Hydrogel-Filled Breast Implants MISTI (Molecular Impact Surface Textured Implants) Gold implants filled with a "bio-oncotic" gel of low molecular weight polyvinylpyrrolidone hydrogel were available in the U.S. from March 1990 to January 1992⁵². In Europe until December 2000, two models of hydrogel implants were available—the PIP hydrogel implant introduced in 1994 (4,000 women in the UK received these implants) and the NovaGold introduced in 1996 (250 women in the U.K. received these implants). MISTI Gold breast implants had a textured silicone elastomer shell⁵³. Among the adverse effects noted with these implants was an increase in implant volume with implantation and capsular contracture^{52, 53}. No information from explanted hydrogel devices on the performance of the silicone elastomer shell has been identified from the published medical literature.

ARE THERE MECHANICAL TESTING TECHNIQUES THAT ARE ABLE TO PREDICT IMPLANT FAILURE AFTER IMPLANTATION?

According to Young and Watson⁶, the mechanical properties of a silicone elastomer breast implant shell are extremely important and the material must be pliable and strong. A shell must be durable, that is, it must be elastic, and it must be resistant to tearing, abrasion, swelling, and fragmentation. The material must also bounce back to its original shape after deformity. Among the characteristics that are commonly measured and relate to the performance of silicone elastomer shells are: amount of swelling; weight gain; volumetric change; stress (force divided by cross-sectional area) and stress to failure (stress required to produce disruption); and strain (percent elongation) and strain to failure (percent elongation to failure)⁵⁴.

Breast implant manufacturers commonly test their device designs to examine performance by visibly examining the silicone elastomer shell (using SEM or optical microscopy); testing for valve or injection site competence; conducting tests of shell integrity (elongation, tensile set, strength of joints, seams, and seals); conducting fatigue tests (looking for tears, cracks, or cuts); conducting impact resistance tests; and evaluating abrasion properties.

Existing testing techniques are sufficient to predict the potential for implant rupture as a result of the most common causes of rupture (trauma, damage during implantation, fold flaw). The effect of long-term implantation in the body on shell performance and the likelihood of rupture cannot be predicted using current testing methodologies. This information is best obtained from explant retrieval and analysis studies. Such studies may ultimately provide information on the magnitude of change in elastomer properties associated with an increased risk of rupture; however, they can provide only limited information on predicting implant failure in the general population of women.

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REDACTED

Note: 9 pages were deleted

REPORT TITLE: Silicone Gel-Filled Breast Implant Five-Year Accelerated Shelf Life Study

REDACTED

REPORT SUMMARY: This report presents the results for the five-year accelerated shelf life study of silicone gel-filled breast implants. Based on the results of the study, there is no statistically significant decrease in physical properties after five years of accelerated aging. This supports a five year expiration date for silicone gel-filled implants.

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REDACTED

Note: 8 pages were deleted

Research Title: The preliminary study of Lipid effects on Silicone gel shell physical properties

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11. DISCUSSION

- 11.1. This preliminary test has shown no statistically significant different between Control and Test break force results, and Control and Test Elongation results from shells exposed to lard at elevated temperature.

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Email Subject: P020056 (Deficiency 3)

Sent to FDA: Tuesday, October 26, 2004

These were drafted for the conference call to illustrate discussion points.

For 3-2 & 3-11:

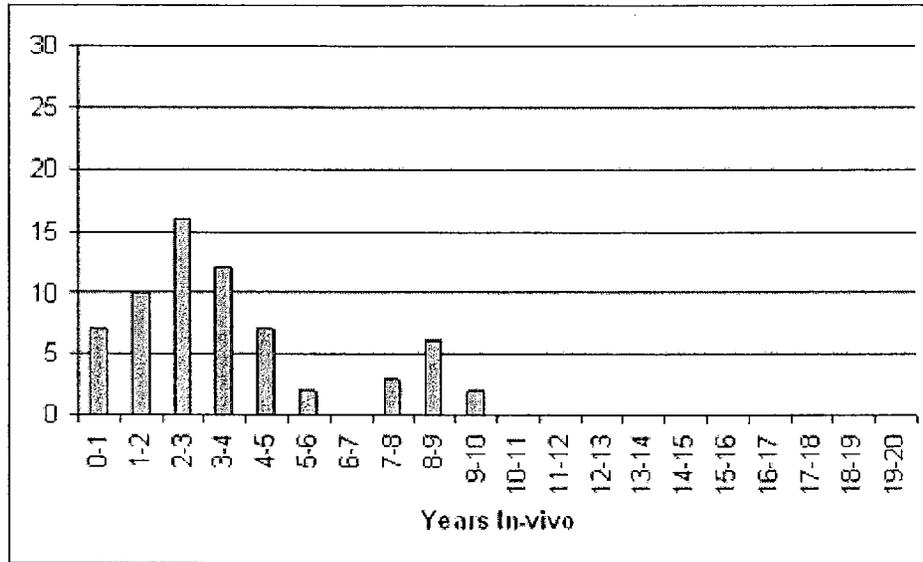
Failure Mode	Average (Yrs)	Min (Yrs)	Max (Yrs)
Style 153 Posterior Sharp Edge Opening (n=36)	4.23	0.19	9.47
Manufacturing Defects (n=6)	8.98	2.28	12.35
Sharp Edge Opening (n=24)	7.15	0.00	19.55
Fold Flaw (n=3)	14.00	9.65	18.73
Surgical Damage (n=30)	2.35	0.00	10.48

For 3-12:

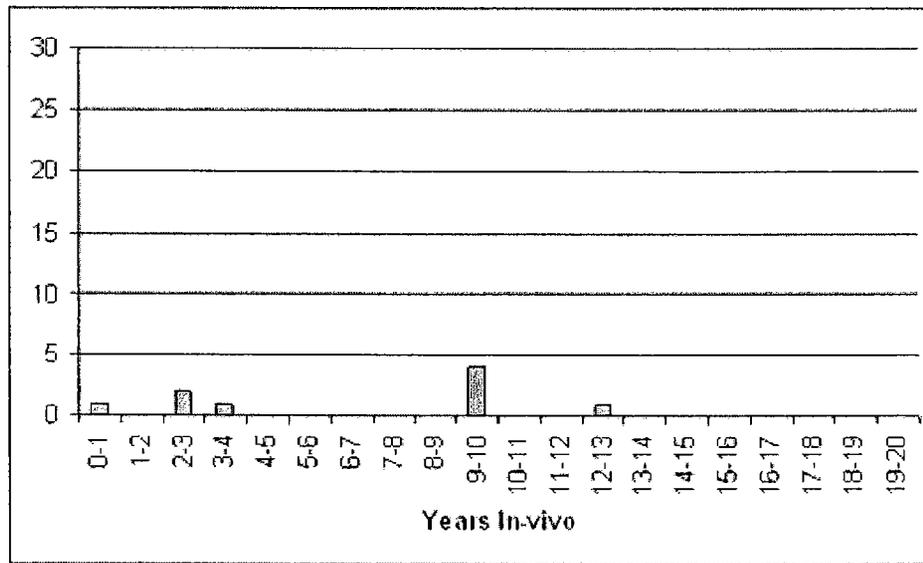
Failure Mode	Average (Yrs)	Minimum (Yrs)	Maximum (Yrs)
Style 153 Posterior Sharp Edge Opening (n=46)	2.55	0.09	5.13
Manufacturing Defects (n=4)	2.03	0.44	3.02
Sharp Edge Opening (n=12)	1.42	0.07	3.97
Fold Flaw (n=1)	0.26	0.26	0.26
Surgical Impact (n=4)	1.15	0.12	2.52
Surgical Damage (n=61)	1.92	0.00	5.08

Combined Info from 3-2/3-12 (with duplicates removed):

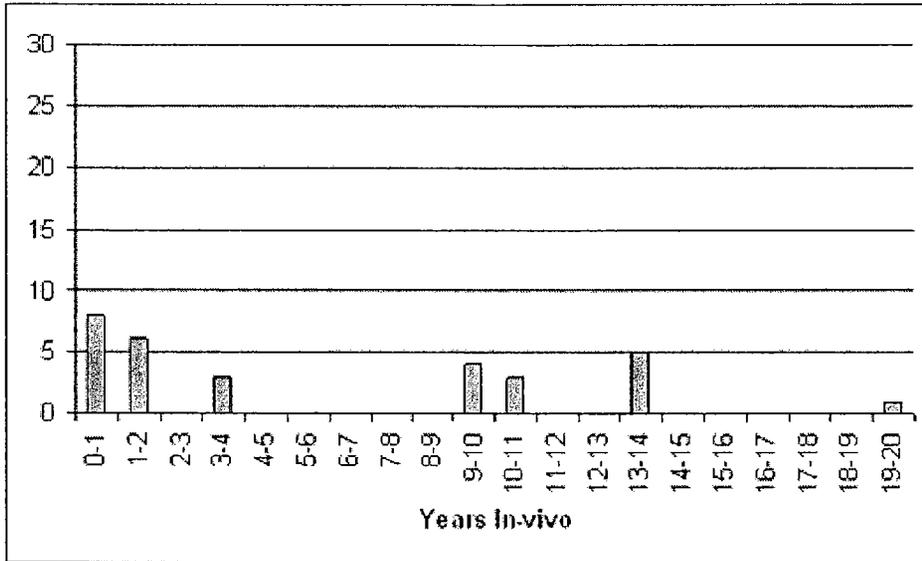
Failure Mode	Average (Yrs)	Minimum (Yrs)	Maximum (Yrs)
Style 153 Posterior Sharp Edge Opening (n=65)	3.58	0.09	9.47
Manufacturing Defects (n=9)	6.63	0.44	12.35
Sharp Edge Opening (n=30)	5.93	0.00	19.55
Fold Flaw (n=4)	10.57	0.26	18.73
Surgical Impact (n=4)	1.15	0.12	2.52
Surgical Damage (n=72)	2.19	0.00	10.48



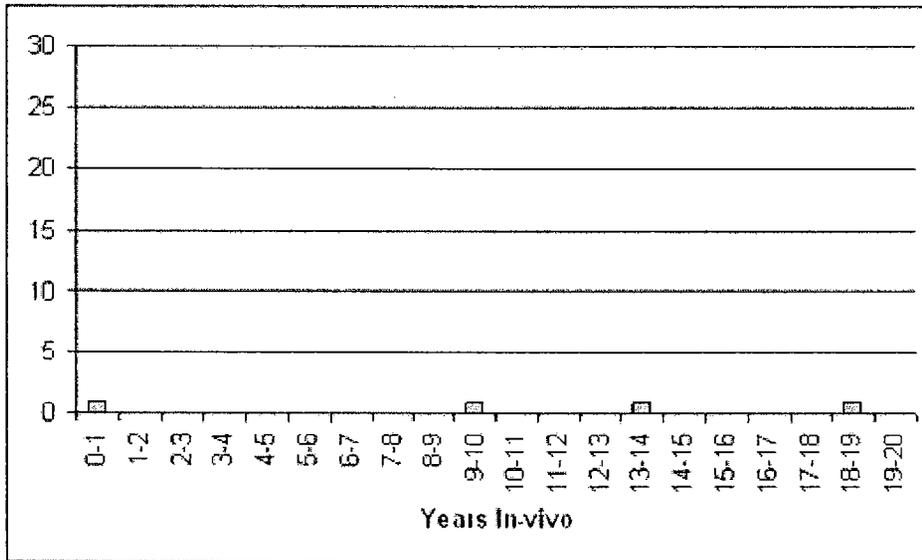
Style 153 Posterior Sharp Edge Opening



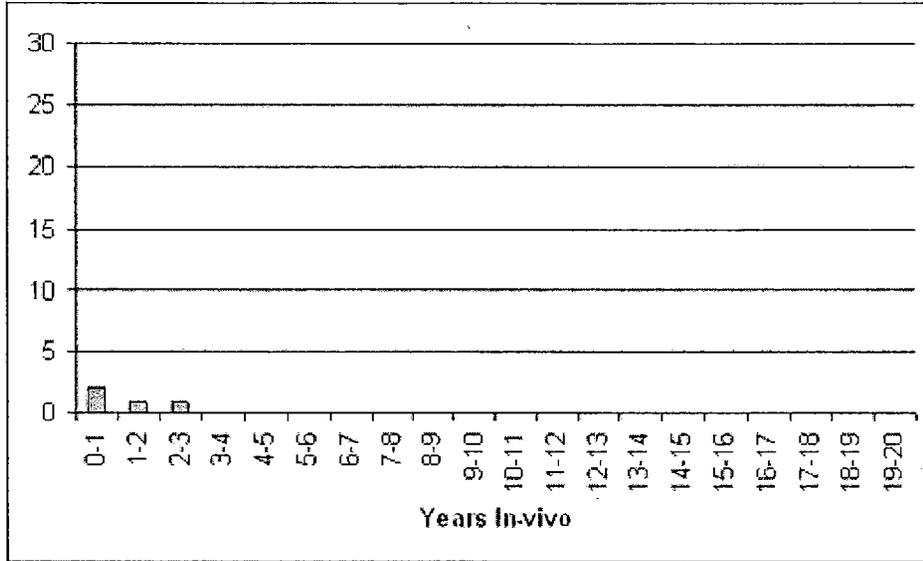
Manufacturing Defects



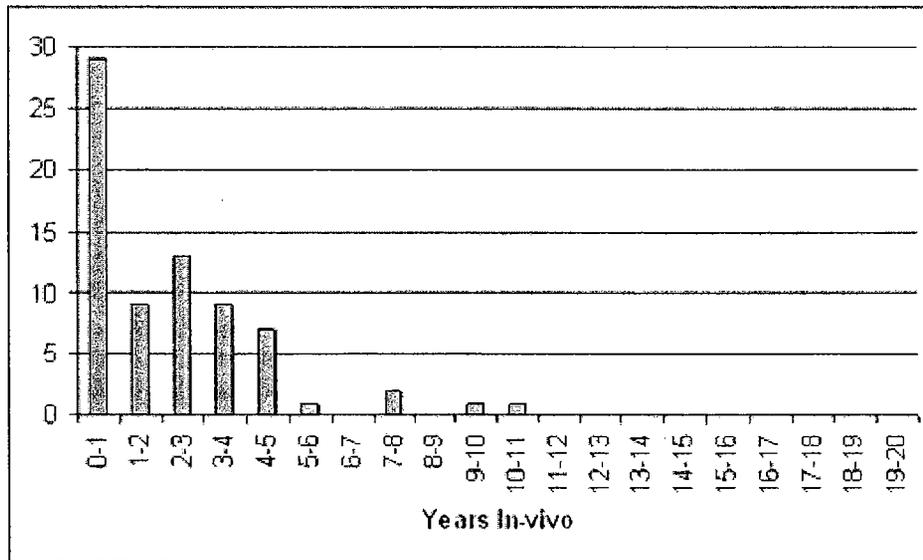
Sharp Edge Openings



Fold Flaw Failure



Surgical Impact



Surgical Damage

REDACTED

Email Subject: P020056 (Deficiency 3)

Sent to FDA: Tuesday, January 4, 2005

Attached is the information you requested below. Please let me know if you have any further questions.

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RESPONSE TO ISSUE 1

Located on the following page is the completed table as requested above, which identifies the percent occurrence of each rupture failure mode over the three time periods specified by FDA:

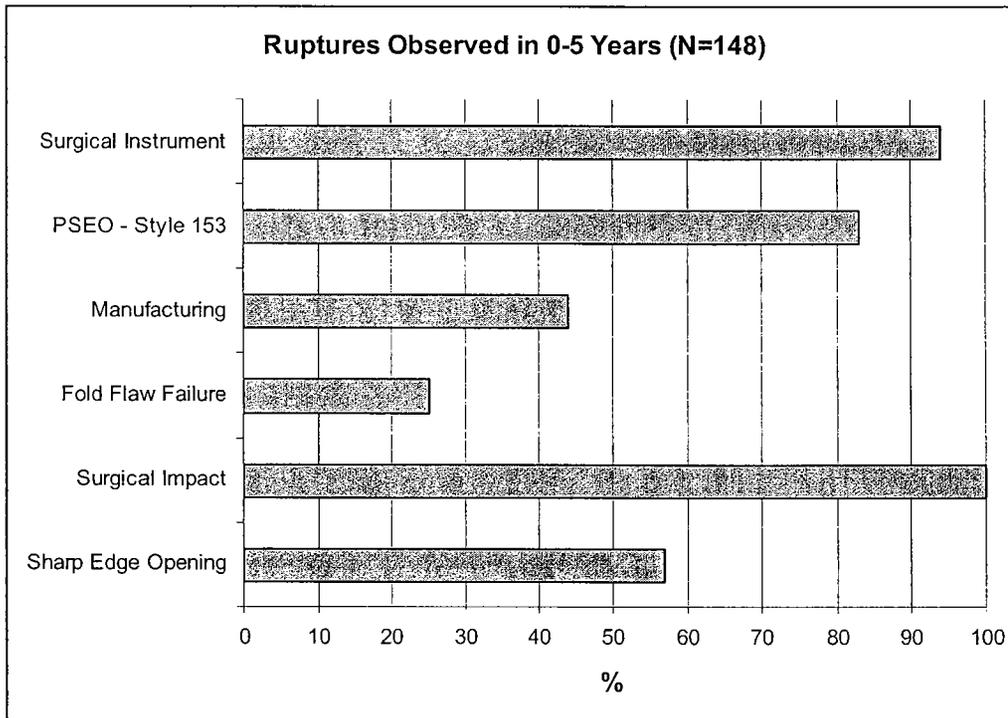
REDACTED

<i>Failure Mode</i>	<i># of Devices Ruptured During Specified In-vivo Time (corresponding %)</i>		
	<i>0-5 years</i>	<i>6-10 years</i>	<i>>10 years</i>
<i>Surgical instrument damage</i>	<i>68 (94%)</i>	<i>4(6%)</i>	<i>0 (0%)</i>
<i>Posterior sharp edge - Style 153 only</i>	<i>54 (83%)</i>	<i>11 (17%)</i>	<i>0 (0%)</i>
<i>Manufacturing</i>	<i>4 (44%)</i>	<i>4 (44%)</i>	<i>1 (12%)</i>
<i>Fold flaw failures</i>	<i>1 (25%)</i>	<i>1 (25%)</i>	<i>2 (50%)</i>
<i>Surgical impact</i>	<i>4 (100%)</i>	<i>0 (0%)</i>	<i>0 (0%)</i>
<i>Sharp edge opening</i>	<i>17 (57%)</i>	<i>7 (23%)</i>	<i>6 (20%)</i>
<i>Total</i>	<i>148 (80%)</i>	<i>27 (15%)</i>	<i>9 (5%)</i>

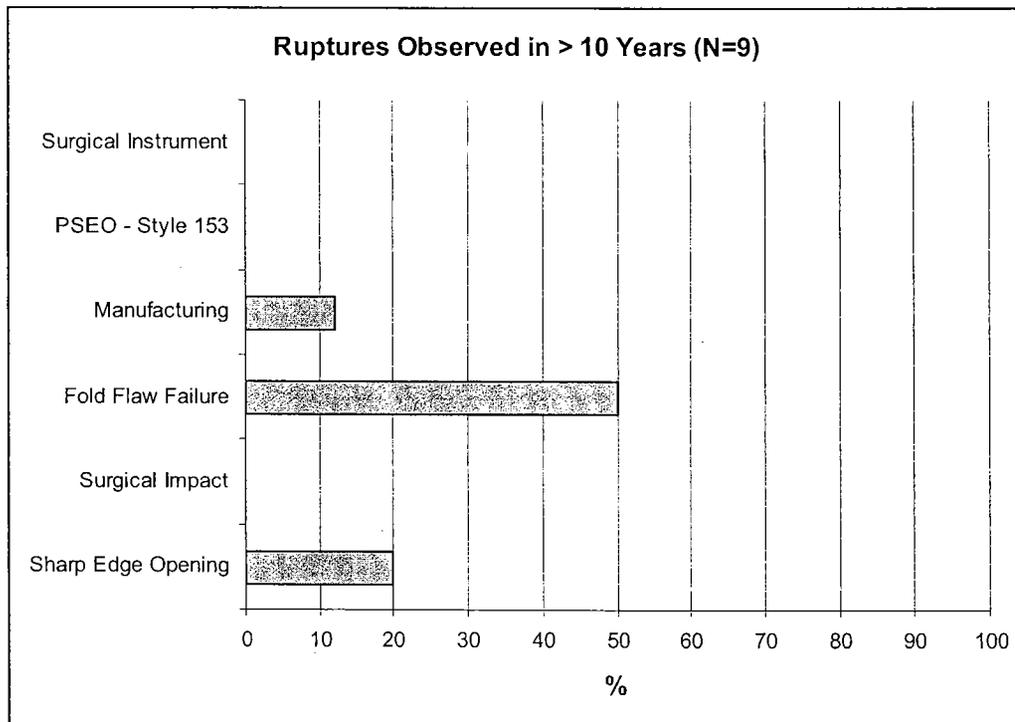
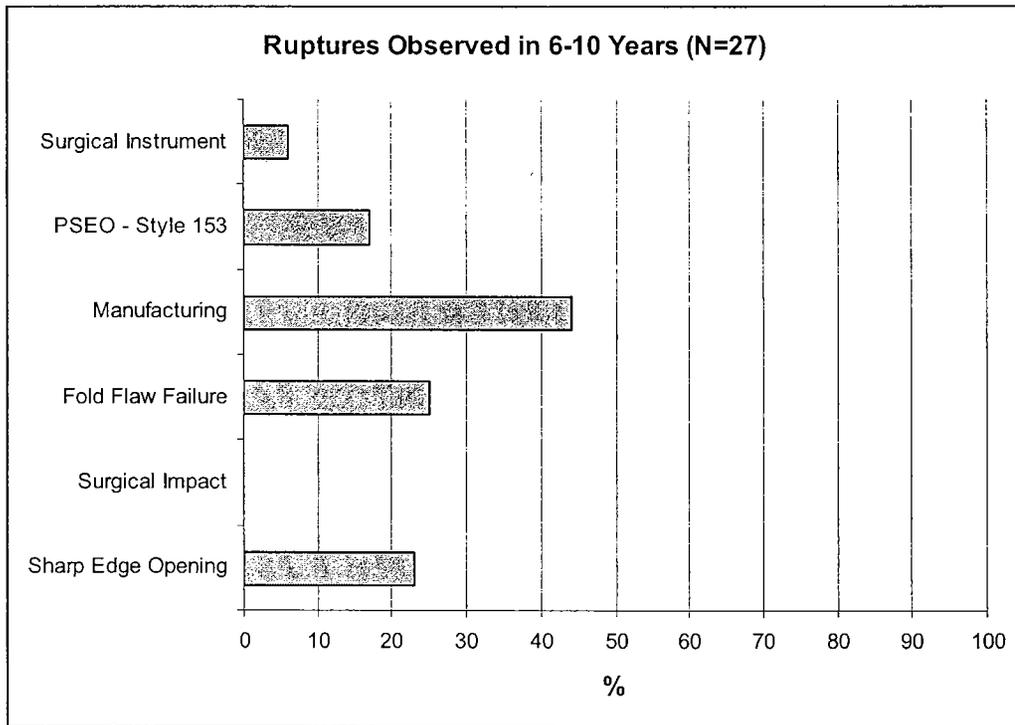
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RESPONSE TO ISSUE 2.

The following graphs correspond to the data presented in the table above. Please note that the abbreviation, "PSEO" in the second bar from the top on each graph represents "posterior sharp edge opening".



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Note: 17 pages were deleted

RESPONSE TO DEFICIENCY 4

General estimating equation (GEE) and other models were used to address FDA's questions a-d above. In accordance with International Conference on Harmonization (ICH) E3, Structure and Content of Clinical Study Reports, Section 11.4.1, output from continuous and categorical models and other analyses included in this response, is available upon request. Definitions for the case report form (CRF) variable names are located in Attachment 4-1. Category assignment for the CTD composites were modeled as previously defined in Inamed's pending PMA as follows:

002060

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Category	CRF variables
General	fever, sgland, wtgain, wtloss, tiredm, pain, fatigue
Joint	jpain, hswell, jswell, stiff
Muscular	mweak, aches, bpain, npain, limbs
Neurological	hdache, think, memory, tingle, balnce, earbzz
Other	dryeye, eyeoth, soresm, drymou, taste, swallow
Skin	hairls, fswell, rash, bruise, bleed, hives, skinp
Gastrop	hburn, cramps, nausea, vomit, consti, runs, bowels, bstool, nohngr, gipain
Urinary	urine, purine

A. FREQUENCIES OF CTD SIGNS AND SYMPTOMS

General estimating equation (GEE) models were used to test the effects of Inamed's silicone-filled breast implants on connective tissue disease (CTD) signs and symptoms for augmentation patients reported in the Core Clinical Study as of the data extraction on May 19th, 2004. The guidance on GEE modeling kindly supplied by [REDACTED] via FDA (Attachment 4-2) was used to test the CTD binary response composite category (general, muscular, neurological, skin, joint, other) versus the independent variables group (baseline, follow-up), and age. Because of violations to the missing completely at random (MCAR) rule, GEE analyses for CTD signs and symptoms in the reconstruction and revision cohorts were not completed. Models that did not converge were not included. The statistical rationale and SAS code are included in Attachment 4-2.

The following table summarizes the frequencies and percentages of reported CTD events by category, cohort, and time. Improvements (decreases) from year 2 to year 4 were seen in 11 subgroups, and increases through year 4 were reported in 13 subgroups.

	AUG			REC			REV		
general	b1	y2	y4	b1	y2	y4	b1	y2	y4
n	55	86	70	50	43	23	39	49	42
%	12	19.5	21	23	23.1	21	17	27.4	26
joint									
n	71	97	90	92	106	54	50	62	64
%	14	22	27	42	57	48	22	34.6	39
muscle									
n	100	125	114	78	75	48	65	72	61
%	20	28.3	34	36	40.3	43	29	40.2	37
skin									
n	44	60	44	29	42	20	20	29	23
%	8.9	13.6	13	13	22.6	18	8.9	16.2	14
neuro									
n	201	208	155	102	108	65	83	89	73
%	41	47.2	46	47	58.1	58	37	49.7	45

002061

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	AUG				REC				REV		
gastrop	bl	y2	y4		bl	y2	y4		bl	y2	y4
n	241	215	179		137	115	78		121	96	98
%	49	48.8	53		63	61.8	70		54	53.6	60
urinary											
n	6	11	12		13	10	3		7	15	11
%	1.2	2.5	3.6		5.9	5.4	2.7		3.1	8.4	6.8
other											
n	62	67	65		52	52	39		32	37	47
%	13	15.2	19		24	28	35		14	20.7	29

The mechanism of CTD signs and symptoms is likely multifactorial, and includes such variables as time and surgical differences. At baseline (Figure 4a-1), the probability of experiencing multiple CTD signs and symptoms increased with age for augmentation patients reporting signs or symptoms in all major CTD categories (general, muscular, neurological, joint). Likewise, the probability of experiencing a CTD sign or symptom increases with age for augmentation patients reporting signs or symptoms in any major CTD category (Figure 4a-2). The reports for urinary, gastrop, other, and skin showed similar aging trends. The major CTD groups were chosen because of their applicability to the fibromyalgia signs and symptoms analysis. However, a broader set of variables than those used in the FMSS definition in response to Deficiency 4b, was included in the major CTD groups. The following CRF variables were captured: mweak, aches, bpain, npain, limbs, jpain, hswell, jswell, stiff, hdache, think, memory, tingle, balnce, earbzz, fever, sgland, wtgain, wtloss, tiredm, pain and fatigue.

As suggested, we divided the age at time of implantation into categories. The descriptive moments for the age group variable at baseline and at the patient's last visit are shown in Tables 4a-1 and 4a-2. The shifts in skewness and location statistics between baseline and follow-up distributions are shown in Figure 4a-3. Adjusting for age in the GEE models as a continuous covariate or classification variable produced similar results.

Increases from baseline in CTD signs and symptoms were seen in almost all categories and significant differences in binary response, regardless of a significant age group result, were found in the augmentation cohort other, muscle, skin and joint categories. When using an interaction term in the model, two categories, skin and muscle were no longer significant. Significant increases for age groups within CTD categories are shown in Tables 4a-3 to 4a-6. Tables 4a-7 through 4a-11 provide cohort frequencies, by baseline and last observation, for important variables.

The general CTD category was analyzed using 3 different definitions: 1) as previously defined in Inamed's pending PMA, 2) same as one (1) but including pain, and 3) same as two (2) but including fatigue. None of the definitions showed a significant change from baseline, although pain, as measured on the visual analog scale increased and peaked at year two. In keeping with the literature, as shown below, 10% to 30% of patients

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suffered back pain after surgery¹⁸. Back pain appears to be related to age and implant size, where older patients with larger implants indicated more back pain.

Year 2

back pain	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	640	79.40	640	79.40
1	166	20.60	806	100.00

Year 4

back pain	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	469	76.51	469	76.51
1	144	23.49	613	100.00

The skin category last observation carried forward analysis showed significant increases from baseline ($p < 0.001$) in older patients, which again supports the literature. Skin disorders are so common among older people that it is often difficult to tell normal changes from those related to a disorder. More than 90% of all older people have some type of skin disorder^{3,5,8}.

As shown below, dry eyes (major other CTD category component) was another subgroup that showed increases from baseline that can be attributed to aging. Tear volume decreases as much as 60% by age 65 from that at age 18. Dry Eye Syndrome affects 75% of people over age 60^{4,9,16}.

Baseline

Dry eye	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	858	91.67	858	91.67
1	78	8.33	936	100.00

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Year 2

Dry eye	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	715	88.71	715	88.71
1	91	11.29	806	100.00

Year 4

Dry eye	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	520	84.83	520	84.83
1	93	15.17	613	100.00

A GEE analysis was performed comparing all scheduled visits (baseline, year 1, year 2, year 4) within the augmentation cohort. Convergence was demonstrated for all categorical analyses.

General findings:

1. The General category GEE analysis showed significant age related changes for all patients ($p=0.04$) and no significant changes from baseline for any of the follow-up time points.
2. The Joint category GEE analysis for all patients showed significant age related changes from baseline ($p < 0.001$) and all follow-up visits showed significant changes from baseline.
3. The Muscular category GEE analysis for all patients showed no significant age related changes from baseline ($p=0.97$) and all follow-up visits showed significant changes from baseline.
4. The Neurological category GEE analysis for all patients showed significant age related changes from baseline ($p=0.016$) and no significant departures from baseline for any of the follow-up time points, except from year 1 to year 2 ($p=0.046$).
5. The Other category GEE analysis for all patients did not show significant age related changes from baseline ($p= 0.51$) and all follow-up visits showed significant changes from baseline.
6. The Skin category GEE analysis for all patients showed significant age related changes from baseline for all patients ($p= 0.01$)
7. The Gastrop category GEE analysis showed no significant age related changes from baseline for all patients ($p= 0.23$) and no significant departures from baseline for any of the follow-up time points.

002064

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8. The Urinary category GEE analysis did not show significant age related changes from baseline for all patients ($p= 0.19$) and all follow-up visits showed significant changes from baseline.

In conclusion, the increases from baseline for some CTD signs and symptoms, reported by the Core augmentation cohort during the follow-up period are for the most part a function of aging. It is also likely that augmentation patients underreported subtle preexisting conditions during their screening period, which manifested for certain predispositions during follow-up. This conjecture is founded in the literature studies on the normal population², which suggest a lower than normal baseline response in the Core augmentation CTD reports. The lack of a suitable control group and incomplete 4-year data presented GEE concerns. The repeated measures (last observation carried forward) and the longitudinal (all scheduled visits) analyses produced similar results.

B. FATIGUE AND FIBROMYALGIA SIGNS AND SYMPTOMS

The probability for experiencing fatigue and/or fibromyalgia signs and symptoms (FMSS) increases with age in patients reported in the Core Clinical Study as of the data extraction on May 19th, 2004. The composite FMSS variable was constructed from Form 4 using the FDA recommended algorithm, with one exception (possible FMSS = fatigue greater than zero and unusual fatigue and aches and back pain or neck pain or chest pain). Including the variable of pain as measured on the visual analog scale (Form 4 Q2) was found to be a redundant measure. The variables selected were those that showed the greatest difference from baseline in order to present a worst case scenario. Figure 4b-1 shows the baseline probability of experiencing possible FMSS versus age, and as shown in Figure 4b-2 is highest at sites that primarily perform reconstruction surgeries, which comprise the majority of the right- upper portion of the curve. The course of FMSS over time suggests an initial below normal disposition, followed by an increase to normal levels^{6,11,13,17} two years post implant, remaining unchanged through year four. Three percent of all patients presented signs and symptoms of fibromyalgia at the two and four year visits.

The odds for experiencing FMSS after controlling for age is consistent with literature²⁰ odds ratios for a normal population, where the literature reports OR 1.03; 95% CI 0.98, 1.08 and the Core study follow-up results show OR 1.01; 95% CI 0.95, 1.08. Likewise, the combined fatigue responses from Inamed's "Activities and Lifestyle" (Form 4 Q4 and Q13), showed an increase of 3.2% from baseline (Tables 4b-1 and 4b-2). This increase is seen as a normal time related event and is consistent with the literature^{14, 15}.

The topic of fatigue has been in the medical literature for hundreds of years. It is thought to be multidimensional with many possible causes^{7,10}. The most common complaint from patients seeking general medical care is fatigue or loss of energy, and chronic fatigue (intractable fatigue lasting more than 6 months and not reversed by sleep) was reported by approximately one quarter of all patients seeking medical care^{7,10}. Many medical conditions were associated with chronic fatigue, such as respiratory, coronary, skeletal-

002065

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muscular and bowel conditions as well as cancers and infections^{1,12,14}. Increases from baseline in reported fatigue were noted in the augmentation and revision cohorts, while the reconstruction cohort reported a decrease in follow-up fatigue problems (Tables 4b-3 and 4b-4).

In conclusion, Core Study fatigue and fibromyalgia analyses results support literature findings that fail to show an association with silicone-filled breast implants. The reconstruction cohort finding is especially encouraging in light of the complexities associated with this type of surgery.

C. CORRELATION ANALYSIS

Tables 4c-1 and 4c-2 show the Pearson Correlation Coefficients for selected variables from dissatisfied patients reported in the Core Clinical Study as of the data extraction on May 19th, 2004. The variables, RASS and LASS (left/right dissatisfied patient assessments) and the categorical variables for connective tissue disease (CTD) signs/symptoms and fibromyalgia signs/symptoms (FMSS) presented in Table 4c-1 were used in the analysis. None of the CTD complaints, i.e. pain and swelling in the joints, redness of the skin, back or neck pain, swelling of the hands or feet, memory problems, headaches or muscle weakness, had an impact on dissatisfaction. The confirmed rupture cohort (Table 4c-2) was tested for the same comparisons as above. No distinctive features relating to silicone breast implants were identifiable in the dissatisfied subgroup for reported fibromyalgia signs and symptoms (FMSS) or CTDs in any of the subgroups examined.

For this correlational analysis, the goal was to determine how much of the variability in reported signs and symptoms was a function of dissatisfaction. The results were less than modest at best. In most cases, no statistical relationship between response and dissatisfaction was determined. Failure to find a relationship using this approach is not surprising given the high patient satisfaction results in Inamed's saline and silicone study findings. Due to the small dissatisfied sample size, the results do not prove that a relationship between dissatisfaction and CTD signs/symptoms and fibromyalgia signs/symptoms does not exist, but simply that we cannot demonstrate it using this approach.

Six patients reported FMSS in the primary rupture dataset, which includes confirmed rupture, unconfirmed rupture, and confirmed non-rupture patients. Three of the six patients who reported FMSS are from the confirmed rupture subgroup, and the other three patients who reported FMSS are from the confirmed non-rupture subgroup (Table 4c-3). The rupture subgroup responses (Table 4c-3) showed no differences when nonparametrically tested (Table 4c-4). Two of the six possible FMSS reports involved one patient who experienced an explantation and another patient who experienced a reoperation. Consistent with literature that discusses fibromyalgia in association with surgery or other physical trauma¹⁸, these surgical events may have contributed to the reports of FMSS in these two patients (Table 4c-5). The consequences of rupture, silent or otherwise, were no different from the remaining cohort members.

002066

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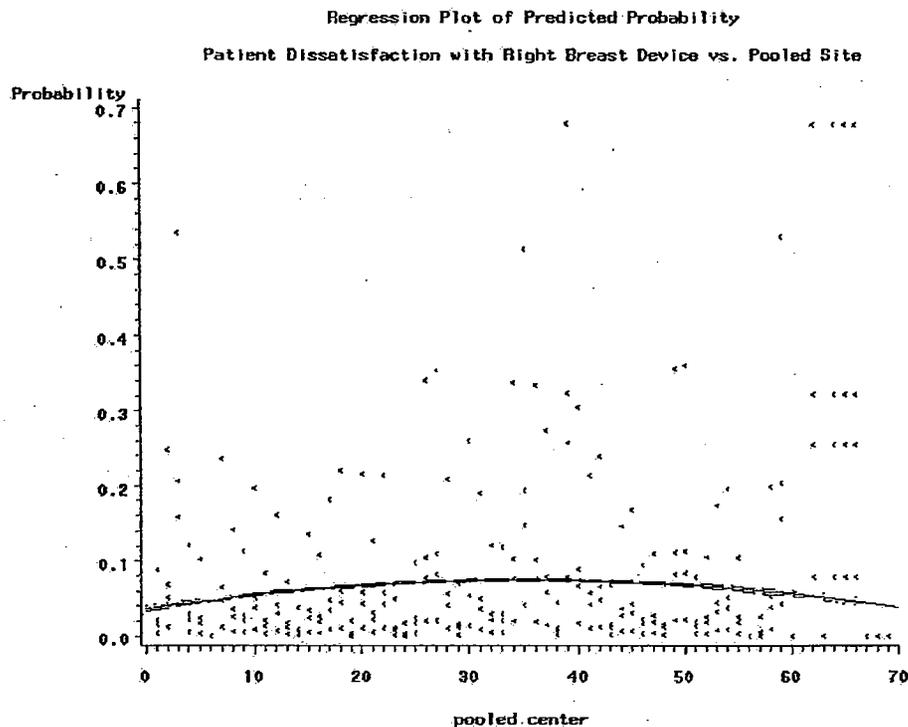
Comparisons between the non-MRI and MRI subgroups are presented in Tables 4c-6 and 4c-7. Significant between group differences were found for: 1) time to rupture, 2) possible FMSS, and 3) many CTD categories. These findings suggest that patients who are in the MRI subgroup may be experiencing possible FMSS and CTD signs/symptoms because they are undergoing explantation surgery more than the non-MRI subgroup. Almost half of the explantation surgeries were performed in the MRI confirmed non-ruptured subgroup, and therefore were unnecessary. The literature is replete with cases of FMSS being associated with surgery or some other type of physical trauma¹⁸.

Results also showed that MRI gives a high number of false positives (~36%). The American Society of Clinical Oncology (annual meeting, Chicago, June 2, 2003)²¹ stated that, "false positive results can lead to unnecessary additional tests, biopsies, and increased patient anxiety". The significant false-positive rate indicates that it may not be prudent to recommend MRI be commonly used for early detection of asymptomatic silent rupture.

There are a number of theories to explain dissatisfaction with silicone-filled breast implant outcomes, including the doctor-patient relationship, beliefs about consequences, and increased access to information via the internet. Patients who experience dissatisfaction or limited success with the outcome most commonly reported conditions associated with chronic pain (back and neck pain, arthritis and rheumatism). The wide variation in outcomes between different centers might be a factor, as shown in the graph below and Figure 4b-2. Factors such as increased body mass index, advanced age, and the presence of baseline co-morbidity are associated with poorer outcomes and a higher risk for a range of complications.

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As inclusion/exclusion criterion, the study relied on self-report of being relatively healthy at baseline. If certain conditions were already present at baseline but not yet formally diagnosed, then it is possible that these will cause subtle changes in how a patient feels about her life. Therefore, it is possible that the dissatisfied group or 'new' CTD patients are enriched with persons who already have early stages of certain conditions or problems. As seen in Figure 4c-1, the probability for experiencing a possible FMSS for the dissatisfied group increased with age when compared to the similar slope for all patients at baseline presented in Figure 4b-1. The increases in probability are most likely a function of normal aging, outcomes that were not ideal, and/or negative life experiences.

Tables 4c-8 through 4c-13 provide examples of the rupture dataset subgroup frequencies for important CTD subgroups. Nothing significant was determined across rupture subgroups and CTD categories or subgroups. Table 4c-14 provides an example of inferential output for the variable, aches, versus the three rupture subgroups of confirmed rupture, unconfirmed rupture and confirmed non-rupture. Across all CTD variables, aches, was the closest to showing a significant difference ($p=0.113$) between the three rupture subgroups.

Complications from secondary procedures were probable contributors to the increases in CTD/FMSS reported above. Patients reporting Form 4 signs and symptoms also reported similar Form 7 complications. The incidence of CTD signs and symptoms, reported

002068

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above is, therefore, likely exaggerated for some common secondary procedure outcomes, i.e. pain, chest pain, bruise, etc.

Complications reported on Form 7 were evaluated by date of resolution for coincidence with Form 4 CTD reports (muscle weakness, back pain, neck pain, fatigue, chest pain, aches). Twenty-nine (~3%) augmentation patients, who reported 3 or more signs and symptoms that may be associated with FMMS (muscle weakness, back pain, neck pain, fatigue, chest pain, aches), also had unresolved complications from a secondary procedure. In a similar fashion, 15 (~7%) reconstruction and 25 (~11%) revision patients had overlapping windows for 3 or more of the selected CTD signs and symptoms reports and unresolved complication reports. A listing of patients with overlapping windows and at least 3 CTD signs and symptoms can be found in Appendix 4 of Attachment B. Due to the overlapping windows for CTD signs and symptoms associated with FMSS and complication reporting, complications were not included in the correlation analysis. All CTD category reports (joint, muscle, general, etc.) showed that the majority of these patients also had unresolved complications at some point per the data collected on Form 7, and therefore also had overlapping windows.

In conclusion, the correlation and subsequent analyses produced nothing remarkable. Scatterplots were examined, and no linear associations between the variables were found. In light of the apparent lack of association, adjustments for the effects of other variables using partial coefficients were not performed.

D. COMPARISON OF CTD SIGNS AND SYMPTOMS DATA BETWEEN INAMED'S SILICONE-FILLED AND SALINE-FILLED BREAST IMPLANT STUDIES

Table 4d-1 shows the change from baseline comparisons for selected connective tissue disease (CTD) variables using the last observation carried forward through 4 years, for patients reported in the Core Clinical Study as of the data extraction on May 19th, 2004, and the 4-year data from the A95/R95 saline study datasets, dated November 1, 2001. Since the A95/R95 saline study does not include a Revision cohort, only the Augmentation (A95) and Reconstruction (R95) cohorts for both the Core and A95/R95 studies were compared. CTD variables that were common to both studies were chosen for analysis. Table 4d-1 shows summary statistics for those variables common to many fibromyalgia signs and symptoms (fatigue, swelling, weakness, aches, back and neck pain), referred to in this analysis (4d) as the "FMSS composite variable".

The greatest change from baseline (least favorable result) for this composite variable was reported in the A95 saline study. Results from probability estimates across time and GEE models, as in Response 4a, can be found in Appendices 5 and 6 of Attachment 4-B. The Augmentation cohort in Core and the A95 saline studies show similar age adjusted response patterns. The Core Reconstruction cohort was not examined using GEE models because of violations to the missing completely at random rule. The Core study Reconstruction cohort change from baseline for the composite variable is more favorable than the saline Augmentation cohort (A95) change from baseline. The R95 saline study showed the most favorable change from baseline results, and the Core study

002069

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Augmentation and Reconstruction cohorts change from baseline results were ranked second and third, in between the worst (A95) and the best (R95) results.

Tables 4d-2 through 4d-5 present baseline and follow-up parametric and nonparametric comparisons between A95 (saline) and Core. Baseline and follow-up response patterns were not different between the two studies for the FMSS composite variable.

Most of the age related CTD changes support post-surgery studies that show an association between back pain and arthritic signs and symptoms with negative life events and age. Comparing back pain in Core and A95 (saline) shows an almost identical pattern of response (Figures 4d-1 through 4d-4); back pain is the CTD variable in both studies that shows the greatest change from baseline (8%).

In conclusion, the risk of connective tissue disease or FMSS was determined to be greater in the A95 (saline) reports versus the Core study reports. Both studies show similar increases from baseline for common CTD/FMSS variables. These increases can be attributed to a variety of explanations, i.e. somatisation, post breast surgery syndrome, site differences, quality of life issues, neuropathic factors or complications from secondary procedures.

SUMMARY

Considering historical and recent results from: 1) the various models used in the Core CTD analyses, i.e. McNemar's GEE, 2) the results from the fibromyalgia signs and symptoms analysis presented in Deficiency 4b, 3) the apparent lack of associations or linear relationships between dependent and independent variables in Deficiency 4c, and 4) the saline study (A95/R95) comparison results discussed in Deficiency 4d, several questions relating to the clinical interpretation come to mind:

1. What clinical conclusions can we infer with some degree of confidence from the response to Deficiency 4?
2. Which model is the best predictor? (What are we left with after all models are compared?)
3. Which conclusions are most likely reproducible?

Examination of the frequencies and probability graphs found in Attachment 4-B, Appendices 1, 2, and 3, provides the pattern of responses that is the basis for the GEE results. Baseline measures and changes from baseline that are less than 5% are probably not reproducible due to error, variation, and instability found in small frequencies. Changes from baseline that approach normal literature values may be due to under-reported baseline measures and may represent a regression towards normality. Therefore, values that are found to be below literature findings for the normal population are suspect. Baseline measures and changes from baseline that are greater than 5% and show agreement in both the Core and saline studies are probably reproducible. Variables analyzed thus far that meet these criteria are: back and neck pain, hand swelling, fatigue, and aches.

002070

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In general, the increases in baseline for some CTD signs and symptoms in Core Study augmentation patients were mainly a function of aging. Furthermore, Core Study analyses are consistent with literature findings that fail to show an association between fatigue and fibromyalgia and silicone breast implants. In addition, the published literature shows a correlation between fibromyalgia signs and symptoms and surgery or physical trauma, as was seen for two of the six possible FMSS reports in Core Study rupture patients. An increase in CTD/fibromyalgia signs and symptoms showed no correlation with patient dissatisfaction or rupture. Finally, the CTD phenomena reported and analyzed through 4 years in the Saline and Core Studies were found to be similar. No significant differences were determined. This indicates that any increase in CTD signs and symptoms detected in women with silicone-filled breast implants is mostly likely not specifically related to the presence of her breast implants.

002071

TABLES AND FIGURES FOR DEFICIENCY 4

Figure 4a-1

**Estimated Baseline Probability versus Age
Membership in General and Joint and Muscle and Neurological Categories
Augmentation Cohort**

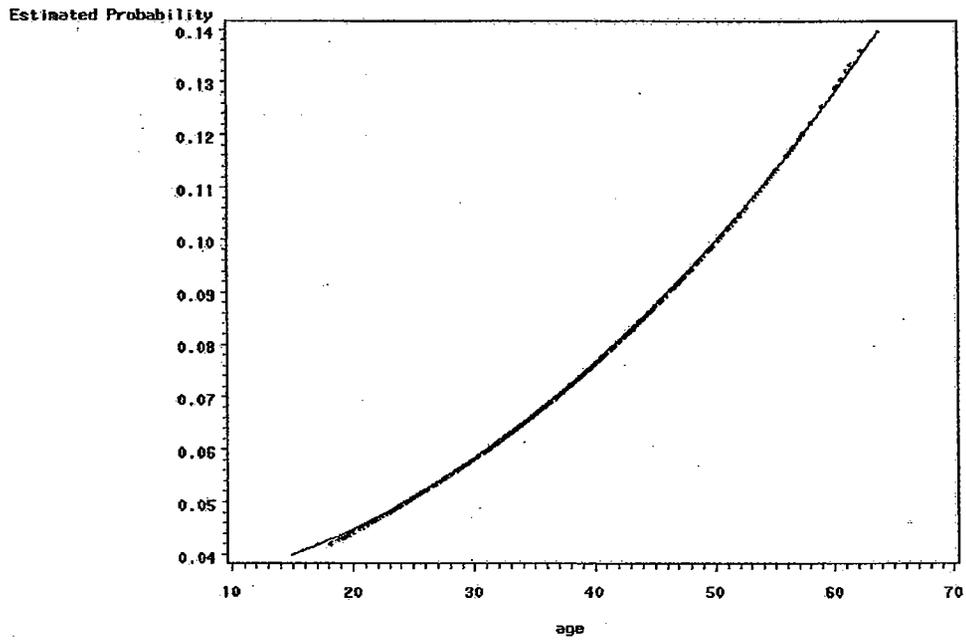


Figure 4a-2

**Estimated Baseline Probability versus Age
Membership in General or Joint or Muscle or Neurological Categories
Augmentation Cohort**

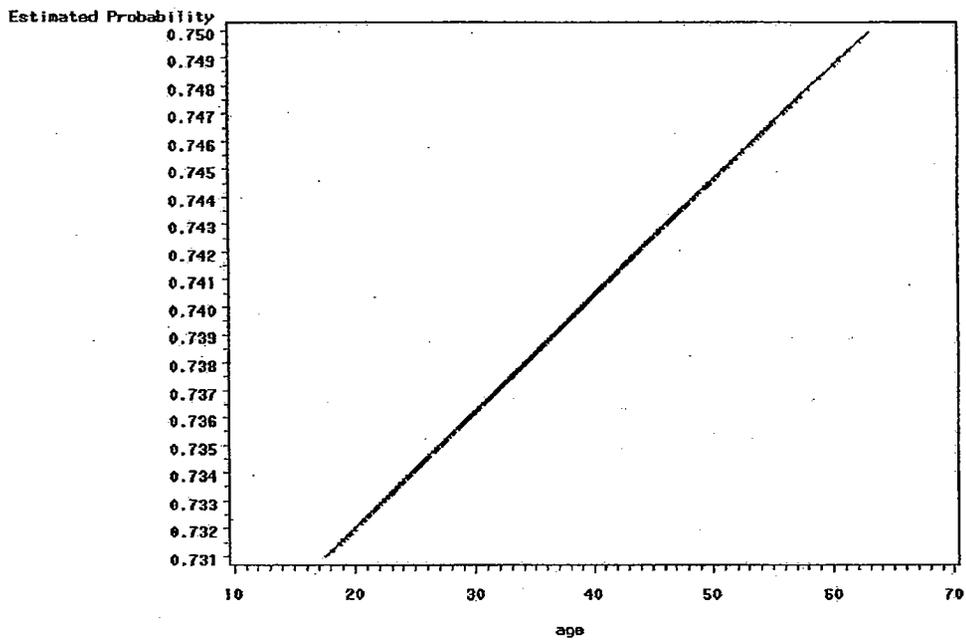


Figure 4a-3

**Percentage of Patients by Age Group Categories
Augmentation Cohort**

Baseline Age Group Categories
Augmentation Cohort

Last Observation Age Group Categories*
Augmentation Cohort

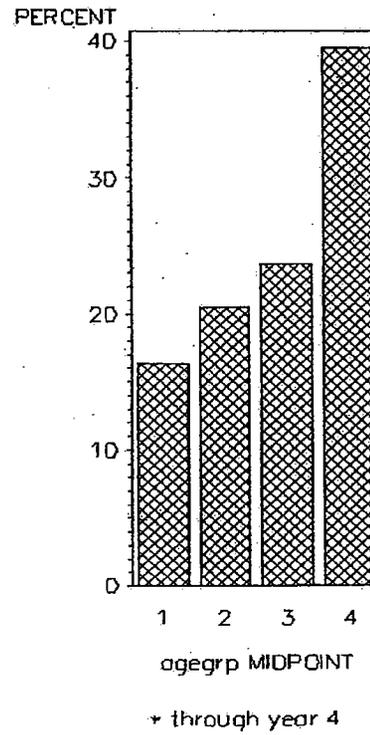
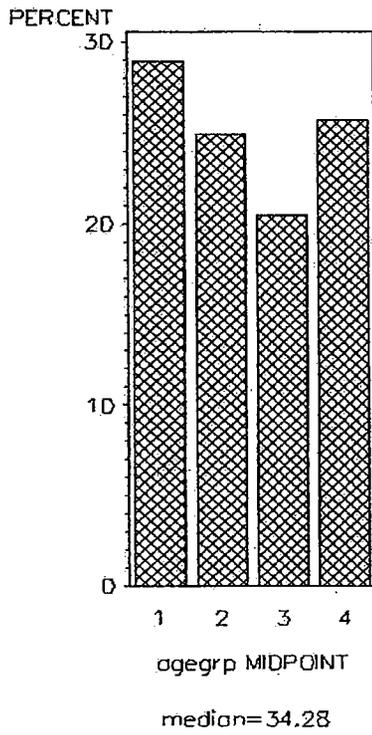


Table 4a-1

**Basic Statistical Measures
Baseline Age Group
Augmentation Cohort**

Moments			
N	494	Sum Weights	494
Mean	2.4291498	Sum Observations	1200
Std Deviation	1.1579343	Variance	1.34081185
Skewness	0.11009292	Kurtosis	-1.436837
Uncorrected SS	3576	Corrected SS	661.020243
Coeff Variation	47.6682955	Std Error Mean	0.05209793

Location		Variability	
Mean	2.429150	Std Deviation	1.15793
Median	2.000000	Variance	1.34081
Mode	1.000000	Range	3.00000

Table 4a-2

**Basic Statistical Measures
Last Observation Age Group
Augmentation Cohort**

Moments			
N	494	Sum Weights	494
Mean	2.86234818	Sum Observations	1414
Std. Deviation	1.11293308	Variance	1.23862083
Skewness	-0.4440344	Kurtosis	-1.2023414
Uncorrected SS	4658	Corrected SS	610.639676
Coeff. Variation	38.8818204	Std. Error Mean	0.05097323

Location		Variability	
Mean	2.862348	Std. Deviation	1.11293
Median	3.000000	Variance	1.23862
Mode	4.000000	Range	3.00000

* through 4 years

Table 4a-3

**Analysis Of GEE Parameter Empirical Standard Error Estimates
Other CTD Category
Augmentation Cohort**

Parameter		Estimate	Standard Error	95% Confidence Limits		Z	Pr > Z
other		0.6280	0.2851	0.0692	1.1867	2.20	0.0276
agegrp	3	-3.0252	0.7175	-4.4314	-1.6190	-4.22	<.0001
agegrp	4	-2.6424	0.5285	-3.6782	-1.6066	-5.00	<.0001

Table 4a-4

**Analysis Of GEE Parameter Empirical Standard Error Estimates
Neurological CTD Category
Augmentation Cohort**

Parameter		Estimate	Standard Error	95% Confidence Limits		Z	Pr > Z
neurologic		0.0777	0.2063	-0.3265	0.4820	0.38	0.7062
agegrp	2	-0.9740	0.3923	-1.7429	-0.2051	-2.48	0.0130

Table 4a-5

**Analysis Of GEE Parameter Empirical Standard Error Estimates
Joint CTD Category
Augmentation Cohort**

Parameter		Estimate	Standard Error	95% Confidence Limits		Z	Pr > Z
joint		0.5390	0.2294	0.0893	0.9887	2.35	0.0188
agegrp	1	-2.9785	0.5456	-4.0478	-1.9092	-5.46	<.0001
agegrp	2	-2.9444	0.7094	-4.3348	-1.5540	-4.15	<.0001
agegrp	3	-1.9273	0.5470	-2.9994	-0.8551	-3.52	0.0004
agegrp	4	-1.6826	0.4117	-2.4895	-0.8757	-4.09	<.0001

Table 4a-6

**Analysis Of GEE Parameter Empirical Standard Error Estimates
Muscle CTD Category
Augmentation Cohort**

Parameter		Estimate	Standard Error	95% Confidence Limits		Z	Pr > Z
muscle		0.2666	0.2044	-0.1340	0.6672	1.30	0.1922
agegrp	2	-3.2296	0.5852	-4.3765	-2.0827	-5.52	<.0001
agegrp	3	-1.4961	0.4979	-2.4719	-0.5202	-3.00	0.0027
agegrp	4	-1.4211	0.3735	-2.1532	-0.6891	-3.81	0.0001

Table 4a-7

**Comparison of Baseline and Follow-up CTDs
Membership in General or Joint or Muscle or Neurological Categories
Patients with Baseline and at Least One Follow-up Entry**

bctd	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	174	19.91	174	19.91
1	700	80.09	874	100.00

ftcd	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	161	18.42	161	18.42
1	713	81.58	874	100.00

Table 4a-8

**Comparison of Baseline and Follow-up CTDs
Membership in General or Joint or Muscle or Neurological Categories
Augmentation Patients with Baseline and at Least One Follow-up Entry**

bctd	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	128	27.35	128	27.35
1	340	72.65	468	100.00

ftcd	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	113	24.15	113	24.15
1	355	75.85	468	100.00

Table 4a-9

**Comparison of Baseline and Follow-up CTDs
Membership in General or Joint or Muscle or Neurological Categories
Reconstruction Patients with Baseline and at Least One Follow-up Entry**

bctd	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	18	7.77	18	7.77
1	190	92.23	208	100.00

fctd	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	15	7.28	15	7.28
1	191	92.72	206	100.00

Table 4a-10

**Comparison of Baseline and Follow-up CTDs
Membership in General or Joint or Muscle or Neurological Categories
Revision Patients with Baseline and at Least One Follow-up Entry**

bctd	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	30	15.00	30	15.00
1	170	85.00	200	100.00

fctd	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	33	16.50	33	16.50
1	167	83.50	200	100.00

Table 4a-11

**Comparison of Baseline and Follow-up CTDs
Membership in General or Joint or Muscle or Neurological Categories
All Patients at Baseline and Those with at Least One Follow-up Entry**

botd	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	188	20.11	188	20.11
1	747	79.89	935	100.00

ftcd	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	163	18.54	163	18.54
1	716	81.46	879	100.00

Figure 4b -1

Baseline Probability of Experiencing FMSS versus Age
All Patients

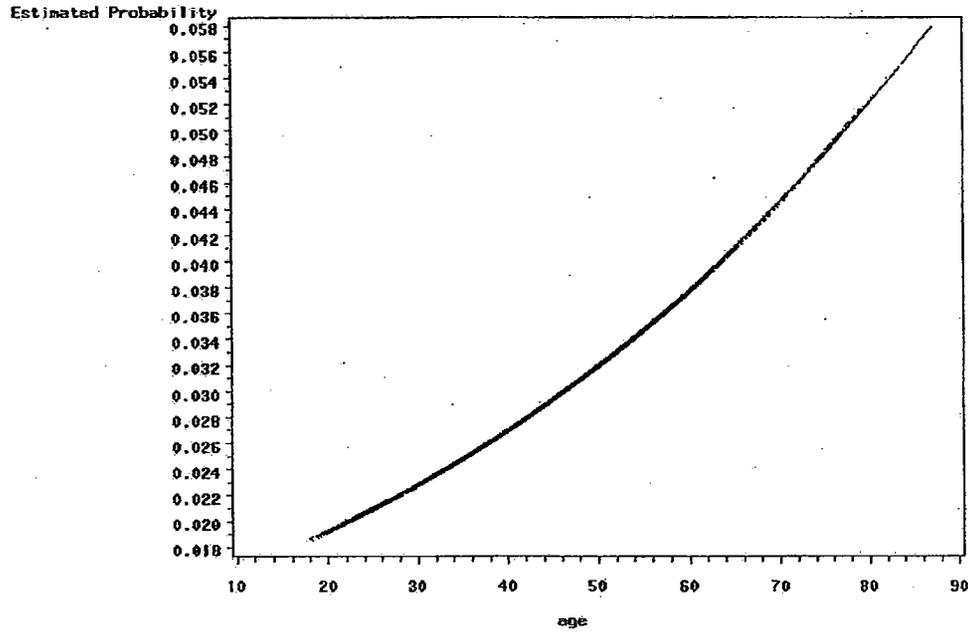


Figure 4b -2

Follow-up Probability of Experiencing FMSS versus Site
All Patients

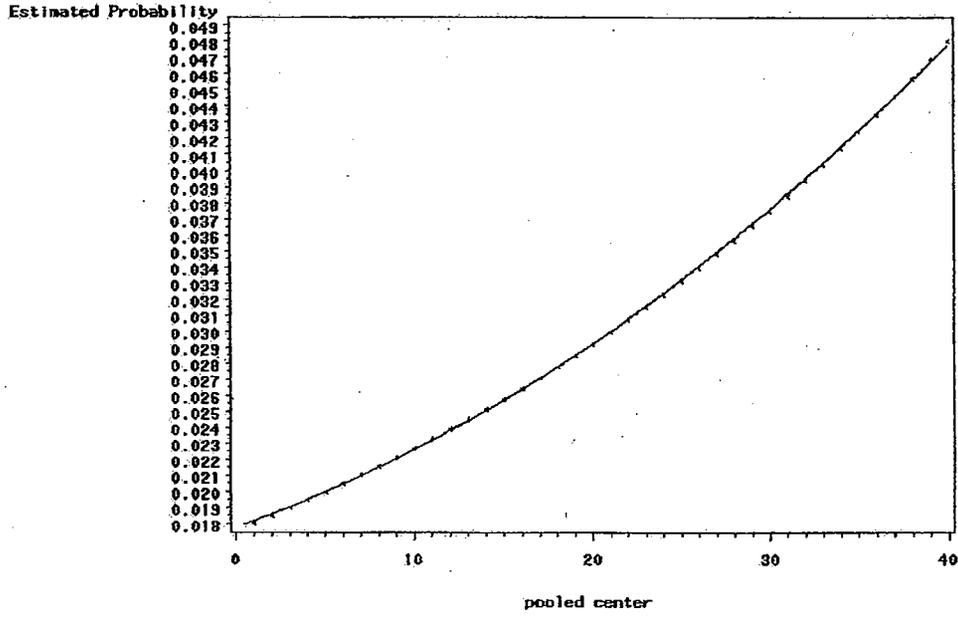


Table 4b -1

**Frequency of Experiencing Baseline Fatigue
All Patients**

BFAT	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	424	45.11	424	45.11
1	516	54.89	940	100.00

Table 4b -2

**Frequency of Experiencing Follow-up Fatigue
Last Observation Carried Forward
All Patients**

FFAT	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	394	41.91	394	41.91
1	546	58.09	940	100.00

Table 4b -3

**Frequency of Experiencing Baseline Fatigue
Reconstruction Cohort**

BFAT	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	66	29.86	66	29.86
1	155	70.14	221	100.00

Table 4b -4

**Frequency of Experiencing Follow-up Fatigue
Last Observation Carried Forward
Reconstruction Cohort**

FFAT	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	73	33.03	73	33.03
1	148	66.97	221	100.00

Figure 4c-1

Estimated Probability of Possible FMSS Dissatisfied Patients

Dissatisfied Patients

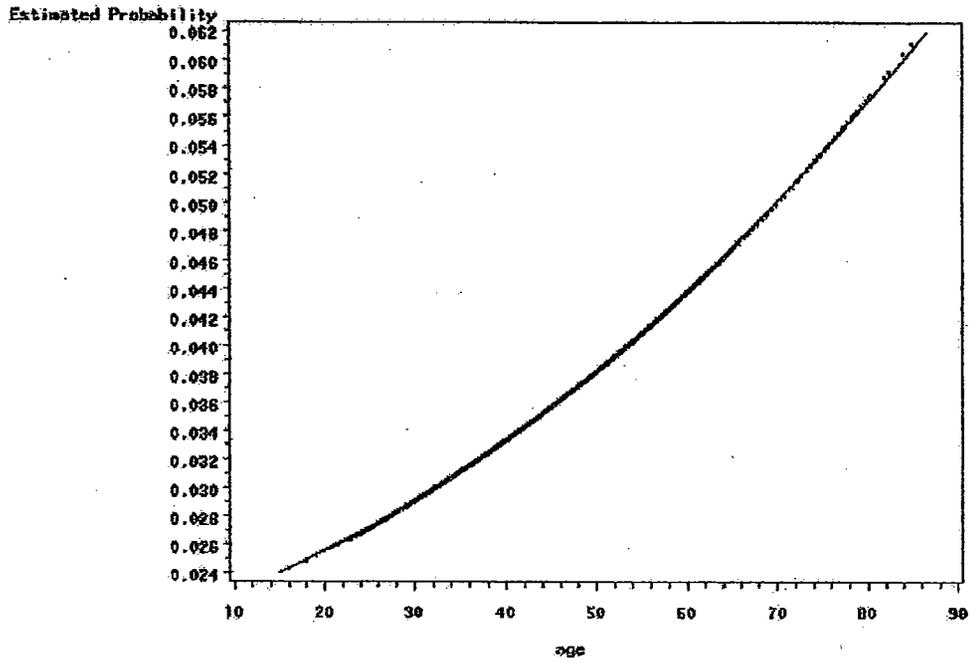


Table 4c-1

**Correlation Coefficients
All Dissatisfied Patients**

Pearson Correlation Coefficients Prob > r under H0: Rho=0									
	RASS	LASS	FMSS	FATIGUE	MUSCLE	JOINT	OTHER	NEUROLOGIC	GENERAL
RASS	1.00000	0.53280 <.0001	0.03714 0.0095	0.03254 0.0230	0.01751 0.2213	0.01173 0.4124	0.04656 0.0011	0.00482 0.7364	0.02711 0.0582
LASS	0.53280 <.0001	1.00000	0.00936 0.5130	0.00529 0.7115	0.00641 0.6542	0.00095 0.9469	0.02620 0.0671	0.02427 0.0899	0.04456 0.0018
FMSS	0.03714 0.0095	0.00936 0.5130	1.00000	0.53476 <.0001	0.27713 <.0001	0.22285 <.0001	0.14146 <.0001	0.19354 <.0001	0.09723 <.0001
FATIGUE	0.03254 0.0230	0.00529 0.7115	0.53476 <.0001	1.00000	0.21179 <.0001	0.17573 <.0001	0.17466 <.0001	0.22639 <.0001	0.18182 <.0001

Table 4c-2

**Correlation Coefficients
Dissatisfied Patients with Confirmed Ruptures**

Pearson Correlation Coefficients Prob > r under H ₀ : Rho=0									
	RASS	LASS	FMSS	FATIGUE	MUSCLE	JOINT	OTHER	NEUROLOGIC	GENERAL
RASS	1.00000 0.0000	0.47131 <.0001	0.09742 0.0595	0.01496 0.7728	0.10452 0.0431	-0.02690 0.8035	0.06991 0.1767	0.03804 0.4826	0.02975 0.5658
LASS	0.47131 <.0001	1.00000	0.03713 0.4735	-0.03502 0.4990	0.05408 0.2962	0.01831 0.7238	0.08685 0.0931	0.07273 0.1599	0.10725 0.0379
FMSS	0.09742 0.0595	0.03713 0.4735	1.00000	0.66090 <.0001	0.31791 <.0001	0.26321 <.0001	0.02972 0.5661	0.24565 <.0001	0.12528 0.0152
FATIGUE	0.01496 0.7728	-0.03502 0.4990	0.66090 <.0001	1.00000	0.27079 <.0001	0.20393 <.0001	0.09825 0.0573	0.20281 <.0001	0.18956 0.0002

Table 4c-3

**Frequency of Possible FMSS in the Rupture Dataset
By Rupture Subgroup
All Silicone gel filled implants**

Rupture Group	Possible FMSS		Total
	0	1	
Confirmed Rupture	22 88.00	3 12.00	25
Unconfirmed Rupture	18 100.00	0 0.00	18
Confirmed Non-rupture	31 91.18	3 8.82	34
Total	71	6	77

Table 4c-4

**Nonparametric Analysis Results of the Rupture Dataset
Rupture Subgroup vs. Possible FMSS**

Statistic	Prob
Chi-Square	0.335
Likelihood Ratio Chi-Square	0.1734
Mantel-Haenszel Chi-Square	0.7328
Fisher's Exact Test	0.4139

Table 4c-5

Possible FMSS by Method of Rupture Confirmation

Possible FMSS	Dx Test (e.g., Ultrasound)	Explant	MRI	Physician Exam	Reoperation	Total
0	8	8	36	17	2	71
	10.39	10.39	46.75	22.08	2.60	92.21
	11.27	11.27	50.70	23.94	2.82	
	88.89	88.89	94.74	94.44	66.67	
1	1	1	2	1	1	6
	1.30	1.30	2.60	1.30	1.30	7.79
	16.67	16.67	33.33	16.67	16.67	
	11.11	11.11	5.26	5.56	33.33	
Total	9	9	38	18	3	77
	11.69	11.69	49.35	23.38	3.90	100.00

Table 4c-6

Test of Equality over Strata
Time to Rupture

Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	5.1639	1	0.0231
Wilcoxon	2.9256	1	0.0872
-2Log(LR)	0.4239	1	0.5150

Table 4c-7

**Analysis of Maximum Likelihood Estimates
Possible FMSS**

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
mi1	1	0.55284	0.24600	5.0505	0.0246	1.738	1.073	2.815

Table 4c-8

Joint Composite Categorical across Rupture Subgroups
By Patient

Joint	Rupture Dataset Subgroup			Total
	CONFIRMED NONRUPTURE	CONFIRMED RUPTURE	UNCONFIRMED RUPTURE	
0	12	10	11	33
	18.46	15.38	16.92	50.77
	36.36	30.30	33.33	
	52.17	40.00	64.71	
1	11	15	6	32
	16.92	23.08	9.23	49.23
	34.38	46.88	18.75	
	47.83	60.00	35.29	
Total	23 35.38	25 38.46	17 26.15	65 100.00

Table 4c-9

BPAIN Subgroup across Rupture Subgroups

BPAIN(Experience - Back Pain)	Rupture Dataset Subgroup			Total
	CONFIRMED NONRUPTURE	CONFIRMED RUPTURE	UNCONFIRMED RUPTURE	
0	14	14	12	40
	21.54	21.54	18.46	61.54
	35.00	35.00	30.00	
	60.87	56.00	70.59	
1	9	11	5	25
	13.85	16.92	7.69	38.46
	36.00	44.00	20.00	
	39.13	44.00	29.41	
Total	23 35.38	25 38.46	17 26.15	65 100.00

Table 4c-10

JPAIN Subgroup across Rupture Subgroups

JPAIN(Experience - Joint Pain)	Rupture Dataset Subgroup			Total
	CONFIRMED NONRUPTURE	CONFIRMED RUPTURE	UNCONFIRMED RUPTURE	
0	20	21	14	55
	30.77	32.31	21.54	
	36.36	38.18	25.45	
	86.96	84.00	82.35	
1	3	4	3	19
	4.62	6.15	4.62	
	30.00	40.00	30.00	
	13.04	16.00	17.65	
Total	23	25	17	65
	35.38	38.46	26.15	

Table 4c-11

Fatigue (VAS) Subgroup across Rupture Subgroups

fatigue	Rupture Dataset Subgroup			Total
	CONFIRMED NONRUPTURE	CONFIRMED RUPTURE	UNCONFIRMED RUPTURE	
0	9	8	9	26
	13.85	12.31	13.85	
	34.62	30.77	34.62	
	39.13	32.00	52.94	
1	14	17	8	39
	21.54	26.15	12.31	
	35.90	43.59	20.51	
	60.87	68.00	47.06	
Total	23	25	17	65
	35.38	38.46	26.15	

Table 4c-12

Pain (VAS) Subgroup across Rupture Subgroups

pain	Rupture Dataset Subgroup			Total
	CONFIRMED NONRUPTURE	CONFIRMED RUPTURE	UNCONFIRMED RUPTURE	
0	12	14	8	34
	18.46	21.54	12.31	52.31
	35.29	41.18	23.53	
	52.17	56.00	47.06	
1	11	11	9	31
	16.92	16.92	13.85	47.69
	35.48	35.48	29.03	
	47.83	44.00	52.94	
Total	23 35.38	25 38.46	17 26.15	65 100.00

Table 4c-13

MWEAK Subgroup across Rupture Subgroups

MWEAK(Experience - Muscle Weakness)	Rupture Dataset Subgroup			Total
	CONFIRMED NONRUPTURE	CONFIRMED RUPTURE	UNCONFIRMED RUPTURE	
0	21	23	17	61
	32.31	35.38	26.15	93.85
	34.43	37.70	27.87	
	91.30	92.00	100.00	
1	2	2	0	4
	3.08	3.08	0.00	6.15
	50.00	50.00	0.00	
	8.70	8.00	0.00	
Total	23 35.38	25 38.46	17 26.15	65 100.00

Table 4c-14
Statistics for ACHES versus Subgroup

Statistic	DF	Value	Prob
Chi-Square	2	4.3629	0.1129
Likelihood Ratio Chi-Square	2	4.3212	0.1153
Mantel-Haenszel Chi-Square	1	0.0073	0.9319

Figure 4d-1

Estimated Probability of Baseline Back Pain
Core Study Augmentation Cohort

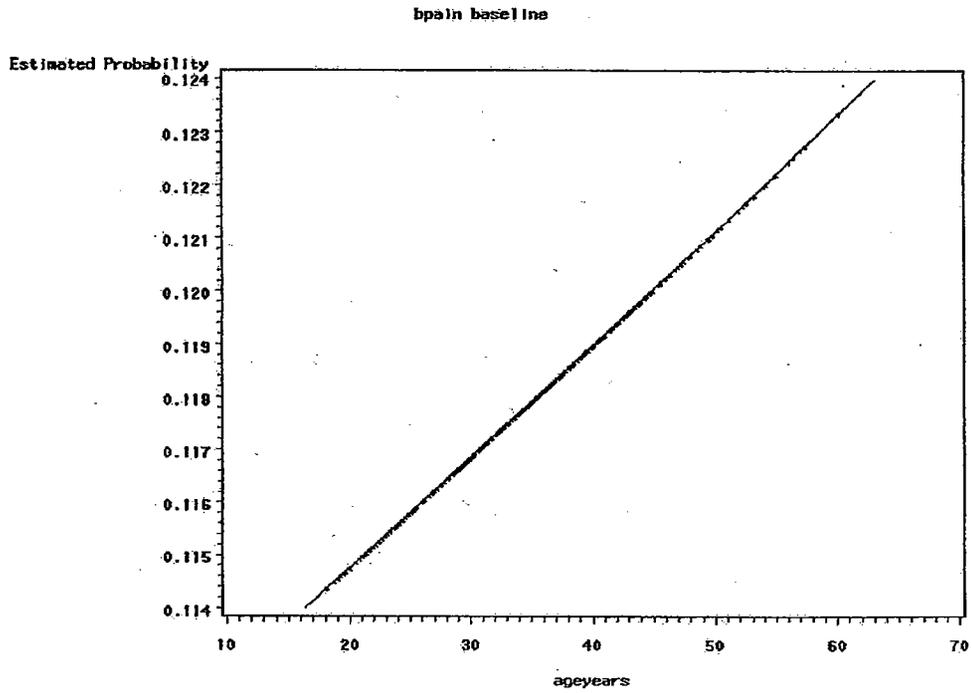


Figure 4d-2

**Estimated Probability of Follow-up Back Pain
Core Study Augmentation Cohort**

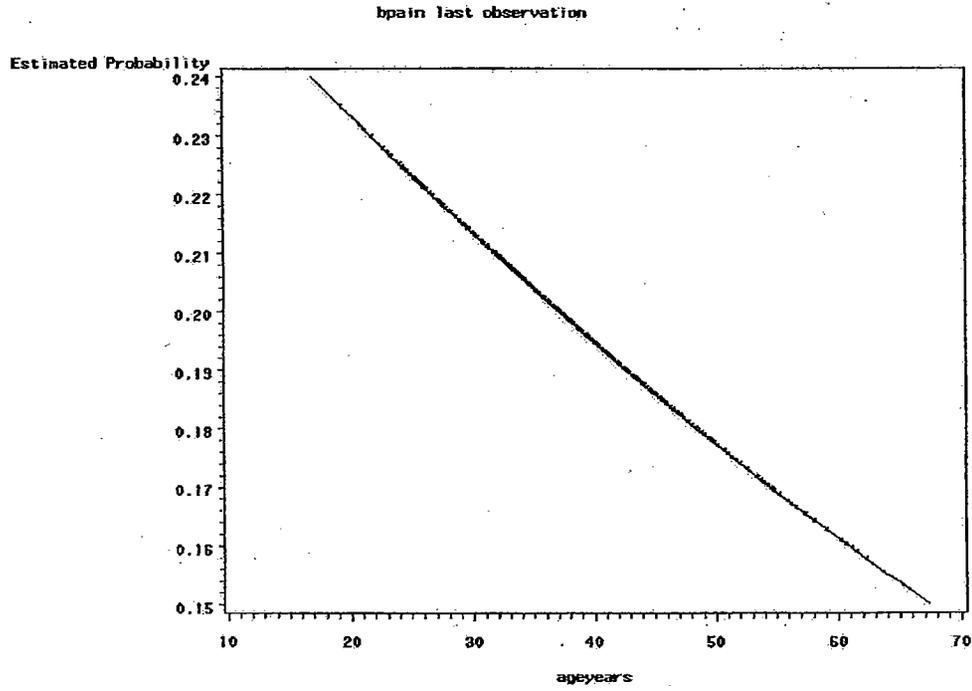


Figure 4d-3

Estimated Probability of Baseline Back Pain
A95 Study

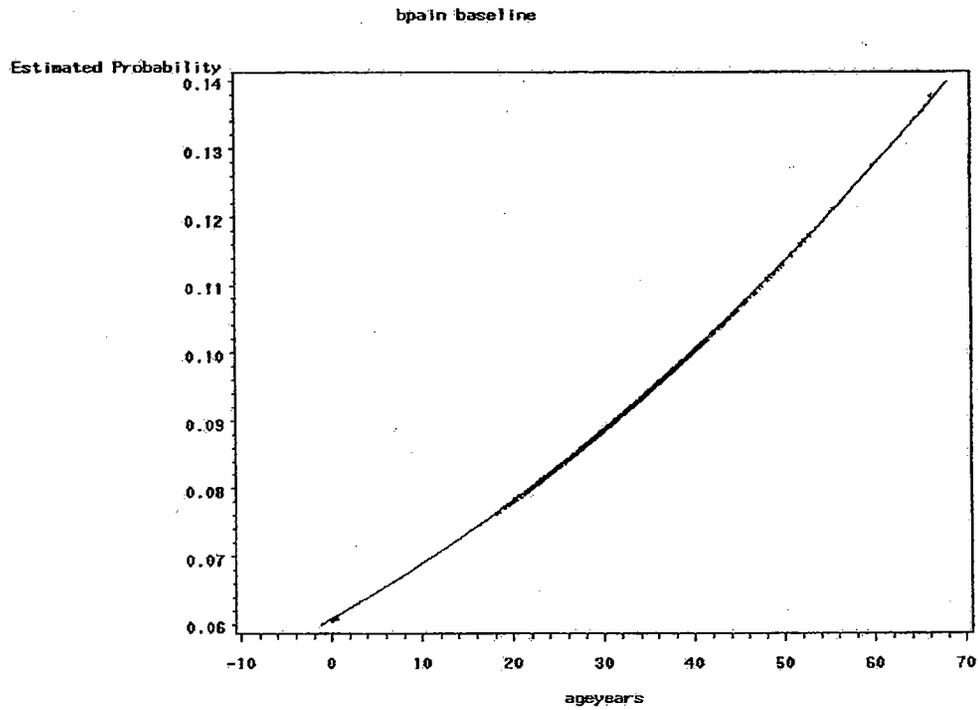


Figure 4d-4

Estimated Probability of Follow-up Back Pain
A95 Study

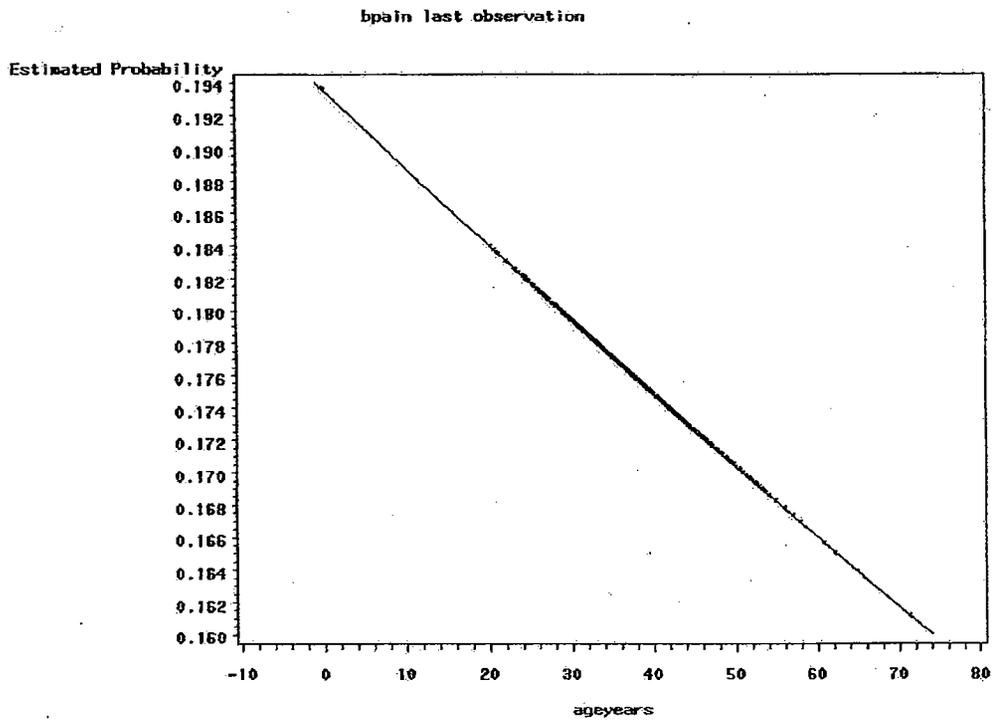


Table 4d-1

Comparison of Saline (s_) and Core (g_) Studies
Common CTD Variables

Variable	AUGMENTATION				RECONSTRUCTION			
	N	Baseline	Last obs	Diff	N	Baseline	Last obs	Diff
s_fatigue	901	0.048	0.128	-0.080	236	0.157	0.093	0.064
s_hswell	901	0.017	0.046	-0.029	236	0.097	0.064	0.034
s_mweak	901	0.003	0.028	-0.024	236	0.047	0.055	-0.008
s_aches	901	0.092	0.150	-0.058	236	0.195	0.212	-0.017
s_bpain	901	0.091	0.176	-0.085	236	0.195	0.182	0.013
s_npain	901	0.063	0.140	-0.077	236	0.093	0.102	-0.008
g_fatigue	494	0.026	0.113	-0.087	221	0.149	0.127	0.023
g_hswell	494	0.012	0.024	-0.012	221	0.059	0.095	-0.036
g_mweak	494	0.002	0.034	-0.032	221	0.063	0.050	0.014
g_aches	494	0.089	0.140	-0.051	221	0.181	0.271	-0.090
g_bpain	494	0.119	0.194	-0.075	221	0.186	0.222	-0.036
g_npain	494	0.079	0.134	-0.055	221	0.104	0.167	-0.063

Table 4d-2

**Parametric Comparison of A95 and Core Study
Baseline FMSS Composite**

T-Tests					
Variable	Method	Variances	DF	t Value	Pr > t
possibase	Pooled	Equal	1393	-1.07	0.2846
possibase	Satterthwaite	Unequal	978	-1.06	0.2908

Equality of Variances					
Variable	Method	Num DF	Den DF	F Value	Pr > F
possibase	Folded F	493	900	1.09	0.2698

Table 4d-3

**Nonparametric Comparison of A95 and Core Study
Baseline FMSS Composite**

Statistic	DF	Value	Prob
Chi-Square	1	1.1464	0.2843
Likelihood Ratio Chi-Square	1	1.1373	0.2862
Continuity Adj. Chi-Square	1	1.0027	0.3166
Mantel-Haenszel Chi-Square	1	1.1456	0.2845

Table 4d-4

**Parametric Comparison of A95 and Core Study
Follow-up FMSS Composite**

T-Tests					
Variable	Method	Variances	DF	t Value	Pr > t
possifoll	Pooled	Equal	1393	0.63	0.5278
possifoll	Satterthwaite	Unequal	1024	0.63	0.5266

Equality of Variances					
Variable	Method	Num DF	Den DF	F Value	Pr > F
possifoll	Folded F	900	493	1.02	0.8041

Table 4d-5

**Nonparametric Comparison of A95 and Core Study
Follow-up FMSS Composite**

Statistic	DF	Value	Prob
Chi-Square	1	0.3993	0.5275
Likelihood Ratio Chi-Square	1	0.4001	0.5270
Continuity Adj. Chi-Square	1	0.3290	0.5663
Mantel-Haenszel Chi-Square	1	0.3990	0.5276

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RESPONSE TO DEFICIENCY 5

In order to address the above request, Inamed examined the percent of patients in each Core Study cohort reporting dissatisfaction, as well as the specific reasons patients provided for their individual dissatisfaction. Complete 3 year data, extracted on May 19, 2004 is reported separately by cohort.

Data is reported by patient for all follow-up visits, and each unique dissatisfaction is only reported once per patient (e.g., a specific reason for dissatisfaction reported bilaterally counts as one report). Some patients specified more than one reason for dissatisfaction; in these cases, each dissatisfaction reason is reported separately in the table, so the sum of dissatisfaction reasons may be greater than the number of patients reporting dissatisfaction.

Overall, across all 3 cohorts the most common reasons women reported for being dissatisfied with their breast implants were capsular contracture (primarily Grades II and III), patient desire for size/style change, asymmetry and malposition.

At the 3-year follow-up visit, 96% of Augmentation patients reported being at least somewhat satisfied with the outcome of their breast implant surgery (Attachment 5-1). Indeed, on a 1 (definitely dissatisfied) to 5 (definitely satisfied) scale, the average satisfaction level for patients was 4.7.

As reported in Table 5-1, through 3 years the most common reason Augmentation patients were dissatisfied was due to capsular contracture (56%). Other common dissatisfaction reasons included asymmetry (17%), implant malposition (11%), ptosis (11%) and patient desire for size/style change (9%).

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Table 5-1

Core Augmentation: Reasons for Patient Dissatisfaction with Implants

Dissatisfaction Specified	Patients (N=54)	
	n	%
Asymmetry	9	17%
Breast Pain	1	2%
Breast Shape	1	2%
Breast Tissue Contour	2	4%
Capsular Contracture - Baker Grade I	1	2%
Capsular Contracture - Baker Grade II	10	19%
Capsular Contracture - Baker Grade III	17	31%
Capsular Contracture - Baker Grade IV	1	2%
Capsular Contracture - unknown grade	1	2%
Implant Malposition	6	11%
Nipple Pain	1	2%
Nipple/Areola Size/Position	2	4%
Patient Desire for Size/Style Change	5	9%
Pregnancy Related Contracture	1	1%
Ptosis	6	11%
Scarring	4	7%
Wrinkling	1	2%
Total	69	127%

At the 3-year follow-up visit, 92% of Reconstruction patients reported being at least somewhat satisfied with the outcome of their breast implant surgery (Attachment 5-1), with an average satisfaction level of 4.4.

Through 3 years, the most common reason Reconstruction patients reported being dissatisfied was due to capsular contracture (28%). This is illustrated in Table 5-2. Other common dissatisfaction reasons included patient desire for size/style change (25%), asymmetry (18%), implant malposition (15%), breast shape (10%) and wrinkling (10%).

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Table 5-2

Core Reconstruction: Reasons for Patient Dissatisfaction with Implants

Dissatisfaction Specified	Patients (N=40)	
	n	%
Asymmetry	7	18%
Breast Pain	3	8%
Breast Shape	4	10%
Capsular Contracture - Baker Grade III	6	15%
Capsular Contracture - Baker Grade IV	5	13%
Implant Malposition	6	15%
Insufficient/Excess Skin	2	5%
Other Complication*	3	8%
Patient Desire for Size/Style Change	10	25%
Ptosis	1	3%
Scarring	1	3%
Wrinkling	4	10%
Total	52	130%

*Other complications include "doesn't feel right", "thinks they are causing shortness of breath/chest pain" and "feel foreign"

At the 3-year follow-up visit, 88% of Revision patients reported being at least somewhat satisfied with the outcome of their breast implant surgery (Attachment 5-1), with an average satisfaction level of 4.4.

Table 5-3 shows that through 3 years, the most common reason for patient dissatisfaction among Revision patients was capsular contracture (50%). Other common dissatisfaction reasons included wrinkling (18%), implant malposition (16%) and patient desire for size/style change (16%).

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**Table 5-3
Core Revision: Reasons for Patient Dissatisfaction with Implants**

Dissatisfaction Specified	Patients (N=50)	
	n	%
Asymmetry	3	6%
Breast Firmness	1	2%
Breast Lump, Mass, Cyst	1	2%
Breast Pain	4	8%
Breast Shape	4	8%
Breast Tissue Contour	1	2%
Capsular Contracture - Baker Grade I	1	2%
Capsular Contracture - Baker Grade II	10	20%
Capsular Contracture - Baker Grade III	12	24%
Capsular Contracture - Baker Grade IV	2	4%
Implant Malposition	8	16%
Implant Palpability	4	8%
Infection	1	2%
Loss of Skin Sensation	1	2%
Nipple/Areola Size/Position	1	2%
Other Complication*	1	2%
Patient Desire for Size/Style Change	8	16%
Ptosis	1	2%
Scarring	2	4%
Seroma	1	2%
Wrinkling	9	18%
Total	76	152%

*Other complication is "not her breasts"

To reiterate, across all follow-up visits through 3 years for Core Study patients, the most common reasons for patients to be dissatisfied with their breast implants were capsular contracture and aesthetic issues such as asymmetry, malposition and the desire for larger or smaller implants.

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RESPONSE TO DEFICIENCY 6

A. COLLECTION OF RETROSPECTIVE LOCAL COMPLICATION DATA

Retrospective data was collected for 717 patients (396 augmentation, 123 reconstruction, and 198 revision). Of the 717 patients, 100 patients were found to have the local complications that required retrospective data collection identified in their medical records. This retrospective data collection resulted in a total of 150 additional complication reports.

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B. TIME POINTS FOR COLLECTION OF RETROSPECTIVE LOCAL COMPLICATION DATA

As FDA noted it was only necessary to collect retrospective local complication data at the 0-4 week and 6-month time points for the affected patients. Of the 150 complications identified retrospectively, 133 had onset during the 0-4 week time point and 17 had onset during the 6-month time point.

C. METHOD OF RETROSPECTIVE DATA COLLECTION

Per the plan discussed with [REDACTED] during a teleconference on December 6, 1999, Study Coordinators at the investigational sites reviewed the applicable patient charts and documented these local complication data on a "Form 7 Complication/Treatment Log" case report form (CRF), stamped "Retrospective". The Principal Investigator at each site verified this information and signed the CRFs, which were then returned to Inamed for processing. This data was collected from sites that utilized the previous version of the Form 7 that did not include collection of these local complications and did not capture these local complications in the "specify other complication" field of the form.

D. KAPLAN-MEIER RISK RATES FOR LOCAL COMPLICATION DATA (RETROSPECTIVE & PROSPECTIVE)

The risk rates at 3 years for the local complications identified by FDA for retrospective collection under the revised CORE Study protocol, are presented separately for those patients for which data were collected prospectively and retrospectively (Attachment 6-1). For most complications, the confidence intervals derived from the retrospective data overlap the confidence intervals derived from the prospective data, except when there were no reports of the corresponding complication prospectively. This situation occurred with the following complications in the Revision cohort:

- Revision: Bruising
 - Prospective Data: 0% (--,--)
 - Retrospective Data: 2.1% (0.1%, 4.1%)
- Revision: Hypertrophic Scarring
 - Prospective Data: 0% (--,--)
 - Retrospective Data: 3.5% (0.7%, 6.2%)
- Revision: Swelling
 - Prospective Data: 0% (--,--)
 - Retrospective Data: 6.4% (2.9%, 9.9%)

For the three types of events noted above, there were no reports in the patients for which these local complication data were collected prospectively, as compared to those patients whose charts were scrutinized for retrospective data. This indicates that although the CRF did not prompt these complications with their own specific check box, they were not underreported in the retrospective patient group because the information was in the chart and readily retrievable.

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It is also important to note that the prospective patient group could not have suffered from underreporting of these local complications because Inamed Clinical Research Associates routinely monitor all patient charts. This monitoring assures that all complications noted on source documents, such as progress notes, are documented on CRFs.

E. POOLING OF RETROSPECTIVE AND PROSPECTIVE LOCAL COMPLICATION DATA

Data collected from these patients both retrospectively and prospectively can be pooled because the data collected retrospectively is as reliable as the data collected prospectively. The information for the retrospective data collection was 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 both groups, regardless of whether the data were collected prospectively or retrospectively. Furthermore, the risk rates for both groups are comparable as demonstrated in response to 6.d. above. Pooling provides increased confidence that an important effect has not been overlooked or underestimated.

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RESPONSE TO DEFICIENCY 7

GEL BLEED TESTING

In response to this deficiency, new gel bleed testing was initiated. The results of the new gel bleed testing are attached in test report, [REDACTED] "Gel Bleed Testing in a Lipid-Rich System", which is provided as Attachment 7-1.

The testing was performed to provide the following information:

- Identity of the gel bleed constituents (including catalysts derived from platinum species and tin);
- The gel constituents bleed rate; and
- The rate change over time.

To mimic a lipid-rich system Inamed developed new gel bleed bench testing employing 3M Empore Extraction Disks, which are comprised of silica coated with octadecyl carbon groups (C-18). In general, the study design followed the ASTM F703 gel bleed methodology. However, instead of using silicone disks as in the ASTM standard, the 3M disks provided a high surface area, with C-18 as the adsorbent, which is closer in nature to the lipids encountered in the body. Consistent with the ASTM standard, a gel-filled

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breast implant was placed over a disk for a period of time. Subsequently, the implant was removed and the disk evaluated for bleed constituents, which were identified and quantified by gas chromatography-mass spectrometry (GC-MS).

For disks of a comparable size, about 6 times less silicone migrated into the 3M disks relative to the silicone disks used in the ASTM gel bleed analysis. The silicone species identified on the 3M disks matched species identified in silicone disk samples from the ASTM study. The silicone constituents of bleed were identified both as cyclic species from D5 to D21 and linear species from MD6M to MD18M. There were only small differences in concentration of silicone species in bleed found in the 3M disks, when compared to the ASTM silicone disks.

The rate of the bleed determined by employing 3M Empore disks was $0.0003 \text{ gm/cm}^2/\text{wk}$ ($0.000263 \text{ gm/cm}^2/\text{wk}$), which is approximately six times less, compared to the rate using the same style device with silicone disks in previous ASTM gel bleed testing. This testing used Inamed's Style 40 silicone-filled breast implant, which was established from previous testing as the worst case implant model.

The rate of change over time was determined to be minimal after 28 days of exposure and was less than the rate of change determined for the ASTM silicone disk methodology throughout the testing period. As anticipated, the silicone shell to silicone disk interface of the ASTM method enhances silicone bleed, compared to the silicone shell to C-18 coated disk of the 3M disk method, reflecting the preference of silicone to associate with itself even in a hydrophobic, lipid-like environment.

There was no evidence that the catalysts, platinum or tin, are contained in the constituents of silicone gel bleed as detected on the 3M disks.

The biocompatibility evaluations of silicone gel previously presented in P020056, confirm the lack of interaction of gel and, hence, gel bleed constituents with tissue. For instance, exposure of gel to a cell monolayer in cytotoxicity testing is not observed to induce cellular distress. Additionally, exposure of gel to paravertebral muscle in the rabbit for 90 days resulted in histological observations considered by the pathologist to demonstrate the non-toxicity of gel implants in rabbit tissue.

Similarly, in the chronic toxicity and carcinogenicity rat study in which capsule histology around a bolus of silicone gel was performed at 12 and 18 months for the satellite groups (chronic toxicity study element) and at 24 months for the main group (cancer study element), the animal studies identified that the presence of gel is well tolerated by the body.

To further address FDA's concerns regarding the potential association between *in vivo* gel bleed and local complications, Inamed compared Core Study risk rates for a number of complications to the risk rates reported in Inamed's 1995 Saline Studies. Table 1

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provides a comparison of complication rates for augmentation patients, and Table 2 provides a comparison of complication rates for reconstruction patients. These comparisons show that in general, patients are at no higher risk of local complications following implantation of Inamed's silicone-filled breast implants than they are following implantation of Inamed's saline-filled breast implants. This demonstrates that there is no reason to believe that local complications are specifically associated with gel bleed.

For all of the complications examined, there are no instances of significantly higher rates in patients with silicone-filled implants versus patients with saline-filled implants, as demonstrated by non-overlapping confidence intervals for the few complications that had slightly higher rates in the Core Study. On the other hand, numerous complications had significantly higher rates for the patients in the Saline Study. Specifically, Core Study patients had significantly lower rates of irritation/inflammation and breast pain than the Saline Study patients in both cohorts. Capsular contracture showed no significant difference in occurrence rates between the two types of implants.

Table 1
Augmentation: 3-Year Complication Rates, Core Study and Saline Study

Complication*	Silicone Patients (N=494)		Saline Patients (N=901)	
	Rate (%)	(95% CI)	Rate (%)	(95% CI)
Reoperation	21.1	(17.4, 24.7)	21.1	(18.4, 23.8)
Capsular Contracture	9.7	(7.0, 12.3)	8.7	(6.8, 10.6)
Implant Removal/Replacement	7.0	(4.7, 9.3)	7.6	(5.8, 9.4)
Breast Pain	6.9	(4.6, 9.2)	15.6	(13.2, 17.9)
Loss of Nipple Sensation	3.5	(1.9, 5.2)	8.4	(6.5, 10.2)
Asymmetry	3.0	(1.4, 4.5)	10.1	(8.1, 12.1)
Implant Malposition	2.9	(1.4, 4.4)	8.2	(6.3, 10.0)
Nipple Hypersensitivity/Paresthesia	1.2	(0.3, 2.2)	9.3	(7.4, 11.2)
Implant Palpability/Visibility	1.1	(0.1, 2.0)	9.2	(7.2, 11.1)
Implant Rupture/Deflation	2.0	(0.7, 3.3)	5.0	(3.5, 6.4)
Wrinkling	0.9	(0.0, 1.7)	10.5	(8.4, 12.6)
Delayed Wound Healing	0.6	(0.0, 1.3)	0.7	(0.1, 1.2)
Skin Hypersensitivity/Paresthesia	0.4	(0.0, 1.0)	7.2	(5.5, 9.0)
Implant Extrusion	0.4	(0.0, 1.0)	0.1	(0.0, 0.4)
Irritation/Inflammation	0	-	2.9	(1.8, 4.0)
Capsule Calcification	0	-	1.2	(0.4, 1.9)

*All complications other than reoperation and implant replacement/removal were assessed with severity ratings. Most rates shown in the table include only complications rated moderate, severe or very severe (excludes mild and very mild ratings). The only complication rates that include all severity ratings are rupture and implant extrusion.

002227

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Table 2
Reconstruction: 3-Year Complication Rates, Core Study and Saline Study

Complication*	Silicone Patients (N=221)		Saline Patients (N=237)	
	Rate (%)	(95% CI)	Rate (%)	(95% CI)
Reoperation	47.2	(40.5, 53.9)	38.7	(32.3, 45.0)
Implant Removal/Replacement	21.6	(16.0, 27.1)	22.5	(17.1, 28.0)
Capsular Contracture	15.1	(10.1, 20.0)	25.3	(19.5, 31.2)
Asymmetry	13.4	(8.7, 18.0)	33.0	(26.6, 39.4)
Implant Malposition	7.5	(4.0, 11.0)	12.2	(7.8, 16.6)
Implant Rupture/Deflation	10.6	(6.2, 15.0)	6.2	(2.9, 9.5)
Breast Pain	5.9	(2.6, 9.1)	15.3	(10.3, 20.2)
Wrinkling	3.4	(0.9, 5.9)	23.3	(17.5, 29.1)
Delayed Wound Healing	1.8	(0.1, 3.6)	2.7	(0.6, 4.9)
Implant Extrusion	1.0	(0.0, 2.3)	2.6	(0.6, 4.7)
Nipple Hypersensitivity/Paresthesia	0.5	(0.0, 1.3)	0.4	(0.0, 1.3)
Implant Palpability/Visibility	0.5	(0.0, 1.3)	20.0	(14.5, 25.5)
Loss of Nipple Sensation	0	-	12.0	(7.4, 16.6)
Irritation/Inflammation	0	-	6.6	(3.3, 9.8)
Skin Hypersensitivity/Paresthesia	0	-	5.6	(2.5, 8.6)
Capsule Calcification	0	-	4.7	(1.9, 7.6)

*All complications other than reoperation and implant replacement/removal were assessed with severity ratings. Most rates shown in the table include only complications rated moderate, severe or very severe (excludes mild and very mild ratings). The only complication rates that include all severity ratings are rupture and implant extrusion.

CONCLUSION

The new gel bleed bench test that Inamed developed to identify and quantify gel bleed constituents in a lipid type environment indicates that the same silicone species are detected as when the ASTM F703 method is used with silicone disks. As previously discussed, the silicone shell to silicone disk interface of the ASTM method enhances silicone bleed, compared to the silicone shell to C-18 coated disk of the 3M disk method, reflecting the preference of silicone to associate with itself even in a hydrophobic, lipid-like environment. Clinically, the local complications associated with patients with silicone gel-filled breast implants are also observed in patients with saline-filled breast implants. As seen from the animal and clinical data, exposure to gel (and, therefore, gel bleed) does not lead to or increase the risk of local complications. Although a degree of gel bleed does exist, both preclinical and clinical findings demonstrate that gel and the subsequent presence of gel bleed are well tolerated by the body and there are no potential clinical local complications that may be associated specifically with gel bleed.

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GEL BLEED TESTING IN A LIPID-RICH SYSTEM

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EXECUTIVE SUMMARY

A new test for gel bleed was developed that uses high surface area, supported C18 as the adsorbent (3M Empore Extraction Disk). This material is closer in nature to the lipids encountered in the body than is the silicone disk used in the previous ASTM F703 bleed test. For silicone disks of a comparable size, about 6 times less silicone material migrated into the 3M disks.

The silicone bleed constituents were identified and quantified by GC-MS both as cyclic species from D5 to D21 and linear species from MD6M to MD18M. These species were found to match the silicone bleed species identified in the ASTM silicone disks samples. Only small differences in the concentrations were observed in the species of silicones in bleed found in the 3M disks, when compared to the ASTM silicone disks. There were larger differences in the relative magnitude of the silicones found in the two materials. The high surface area 3M disks used as controls were extremely efficient at capturing volatized, low molecular weight silicones from the local environment. Thus, the magnitude of bleed of these materials could not be determined: a larger quantity of low molecular silicones ($< D_8$) were found in the controls than in the experimental disks. Medium molecular weight silicones partitioned slightly more effectively into the C18 disks than into the ASTM silicone disks ($D_8 \rightarrow D_{12}$). By contrast, slightly higher molecular weight species ($> D_{12}$) were found in the silicone disks of the ASTM method.

This test provides a complementary method to the ASTM F703 tests. Less silicone was observed to bleed from the implants in this test employing lipid-like materials. The calculated rate of bleed was $0.0003 \text{ gm/cm}^2/\text{wk}$ approximately six times less than that using silicone disk.

The rate of change over time was determined to be minimal after 28 days of exposure and was less than the rate of change determined for the ASTM silicone disk methodology throughout the testing period.

There was no evidence that the catalysts, platinum or tin, are contained in the constituents of silicone gel bleed as detected on the 3M disks.

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RESPONSE TO DEFICIENCY 9

A. SCREENING FOR SILENT RUPTURE

Specific labeling instructions to physicians and patients, regarding recommendations for the method(s) and frequency of screening for rupture, have been added to the draft product insert (DFU) provided in Attachment 9-1 and the draft patient brochures provided in Attachments 9-2, 9-3 and 9-4.

The text of this addition in the draft DFU is:

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, Holmich 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.

The text of the addition noted below is located in the "Rupture" section of the draft documents ***Making an Informed Decision; Silicone Filled Breast Implant Surgery***:

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.

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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.

B. CLINICAL MANAGEMENT OF RUPTURE

Specific labeling instructions to physicians and patients, regarding the clinical management of suspicious and confirmed rupture, along with the information from which the instructions are based, were added to the draft product insert (DFU) provided in Attachment 9-1 and the draft patient brochures provided in Attachments 9-2, 9-3 and 9-4.

The text of this addition in the draft DFU is:

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. Holmich 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.

The text of the addition noted below is located in the "Rupture" section of the draft documents *Making an Informed Decision; Silicone Filled Breast Implant Surgery*:

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

002547

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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.

C. OFFSPRING

Specific labeling to physicians and patients, regarding the potential health consequences to offspring from women implanted with our device (i.e., second generation effects), was previously provided in labeling approved by the Agency for the Core and Adjunct Studies. This has been revised in the draft product insert (DFU) provided in Attachment 9-1 and the draft patient brochures provided in Attachments 9-2, 9-3 and 9-4.

The text of this addition in the draft DFU is:

Second-Generation Effects

The concern that children born to mothers with silicone breast implants are at risk of developing adverse health outcomes stems from reports of children born to or breastfed by such women who developed swallowing difficulties, irritability, nonspecific skin rashes, fatigue, and other symptoms (Levine and Ilowite 1994, Levine et al. 1196). However, epidemiological investigations have not found any increased risk of adverse health outcomes, including occurrence of esophageal disorders, connective tissue disease, and congenital malformations in children

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born to women with breast implants (Kjoller et al. 1998, Kjoller et al. 2002, Signorello et al. 2001).

The text of this addition in the draft documents *Making an Informed Decision; Silicone Filled Breast Implant Surgery* is:

Effects on Children of Women with Breast Implants

The concern that children born to mothers with silicone breast implants are at risk of developing health problems stems from reports of children born to or breastfed by such women who developed swallowing difficulties, irritability, nonspecific skin rashes, fatigue, and other symptoms. However, epidemiological investigations have not found any increased risk of adverse health outcomes, including occurrence of esophageal disorders, connective tissue disease, and congenital malformations in children born to women with breast implants.

D. BREAST FEEDING

Specific labeling to physicians and patients, regarding the potential health consequences to offspring nursed by women implanted with our device, was previously provided in labeling approved by the Agency for the Core and Adjunct Studies. This has been revised in the draft product insert (DFU) provided in Attachment 9-1 and the draft patient brochures provided in Attachments 9-2, 9-3 and 9-4.

The text of this addition in the draft DFU is:

Effects on Breast Milk

At this time it is not known if a small amount of silicone may diffuse from the silicone-filled breast implant and find its way into breast milk. If this occurs, it is not known what effect it may have on the nursing infant. There have been some studies that reported evidence of esophageal dysmobility and gastrointestinal effects in breastfed children of women with implants, but there is insufficient evidence that this is a result of exposure to silicone. There is evidence that silicon concentrations in breast milk are the same in mothers with and without breast implants (Lugowski et al. 1998). The American Academy of Pediatrics prepared a statement on the transfer of drugs and other chemicals into human milk in September 2001, which concluded "The Committee on Drugs does not feel that the evidence currently justifies classifying silicone implants as a contraindication to breastfeeding."

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The text of this addition in the draft documents *Making an Informed Decision; Silicone Filled Breast Implant Surgery* is:

BREAST IMPLANTS MAY AFFECT YOUR ABILITY TO BREAST FEED.

Breast implant surgery may affect your ability to breast feed because the surgery may sever nerves that stimulate the body to release the hormones that trigger milk release. In addition, an incision around the nipple, which may be done to make the surgical scar less noticeable, also may sever ducts that drain milk from the mammary gland, such that even if the mother has an adequate milk supply, it may be difficult for the milk to drain into the nipple. Also, breast implants will not prevent a woman's breasts from sagging after pregnancy.

At this time it is not known if a small amount of silicone may diffuse (pass through) from the silicone-filled breast implant and find its way into breast milk. If this occurs, it is not known what effect it may have on the nursing infant. Although there are no current methods for detecting silicone levels in breast milk, a study measuring silicon (one component in silicone) levels did not indicate higher levels in breast milk from women with silicone-filled breast implants when compared to women without implants.

E. GEL RUPTURE

Specific labeling instructions to physicians and patients, regarding the potential systemic health consequences of extracapsular and migrated gel rupture, were added to the draft product insert (DFU) provided in Attachment 9-1 and the draft patient brochures provided in Attachments 9-2, 9-3 and 9-4.

The text of this addition in the draft DFU is:

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 (Holmich et al. 2001, Berg et al. 2002, Herborn et al. 2002, Holmich 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

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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. Holmich 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.

The text of the addition noted below is located in the "Rupture" section of the draft documents *Making an Informed Decision; Silicone Filled Breast Implant Surgery*, and is embedded in the third paragraph added in response to Deficiency 9b:

Rupture

...There is no evidence that silicone gel that moves beyond the breast capsule causes any symptoms or disease elsewhere in the body. (Note: Additional language was added to the draft patient labeling regarding CTD signs and symptoms as described below.)

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.

F. CTD SIGNS AND SYMPTOMS

Specific labeling to physicians and patients, regarding the CTD signs and symptoms data from our response to Deficiency 4, has been added to the draft product insert (DFU) provided in Attachment 9-1 and to the draft patient brochures provided in Attachments 9-2, 9-3 and 9-4.

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The text of this addition in the draft DFU is:

Systemic (CTD) Diseases

Concern over the association of breast implants to the development of autoimmune or connective tissue diseases, such as lupus, scleroderma, or rheumatoid arthritis, was raised because of cases reported in the literature with small numbers of women with implants. Several large epidemiological studies of women with and without implants indicate that these diseases are no more common in women with implants than in those women without implants.

Some patients in INAMED's Core Clinical Study showed an increase over time in some CTD signs and symptoms and those CTD signs and symptoms specific to fibromyalgia, such as fatigue, swelling, weakness, aches, back and neck pain. However, patients with INAMED's saline-filled implants showed similar increases in these signs and symptoms. This indicates that the increased signs and symptoms are most likely not caused by the silicone-filled breast implants and may be attributed to other factors such as aging.

The text of this addition in the draft documents *Making an Informed Decision; Silicone Filled Breast Implant Surgery* is:

Connective Tissue Disease

Concern over the association of breast implants to the development of autoimmune or connective tissue diseases, such as lupus, scleroderma, or rheumatoid arthritis, was raised because of cases reported in the literature with small numbers of women with implants. Several large epidemiological studies of women with and without implants indicate that these diseases are no more common in women with implants than in those women without implants

Some patients in INAMED's Core Clinical Study showed an increase over time in some CTD signs and symptoms and those CTD signs and symptoms specific to fibromyalgia, such as fatigue, swelling, weakness, aches, back and neck pain. However, patients with INAMED's saline-filled implants showed similar increases in these signs and symptoms. This indicates that the increased signs and symptoms are most likely not caused by the silicone-filled breast implants and may be attributed to other factors such as aging.

G. GEL BLEED

Specific labeling to physicians and patients, regarding the potential clinical local complications (e.g., chronic inflammation, chronic pain, capsular contracture) that may be associated with gel bleed and the results of the gel bleed testing, has been added to the draft product insert (DFU) provided in Attachment 9-1 and the draft patient brochures provided in Attachments 9-2, 9-3 and 9-4.

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The text of this addition in the draft DFU is:

Local complications potentially associated with gel diffusion (bleed)

There is no evidence from the medical literature or from Inamed's own testing suggesting that gel bleed (diffusion) may be associated with local complications in breast implant patients. In addition, clinical study patients in Inamed's Core clinical study for silicone-filled breast implants were at no higher risk of local complications when compared to the risk of local complications reported in Inamed's 1995 saline-filled breast implant clinical study. INAMED conducted *in-vitro* testing in order to mimic a lipid-rich *in-vivo* environment to determine bleed rate over time, and to identify the constituents of gel diffusion (bleed). There was no evidence that the catalysts, platinum or tin, are contained in the constituents of silicone gel bleed under the conditions of the test method.

The text of this addition in the draft documents *Making an Informed Decision; Silicone Filled Breast Implant Surgery* is:

Gel Bleed

There is no evidence from the medical literature or from Inamed's own testing suggesting that gel bleed (gel components passing through the shell) may be associated with local complications in breast implant patients. In addition, clinical study patients in Inamed's Core clinical study for silicone-filled breast implants were at no higher risk of local complications when compared to the risk of local complications reported in Inamed's 1995 saline-filled breast implant clinical study.

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

002553

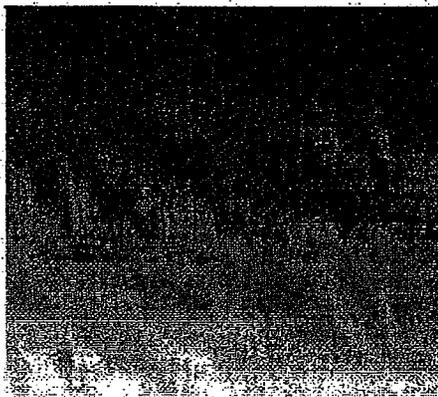
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Directions for Use

BIOCELL[®]
Textured
and
Smooth

SILICONE-FILLED
BREAST IMPLANTS



INAMED
AESTHETICS

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician

Table of Contents

SECTION	PAGE
Introduction	
Directions to the Surgeon	
Information to be Discussed with the Patient	
Device Description	
Indications	
Contraindications	
Warnings	
Precautions	
Special Considerations to be Discussed with the Patient	
Preclinical Study Information	
Clinical Studies	
Study Design	
Safety Outcomes	
Potential Adverse Events	
Effectiveness Outcomes	
Instructions for Use	
Single Use	
Product Identification	
Surgical Planning	
Preliminary Product Examination	
Sterile Product	
Surgical Procedure	
Documentation the Physician Should Provide to the Patient	
Specific Product Information	
BIOCELL [®] Delivery Assistance Sleeve	
Returned Goods Policy	
Reporting and Return of Explanted Devices	
ConfidencePlus [™] Breast Implant Replacement Program	
Product Ordering	

INTRODUCTION

• **DIRECTIONS TO THE SURGEON**

This document contains information that is essential to the patient consultation process. Please familiarize yourself with the content of this document and resolve any questions or concerns prior to proceeding with use of the device.

The information supplied in this Direction for Use document is intended to provide an overview of the appropriate use of INAMED silicone-filled breast implants, contraindications for use, warnings, including surgical techniques that should be avoided as it may compromise implant integrity, precautions, adverse and potential adverse events, as well as a clinical study summary.

Patient Counseling Information

Sections of this *Directions for Use* document indicated by "***Patient Counseling Information***" contain points that the physician should review when counseling the patient about silicone-filled breast implants and breast implant surgery.

• **INFORMATION TO BE DISCUSSED WITH THE PATIENT**

WARNINGS, PRECAUTIONS, ADVERSE EVENTS

Patient Counseling Information

Breast implant surgery is known to provide satisfaction to patients, *HOWEVER*, as with any surgical procedure, it is *NOT* without risks. Breast implantation is an elective procedure, and the patient must be well counseled on the risk/benefit relationship.

Before the decision to proceed with surgery, the surgeon or a designated patient counselor should inform the patient of the warnings, precautions, and adverse reactions listed in this *Directions for Use* document. The physician should advise the patient that medical management of serious adverse reactions may include explantation.

INFORMED CONSENT

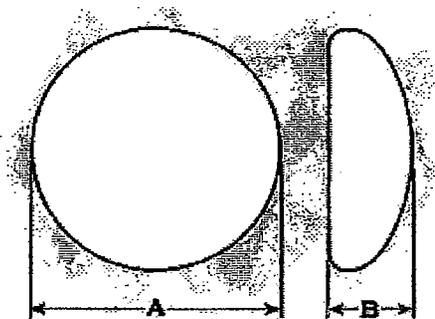
Patient Counseling Information

Each patient should read, understand, sign, and date the document ***Making an Informed Decision; Silicone Filled Breast Implant Surgery*** supplied by INAMED Corporation, which contains important information on the benefits and possible risks associated with silicone-filled breast implant surgery.

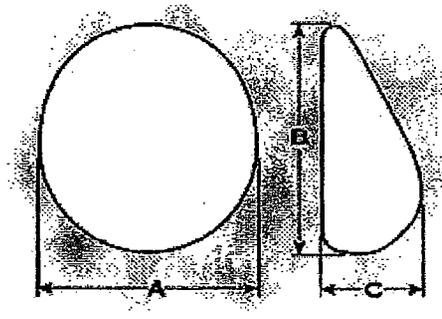
DEVICE DESCRIPTION

INAMED Aesthetics Silicone-Filled Breast Implants are constructed with barrier shell technology resulting in a low diffusion silicone elastomer shell and are filled with a soft, cohesive silicone gel. INAMED Aesthetics Silicone-Filled Breast Implants are available in both smooth and BIOCELL[®] surface textures in round and shaped designs.

Refer to the INAMED Aesthetics product catalog for a complete list of implant options and sizes.



A = Width; B = Projection
Round Breast Implant



A = Width; B = Height; C = Projection
Shaped Breast Implant

INDICATIONS

- **Breast Augmentation.**
A woman must be at least 18 years old for breast augmentation.
- **Breast Reconstruction**
- **Breast Revision**

CONTRAINDICATIONS

Patient Groups in which the product is contraindicated:

- **Women with existing malignant or pre-malignant cancer of the breast without adequate treatment**
- **Women with an active infection anywhere in the body**
- **Women who are currently pregnant or nursing**
- **Augmentation in women under the age of 18 years**

Surgical Practices in which product use is contraindicated due to compromise of product integrity:

- **Alteration:** Do not alter the implant.
- **Stacking of implants:** Do not place more than one implant per breast.
- **Reuse:** See "Instructions for Use" section.

WARNINGS

AVOID DAMAGE DURING SURGERY

- ***Care should be taken to avoid the use of excessive force and to minimize handling of the implant during surgical insertion.***

Based on analyses of explanted ruptured silicone-filled breast implants, observations of surgeries, and a review of the published literature, INAMED believes that the forcing of implants through small incisions may result in localized weakening of the breast implant shell potentially leading to shell damage and possible implant rupture.

- ***Care should be taken when using surgical instruments in proximity with the breast implant, including scalpel, sutures, and dissection instrumentation.***

Silicone-filled breast implants are prone to unintended instrument trauma during implantation or during explantation (Brandon et al. 2001, Young and Watson 2001). Failure can result from damage by scalpels, suture needles, hypodermic needles, hemostats, and Adson forceps and has been observed in explanted device shells using scanning electron microscopy (Brandon et al. 2001).

- ***Use care in subsequent procedures such as open capsulotomy, breast pocket revision, hematoma/seroma aspiration, and biopsy/lumpectomy to avoid damage to the implant.***

Re-positioning of the implant during subsequent procedures should be carefully evaluated by the medical team and care taken to avoid contamination of the implant before placement back in the pocket. Use of excessive force during removal and replacement can contribute to localized weakening of the breast implant shell potentially leading to decreased device performance.

- ***Do not contact the implant with disposable, capacitor-type cautery devices.***
- ***Do not insert or attempt to repair a damaged prosthesis.***

CLOSED CAPSULOTOMY

DO NOT treat capsular contracture by forceful external compression, which will likely result in implant damage, rupture, folds, and/or hematoma.

SINGLE USE DEVICES

Breast implants are single use devices only. Do not resterilize or reuse.

MICROWAVE DIATHERMY

The use of microwave diathermy in patients with breast implants is not recommended, as it has been reported to cause tissue necrosis, skin erosion, and extrusion of the implant

PRECAUTIONS

SPECIFIC POPULATIONS

Safety and Effectiveness have not been established in patients with:

- Conditions or medications that interfere with wound healing ability (such as poorly controlled diabetes) or blood clotting (such as concurrent Coumadin® therapy)
- Reduced blood supply to breast tissue
- Autoimmune diseases such as lupus and scleroderma
- A compromised immune system (e.g., currently receiving immunosuppressive therapy)

MAMMOGRAPHY

Patient Counseling Information

Breast implants may complicate the interpretation of mammographic images by obscuring underlying breast tissue and/or by compressing overlying tissue. The ability of mammography to detect cancer or implant rupture in patients with breast implants has been evaluated in numerous studies. Standard compression mammography is insufficient by itself to detect many palpable tumors (Carlson et al. 1993), but the detection rate improves when combined with displacement techniques (Eklund et al. 1988). Accredited mammography centers and use of displacement techniques are needed to adequately visualize breast tissue in the implanted breast. Radiologists should be experienced with the most current radiological techniques and equipment for imaging breasts with implants.

Presurgical mammography with a follow-up mammogram 6 months to 1 year following surgery may be performed to establish a baseline for future routine mammography.

RADIATION TO THE BREAST

INAMED has not tested the *in vivo* effects of radiation therapy in patients who have breast implants. The literature suggests that radiation therapy may increase the likelihood of capsular contracture, necrosis, and extrusion.

LONG-TERM EFFECTS

Patient Counseling Information

Although clinical study follow-up data has been collected through 4 years, the long-term safety and effectiveness of INAMED's Silicone-Filled Breast Implants has not been established. INAMED is monitoring the long-term (i.e., 10-year) risk of implant rupture, reoperation, implant removal, breast disease and other local and systemic complications.

SPECIAL CONSIDERATIONS TO BE DISCUSSED WITH THE PATIENT

Patient Counseling Information

The following information should be discussed with patients prior to their decision to proceed with surgery:

- ***Professional Care*** – Patients should be advised that follow-up exams as prescribed by their plastic surgeon are recommended to monitor the status of their breast implants.
- ***Reoperation*** – Patients should be advised that additional surgery to their breast and/or implant may be necessary over the course of their life.
- ***Explantation*** – Patients should be advised that implants are not considered life-time devices, and they will potentially undergo implant removal, with or without replacement, over the course of their life. Patients should also be advised that the changes to their breast following explantation are irreversible.
- ***Mammography*** - Patients should be instructed to inform their mammographers about the presence, type, and placement of their implants. Patients should be advised to request diagnostic mammography rather than screening mammography.
- ***Lactation*** – Patients should be advised that breast implants may interfere with the ability to successfully breast feed.
- ***Infection*** – In rare instances, acute infection may occur in a breast with implants. The signs of acute infection include erythema, tenderness, fluid accumulation, pain and fever. Very rarely, Toxic Shock Syndrome, a potentially life-threatening condition, has been reported in women after breast implant surgery. It is characterized by symptoms that occur suddenly and include high fever (102°F, 38.8°C or higher), vomiting, diarrhea, a sunburn-like rash, red eyes, dizziness, lightheadedness, muscle aches, and drops in blood pressure, which may cause fainting. Patients should be advised to contact a physician immediately for diagnosis and treatment for any of these symptoms.
- ***Avoiding Damage during Treatment*** – Patients should be instructed to inform other treating physicians of the presence of implants to minimize the risk of damage to the implants.
- ***Smoking*** – Patients should be informed that smoking may interfere with the healing process.

- ***Cosmetic Dissatisfaction*** – Patients should be informed that dissatisfaction with cosmetic results related to such things as scar deformity, hypertrophic scarring, capsular contracture, asymmetry, displacement, incorrect size, unanticipated contour, and palpability may occur. Careful surgical planning and technique can minimize, but not preclude, the risk of such results. Pre-existing asymmetry may not be entirely correctable. Physiological and behavioral differences among patients and variations in surgical techniques and medical treatments account for a wide variety of responses to silicone-filled breast implant surgery. Revision surgery may be indicated to maintain patient satisfaction but carries additional considerations and risks.
- ***Breast Examination Techniques*** – Patients should be instructed to follow the most current medical recommendations regarding breast examination and mammography frequency appropriate for their age and medical history. To maximize the effectiveness of breast self examinations for any palpable lesions, patients should be instructed how to distinguish the implant from breast tissue.
- ***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, Holmich 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.
- ***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. Holmich 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.

COMPLICATIONS

Patient Counseling Information

The following is a list of potential adverse events that may occur with breast implant surgery. Some of these adverse events are reported in Tables 1 and 6 below. The risks include: implant rupture, additional surgery, capsular contracture, infection, Toxic Shock Syndrome (TSS), necrosis, hematoma, seroma, extrusion, breast pain, changes in nipple sensation, changes in breast sensation, dissatisfaction with cosmetic results (wrinkling, folding, displacement, asymmetry, palpability, visibility, ptosis), calcific deposits, irritation/inflammation, delayed wound healing, hypertrophic scarring, breast tissue atrophy/chest wall deformity, difficulty/inability in breast feeding, and inability to adequately visualize breast lesions with mammography.

In addition to these potential adverse events, there has been discussion in the scientific and regulatory communities regarding the potential for silicone-filled breast implants to be associated with certain systemic diseases or concerns.

- **Systemic (CTD) Diseases**

Concern over the association of breast implants to the development of autoimmune or connective tissue diseases, such as lupus, scleroderma, or rheumatoid arthritis, was raised because of cases reported in the literature with small numbers of women with implants. Several large epidemiological studies of women with and without implants indicate that these diseases are no more common in women with implants than in those women without implants.

Some patients in INAMED's Core Clinical Study showed an increase over time in some CTD signs and symptoms and those CTD signs and symptoms specific to fibromyalgia, such as fatigue, swelling, weakness, aches, back and neck pain. However, patients with INAMED's saline-filled implants showed similar increases in these signs and symptoms. This indicates that the increased signs and symptoms are most likely not caused by the silicone-filled breast implants and may be attributed to other factors such as aging.

- **Suicide**

Some investigators have raised concerns that the risk of suicide is increased in patients with silicone-filled breast implants (Brinton et al. 2001, Koot et al. 2003, Pukkala et al. 2003, Jacobsen et al. 2003). The studies are not designed to account for very significant potential confounding factors that are likely to affect a woman's predisposition for suicidal tendencies and that are widely acknowledged to be more prevalent among women who seek breast implants (e.g., cigarette smoking, alcohol consumption, weight, parity, low self-esteem, depression, or other psychiatric/emotional disorders) (McLaughlin et al. 2003, McLaughlin et al. 2004).

- **Cancer**

Published clinical studies indicate that breast cancer is no more common in women with implants than those without implants (Institute of Medicine 2000, McLaughlin et al. 1994, Friis et al. 1997, Møller et al. 2000). Furthermore, basic animal toxicological studies as discussed in INAMED's Summary of Safety & Effectiveness Data (SSED) document (www.tdb.gov) do not find pathology that would support a causation of human carcinogenicity by silicone breast implants.

- **Effects on Breast Milk**

At this time it is not known if a small amount of silicone may diffuse from the silicone-filled breast implant and find its way into breast milk. If this occurs, it is not known what effect it may have on the nursing infant. There have been some studies that reported evidence of esophageal dysmobility and gastrointestinal effects in breastfed children of women with implants, but there is insufficient evidence that this is a result of exposure to silicone. There is evidence that silicon concentrations in breast milk are the same in mothers with and without breast implants (Lugowski et al. 1998). The American Academy of Pediatrics prepared a statement on the transfer of drugs and other chemicals into human milk in September 2001, which concluded "The Committee on Drugs does not feel that the evidence currently justifies classifying silicone implants as a contraindication to breastfeeding."

- **Second-Generation Effects**

The concern that children born to mothers with silicone breast implants are at risk of developing adverse health outcomes stems from reports of children born to or breastfed by such women who developed swallowing difficulties, irritability, nonspecific skin rashes, fatigue, and other symptoms (Levine and Ilowitz 1994, Levine et al. 1996). However, epidemiological investigations have not found any increased risk of adverse health outcomes, including occurrence of esophageal disorders, connective tissue disease, and congenital malformations in children born to women with breast implants (Kjoller et al. 1998, Kjoller et al. 2002, Signorello et al. 2001).

- **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 (Holmich et al. 2001, Berg et al. 2002, Herborn et al. 2002, Holmich 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. Holmich 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 risk of systemic disease in breast implant patients.

- **Local complications potentially associated with gel diffusion (bleed)**

There is no evidence from the medical literature or from Inamed's own testing suggesting that gel bleed (diffusion) may be associated with local complications in breast implant patients. In addition, clinical study patients in Inamed's Core clinical study for silicone-filled breast implants were at no higher risk of local complications when compared to the risk of local complications reported in Inamed's 1995 saline-filled breast implant clinical study. INAMED conducted *in-vitro* testing in order to mimic a lipid-rich *in-vivo* environment to determine bleed rate over time, and to identify the constituents of gel diffusion (bleed). There was no evidence that the catalysts, platinum or tin, are contained in the constituents of silicone gel bleed under the conditions of the test method.

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PRECLINICAL STUDY INFORMATION

Preclinical study of INAMED's Silicone-Filled Breast implants revealed that the materials of which the device is made are biocompatible, the silicone elastomer shell is durable, and there is a low potential for filler bleed. A summary of preclinical studies conducted including chemistry, toxicology, and physical/mechanical testing can be found in the SSED document on the FDA website at www.tdb.gov.

CLINICAL STUDIES

CORE CLINICAL STUDY

Study Design

The safety and effectiveness of INAMED Silicone-Filled Breast Implants were evaluated in three open-label, multicenter clinical studies: the 1990 Augmentation/Reconstruction Study (AR90), the Core Study and the Adjunct Study. Because the 1990 Study utilized devices and surgical practices that are no longer current, these data are not reported below.

The Core Study was designed as a 10-year study to assess safety and effectiveness. Patients studied were those seeking implant surgery for breast augmentation, breast reconstruction, or revision of an existing breast implant. Follow-up was at 0-4 weeks, 6 months, and annually through 10 years, and is currently ongoing. Safety assessments consisted of adverse event rates and rates of secondary surgical treatment. Effectiveness assessments consist of patient satisfaction, breast size change, and measures of body esteem/self esteem/body image.

Patient Accounting and Baseline Demographic Profile

The Core Study enrolled 494 augmentation patients, 221 reconstruction patients, and 225 revision patients. Of those patients expected to be seen, 86% of the augmentation patients, 94% of the reconstruction patients, and 87% of the revision patients were seen for their 3-year follow-up visit. *[Note that 3-year data are the most current data available.]*

Demographic information obtained from the Core Study revealed that over 80% of patients were Caucasian and most study participants were married (49% of augmentation patients, 75% of reconstruction patients, and 64% of revision patients). Approximately half were employed in professional occupations and more than three fourths had at least some college education. The median patient age was 34 years for augmentation patients, 50 years for reconstruction patients, and 44 years for revision patients. *[Note that 3-year data are the most current data available.]*

With respect to surgical baseline factors in the Core Study, for augmentation patients, the most frequently used devices were round, with a smooth surface somewhat more common than textured. The most common incision sites were inframammary and periareolar, and the most frequent placement of the implant was submuscular. For reconstruction patients, the most frequently used devices were shaped with a textured surface, the most common incision site was the mastectomy scar, and the most frequent placement of the implant was submuscular. For revision patients, the most frequently used devices were round, and the textured surface (round and shaped) was more common than smooth. The most common incision site was inframammary, and the most frequent placement of the implant was submuscular.

SAFETY OUTCOMES

Adverse Events

The cumulative Kaplan-Meier risk of first occurrence of adverse events (and 95% confidence interval) reported in greater than 1% of patients is shown in **Table 1** based on indication.

Table 1
3-Year Cumulative First Occurrence Kaplan-Meier Adverse Event Risk Rates (95% Confidence Interval), By Patient

Complication	Augmentation N = 494		Reconstruction N = 221		Revision N = 225	
	Rate (%)	(95% CI)	Rate (%)	(95% CI)	Rate (%)	(95% CI)
Reoperation*	21.1	(17.4, 24.7)	47.2	(40.5, 53.9)	35.1	(28.7, 41.6)
Capsular Contracture	9.7	(7.0, 12.3)	15.1	(10.1, 20.0)	14.1	(9.4, 18.9)
Implant Replacement/Removal*	7.0	(4.7, 9.3)	21.6	(16.0, 27.1)	12.9	(8.3, 17.4)
Breast Pain	6.9	(4.6, 9.2)	5.9	(2.6, 9.1)	6.6	(3.2, 9.9)
Swelling	6.7	(4.5, 9.0)	4.6	(1.8, 7.3)	5.5	(2.5, 8.6)
Loss of Nipple Sensation	3.5	(1.9, 5.2)	0	—	0	—
Asymmetry	3.0	(1.4, 4.5)	13.4	(8.7, 18.0)	4.5	(1.6, 7.4)
Implant Malposition	2.9	(1.4, 4.4)	7.5	(4.0, 11.0)	4.8	(1.9, 7.7)
Hypertrophic/Abnormal Scarring	2.7	(1.3, 4.2)	3.9	(1.2, 6.5)	4.5	(1.6, 7.3)
Ptosis	1.9	(0.7, 3.1)	<1	<1	<1	<1
Seroma/Fluid Accumulation	1.2	(0.3, 2.2)	1.8	(0.1, 3.6)	5.2	(2.2, 8.2)
Skin Rash	1.2	(0.3, 2.2)	1.4	(0.0, 2.9)	1.0	(0.0, 2.3)
Hematoma	1.2	(0.3, 2.2)	<1	<1	1.4	(0.0, 2.9)
Nipple Hypersensitivity/Paresthesia	1.2	(0.3, 2.2)	<1	<1	0	—
Implant Palpability/Visibility	1.1	(0.1, 2.0)	<1	<1	2.9	(0.6, 5.1)
Loss of Skin Sensation	1.1	(0.1, 2.0)	0	—	<1	<1
Implant Rupture	2.0	(0.4, 1.7)	11.0	(4.1, 9.8)	5.0	(1.0, 4.3)
Bruising	<1	<1	1.4	(0.0, 2.9)	1.8	(0.1, 3.5)
Tissue or Skin Necrosis	<1	<1	3.8	(1.2, 6.3)	1.4	(0.0, 3.0)
Wrinkling/Rippling	<1	<1	3.4	(0.9, 5.9)	5.4	(2.3, 8.6)
Redness	<1	<1	2.0	(0.1, 3.8)	<1	<1
Delayed Wound Healing	<1	<1	1.8	(0.1, 3.6)	<1	<1
Infection	<1	<1	1.9	(0.1, 3.7)	1.8	(0.1, 3.6)

* All complications other than reoperation and implant replacement/removal were assessed with severity ratings. Most rates shown in the table include only complications rated moderate, severe or very severe (excludes mild and very mild ratings). The only complication rates that include all severity ratings are rupture, pneumothorax and implant extrusion.

Reoperation

Of the 494 augmentation patients in the Core Study, at least one additional operation after the initial implantation (reoperation) was performed on 101 patients (20.4%) through 3 years. A total of 123 reoperations were performed on augmentation patients over 3 years.

Of the 221 reconstruction patients in the Core Study, at least one reoperation was performed on 102 patients (46.2%) through 3 years. A total of 144 reoperations were performed on reconstruction patients over 3 years, excluding planned procedures such as nipple reconstruction and nipple tattoo.

Of the 225 revision patients in the Core Study, at least one reoperation was performed on 75 patients (33.3%) through 3 years. A total of 115 reoperations were performed on revision patients over 3 years.

Table 2 shows the types of reoperations performed through 3 years in the Core Study based on the total number of reoperations.

Table 2
Types of Reoperations through 3 Years

Type of Reoperation	Augmentation N = 123 Reoperations		Reconstruction N = 144 Reoperations		Revision N = 115 Reoperations	
	n	percent	n	percent	n	percent
Implant Replacement/Removal ²	33	27	47	34	29	25
Capsule Procedure ³	29	24	21	15	24	21
Scar Revision	14	11	25	17	13	11
Mastopexy	14	11	3	2	9	8
Biopsy	11	9	5	4	5	4
Aspiration of Hematoma/Seroma	9	7	9	6	10	9
Reposition Implant	4	3	6	4	2	2
Wound Repair	3	2	9	6	4	4
Pocket Revision	3	2	4	3	6	5
Revision of Nipple Reconstruction/Tattoo	1	1	6	4	8	7
Removal of Excess Tissue/Lesion/Cyst	1	1	2	1	2	2
Surgical Exploration of Breast Area/Implant	1	1	1	1	1	1
Liposuction	0	0	5	4	1	1
Breast Reduction	0	0	1	1	1	1
Total	123	100	144	100	115	100

¹Primary procedure performed

²Some removals were replaced with an INAMED implant, while others were replaced with a non-INAMED implant

³Capsule Procedure includes capsulectomy, capsulotomy, and capsulorrhaphy

Implant Removal

Of the 494 augmentation patients in the Core Study, there were 33 patients (6.7%) who had 62 implants removed through 3 years. Of the 62 augmentation implants removed through 3 years, 82% were replaced.

Of the 221 reconstruction patients in the Core Study, there were 46 patients (20.8%) who had 56 implants removed through 3 years. Of the 56 reconstruction implants removed through 3 years, 91% were replaced.

Of the 225 revision patients in the Core Study, there were 27 patients (12.0%) who had 46 implants removed through 3 years. Of the 46 revision implants removed through 3 years, 89% were replaced.

The primary reason for implant removal is shown in Table 3 below based on the number of implants removed.

Table 3
Reasons for Implant Removal Through 3 Years

Primary Reason for Implant Removal	Augmentation N = 62 Implants		Reconstruction N = 56 Implants		Revision N = 46 Implants	
	n	percent	n	percent	n	percent
Capsular Contracture	25	40	11	20	8	17
Style/Size Change (Patient Request)	11	18	4	7	11	24
Silicone Anxiety (Patient Request)	7	11	0	0	0	0
Asymmetry	4	6	11	20	1	2
Malposition	4	6	10	18	8	17
Ptosis	4	6	0	0	4	9
Implant Rupture	2	3	7	13	6	13
Nipple Complications	2	3	1	2	0	0
Hematoma/Seroma	1	2	3	5	0	0
Breast Cancer	1	2	1	2	0	0
Extrusion	1	2	1	2	0	0
Wrinkling	0	0	3	5	0	0
Pain	0	0	2	4	1	2
Breast Tissue Contour Deformity	0	0	1	2	2	4
Injury (Iatrogenic or Traumatic)	0	0	1	2	0	0
Infection	0	0	0	0	2	4
Unsatisfactory Scar	0	0	0	0	2	4
Delayed Wound Healing	0	0	0	0	1	2
Total	62	100	56	100	46	100

CTD and Breast Disease

Tables 4 and 5 summarize post-implant observations from the Core Study pertaining to connective tissue/autoimmune disease (CTD) and breast disease (including breast carcinoma). These data should be interpreted with caution in that there was no comparison group of similar women without implants. CTD reports were based on a diagnosis by a physician.

Table 4
Reports of CTD through 3 Years, By Patient

Rheumatic Disease	No. of Confirmed Reports in Patients		
	Augmentation	Reconstruction	Revision
Rheumatoid Arthritis	2	0	0
Systemic Sclerosis/Scleroderma	0	1	0
Fibromyalgia	0	0	1

Table 5
Risk of Breast Disease through 3 Years, By Patient

Breast Disease Observation	Rate (%) of Confirmed Reports in Patients		
	Augmentation	Reconstruction	Revision
Benign	6.4	5.1	9.0
Malignant	<1	5.2	0
Unknown Outcome	1.8	2.1	1.0

Effectiveness Outcomes

Core Study

Effectiveness of silicone-filled breast implants was assessed in the Core Study by a variety of outcomes, including bra cup size change (augmentation patients only), patient satisfaction, body image, body esteem, and self concept. These outcomes were assessed for patients with both original and replacement silicone devices before implantation and at 2 years after surgery, except for bra size which was measured within the first year and a half after surgery and based only on original silicone devices. Satisfaction was measured at every follow-up visit through 3 years.

Augmentation

408 of the original 494 augmentation patients (83%) at 18 months were included in an analysis of cup size (17% did not provide data because pre/post measurements were not obtained or replacement/removal occurred prior to obtaining a post measurement). Of these 408 patients, the following shows the percentage of patients experiencing various changes in cup size:

- Increase by 1 cup size: 41%
- Increase by 2 cup sizes: 45%
- Increase by more than 2 cup sizes: 8%
- No Increase: 6%

410 of the original 494 augmentation patients (83%) were included in an analysis of satisfaction at 3 years. Of these 410 patients, 96% indicated being satisfied with their breast implants at 3 years. Furthermore, augmentation patients showed a statistically significant increase in satisfaction with breast size and shape after implantation.

The Quality-of-Life patient surveys showed that augmentation patients scored higher (better) than the general U.S. female population on the SF-36 scales, which measure general health-related quality of life. However, after 2 years, patients showed a slight worsening in their SF-36 scores possibly due to the increase in patient age or other lifestyle changes. Although they did worsen, they continued to remain higher than the U.S. female population. The following two scales showed no change over the 2 years: The Tennessee Self Concept Scale (which measures overall self concept) and The Rosenberg Self Esteem Scale (which measures overall self esteem). The Body Esteem Scale (which measures overall self esteem related specifically to one's body) showed a slight improvement over the 2 years. The scales described above have been validated and are widely used in various research fields. All scales contain multiple questions that are answered by the patient on the Quality-of-Life patient surveys obtained during the course of the study; a composite score for each scale is created using the responses to each of the individual questions in each scale. The

conclusions drawn above are the result of comparing each patient's baseline composite score to her corresponding 2-year composite score.

Reconstruction

185 of the original 221 reconstruction patients (84%) were included in an analysis of satisfaction at 3 years. Of these 185 patients, 92% indicated being satisfied with their breast implants at 3 years. Reconstruction patients also showed a statistically significant increase in satisfaction with breast size and shape after implantation.

The Quality-of-Life patient surveys showed that reconstruction patients scored higher (better) than the general U.S. female population on the SF-36 scales, which measure general health-related quality of life. After 2 years, patients showed no change from baseline in most of the general health-related attributed measured by the SF-36 indicating that their general health related quality of life remained higher than the U.S. female population. The following two scales showed no change over the 2 years: The Tennessee Self Concept Scale (which measures overall self concept) and The Rosenberg Self Esteem Scale (which measures overall self esteem). Furthermore, The Body Esteem Scale (which measures overall self esteem related specifically to one's body) showed a no change over the 2 years post-implantation. The scales described above have been validated and are widely used in various research fields. All scales contain multiple questions that are answered by the patient on the Quality-of-Life patient surveys obtained during the course of the study; a composite score for each scale is created using the responses to each of the individual questions in each scale. The conclusions drawn above are the result of comparing each patient's baseline composite score to her corresponding 2-year composite score.

Revision

183 of the original 225 revision patients (81%) were included in an analysis of satisfaction at 3 years. Of these 183 patients, 88% indicated being satisfied with their breast implants at 3 years. Revision patients also showed a statistically significant increase in satisfaction with breast size and shape after implantation.

The Quality-of-Life patient surveys showed that revision patients scored higher (better) than the general U.S. female population on many of the SF-36 scales, which measure general health-related quality of life. However, after 2 years, patients showed a slight worsening in their SF-36 scores possibly due to the increase in patient age or other lifestyle changes. Although they did worsen, they continued to remain higher than the U.S. female population. The following two scales showed a decrease (worsening) over the 2 years: The Tennessee Self Concept Scale (which measures overall self concept) and The Rosenberg Self Esteem Scale (which measures overall self esteem). However, The Body Esteem Scale (which measures overall self esteem related specifically to one's body) showed a no change over the 2 years post-implantation; this scale may be more informative in measuring the impact of breast implants because it is specific to the patient's body. The scales described above have been validated and are widely used in various research fields. All scales contain

002576

multiple questions that are answered by the patient on the Quality-of-Life patient surveys obtained during the course of the study; a composite score for each scale is created using the responses to each of the individual questions in each scale. The conclusions drawn above are the result of comparing each patient's baseline composite score to her corresponding 2-year composite score.

ADJUNCT STUDY

Study Design

The Adjunct Study was designed as a prospective 5-year study to assess safety outcomes for a large number of patients. Patients studied were those seeking breast reconstruction or revision of an existing implant for medical reasons. Follow-up was at 1, 3, and 5 years and is currently ongoing. Safety assessments consisted of adverse event rates and rates of secondary surgical treatment.

Patient Accounting and Baseline Demographic Profile

The Adjunct Study enrolled 22,884 reconstruction patients and 23,575 revision patients over 6 years. Of those reconstruction patients expected to be seen, 9,198 (55.6%) returned for their 1-year follow-up visit and 2,552 (34.8%) returned for their 3-year follow-up visit. Of those revision patients expected to be seen, 9,006 (49.0%) returned for their 1-year follow-up visit and 2,833 (29.1%) returned for their 3-year follow-up visit.

Demographic information obtained from the Adjunct Study revealed that approximately 60% of participants were married, more than 40% were employed in professional occupations, and more than 70% had at least some college education. The median patient age was 42 years for reconstruction patients and 46 years for revision patients.

With respect to surgical baseline factors in the Adjunct Study, for both reconstruction and revision patients, the most frequently used devices were round with a fairly equal distribution of smooth and textured surface.

Safety Outcomes

Adverse Events

The cumulative Kaplan-Meier risk of first occurrence of adverse events (and 95% confidence interval) reported in greater than 1% of patients is shown in **Table 6** based on indication.

Table 6
3-Year Cumulative First Occurrence Kaplan-Meier
Adverse Event Risk Rates (95% Confidence Interval), By Patient

Complication	Reconstruction N = 22,884		Revision N = 23,575	
	Rate (%)	(95% CI)	Rate (%)	(95% CI)
Reoperation*	38.6	(37.4, 39.8)	29.5	(28.4, 30.5)
Implant Replacement/Removal*	23.2	(22.1, 24.3)	19.9	(18.9, 20.9)
Capsular Contracture	12.2	(11.2, 13.1)	14.8	(13.9, 15.8)
Asymmetry	10.2	(9.3, 11.0)	8.7	(7.9, 9.4)
Wrinkling	5.8	(5.1, 6.5)	8.9	(8.2, 9.7)
Implant Malposition	5.6	(5.0, 6.3)	5.6	(5.0, 6.3)
Implant Palpability/Visibility	5.5	(4.8, 6.1)	8.6	(7.9, 9.4)
Breast Pain	4.5	(3.9, 5.1)	6.0	(5.3, 6.6)
Loss of Nipple Sensation	3.5	(3.0, 4.0)	3.1	(2.6, 3.6)
Hypertrophic Scarring	2.0	(1.6, 2.4)	1.9	(1.5, 2.2)
Capsule Calcification	1.7	(1.3, 2.1)	2.3	(1.9, 2.7)
Skin Hypersensitivity/Paresthesia	1.6	(1.3, 2.0)	1.6	(1.3, 2.0)
Swelling	1.4	(1.1, 1.7)	1.6	(1.3, 1.9)
Nipple Hypersensitivity/Paresthesia	1.1	(0.8, 1.4)	1.0	(0.7, 1.3)
Implant Rupture*	<1	<1	<1	<1

*All complications other than reoperation and implant replacement/removal were assessed with severity ratings. Most rates shown in the table include only complications rated moderate, severe or very severe (excludes mild and very mild ratings). The only complication rates that include all severity ratings are rupture, pneumothorax and implant extrusion.

Effectiveness Outcomes

Effectiveness of silicone-filled breast implants was assessed in the Adjunct Study by patient reports of satisfaction at 1 and 3 years post-implant. Because this study continued to enroll patients over a 6-year period, many of the enrolled patients have not yet reached their 3-year follow-up visit. Thus, satisfaction data was available from a much smaller number of patients at 3 years than at 1 year.

For reconstruction patients, 9,090 of the original 22,884 patients (40%) were included in an analysis of satisfaction at 1 year post-implant; 60% were not included because these patients had not yet reached the 1-year follow-up time point, satisfaction data was not obtained at the 1-year visit, or implant replacement/removal occurred prior to 1 year). Of these 9,090 reconstruction patients, 93% indicated being satisfied with

their breast implants at 1 year. Satisfaction data was obtained from 2,599 reconstruction patients at 3 years post-implant. 94% of these patients indicated they were satisfied with their breast implants at 3 years.

For revision patients, 8,808 of the original 23,575 patients (37%) were included in an analysis of satisfaction at 1 year post-implant. Of these 8,808 revision patients, 91% indicated being satisfied with their breast implants at 1 year. Satisfaction data were obtained from 2,828 revision patients at 3 years post-implant. 91% of these patients indicated they were satisfied with their breast implants at 3 years.

INSTRUCTIONS FOR USE

NOTE: Back-up breast implants should be available during the procedure.
DO NOT Stack more than one implant per breast.

Single Use

This product is intended for **single use only**. Do not reuse explanted implants.

Product Identification

Product identification stickers accompany each device within the internal product packaging. The stickers provide product-specific information and are designed to be attached to the patient's chart for identification purposes.

Surgical Planning

INAMED relies on the surgeon to know and follow the proper surgical procedures with INAMED Silicone-Filled Breast Implants. Proper surgical planning such as allowance for adequate tissue coverage, implant site (i.e., submuscular vs. subglandular), incision site, implant type, etc., should be made preoperatively. The surgeon must carefully evaluate breast implant size and contour, incision placement, pocket dissection, and implant placement criteria with respect to the patient's anatomy and desired physical outcome. Planning should include clear delineation of aesthetic goals to ensure mutual understanding between surgeon and patient. The surgeon should observe current and accepted techniques to minimize the risk of adverse, and potentially disfiguring, reactions.

Preliminary Product Examination

How to Open Sterile Product Package

Remove the sterile breast implant from its package in an aseptic environment and using talc-free gloved hands. **DO NOT** expose the breast implant to lint, talc, sponge, towel, or other contaminants.

1. Peel open the lid of the outer thermoform package.
2. Invert the outer thermoform package over the sterile field, allowing the sealed inner thermoform package to gently fall into the field.

3. Peel open the lid of the inner thermoform package using the pull-tab.
4. Gently retrieve the breast implant. Prior to use, keep the breast implant in the inner thermoform package to prevent contact with airborne and surgical field particulate contaminants.

Examination of Silicone-Filled Breast Implants

Prior to use, examine the breast implant for evidence of any particulate contamination, damage, or loss of shell integrity. If satisfactory, return the breast implant to the inner thermoform tray and cover it with the lid until implanted to prevent contact with airborne contaminants.

DO NOT implant any device that may appear to have particulate contamination, damage, or loss of shell integrity. A sterile back-up implant must be readily available at the time of surgery.

DO NOT implant any device that may appear to have leaks or nicks.

DO NOT implant damaged or contaminated breast implants.

Sterile Product

Each sterile silicone-filled breast implant is supplied in a sealed, double primary package. Style-specific sterile product accessories are also supplied within the product packaging. Sterility of the implant is maintained only if the thermoform packages, including the package seals, are intact. Use standard procedures to maintain sterility during transfer of the breast implant to the sterile field. Remove the breast implant and accessories from their packages in an aseptic environment and using talc-free gloved hands.

DO NOT use the product if the thermoform packages or seals have been damaged.

DO NOT resterilize the product.

Avoid unnecessary exposure of the breast implant to lint, talc, sponge, towel, skin oils, and other contaminants.

Prior to use, keep the breast implant in the inner thermoform and covered to prevent contact with airborne and surgical field particulate contaminants.

Method for Removing Ruptured Silicone from the Surgical Pocket

In the event of breast implant rupture, the following technique is useful for removal of the silicone mass. Wearing double talc-free surgical gloves on one hand, use the index finger to penetrate the silicone mass. With the other hand, exert pressure on the breast to facilitate manipulation of the silicone mass into the double-gloved hand. Once the silicone is in hand, pull the outer glove over the silicone mass and remove. To remove any residual silicone, blot the surgical pocket with gauze sponges. Avoid contact between surgical instruments and the silicone. If contact occurs, use isopropyl alcohol to remove the silicone from the instruments. Ruptured breast implants must be reported and should be returned to INAMED. In the event of breast implant rupture, contact INAMED Product Support Department at 800.624.4261.

Surgical Procedure Placement

Ensure incision is sufficiently large to facilitate insertion without excessive manipulation and handling of the device and to avoid damage to the device. Inadequate pocket dissection increases the risk of rupture and implant malposition.

A sterile BIOCELL® Delivery Assistance Sleeve is available separately and can be used to assist with placement of the breast implant. Use of this sleeve for insertion of BIOCELL® textured breast implants provides a shell/tissue interface with less friction. Insert the implant into one end of the sleeve. Insert the proximal end of the sleeve into the surgically prepared pocket. With the tissue retracted, the sleeve can be twisted at its distal end to gently guide the breast implant into the pocket. Once the breast implant is inserted, gently remove the sleeve.

DO NOT use lubricants to facilitate placement. Their use creates the risk of pocket contamination and may also affect the tissue-capsule interface.

DO NOT damage the breast implant with sharp surgical instruments such as needles and scalpels, blunt instruments such as clamps and forceps, or by overhandling and manipulation during introduction into the surgical pocket.

DO NOT use excessive force during breast implant placement.

DO NOT manipulate the implant for either radial expansion, compression or dissection of the pocket.

Breast augmentation with silicone-filled implants can be carried out through several different incisions including inframammary, periareolar, or transaxillary. Some surgeons advocate a "no-touch" technique, which requires significant attention to minimizing contact between the patient's skin and the implant. Pocket dissection should be planned out preoperatively and be performed accurately and with minimal trauma. Excellent hemostasis is important to avoid postoperative hematoma. The implant may be placed subglandularly or subpectorally depending upon the balance of cosmetic and medical considerations in any given patient. The size and shape of the device may be determined preoperatively by means of dimensional planning or intraoperatively with the help of temporary sizer devices. It is important to maintain proper orientation of any shaped implant.

The incision for the placement of the implant should be securely closed and in several layers, whenever possible. Drains are optional.

Breast Reconstruction is generally carried out in the mastectomy scar. Special care must be used in breast reconstruction to make sure that appropriate amounts of healthy tissue are available to cover the implant and that the implant be properly sized and positioned based upon careful preoperative planning.

Educational materials are available through the INAMED Customer Care Department to supplement surgical knowledge of the dimensional techniques intended for use with INAMED Aesthetics breast implants.

Maintaining Hemostasis/Avoiding Fluid Accumulation

Postoperative hematoma and seroma may be minimized by meticulous attention to hemostasis during surgery, and possibly also by postoperative use of a closed drainage system. Persistent, excessive bleeding must be controlled before implantation.

Any postoperative evacuation of hematoma or seroma must be conducted with care to avoid breast implant contamination or damage from sharp instruments.

DOCUMENTATION THE PHYSICIAN SHOULD PROVIDE TO THE PATIENT

Breast implantation is an elective procedure and the patient must be well counseled on the risk-benefit relationship. The surgeon should provide each prospective patient with the following:

- ***Making an Informed Decision: Silicone-Filled Breast Implant Surgery***
This brochure should be used to facilitate patient education in the risks and benefits of silicone-filled breast implant surgery. The patient should be advised to wait a week after reviewing and considering this information before deciding whether to have augmentation surgery.
- ***Device Identification Card***
Enclosed with each silicone-filled breast implant is a Device Identification Card. To complete the Device Identification Card, place one device identification sticker for each implant on the back of the card. Stickers are located on the internal product packaging attached to the label. If a sticker is unavailable, the lot number, catalog number and description of the device may be copied by hand from the device label. Patients should be provided with these cards for personal reference.
- ***Medical Device Registration***
INAMED Corporation maintains a device registry to identify patients who have INAMED's silicone-filled breast implants. The registry is designed to collect demographic and contact information for patients who are implanted with INAMED's silicone-filled breast implants. Information collected in the device registry may be provided, with patient consent, to research institutions engaged in large scale epidemiological studies.

INAMED strongly suggests that all patients receiving silicone-filled breast implants be registered in this database.

Successful device registration begins with the **Medical Device Registration Form** that is supplied with every breast implant. Stickers with product-specific

information are provided for quick completion of the form and are located on the internal product packaging attached to the label. If stickers are unavailable, the lot number, catalog number and description of each device may be copied by hand from the device label. The surgeon, medical facility or health care staff should fill out the top portion of the Medical Device Registration Form and then supply the entire form, along with the Device ID Card, to the patient. The patient should then complete the **Medical Device Registration Form** and return it to INAMED Corporation in the postage paid envelope provided.

SPECIFIC PRODUCT INFORMATION

BIOCELL® Delivery Assistance Sleeve

Sterile BIOCELL® Delivery Assistance Sleeves are available from your INAMED Aesthetics Sales Representative or Customer Care Department at 800.766.0171.

Returned Goods Policy

Product returns should be handled through an INAMED Aesthetics Sales Representative or through the Customer Care Department at 800.766.0171. Return value is based on time limitations. All package seals must be intact to be eligible for return. Returned products may be subject to a restocking charge. Certain products are non-returnable, including Zyderm® and Zyplast®.

Reporting and Return of Explanted Devices

The reason for explantation should be reported and the explanted device returned to INAMED Corporation. In the event of such an explantation, please contact Product Support at 800.624.4261 for an Explant Kit and explant return instructions.

ConfidencePlus™ Limited Warranties

The ConfidencePlus™ Limited Warranties provide lifetime replacement and limited financial reimbursement in the event of loss of shell integrity resulting in implant deflation or rupture, subject to certain conditions as fully discussed in the ConfidencePlus™ literature. For more information, please contact Product Support at 800.624.4261.

Product Ordering

To order directly in the U.S.A or for product information, please contact your local INAMED Aesthetics Sales Representative or the INAMED Customer Care Department at 800.766.0171.

INAMED, the INAMED logo, BIOCELL, BioDIMENSIONAL, BIOSPAN, ZYDERM and ZYPLAST, ConfidencePlus are registered trademarks and/or trademarks of INAMED Corporation.

These products are covered by one or more of the following U.S. Patents: 5,480,430; 5,007,929; 4,889,744 and 4,859,712 and/or foreign patents corresponding thereto.



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MAKING AN INFORMED DECISION

SILICONE-FILLED BREAST IMPLANT AUGMENTATION

 **INAMED**
AESTHETICS

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INTRODUCTION

TO THE PATIENT

The information contained in this booklet, *Making an Informed Decision, Silicone filled Breast Implant Surgery*, is designed to provide you with an understanding of the risks and benefits of surgery with silicone filled breast implants as well as provide an overview of the experience of patients in the INAMED Core Clinical Study.

Please review this information to ensure your preoperative consultation is effective and comprehensive. Make notes about issues that you would like to further discuss with your plastic surgeon, and ask questions. Give yourself time to consider your choices and proceed with surgery only after you are satisfied that the decision is right for you.

TO THE HEALTHCARE PROFESSIONAL

Discussion of the content of this document is an important part of the informed decision making process for the patient. Please take time to familiarize yourself with the information presented here and incorporate it into your pre-operative discussion.

For your convenience a signature block is provided as a means of documenting the preoperative discussion in the patient's file.

After removing the signature block, please give this book to the patient for her records.

Making an Informed Decision

Silicone Filled Breast Implant surgery

Augmentation

I have reviewed the information presented in *Making an Informed Decision Silicone Filled Breast Implant Surgery, Augmentation*. My concerns and questions have been addressed by my doctor and I have considered alternatives to augmentation surgery including use of external prostheses or surgery with saline-filled breast implants.

I am choosing to proceed with silicone filled breast implant surgery.

Patient Name

Patient Signature

Date

Surgeon Name

Surgeon Signature

Date

002588

TABLE OF CONTENTS

SO, YOU'RE CONSIDERING SILICONE-FILLED BREAST IMPLANT SURGERY

WHAT GIVES THE BREAST ITS SHAPE?

WHAT IS SILICONE?

WHAT IS A SILICONE-FILLED BREAST IMPLANT?

WHAT TYPES OF SILICONE-FILLED BREAST IMPLANTS ARE AVAILABLE FROM INAMED?

ARE SILICONE-FILLED BREAST IMPLANTS RIGHT FOR YOU?

WHAT ARE THE BENEFITS OF BREAST AUGMENTATION SURGERY?

WHAT YOU NEED TO KNOW BEFORE BREAST AUGMENTATION SURGERY?

WHAT EVIDENCE IS THERE THAT INAMED SILICONE-FILLED IMPLANTS ARE SAFE AND EFFECTIVE?

SOME PRACTIAL ASPECTS OF BREAST AUGMENTATION SURGERY

REGISTERING YOUR BREAST IMPLANT

WHAT YOU NEED TO KNOW AFTER THE SURGERY

HOW TO RECEIVE MORE INFORMATION

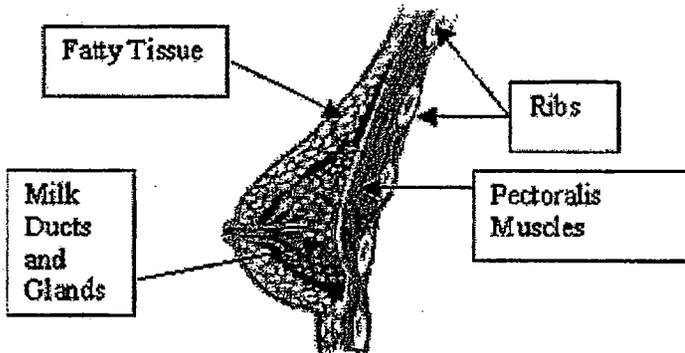
GLOSSARY OF MEDICAL/TECHNICAL TERMS

SO, YOU'RE CONSIDERING SILICONE-FILLED BREAST IMPLANT SURGERY

If you are a woman, 18-years of age or older, you may be considering breast implant surgery to enhance your appearance. This is referred to as breast augmentation. INAMED Aesthetics has prepared this patient information booklet to help you better understand the breast implant procedure and assist you in making an informed decision about breast augmentation surgery. It will help to answer some of the questions you may have about the surgery and about breast implants in general. It will also provide you with specific information about the INAMED silicone-filled breast implant product line.

This educational booklet can not and should not take the place of discussing your surgery with your plastic surgeon. Make sure to speak with your surgeon about your expectations of the results, as well as what you can expect regarding the length of the surgery, your recovery, and any potential complications of the surgery. Ask questions. You and your surgeon will work together to help you to achieve the body image you desire.

WHAT GIVES THE BREAST ITS SHAPE?



The breast consists of milk ducts and glands, surrounded by fatty tissue that provides its shape and feel. Beneath the breast is the pectoralis major muscle (chest muscle) of the chest wall.

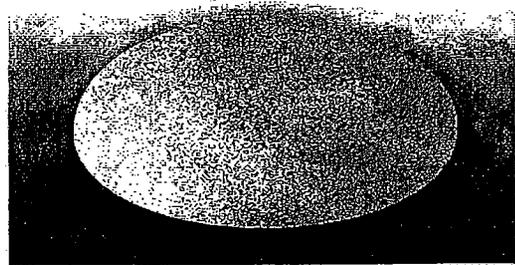
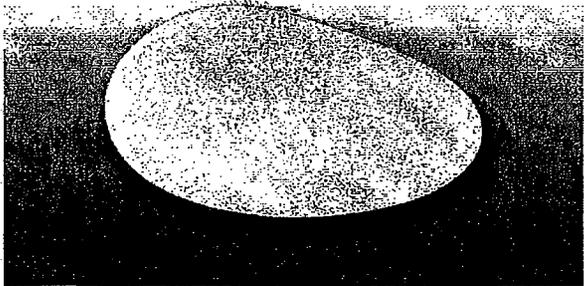
Women may choose breast augmentation surgery because they believe that their breasts are smaller than they desire or because their breasts are misshapen or asymmetrical. They may also choose breast augmentation surgery because their breasts have begun to droop or sag as a result of pregnancy (when the milk glands are temporarily enlarged), rapid weight loss, or the effects of gravity that accompanies aging.

WHAT IS SILICONE?

Silicones are a family of compounds, made from silicon, a naturally occurring element. Silicones have been part of the consumer industry for over 50 years and because they can be manufactured in various ways, silicones appear in a wide variety of products most of us use every day. Medical devices utilizing silicone include artificial joints, facial implants, catheters, tissue expanders and breast implants.

WHAT IS A SILICONE-FILLED BREAST IMPLANT?

A silicone-filled breast implant is a sac (implant shell) made of silicone elastomer (rubber) and filled with silicone gel. It is surgically implanted either under your breast tissue and above your chest muscle or below your chest muscle. Your plastic surgeon will discuss with you the best positioning for your implants.

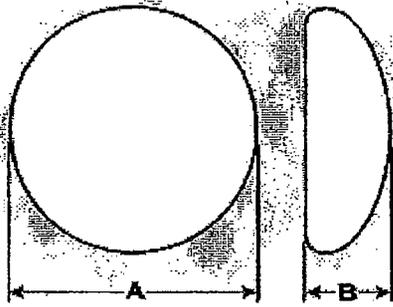


WHAT TYPES OF SILICONE-FILLED BREAST IMPLANTS ARE AVAILABLE FROM INAMED?

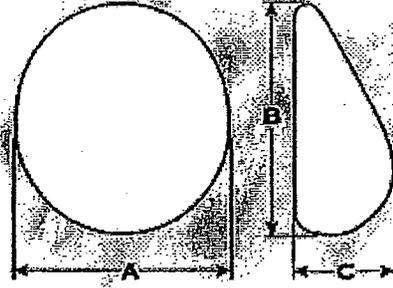
Breast implants come in a variety of shapes, surface textures, and sizes. INAMED manufactures several styles of round and one style of shaped silicone-filled breast implant (see below). They are available with smooth shell surfaces or textured shell surfaces. Your plastic surgeon will discuss with you the implant design that will best help you achieve your desired outcome.

Round Breast Implants:	
Style 10:	Smooth shell surface, moderate projection
Style 20:	Smooth shell surface, full projection
Style 40:	Smooth shell surface, standard projection
Style 45:	Smooth shell surface, full projection
Style 110:	BIOCELL® Textured shell surface, moderate projection
Style 120:	BIOCELL® Textured shell surface, full projection

Shaped Breast Implants:



A = Width; B = Projection
Round Breast Implant



A = Width; B = Height; C =
Projection
Shaped Breast Implant

Style 153:	BIOCELL® Textured shell surface, double lumen, full height, full projection
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ARE SILICONE-FILLED BREAST IMPLANTS RIGHT FOR YOU?

In order to help you achieve your cosmetic goals safely, silicone-filled implants should not be used in women under the age of 18, in women with existing malignant or pre-malignant cancer of the breast who have not been successfully treated, in women with an active infection anywhere in the body, and in women who are currently pregnant or nursing.

In addition, silicone-filled breast implants have not been clinically tested in women with autoimmune diseases like lupus or scleroderma, in women with conditions that could interfere with wound healing and blood clotting, in women with a weakened immune system (such as women receiving immunosuppressive therapy), and in women with a reduced blood supply to the breast tissue. If you have any of these conditions or other serious health problems, you should discuss with your surgeon whether breast augmentation surgery is appropriate for you.

WHAT ARE THE BENEFITS OF BREAST AUGMENTATION SURGERY?

The obvious benefit of silicone-filled breast implants is an increased bra cup size, but women who have breast implants also report an improved body image.

WHAT YOU NEED TO KNOW BEFORE BREAST AUGMENTATION SURGERY

Before you agree to any surgical procedure, you need to fully understand the potential health risks that are associated with the surgery. If you are considering breast augmentation, you also need to understand the potential health risks that may be associated with the long-term implantation of breast implants. These are described below.

THERE ARE RISKS ASSOCIATED WITH THE IMPLANT SURGERY.

All surgery carries some risk. The most commonly reported surgery-related risks for breast augmentation surgery are infection, bleeding, seroma, scarring, anesthesia, and pain.

Scarring

Most scars following breast augmentation are pale thin lines. However, they may become red, firm, and elevated. Some scars fade with time but scar revision may be desired.

Infection

Infection occurs very rarely following breast implant surgery. Most infections resulting from surgery appear within a few days to weeks after the operation, although infection is possible at any time after surgery. Infections with an implant present are harder to treat than infections in normal body tissues. Infections are typically treated with antibiotics, but if the infection does not respond to antibiotics, the implant may have to be removed. Another implant may be placed after the infection is resolved. In very rare instances, Toxic Shock Syndrome, a potentially life threatening condition, has been noted in women after breast implant surgery. Symptoms include sudden fever, vomiting, diarrhea, fainting, dizziness, and/or sunburn-like rash. You should see your surgeon immediately for diagnosis and treatment for this condition.

Hematoma

Bleeding (hematoma) occurs in 2-4% of breast implant procedures. It is usually seen soon after surgery, however, it can occur at any time after injury to the breast. While the body absorbs small hematomas, large ones will require the placement of surgical drains for proper healing. A small scar can result from surgical draining. Implant rupture can occur from surgical draining if damage to the implant occurs during the draining procedure.

Seroma

Seroma is a collection of the watery portion of the blood (in this case, around the implant or around the incision). While the body absorbs small seromas, large ones will require the placement of surgical drains for proper healing. A small scar can result from surgical draining. Implant rupture can occur from surgical draining if damage to the implant occurs during the draining procedure.

Anesthesia

As with all surgeries, there is a risk that you will experience an adverse reaction to the anesthesia.

Pain

Pain of varying intensity and duration may occur and persist following breast implant surgery. In addition, improper size, placement, surgical technique, or capsular contracture may result in pain associated with nerve entrapment or interference with muscle motion. You should inform your surgeon if you experience severe pain.

YOU MAY NOT BE PLEASED WITH THE COSMETIC OUTCOME.

Dissatisfying results such as wrinkling, asymmetry (one breast is larger or smaller or a different shape than the other), implant displacement (shifting), incorrect size,

002594

unanticipated shape, implant palpability (ability to feel the implant under the skin), scar deformity, and/or hypertrophic (irregular, raised scar) scarring, may occur. Careful surgical planning and technique can minimize but not always prevent such results.

YOU MAY REQUIRE ADDITIONAL SURGERY AND SURGEON VISITS.

Breast implants are not considered lifetime devices. You may undergo implant removal with or without implant replacement during your lifetime.

MANY OF THE CHANGES TO YOUR BREAST FOLLOWING IMPLANTATION ARE IRREVERSIBLE.

If you later choose to have your implant(s) removed, you may experience unacceptable dimpling, puckering, or wrinkling of the skin or other cosmetic changes of the breast.

BREAST IMPLANTS MAY AFFECT YOUR ABILITY TO BREAST FEED.

Breast implant surgery may affect your ability to breast feed because the surgery may sever nerves that stimulate the body to release the hormones that trigger milk release. In addition, an incision around the nipple, which may be done to make the surgical scar less noticeable, also may sever ducts that drain milk from the mammary gland, such that even if the mother has an adequate milk supply, it may be difficult for the milk to drain into the nipple. Also, breast implants will not prevent a woman's breasts from sagging after pregnancy.

At this time it is not known if a small amount of silicone may diffuse (pass through) from the silicone-filled breast implant and may find its way into breast milk. If this occurs, it is not known what effect it may have on the nursing infant. Although there are no current methods for detecting silicone levels in breast milk, a study measuring silicon (one component in silicone) levels did not indicate higher levels in breast milk from women with silicone-filled breast implants when compared to women without implants.

BREAST IMPLANTS MAKE ROUTINE SCREENING MAMMOGRAPHY MORE DIFFICULT.

The presence of breast implants may interfere with finding breast cancer during mammography and also may make it difficult to perform mammography. Therefore, it is essential that you tell your mammography technologist that you have an implant before the procedure. The technologist can use special techniques to minimize the possibility of rupture and to get the best possible views of the breast tissue. You

002595

may wish to undergo a preoperative mammogram and another one 6 months to one year after implantation to establish a baseline.

Because the breast is squeezed during mammography, it is possible for an implant to rupture during the procedure. More x-ray views are necessary with these special techniques; therefore, women with breast implants will receive more radiation. However, the benefit of the mammogram in finding cancer outweighs the risk of the additional x-rays.

In addition to routine mammograms, women should perform a breast self-examination monthly on the implanted breast. In order to do this effectively, you should ask your surgeon to help you distinguish the implant from your breast tissue. Any new lumps or an abnormal finding on the mammogram should be evaluated with a biopsy. If a biopsy is performed, care must be taken to avoid puncturing the implant.

YOUR HEALTH INSURANCE PREMIUMS MAY INCREASE, COVERAGE MAY BE DROPPED, AND/OR FUTURE COVERAGE MAY BE DENIED.

Treatment of complications may not be covered as well. You should check with your insurance company regarding these coverage issues.

THE LONG-TERM SAFETY AND EFFECTIVENESS OF BREAST IMPLANTS HAVE NOT BEEN STUDIED.

INAMED is monitoring the long-term (10-year) chance of implant rupture, reoperation, implant removal, and capsular contracture (hardening of the tissues around the implant). INAMED is also conducting mechanical testing to assess the long-term likelihood of implant rupture. As new information becomes available, INAMED will issue an updated version of this brochure.

YOU HAVE OTHER OPTIONS.

There are alternatives to breast augmentation with a silicone-filled breast implant. You may choose to have no treatment at all and accept your breasts as they are. You may choose to wear a padded bra or external prostheses. You may choose to have saline-filled implants implanted.

SOME LOCAL COMPLICATIONS CAN OCCUR IN IMPLANTED BREASTS.

Local complications are sometimes observed in the breasts of women with silicone-filled implants. These include capsular contracture, rupture, calcification, implant extrusion, wound healing problems or tissue necrosis, visible skin wrinkling and rippling, changes in nipple and skin sensation, pain, malposition, asymmetry, breast tissue atrophy, and re-operation.

Capsular Contracture

The scar tissue or capsule that normally forms around the implant may tighten and squeeze the implant and is called capsular contracture. Capsular contracture may be more common following infection, hematoma, and seroma. It is also more common with subglandular placement (behind the mammary gland and on top of the chest muscle). Symptoms range from mild firmness and mild discomfort to severe pain, distorted shape, palpability of the implant, and/or movement of the implant.

Capsular contracture may occur on one side, both sides, or not at all. In severe cases, the disfigurement or discomfort resulting from capsular contracture may require surgery to remove the scar tissue around the implant and/or implant replacement. In some cases, the contracture may not be correctable and implant removal of the implant and capsule tissue may be necessary. Closed capsulotomy is not recommended due to concerns about implant rupture and localized bleeding. The occurrence of capsular contracture is not predictable, however, the chance of it happening increases with time. Capsular contracture may happen again after these additional surgeries.

Rupture

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.

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.

Gel Bleed

There is no evidence from the medical literature or from Inamed's own testing suggesting that gel bleed (gel components passing through the shell) may be associated with local complications in breast implant patients. In addition, clinical study patients in Inamed's Core clinical study for silicone-filled breast implants were at no higher risk of local complications when compared to the risk of local complications reported in Inamed's 1995 saline-filled breast implant clinical study.

Calcium Deposits

Deposits of calcium can be seen on mammograms and although they are benign, they can be mistaken for possible cancer, resulting in additional surgery for biopsy and/or removal of the implant to distinguish the calcium deposits from cancer.

Implant Extrusion

If the skin or breast tissue covering the implant is very thin and/or there is a problem with healing, the implant may break through the skin and become exposed. This will require removal of the implant.

Wound Healing Problems or Tissue Necrosis

Some patients experience delayed healing of the incision site or they may not heal well. This can result in an unattractive scar and if the implant is exposed, further surgery will be required. Tissue breakdown or necrosis (the formation of dead tissue around the implant) will delay wound healing, may cause wound infection, and may require surgical correction and/or implant removal. Permanent scar deformity may occur following necrosis. Factors associated with increased necrosis include infection, use of steroids in the surgical pocket, smoking, chemotherapy/radiation, and excessive heat or cold therapy.

Visible Skin Wrinkling and Rippling

Visible rippling can result when an implant pulls on the overlying tissues or when the natural folds in the implant are visible through the skin. Removal and replacement of the implant may correct this problem.

Change in Nipple and Skin Sensation

Some change in nipple sensation is not unusual right after surgery and, after several months, most patients have normal sensation. Only rarely does permanent loss of nipple and skin sensation or hypersensitivity occur. The range of changes varies from intense sensitivity to no feeling in the nipple or breast following surgery. Changes in feeling can be temporary or permanent and may affect your sexual response or your ability to nurse a baby.

Pain

Pain of varying intensity and duration may occur and persist following breast implant surgery. In addition, improper size, placement, surgical technique, or capsular contracture may result in pain associated with nerve entrapment or interference with muscle motion. You should tell your surgeon about severe pain.

Malposition

Breast malposition may result from shifting after initial placement, excessive sagging or stretching of the lower breast, or capsular contracture. Removal and replacement of the implant may correct this problem.

Asymmetry

Asymmetry (differences in size or shape between breasts) can result from some of the above-mentioned complications. Most women's breasts have at least some asymmetry, even without implants. Removal and replacement of the implant may correct this problem.

Breast Tissue Atrophy

Pressure from breast implants may cause the surrounding tissue to thin or shrink and this may result in the implant becoming more visible or palpable. This can occur while implants are still in place or following implant removal without replacement.

Re-operation

Implanted devices do not last forever, and like many other implanted devices breast implants may need to be replaced or removed after a period of time. The rates of re-operation reported in the literature for noncosmetic reasons range from 10 to 30%. Patients should expect to have additional surgery at some point to replace or remove the implant. Also, problems such as rupture, capsular contracture, infection,

shifting, and calcium deposits can require removal of the implants. Many women decide to have the implants replaced, but some women do not. If you choose not to, you may have cosmetically unacceptable dimpling and/or puckering of the breast following removal of the implant.

THERE IS A CONCERN THAT BREAST IMPLANTS INCREASE THE RISK OF CERTAIN DISEASES OR EVENTS.

There has been discussion in the scientific and regulatory communities regarding the potential for silicone-filled breast implants to be associated with certain systemic diseases or concerns. The strength of these associations between breast implants and connective tissue disease, cancer, nervous system effects, effects on children, and suicide is discussed below.

Connective Tissue Disease

Concern over the association of breast implants to the development of autoimmune or connective tissue diseases, such as lupus, scleroderma, or rheumatoid arthritis, was raised because of cases reported in the literature with small numbers of women with implants. Several large epidemiological studies of women with and without implants indicate that these diseases are no more common in women with implants than those in women without implants.

Some patients in INAMED's Core Clinical Study showed an increase over time in some CTD signs and symptoms and those CTD signs and symptoms specific to fibromyalgia, such as fatigue, swelling, weakness, aches, back and neck pain. However, patients with INAMED's saline-filled implants showed similar increases in these signs and symptoms. This indicates that the increased signs and symptoms are most likely not caused by the silicone-filled breast implants and may be attributed to other factors such as aging.

Cancer and Benign Breast Disease

The overwhelming majority of epidemiological studies indicate that cancer and benign breast disease are no more common in women with implants than those without implants, thus offering compelling scientific evidence of a lack of association between breast implants and cancers.

Nervous System Effects

Most investigators report no causal relationship between the presence of breast implants and neurological effects including Meniere's disease, hearing loss, and neurological disease, including multiple sclerosis and Guillain-Barre syndrome.

Effects on Children of Women with Breast Implants

The concern that children born to mothers with silicone breast implants are at risk of developing health problems stems from reports of children born to or breastfed by such women who developed swallowing difficulties, irritability, nonspecific skin rashes, fatigue, and other symptoms. However, epidemiological investigations have not found any increased risk of adverse health outcomes, including occurrence of esophageal disorders, connective tissue disease, and congenital malformations in children born to women with breast implants.

Suicide

Some investigators have raised concerns that the risk of suicide is increased in patients with silicone-filled breast implants. However, their studies do not consider other factors that are likely to affect a woman's predisposition for suicidal tendencies and that are widely acknowledged to be more common among women who seek breast implants, such as cigarette smoking, alcohol consumption, weight, parity, low self-esteem, depression, or other psychiatric/emotional disorders.

WHAT EVIDENCE IS THERE THAT INAMED SILICONE-FILLED IMPLANTS ARE SAFE AND EFFECTIVE?

Although you will experience your own risks (complications) and benefits following breast implant surgery, this section describes the specific complications and benefits of INAMED silicone-filled breast implants. INAMED's studies indicate, for example, that about 1 in 5 augmentation patients (21%) can expect to experience additional breast surgery at some point through 3 years after implant surgery. The information below provides more details about the complications and benefits you may experience.

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.

STUDIES IN WOMEN

INAMED conducted clinical studies testing of its silicone-filled breast implants to determine the short-term and most common complications as well as benefits of its implants. The Core Clinical Study was designed as a 10-year study to assess all complications as well as patient satisfaction, body image, body esteem, and self

002601

concept. Patients were followed annually, and data through 3 years after implantation are currently available. The Core Study enrolled 494 augmentation patients. Of the women expected to be seen at the 3-year follow-up visit, 86% were seen.

Complications Reported in the Core Study

The local complications observed in women at 3 years are presented in the table below. The rates reflect the number of augmentation patients out of 100 who experienced the listed complication at least once within the first 3 years after implantation. Some complications occurred more than once for some patients. The most common complication experienced within the first 3 years of implantation was capsular contracture (10% or 10 patients out of 100). Some complications required patients to undergo an additional breast surgery in order to address the complication. The following table shows all complications (i.e., those that lead to additional surgery and those that did not.)

Complication	3-Year Complication Rate
Capsular Contracture	10%
Breast Pain	7%
Swelling	7%
Asymmetry, Implant Malposition, Loss of Nipple Sensation, Ptosis, Scarring	2-5%
Rupture	2%
Hematoma, Implant Palpability/Visibility, Loss of Skin Sensation, Nipple Hypersensitivity/Paresthesia, Seroma/Fluid Accumulation, Skin Rash	1%
Bruising, Delayed Wound Healing, Implant Extrusion*, Infection, Lymphedema, Other Nipple Complications, Pneumothorax*, Redness, Skin Hypersensitivity/Paresthesia, Tissue or Skin Necrosis, Wrinkling	<1%
Capsule Calcification, Irritation, Lymphadenopathy, Other Complications	0%

*All complications were assessed with severity ratings. Most rates shown in the table include only complications rated moderate, severe, or very severe (excludes mild and very mild ratings). The only complication rates that include all severity ratings are rupture, pneumothorax, and implant extrusion.

Additional Surgeries

Some of the complications reported in the above table led to an additional surgery and some additional surgeries involved removal of the implant. A patient has a 21% risk of additional surgery through 3 years and 7% risk of implant removal through 3 years.

Through 3 years, 101 augmentation patients had at least one additional surgery, and some patients required multiple surgeries. A total of 123 additional surgeries were performed through 3 years. Although some complications lead to an additional surgery, it is important to note that many complications do not require additional surgery and many additional surgeries are performed without removal of the implant. 33 of the 101 patients (33%) had an implant removed. For example, in the previous table a patient's risk of capsular contracture is 11%, but in the table below a patient's risk of a capsular contracture that requires additional surgery is less, at 6%, and a patient's risk of having the implant removed to treat the capsular contracture is even lower at 2%. The following table describes a patient's risk of having an additional surgery or implant removal for the complications listed in the previous table..

(Because rupture is addressed in the next section, it is not included in the following table.)

Complication	% Risk of Complication Leading to Additional Surgery	% Risk of Complication Leading to Removal/Replacement
Asymmetry	1.7%	1.3%
Breast Pain	0.2%	0.2%
Capsular Contracture	7.2%	3.4%
Hematoma	2.1%	0.2%
Scarring	3.4%	0%
Implant Malposition	4.4%	1.3%
Implant Palpability	0%	0%
Loss of Skin Sensation	0%	0%
Nipple Complication	0.4%	0%
Ptosis	4.3%	0.7%
Skin Rash	0%	0%
Swelling	0%	0%
Patient Request for Style/Size Change	4.1%	4.1%
Need for Biopsy	2.8%	0.2%
Patient Request due to Media Anxiety	0.9%	0.9%
Other	0.9%	0.2%
Delayed Wound Healing	0.4%	0.0%
Extrusion	0.2%	0.2%
Wrinkling/Rippling	0.2%	0.2%
Necrosis	0.2%	0.0%

Rupture

Through 3 years, both silent and symptomatic (i.e., non-silent) ruptures have been detected in the augmentation patients. The 3-year rates of these events are described as 2% risk of any rupture, 2% risk of silent rupture, and 0% risk of symptomatic rupture.

The risks presented above are calculated by-implant rather than by-patient because the complication is implant-specific. Furthermore, the risks include some implants that have not yet been assessed to determine if they are actual ruptures because they have not been explanted.

Some silent ruptures were discovered via MRI. A portion of the study participants underwent routine screening with MRI. Of all the implants in the Core Study that were diagnosed as ruptured via MRI, 36-37% proved to be intact.

Other Events

Through 3 years, events other than the complications described in the previous tables above were collected in the Core Clinical Study. Some of these events, such as breast cancer and CTD, can occur in non-implanted patients. Therefore, without a comparison group of women with similar characteristics (such as age, race, etc.) and without breast implants, no conclusions can be made about the relationship between breast implants and some of these other events. These events are described in the following table.

Event	Augmentation 3-Year Rate
Biopsy Procedure	3%
Malignant Breast Cancer	<1%
Benign Breast Cancer	6%
Unknown Breast Cancer (i.e., not yet diagnosed)	2%
CTD - Rheumatoid Arthritis	<1%
Implant Removal due to Patient Request for Size/Style Change	4%
Implant Removal due to Patient's Request	<1%

Benefits of Implantation

The benefits of silicone-filled breast implants were assessed by a variety of outcomes, including bra cup size change and assessments of patient satisfaction, body image, body esteem, and self concept. These outcomes were assessed for patients with both original and replacement silicone devices before implantation and at every follow-up visit, except for bra size and quality-of-life concepts. Bra size was measured within the first year and a half after surgery. Quality-of-life concepts were measured at baseline and at follow-up visits 1, 2, and 4 years after implantation.

411 of the original 494 augmentation patients were included in an analysis of cup size (some did not provide data because pre/post measurements were not obtained or replacement/removal occurred prior to obtaining a post measurement). Of these 411 patients, the following shows the percentage of patients experiencing various changes in cup size: 41% increased by 1 cup size; 45% increased by 2 cup sizes; 8% increased by more than 2 cup sizes; and 6% had no increase or decreased.

341 of the original 494 patients were included in an analysis of satisfaction at 4 years. Of these 341 patients, 95% indicated being satisfied with their breast implants at 4 years. Furthermore, augmentation patients showed a statistically significant increase in satisfaction with breast size and shape after implantation.

The Quality-of Life patient surveys showed that augmentation patients scored higher (better) than the general U.S. female population on questions measuring general health-related quality of life. However, after 2 years, augmentation patients showed a slight worsening in these general scores possibly due to the increase in patient age or other lifestyle changes. Although they did worsen, they continued to remain higher than the U.S. female population. Patient responses to questions regarding overall self-concept and overall self-esteem did not change (did not increase or decrease self concept/esteem) over the 2 years after receiving implants. However, patient responses to questions regarding overall self-esteem related specifically to one's body did increase over the 2 years after receiving implants, indicating an improved body-related esteem.

SOME PRACTICAL ASPECTS OF BREAST IMPLANTATION SURGERY

When considering breast augmentation surgery, it is important for you to have confidence in your plastic surgeon and the surgical approach and device design he or she has chosen for you. The following information provides you with some information relating to the more practical aspects of breast implantation surgery.

CHOOSING A PLASTIC SURGEON

When choosing a surgeon who is experienced with breast implantation, you should know the answers to the following questions:

1. How many breast augmentation implantation procedures does he/she perform each year?
2. How many years has he/she performed breast implantation procedures?
3. Is he/she board certified, and if so, with which board?
4. In which states is he/she licensed to practice surgery? (Note that some states provide information on disciplinary action and malpractice claims/settlements to prospective patients either by request or on the worldwide web.)
5. What is the most common complication he/she encounters with breast implantation?
6. What is his/her reoperation rate with breast implantation and what is the most common type of reoperation he/she performs?

QUESTIONS TO ASK THE PLASTIC SURGEON ABOUT BREAST AUGMENTATION

The following list of questions may help to remind you of topics to discuss with your surgeon. You may have additional questions as well:

002605

1. What are the risks and complications associated with having breast implants?
2. How many additional operations on my implanted breast(s) can I expect over my lifetime?
3. How will my breasts look if I decide to have the implants removed without replacement?
4. What shape, size, surface texturing, incision site, and placement site is recommended for me?
5. How will my ability to breast feed be affected?
6. How can I expect my implanted breasts to look over time?
7. How can I expect my implanted breasts to look after pregnancy? After breast feeding?
8. What are my options if I am dissatisfied with the cosmetic outcome of my implanted breasts?
9. What alternate procedures or products are available if I choose not to have breast implants?
10. Do you have before and after photos I can look at for each procedure and what results are reasonable for me?

WHAT SIZE AND DESIGN OF IMPLANT TO CHOOSE

Familiarize yourself with the following options in breast implant surgery and be prepared to discuss with your surgeon the following issues:

Implant Shape and Size

Depending on the desired shape you wish to achieve, you and your surgeon may choose a round or contoured implant shape. Generally, the larger you want your cup size, the larger the breast implant the surgeon will consider (measured in cubic centimeters, or cc's). Contoured implants that are placed submuscularly (under your chest muscle) may assume a round shape after implantation.

Your surgeon will also evaluate your existing tissue to determine if you have enough to cover the breast implant. If you desire a breast implant size too large for your tissue, the surgeon may warn you that breast implant edges may be apparent or visible post-operatively. You may even risk surgical complications. Also, excessively large breast implants may speed up the effects of gravity and result in earlier droop or sag.

Implant Surface Texturing

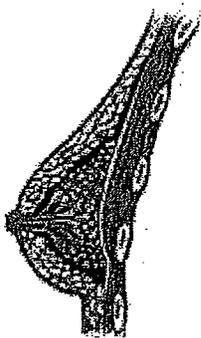
Textured surface implants were designed to reduce the chance of capsular contracture. Some information in the literature with small numbers of patients suggests that surface texturing reduces the chance of severe capsular contracture, but clinical information from studies of a large number of women with INAMED implants shows no difference in the likelihood of developing capsular contracture with textured implants compared to smooth-surfaced implants.

Palpability

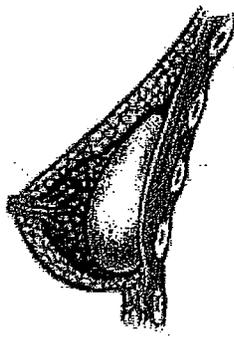
The following may cause implants to be more palpable (more easily felt): textured implants, larger implants, subglandular placement, and the amount of skin/tissue available to cover the implant.

Implant Placement

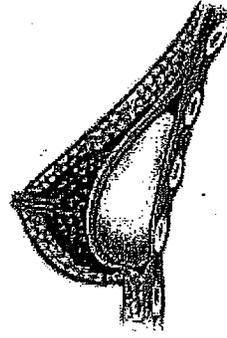
The breast implant can be placed either partially under the pectoralis major muscle (submuscular) or on top of the muscle and under the breast glands (subglandular) depending on the thickness of your breast tissue and its ability to adequately cover the breast implant. You should discuss with your surgeon the pros and cons of the implant placement selected for you.



Breast before
augmentation



Breast after
subglandular
augmentation



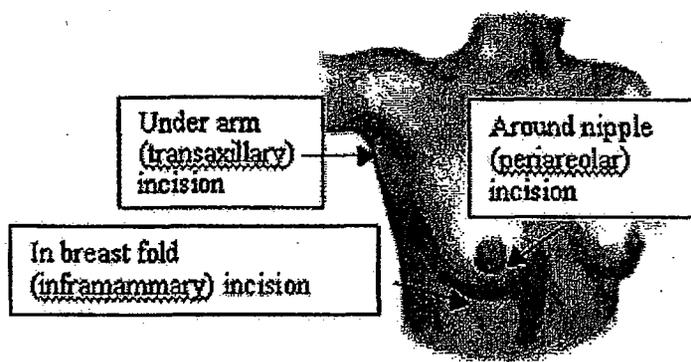
Breast after
submuscular
augmentation

The submuscular placement may make surgery last longer, may make recovery longer, may be more painful, and may make it more difficult to have some reoperation procedures than the subglandular placement. The possible benefits of this placement are that it may result in less palpable implants, less capsular contracture, and easier imaging of the breast with mammography.

The subglandular placement may make surgery and recovery shorter, may be less painful, and may be easier to access for reoperation than the submuscular placement. However, this placement may result in more palpable implants, more capsular contracture, and more difficult imaging of the breast with mammography.

Incision Sites

There are three common incision sites: under the arm (axillary), around the nipple (periareolar), or within the breast fold (inframammary). If the incision is made under the arm, the surgeon may use a probe fitted with a miniature camera, along with minimally invasive (very small) instruments, to create a "pocket" for the breast implant.



Periareolar

This incision is most concealed, but is associated with a higher likelihood of inability to successfully breast feed, as compared to the other incision sites.

Inframammary

This incision is less concealed than periareolar and associated with less difficulty than the periareolar incision site when breast feeding.

Axillary

This incision is less concealed than periareolar and associated with less difficulty than the periareolar incision site when breast feeding.

Umbilical/endoscopic

This incision site has not been studied and is not recommended.

Surgical Setting and Anesthesia

Augmentation surgery is usually performed on an outpatient basis, either in a hospital operating room, surgery center, or surgical suite in the surgeon's office. General anesthesia is commonly used, and local anesthesia is also an option. The surgery usually lasts 1 to 2 hours. Your surgeon will make an incision and create a pocket for the breast implant. Then, the breast implant will be placed in the pocket and positioned. Finally, the incision will be closed, usually with stitches, and possibly taped.

Insurance

Insurance does not cover breast augmentation and may not cover reoperation (additional surgery) and additional surgeon's visits following augmentation.

REGISTERING YOUR BREAST IMPLANT

INAMED Corporation maintains a device registry to identify patients who have INAMED's silicone-filled breast implants. The registry is designed to collect demographic and contact information for patients who are implanted with INAMED's silicone-filled breast implants. In addition, registration of your device can assist INAMED in handling problems you experience with your implants and in processing ConfidencePlus™ claims.

With patient consent, information collected in the device registry may be provided to assist with national breast implant surveys conducted by, for example, the National Institutes of Health (NIH).

INAMED strongly recommends that all patients receiving silicone-filled breast implants be registered in this database.

Successful device registration begins with the **Medical Device Registration Form** that is supplied with every breast implant. After surgery your doctor should provide you with the Medical Device Registration Form. The top portion of the form will have been completed with device specific information. The rest of the form should be completed by you and returned to INAMED Corporation in the postage paid envelope provided.

Device Identification Card

You will also be given a device identification card with the style and serial number of your breast implant(s). This card is for your permanent record and should be kept in a safe place. In the event you have a concern or problem with your implant you can use this card to describe the implant to your health care provider or to INAMED.

WHAT YOU NEED TO KNOW AFTER THE SURGERY

Once your surgery is complete, there are a few things you can do to minimize the likelihood that you will experience serious complications.

TAKING CARE OF YOUR IMPLANTS AND YOURSELF

You will probably feel somewhat tired and sore for several days following the operation, and your breasts may remain swollen and sensitive to physical contact for a month or longer. You may also experience a feeling of tightness in the breast area as your skin adjusts to your new breast size.

Post-operative care may involve the use of a post-operative bra, compression bandage, or jogging bra for extra support and positioning while you heal. At your surgeon's recommendation, you will most likely be able to return to work within a few days, although you should avoid any strenuous activities that could raise your pulse and blood pressure for at least a couple of weeks. Your surgeon may also recommend breast massage exercises. If you experience fever, or noticeable swelling and/or redness in your implanted breast(s), you should contact your surgeon immediately.

Once you are healed, you should be routinely monitored for implant ruptures with physical examination by your physician and MRI. Your physician may recommend removal of confirmed or suspected ruptured devices.

IF YOU EXPERIENCE A PROBLEM

You should report any problems that you notice with your implants immediately to your plastic surgeon. If you believe that you have experienced a serious problem(s) related to your breast implants, you should have your health professional report the problem(s) to FDA. You may also report any serious problem directly through the FDA's MedWatch voluntary reporting system. An adverse event is serious and should be reported when it results in an initial or prolonged hospitalization, disability, congenital anomaly, or medical or surgical intervention. This information reported to MedWatch is entered into databases to be used to follow safety trends (patterns) of a device and to determine whether further follow-up of any potential safety issues related to the device is needed.

To report, use MedWatch form 3500 which may be obtained through FDA's website at <http://www.fda.gov/medwatch/index.html>. You may also call 1.888.463.INFO.FDA (1.888.463.6332), from 10:00am-4:00pm Eastern Time, Monday through Friday to receive an additional FDA MedWatch Package. Keep a copy of the MedWatch form completed by your surgeon for your records.

IF YOU NEED TO REPLACE A FAILED IMPLANT

The ConfidencePlus™ Limited Warranties provide lifetime replacement and limited financial reimbursement in the event of loss of shell integrity resulting in implant deflation or rupture, subject to certain conditions as fully discussed in the ConfidencePlus™ literature. For more information, please contact Product Support at 800.624.4261.

002611

HOW TO RECEIVE MORE INFORMATION

If after reading this booklet, you have additional questions about breast implants or breast implant surgery, there are a number of resources available to you.

TOLL-FREE NUMBER

If you are a patient or a prospective patient and wish to speak to an INAMED Aesthetics Breast Implant Support Specialist to inquire about breast implants or discuss any concerns, call toll free at 800.362.4426.

GENERAL RESOURCES ABOUT IMPLANTS

Upon request to INAMED or to your plastic surgeon, you will be provided with a copy of the Directions for Use (package insert). For more detailed information on the preclinical and clinical studies conducted by INAMED, you are referred to the Summary of Safety and Effectiveness Data for this product at <http://www.fda.gov/cdrh/pdf/TBD.html>.

You will also be given a device identification card with the style and serial number of your breast implant(s).

ADDITIONAL RESOURCES

INAMED Aesthetics
1-800-624-4261
www.inamedaesthetics.com

Institute of Medicine Report on the Safety of Silicone Implants
www.nap.edu/catalog/9618.html

Food and Drug Administration
1-888-INFO-FDA or 301-827-3990
www.fda.gov/cdrh/breastimplants/

FDA Breast Implant Consumer Handbook - 2004
<http://www.fda.gov/cdrh/breastimplants/indexbip.html>
<http://www.fda.gov/cdrh/breastimplants/indexbip.PDF>

002612

GLOSSARY OF MEDICAL/TECHNICAL TERMS

Areola	The pigmented or darker colored area of skin surrounding the nipple of the breast.
Asymmetry	A lack of proportion of shape, size and position on opposite sides of the body.
Autoimmune Disease	A disease in which the body mounts an "attack" disease response to its own tissues or cell types. Normally, the body's immune mechanism is able to distinguish clearly between what is a normal substance and what is foreign. In autoimmune diseases, this system becomes defective and produces antibodies against normal parts of the body, causing tissue injury. Certain diseases such as rheumatoid arthritis and scleroderma are considered to be autoimmune diseases.
Axillary	Pertaining to the armpit area.
Bilateral	Pertaining to both the left and right breast.
Biopsy	Removal and examination of sample tissue for diagnosis.
Breast Augmentation	Enlargement of the breast by surgical implantation of a breast implant or patient's own tissue.
Breast Reconstruction	Surgical restoration of natural breast contour and mass following mastectomy, trauma or injury.
Breast Revision	Revision surgery is a plastic surgery procedure to correct or refine the outcome of a previous breast surgery. The revision may involve the replacement of a breast implant.
Capsular Contracture	Tightening of the tissue surrounding a breast implant which results in a firmer breast.
Capsulectomy	Surgical removal of the entire capsule surrounding a breast implant.
Capsulotomy	Closed Capsulotomy: Compression on the outside of the breast to break the capsule and relieve contracture. Open Capsulotomy: Surgically cutting or removing part of the capsule through an incision.
Carcinoma	Invasive malignant tumor.
Congenital Anomaly	Abnormality existing at birth.
Connective Tissue Disease (CTD)	A disease or group of diseases affecting connective tissue. The cause of these diseases are unknown. The diseases are grouped together on the basis of clinical signs, symptoms, and laboratory abnormalities.
Rupture	Refers to loss of silicone gel from a silicone-filled breast implant due to a tear or cut in the implant shell.
Displacement	Shifting from the original position.
Epidemiological	Pertaining to the cause, distribution and control of disease in populations.
Extrusion	A breast implant or tissue expander being pressed out of the body.

Fibrous Tissue	Tissue resembling fibers.
Gel Bleed	Gel components passing through the shell.
Hematoma	A swelling or mass of blood (usually clotted) confined to an organ, tissue, or space and caused by a break in a blood vessel.
Immune Response	The reaction of the body to substances that are foreign or are interpreted as being foreign.
Inframammary	Below the breast.
Inframammary Fold	The crease at the base of the breast and the chest wall.
Inframammary Incision	A surgical incision at the inframammary fold.
In-Patient Surgery	Surgery performed in a hospital requiring an overnight stay
Latissimus Dorsi	Two triangular muscles running from the spinal column to the shoulder.
Mammoplasty	Plastic surgery of the breast.
Mammary	Pertaining to the breast.
Mammography	Use of radiography (X-rays) of the breast to detect breast cancer. Recommended as a screening technique for early detection of breast cancer.
Mastectomy	Surgical removal of the breast. Subcutaneous Mastectomy: Removal of breast tissue, preserving the skin and nipple. Partial Mastectomy: Removal of primary tumor and a wide margin of tissue, may include the overlying skin and the muscle fibrous tissue (fascia) underlying the tumor. Total (Simple) Mastectomy: Removal of breast tissue and the nipple; sometimes accompanied by armpit (axillary) node dissection. Modified Radical Mastectomy: Removal of breast tissue, nipple, and fascia of chest (pectoralis) muscle with axillary node dissection.
Mastopexy	Plastic surgery to move sagging (ptotic) breasts into a more elevated position.
Necrosis	Death of tissue. May be caused by insufficient blood supply, trauma, radiation, chemical agents or infectious disease.
Oncologist	A specialist in the branch of medicine dealing with the study and treatment of tumors.
Out-Patient Surgery	Surgery performed in a hospital or surgery center not requiring an overnight stay.
Palpate/Palpability	To feel with the hand.
Pectoralis	The major muscle of the chest.
Plastic Surgery	Surgery intended to improve, restore, repair, or reconstruct portions of the body following trauma, injury or illness.

002614

Prosthesis	An artificial device used to replace or represent a body part.
Ptosis	Sagging of the breast usually due to normal aging, pregnancy or weight loss.
Rectus Abdominus	Major abdominal (stomach) muscle.
Saline	A solution of sodium chloride (salt) and water.
Seroma	Localized collection of serum (the watery portion of blood), that resembles a tumor.
Serratus	Muscle located beneath the chest's pectoralis major and minor muscles and the rib cage.
Silicone Elastomer	A type of silicone that has elastic properties similar to rubber.
Subglandular Placement	Placement of the breast implant behind the skin and mammary gland, but on top of the chest (pectoralis) muscle. Also called prepectoral or retromammary placement.
Submuscular Placement	Placement of the breast implant under the chest (pectoralis) muscle, or under the pectoralis and serratus muscles. Also called retropectoral or subpectoral placement.
Surgical Incision	Cut made in tissue for surgical purposes.
Transaxillary Incision	Incision across the long axis of the armpit (axilla).
Umbilical	Pertaining to the belly button.
Unilateral	Affecting only left or right breast.

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MAKING AN INFORMED DECISION

SILICONE-FILLED BREAST IMPLANT RECONSTRUCTION

 **DINAMED**
AESTHETICS

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INTRODUCTION

TO THE PATIENT

The information contained in this booklet, *Making an Informed Decision, Silicone-filled Breast Implant Surgery*, is designed to provide you with an understanding of the risks and benefits of surgery with silicone filled breast implants as well as provide an overview of the experience of patients in the INAMED Core Clinical Study.

Please review this information to ensure your preoperative consultation is effective and comprehensive. Make notes about issues that you would like to further discuss with your plastic surgeon, and ask questions. Give yourself time to consider your choices and proceed with surgery only after you are satisfied that the decision is right for you.

TO THE HEALTHCARE PROFESSIONAL

Discussion of the content of this document is an important part of the informed decision making process for the patient. Please take time to familiarize yourself with the information presented here and incorporate it into your pre-operative discussion.

For your convenience a signature block is provided as a means of documenting the preoperative discussion in the patient's file.

After removing the signature block, please give this book to the patient for her records.

Making an Informed Decision

Silicone Filled Breast Implant surgery

Reconstruction

I have reviewed the information presented in *Making an Informed Decision Silicone Filled Breast Implant Surgery, Reconstruction*. My concerns and questions have been addressed by my doctor and I have considered alternatives to reconstruction surgery including use of external prostheses or surgery with saline-filled breast implants.

I am choosing to proceed with silicone filled breast implant surgery.

Patient Name

Patient Signature

Date

Surgeon Name

Surgeon Signature

Date

002619

TABLE OF CONTENTS

SO, YOU'RE CONSIDERING SILICONE-FILLED BREAST IMPLANT SURGERY

WHAT GIVES THE BREAST ITS SHAPE?

WHAT IS SILICONE?

WHAT IS A SILICONE-FILLED BREAST IMPLANT?

WHAT TYPES OF SILICONE-FILLED BREAST IMPLANTS ARE AVAILABLE FROM INAMED?

ARE SILICONE-FILLED BREAST IMPLANTS RIGHT FOR YOU?

WHAT ARE THE BENEFITS OF BREAST RECONSTRUCTION SURGERY?

WHAT YOU NEED TO KNOW BEFORE BREAST RECONSTRUCTION SURGERY?

WHAT EVIDENCE IS THERE THAT INAMED SILICONE-FILLED IMPLANTS ARE SAFE AND EFFECTIVE?

SOME PRACTIAL ASPECTS OF BREAST RECONSTRUCTION SURGERY

REGISTERING YOUR BREAST IMPLANT

WHAT YOU NEED TO KNOW AFTER THE SURGERY

HOW TO RECEIVE MORE INFORMATION

GLOSSARY OF MEDICAL/TECHNICAL TERMS

SO, YOU'RE CONSIDERING SILICONE-FILLED BREAST IMPLANT SURGERY

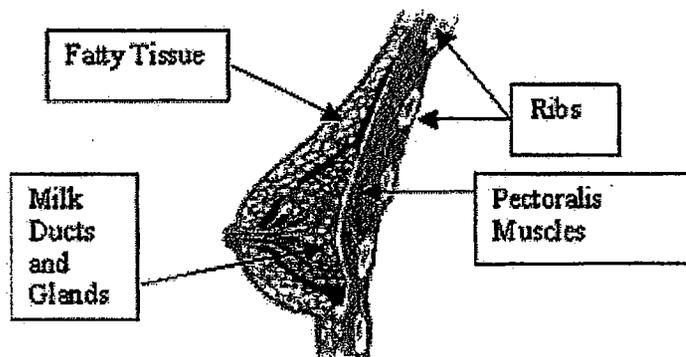
You may be considering breast implant surgery to restore your breast shape after a mastectomy or an injury that resulted in either partial or total loss of the breast(s) or to correct a birth defect. This is referred to as breast reconstruction. Whether you decide to have breast reconstruction depends on your own individual case, medical condition, general health, lifestyle, emotional state, and breast size and shape. You may wish to speak with your family, friends, breast implant support groups, and breast cancer support groups to help you in making this decision.

If you are considering breast reconstruction and do not have a plastic surgeon, ask your general surgeon for a referral for the names of experienced, board certified plastic surgeons in your area. Your general surgeon, plastic surgeon, and oncologist should work together to plan your mastectomy and reconstruction procedure to give you the best possible result.

INAMED has prepared this patient information booklet to help you better understand the breast implant procedure and assist you in making an informed decision about breast reconstruction surgery. It will help to answer some of the questions you may have about the surgery and about breast implants in general. It will also provide you with specific information about the INAMED silicone-filled breast implant product line.

This educational booklet can not and should not take the place of discussing your surgery with your plastic surgeon. Make sure to speak with your surgeon about your expectations of the results, as well as what you can expect regarding the length of the surgery, your recovery, and any potential complications of the surgery. Ask questions. You and your surgeon will work together to help you to achieve the body image you desire.

WHAT GIVES THE BREAST ITS SHAPE?



The breast consists of milk ducts and glands, surrounded by fatty tissue that provides its shape and feel. Beneath the breast is the pectoralis major muscle (chest muscle) of the chest wall.

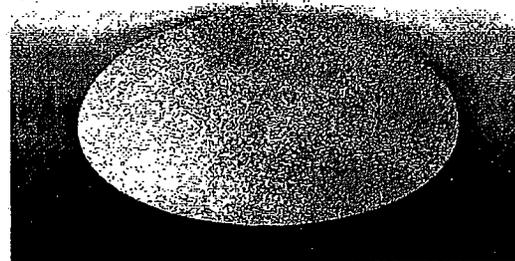
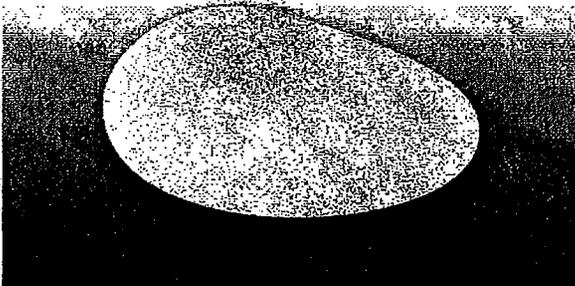
Women may choose breast reconstruction because they wish to restore breast shape following a mastectomy or injury to the breast or to correct a birth defect.

WHAT IS SILICONE?

Silicones are a family of compounds, made from silicon, a naturally occurring element. Silicones have been part of the consumer industry for over 50 years and because they can be manufactured in various ways, silicones appear in a wide variety of products most of us use everyday. Medical devices utilizing silicone include artificial joints, facial implants, catheters, tissue expanders and breast implants.

WHAT IS A SILICONE-FILLED BREAST IMPLANT?

A silicone-filled breast implant is a sac (implant shell) made of silicone elastomer (rubber) and filled with silicone gel. It is surgically implanted either under your breast tissue and above your chest muscle or below your chest muscle. Your plastic surgeon will discuss with you the best positioning for your implants.



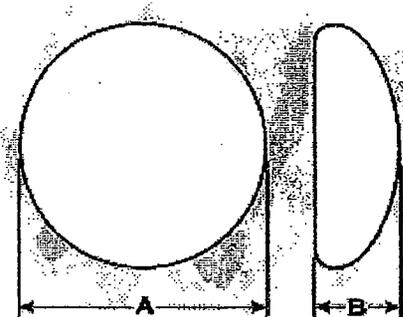
WHAT TYPES OF SILICONE-FILLED BREAST IMPLANTS ARE AVAILABLE FROM INAMED?

Breast implants come in a variety of shapes, surface textures, and sizes. INAMED manufactures several styles of round and one style of shaped silicone-filled breast implant (see below). They are available with smooth shell surfaces or textured shell surfaces. Your plastic surgeon will discuss with you the implant design that will best help you achieve your desired outcome.

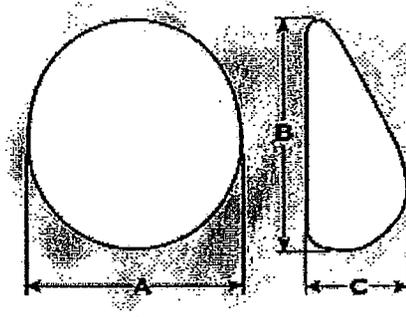
Round Breast Implants:	
Style 10:	Smooth shell surface, moderate projection
Style 20:	Smooth shell surface, full projection
Style 40:	Smooth shell surface, standard projection
Style 45:	Smooth shell surface, full projection
Style 110:	BIOCELL® Textured shell surface, moderate projection
Style 120:	BIOCELL® Textured shell surface, full projection

Shaped Breast Implants:

Style 153:	BIOCELL® Textured shell surface, double lumen, full height, full projection
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A = Width; B = Projection
Round Breast Implant



A = Width; B = Height; C =
Projection
Shaped Breast Implant

ARE SILICONE-FILLED BREAST IMPLANTS RIGHT FOR YOU?

In order to help you achieve your cosmetic goals safely, silicone-filled implants should not be used in women under the age of 18, in women with existing malignant or pre-malignant cancer of the breast who have not been successfully treated, in women with an active infection anywhere in the body, and in women who are currently pregnant or nursing.

In addition, silicone-filled breast implants have not been clinically testing in women with autoimmune diseases like lupus or scleroderma, in women with conditions that could interfere with wound healing and blood clotting, in women with a weakened immune system (such as women receiving immunosuppressive therapy), and in women with a reduced blood supply to the breast tissue. If you have any of these conditions or other serious health problems you should discuss with your surgeon whether breast reconstruction surgery is appropriate for you.

WHAT ARE THE BENEFITS OF BREAST RECONSTRUCTION SURGERY?

The benefits of breast reconstruction with silicone-filled breast implants are an improved cosmetic appearance and an improved body image and an increased self esteem.

WHAT YOU NEED TO KNOW BEFORE BREAST RECONSTRUCTION SURGERY

Before you agree to any surgical procedure, you need to fully understand the potential health risks that are associated with the surgery. If you are considering breast reconstruction, you also need to understand the potential health risks that may be associated with the long-term implantation of breast implants. These are described below.

THERE ARE RISKS ASSOCIATED WITH THE IMPLANT SURGERY.

All surgery carries some risk. The most commonly reported surgery-related risks for breast augmentation surgery are infection, bleeding, seroma, scarring, anesthesia, and pain.

Scarring

Most scars following breast augmentation are pale thin lines. However, they may become red, firm, and elevated. Some scars fade with time but scar revision may be desired.

Infection

Infection occurs very rarely following breast implant surgery. Most infections resulting from surgery appear within a few days to weeks after the operation, although infection is possible at any time after surgery. Infections with an implant present are harder to treat than infections in normal body tissues. Infections are typically treated with antibiotics, but if the infection does not respond to antibiotics, the implant may have to be removed. Another implant may be placed after the infection is resolved. In very rare instances, Toxic Shock Syndrome, a potentially life threatening condition, has been noted in women after breast implant surgery. Symptoms include sudden fever, vomiting, diarrhea, fainting, dizziness, and/or sunburn-like rash. You should see your surgeon immediately for diagnosis and treatment for this condition.

Hematoma

Bleeding (hematoma) occurs in 2-4% of breast implant procedures. It is usually seen soon after surgery, however, it can occur at any time after injury to the breast. While the body absorbs small hematomas, large ones will require the placement of surgical drains for proper healing. A small scar can result from surgical draining. Implant rupture can occur from surgical draining if damage to the implant occurs during the draining procedure.

Seroma

Seroma is a collection of the watery portion of the blood (in this case, around the implant or around the incision). While the body absorbs small seromas, large ones will require the placement of surgical drains for proper healing. A small scar can result from surgical draining. Implant rupture can occur from surgical draining if damage to the implant occurs during the draining procedure.

Anesthesia

As with all surgeries, there is a small risk that you will experience an adverse reaction to the anesthesia.

Pain

Pain of varying intensity and duration may occur and persist following breast implant surgery. In addition, improper size, placement, surgical technique, or capsular contracture may result in pain associated with nerve entrapment or interference with muscle motion. You should inform your surgeon if you experience severe pain.

YOU MAY NOT BE PLEASED WITH THE COSMETIC OUTCOME.

Dissatisfying results such as wrinkling, asymmetry (one breast is larger or smaller or a different shape than the other), implant displacement (shifting), incorrect size, unanticipated shape, implant palpability (ability to feel the implant under the skin), scar deformity, and/or hypertrophic (irregular, raised scar) scarring, may occur. Careful surgical planning and technique can minimize but not always prevent such results.

YOU MAY REQUIRE ADDITIONAL SURGERY AND SURGEON VISITS.

Breast implants are not considered lifetime devices. You may undergo implant removal with or without implant replacement during your lifetime.

MANY OF THE CHANGES TO YOUR BREAST FOLLOWING IMPLANTATION ARE IRREVERSIBLE.

If you later choose to have your implant(s) removed, you may experience unacceptable dimpling, puckering, or wrinkling of the skin or other cosmetic changes of the breast.

BREAST IMPLANTS MAY AFFECT YOUR ABILITY TO BREAST FEED.

Breast implant surgery may affect your ability to breast feed because the surgery may sever nerves that stimulate the body to release the hormones that trigger milk release. In addition, an incision around the nipple, which may be done to make the surgical scar less noticeable, also may sever ducts that drain milk from the mammary gland, such that even if the mother has an adequate milk supply, it may be difficult for the milk to drain into the nipple. Also, breast implants will not prevent a woman's breasts from sagging after pregnancy.

At this time it is not known if a small amount of silicone may diffuse (pass through) from the silicone-filled breast implant and may find its way into breast milk. If this occurs, it is not known what effect it may have on the nursing infant. Although there are no current methods for detecting silicone levels in breast milk, a study measuring silicon (one component in silicone) levels did not indicate higher levels in breast milk from women with silicone-filled breast implants when compared to women without implants.

BREAST IMPLANTS MAKE ROUTINE SCREENING MAMMOGRAPHY MORE DIFFICULT.

The presence of breast implants may interfere with finding breast cancer during mammography and also may make it difficult to perform mammography. Therefore, it is essential that you tell your mammography technologist that you have an implant before the procedure. The technologist can use special techniques to minimize the possibility of rupture and to get the best possible views of the breast tissue. You may wish to undergo a preoperative mammogram and another one 6 months to one year after implantation to establish a baseline.

Because the breast is squeezed during mammography, it is possible for an implant to rupture during the procedure. More x-ray views are necessary with these special techniques; therefore, women with breast implants will receive more radiation. However, the benefit of the mammogram in finding cancer outweighs the risk of the additional x-rays.

In addition to routine mammograms, women should perform a breast self-examination monthly on the implanted breast. In order to do this effectively, you should ask your surgeon to help you distinguish the implant from your breast tissue. Any new lumps or an abnormal finding on the mammogram should be evaluated with a biopsy. If a biopsy is performed, care must be taken to avoid puncturing the implant.

YOUR HEALTH INSURANCE PREMIUMS MAY INCREASE, COVERAGE MAY BE DROPPED, AND/OR FUTURE COVERAGE MAY BE DENIED.

Treatment of complications may not be covered as well. You should check with your insurance company regarding these coverage issues.

THE LONG-TERM SAFETY AND EFFECTIVENESS OF BREAST IMPLANTS HAVE NOT BEEN STUDIED.

INAMED is monitoring the long-term (10-year) chance of implant rupture, reoperation, implant removal, and capsular contracture (hardening of the tissues around the implant). INAMED is also conducting mechanical testing to assess the long-term likelihood of implant rupture. As new information becomes available, INAMED will issue an updated version of this brochure.

YOU HAVE OTHER OPTIONS.

There are alternatives to breast reconstruction with a silicone-filled breast implant. You may choose to have no treatment at all and accept your breast as they are. You may choose to wear an external prosthesis. Breast forms are available in a variety of shapes, sizes, and materials such as foam, cotton, and silicone. Custom prostheses are also available to match the size and shape of your breast. You may choose to have saline-filled implants implanted.

Breast reconstruction can also be accomplished using your own tissues (a tissue flap) or a combination of the tissues and a prosthesis. The breast can be reconstructed by surgically moving a section of skin, fat and muscle from one area of your body to another. The section of tissue may be taken from such areas as your abdomen, upper back, upper hip, or buttocks. The tissue flap may be left attached to the blood supply and moved to the breast area through a tunnel under the skin (a pedicled flap) or it may be removed completely and reattached to the breast area by microsurgical techniques (a free flap). Operating time is generally longer with free flaps, because of the microsurgical requirements. Flap surgery requires a hospital stay of several days and generally a longer recovery time than implant reconstruction. Flap surgery also creates scars at the site where the flap was taken and on the reconstructed breast. However, flap surgery has the advantage of being able to replace tissue in the chest area. This may be useful when the chest tissues have been damaged and are not suitable for tissue expansion. Another advantage of flap procedures over implantation is that alteration of the unaffected breast is generally not needed to improve symmetry. The most common types of tissue flaps are the TRAM (transverse rectus abdominus musculocutaneous flap) (which uses tissue from the abdomen) and the latissimus dorsi flap (which uses tissue from the upper back). Flap surgery, particularly the TRAM flap, is a major operation, and more extensive than your mastectomy operation. It requires good general health and strong emotional motivation. If you are very overweight, smoke cigarettes, have had previous surgery at the flap site, or have any circulatory problems, you may not be a good candidate for a tissue flap procedure. Also, if you are very thin, you may

002627

not have enough tissue in your abdomen or back to create a breast mound with this method.

SOME LOCAL COMPLICATIONS CAN OCCUR IN IMPLANTED BREASTS.

Local complications are sometimes observed in breast of women with silicone-filled implants. These include capsular contracture, rupture, calcification, implant extrusion, wound healing problems or tissue necrosis, visible skin wrinkling and rippling, changes in nipple and skin sensation, pain, malposition, asymmetry, breast tissue atrophy, and re-operation.

Capsular Contracture

The scar tissue or capsule that normally forms around the implant may tighten and squeeze the implant and is called capsular contracture. Capsular contracture may be more common following infection, hematoma, and seroma. It is also more common with subglandular placement (behind the mammary gland and on top of the chest muscle). Symptoms range from mild firmness and mild discomfort to severe pain, distorted shape, palpability of the implant, and/or movement of the implant.

Capsular contracture may occur on one side, both sides, or not at all. In severe cases, the disfigurement or discomfort resulting from capsular contracture may require surgery to remove the scar tissue around the implant and/or implant replacement. In some cases, the contracture may not be correctable and implant removal of the implant and capsule tissue may be necessary. Closed capsulotomy is not recommended due to concerns about implant rupture and localized bleeding. The occurrence of capsular contracture is not predictable, however, the chance of it happening increases with time. Capsular contracture may happen again after these additional surgeries.

Rupture

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.

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.

Gel Bleed

There is no evidence from the medical literature or from Inamed's own testing suggesting that gel bleed (gel components passing through the shell) may be associated with local complications in breast implant patients. In addition, clinical study patients in Inamed's Core clinical study for silicone-filled breast implants were at no higher risk of local complications when compared to the risk of local complications reported in Inamed's 1995 saline-filled breast implant clinical study.

Calcium Deposits

Deposits of calcium can be seen on mammograms and although they are benign, they can be mistaken for possible cancer, resulting in additional surgery for biopsy and/or removal of the implant to distinguish the calcium deposits from cancer.

Implant Extrusion

If the skin or breast tissue covering the implant is very thin and/or there is a problem with healing, the implant may break through the skin and become exposed. This will require removal of the implant.

Wound Healing Problems or Tissue Necrosis

Some patients experience delayed healing of the incision site or they may not heal well. This can result in an unattractive scar and if the implant is exposed, further surgery will be required. Tissue breakdown or necrosis (the formation of dead tissue around the implant) will delay wound healing, may cause wound infection, and may require surgical correction and/or implant removal. Permanent scar deformity may occur following necrosis. Factors associated with increased necrosis include infection, use of steroids in the surgical pocket, smoking, chemotherapy/radiation, and excessive heat or cold therapy.

Visible Skin Wrinkling and Rippling

Visible rippling can result when an implant pulls on the overlying tissues or when the natural folds in the implant are visible through the skin. Removal and replacement of the implant may correct this problem.

Change in Nipple and Skin Sensation

Some change in nipple sensation is not unusual right after surgery and after several months, most patients have normal sensation. Only rarely does permanent loss of nipple and skin sensation or hypersensitivity occur. The range of changes varies from intense sensitivity to no feeling in the nipple or breast following surgery. Changes in feeling can be temporary or permanent and may affect your sexual response or your ability to nurse a baby.

Pain

Pain of varying intensity and duration may occur and persist following breast implant surgery. In addition, improper size, placement, surgical technique, or capsular contracture may result in pain associated with nerve entrapment or interference with muscle motion. You should tell your surgeon about any severe pain you may experience.

Malposition

Breast malposition may result from shifting after initial placement, excessive sagging or stretching of the lower breast, or capsular contracture. Removal and replacement of the implant may correct this problem.

Asymmetry

Asymmetry (differences in size or shape between breasts) can result from some of the above-mentioned complications. Most women's breasts have at least some asymmetry, even without implants. Removal and replacement of the implant may correct this problem.

Breast Tissue Atrophy

Pressure from breast implants may cause the surrounding tissue to thin or shrink and this may result in the implant becoming more visible or palpable. This can occur while implants are still in place or following implant removal without replacement.

Re-operation

Implanted devices do not last forever, and like many other implanted devices may need to be replaced or removed after a period of time. The rates of re-operation reported in the literature for noncosmetic reasons range from 10 to 30%. Patients should expect to have additional surgery at some point to replace or remove the implant. Also, problems such as rupture, capsular contracture, infection, shifting, and calcium deposits can require removal of the implants. Many women decide to have the implants replaced, but some women do not. If you choose not to, you may have cosmetically unacceptable dimpling and/or puckering of the breast following removal of the implant.

THERE IS A CONCERN THAT BREAST IMPLANTS INCREASE THE RISK OF CERTAIN DISEASES OR EVENTS.

There has been discussion in the scientific and regulatory communities regarding the potential for silicone-filled breast implants to be associated with certain systemic diseases or concerns. The strength of these associations between breast implants and connective tissue disease, cancer, nervous system effects, effects on children, and suicide is discussed below.

Connective Tissue Disease

Concern over the association of breast implants to the development of autoimmune or connective tissue diseases, such as lupus, scleroderma, or rheumatoid arthritis, was raised because of cases reported in the literature with small numbers of women with implants. Several large epidemiological studies of women with and without implants indicate that these diseases are no more common in women with implants than those in women without implants.

Some patients in INAMED's Core Clinical Study showed an increase over time in some CTD signs and symptoms and those CTD signs and symptoms specific to fibromyalgia, such as fatigue, swelling, weakness, aches, back and neck pain. However, patients with INAMED's saline-filled implants showed similar increases in these signs and symptoms. This indicates that the increased signs and symptoms are most likely not caused by the silicone-filled breast implants and may be attributed to other factors such as aging.

Cancer and Benign Breast Disease

The overwhelming majority of epidemiological studies indicate that cancer and benign breast disease are no more common in women with implants than those without implants, thus offering compelling scientific evidence of a lack of association between breast implants and cancers.

Nervous System Effects

Most investigators report no causal relationship between the presence of breast implants and neurological effects including Meniere's disease, hearing loss, and neurological disease, including multiple sclerosis and Guillain-Barre syndrome.

Effects on Children of Women with Breast Implants

The concern that children born to mothers with silicone breast implants are at risk of developing health problems stems from reports of children born to or breastfed by such women who developed swallowing difficulties, irritability, nonspecific skin rashes, fatigue, and other symptoms. However, epidemiological investigations have not found any increased risk of adverse health outcomes, including occurrence of esophageal disorders, connective tissue disease, and congenital malformations in children born to women with breast implants.

Suicide

Some investigators have raised concerns that the risk of suicide is increased in patients with silicone-filled breast implants. However, their studies do not consider other factors that are likely to affect a woman's predisposition for suicidal tendencies and that are widely acknowledged to be more common among women who seek breast implants, such as cigarette smoking, alcohol consumption, weight, parity, low self-esteem, depression, or other psychiatric/emotional disorders.

WHAT EVIDENCE IS THERE THAT INAMED SILICONE-FILLED IMPLANTS ARE SAFE AND EFFECTIVE?

Although you will experience your own risks (complications) and benefits following breast implant surgery, this section describes the specific complications and benefits of INAMED silicone-filled breast implants. INAMED's studies of women seeking reconstruction with silicone-filled breast implants indicate, for example, that about 1 in 2 reconstruction patients (47%) can expect to experience additional breast surgery at some point through 3 years after implant surgery. The information below provides more details about the complications and benefits you may experience.

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.

STUDIES IN WOMEN

INAMED conducted clinical studies testing of its silicone-filled breast implants to determine the short-term and most common complications as well as the benefits of its implants. The Core Clinical Study was designed as a 10-year study to assess all complications as well as patient satisfaction, body image, body esteem, and self concept. Patients were followed annually, and data through 3 years after implantation are currently available. The Core Study enrolled 221 reconstruction patients. Of those reconstruction patients available to be seen at the 3-year follow-up visit, 94% were seen.

Complications Reported in the Core Study

The 3-year complication rates are shown from the most common to the least common in the table below. The rates reflect the number of reconstruction patients out of 100 who experienced the listed complication at least once within the first 3 years after implantation. Some complications occurred more than once for some patients. The two most common complications experienced within the first 3 years of implantation were capsular contracture (15% or 15 patients out of 100) and asymmetry (13% or 13 patients out of 100). Some complications required patients to undergo an additional breast surgery in order to address the complication. The following table shows all complications (i.e., those that lead to additional surgery and those that did not.)

Complication	3-Year Complication Rate
Capsular Contracture	15%
Asymmetry	13%
Implant Malposition	8%
Rupture	7%
Breast Pain	6%
Scarring, Redness, Seroma/Fluid Accumulation, Tissue or Skin Necrosis, Wrinkling, Delayed Wound Healing, Swelling	2-5%
Hematoma, Skin Rash, Implant Extrusion*, Infection, Bruising	1%
Nipple Hypersensitivity/Paresthesia, Complications, Pneumothorax*, Ptosis, Implant Palpability/Visibility	<1%
Not Occurring: Capsule Calcification, Irritation, Lymphadenopathy, Lymphedema, Loss of Skin Sensation, Skin Hypersensitivity/Paresthesia, Loss of Nipple Sensation, Other Nipple Complications, Other Complications	0%

*All complications were assessed with severity ratings. Most rates shown in the table include only complications rated moderate, severe, or very severe (excludes mild and very mild ratings). The only complication rates that include all severity ratings are rupture, pneumothorax, and implant extrusion.

Additional Surgeries

Some of the complications reported in the above table led to an additional surgery and some additional surgeries involved removal of the implant. A patient's risk of an additional surgery or implant removal is 47% risk of additional surgery through 3 years and 22% risk of implant removal through 3 years.

Through 3 years, 102 reconstruction patients had at least one additional surgery, and some patients required multiple surgeries. A total of 144 additional surgeries were performed through 4 years. Although some complications led to an additional surgery, many complications do not require additional surgery and many additional surgeries are performed without removal of the implant. 46 of the 101 patients had an implant removed. For example, a patient's risk of capsular contracture is 15%; however, a patient's risk of a capsular contracture that requires additional surgery is less, at 6%, and a patient's risk of having the implant removed to treat the capsular contracture is even lower at 2%. The following table describes a patient's risk of having an additional surgery or implant removal for the complications listed in the previous table.

(Because rupture is addressed in the next section, it is not included in the following table.)

Complication	% Risk of Complication Leading to Additional Surgery	% Risk of Complication Leading to Removal/Replacement
Asymmetry	12.1%	9.2%
Breast Pain	<1%	<1%
Capsular Contracture	6%	2%
Hematoma	1%	<1%
Scarring	14.7%	0.5%
Implant Malposition	15.8%	6.8%
Implant Palpability	0%	0%
Loss of Skin Sensation	0%	0%
Nipple Complication	0%	0%
Ptosis	2.9%	1.0%
Skin Rash	0%	0%
Swelling	0%	0%
Patient Request for Style/Size Change	10.1%	9.6%
Other	5.5%	4.0%
Breast Tissue Contour Deformity	3.8%	1.1%
Need for Biopsy	3.1%	0.5%
Delayed Wound Healing	2.3%	0%
Breast Cancer	1.0%	1.0%
Wrinkling/Rippling	1.0%	1.0%
Extrusion	1.0%	0.5%
Injury (surgery related or traumatic)	0.5%	0.5%
Necrosis	0.5%	0.0%

Rupture

Through 3 years, both silent and symptomatic (i.e., non-silent) ruptures have been detected in the reconstruction patients. The 3-year rates of these events are described as 11% risk of any rupture, 10% risk of silent rupture, and < 1% risk of symptomatic rupture. These risks are calculated by-implant rather than by-patient because the complication is implant-specific.

Some silent ruptures were discovered using MRI. A portion of the study participants underwent routine screening with MRI. Of the implants that were diagnosed as ruptured and later explanted, the Core Study showed 36-37% of the MRI-diagnosed implants to be intact.

Other Events

Through 3 years, events other than the complications described in the previous tables above were collected in the Core Clinical Study. Some of these events, such as breast cancer and connective tissue disease, can occur in non-implanted patients. Therefore, without a comparison group of women with similar characteristics (such as age, race, etc.) and without breast implants, no conclusions can be made about the relationship between breast implants and some of these other events. These events are described in the following table.

Event	Reconstruction 3-Year Rate
Biopsy Procedure	3%
Malignant Breast Cancer	0%
Benign Breast Cancer	9%
Unknown Breast Cancer (i.e., not yet diagnosed)	1%
CTD – Systemic Sclerosis/Scleroderma	<1%
Implant Removal due to Patient Request for Size/Style Change	10%
Implant Removal due to Patient's Request	0%

Benefits of Implantation

The benefits of silicone-filled breast implants were assessed by a variety of outcomes, including patient satisfaction, body image, body esteem, and self concept. These outcomes were assessed for patients with both original and replacement silicone devices before implantation and at every follow-up visit, except for quality-of-life concepts which was measured at baseline and at follow-up visit 1, 2, and 4 years.

185 of the original 221 patients were included in an analysis of satisfaction at 3 years. Of these 185 patients, 92% indicated being satisfied with their breast implants at 4 years.

The Quality-of Life patient surveys showed that reconstruction patients scored higher (better) than the general U.S. female population on questions measuring general health-related quality of life. After 2 years, the patients responses to the general health related quality of life did not change, this indicated they remained higher than the U.S. female population. Patient responses to questions regarding overall self-concept and overall self esteem (did not increase or decrease self concept/esteem) over the 2 years after receiving implants. Furthermore, patient

002636

responses to questions regarding overall self esteem related specifically to one's body remained constant over the 2 years after receiving implants.

SOME PRACTICAL ASPECTS OF BREAST RECONSTRUCTION SURGERY

When considering breast augmentation surgery, it is important for you to have confidence in your plastic surgeon and the surgical approach and device design he or she has chosen for you. The following information provides you with some information relating to the more practical aspects of breast implantation surgery.

CHOOSING A PLASTIC SURGEON

When choosing a surgeon who is experienced with breast implantation, you should know the answers to the following questions:

1. How many breast reconstruction implantation procedures does he/she perform per year?
2. How many years has he/she performed breast implantation procedures?
3. Is he/she board certified, and if so, with which board?
4. In which states is he/she licensed to practice surgery? Note that some states provide information on disciplinary action and malpractice claims/settlements to prospective patients either by request or on the worldwide web.
5. What is the most common complication he/she encounters with breast implantation?
6. What is his/her reoperation rate with breast implantation and what is the most common type of reoperation he/she performs?

QUESTIONS TO ASK THE PLASTIC SURGEON ABOUT BREAST RECONSTRUCTION

The following list of questions may help to remind you of topics to discuss with your surgeon. You may have additional questions as well.

1. What are all my options for breast reconstruction?
2. What are the risks and complications of each type of breast reconstruction surgery and how common are they?
3. What if my cancer recurs or occurs in the other breast?
4. Will reconstruction interfere with my cancer treatment?
5. How many steps are there in each procedure and what are they?
6. How long will it take to complete my reconstruction?

002637

7. How much experience do you have with each procedure?
8. Do you have before and after photos I can look at for each procedure and what results are reasonable for me?
9. What will my scars look like?
10. What kind of changes in my implanted breast can I expect over time?
11. What kind of changes in my implanted breast can I expect with pregnancy?
12. What are my options if I am dissatisfied with the cosmetic outcome of my implanted breast?
13. Can I talk with other patients about their experiences?
14. What is the estimated total cost of each procedure?
15. How much will my health insurance carrier cover, especially any complication that may require surgery?
16. How much pain or discomfort will I feel, and for how long?
17. How long will I be in the hospital?
18. Will I need blood transfusions, and can I donate my own blood?
19. When will I be able to resume my normal activity (or sexual activity, or athletic activity)?

WHAT SIZE AND DESIGN OF IMPLANT TO CHOOSE

Familiarize yourself with the following options in breast implant surgery and be prepared to discuss with your surgeon the following issues:

Implant Shape and Size

Depending on the desired shape you wish to achieve, you and your surgeon may choose a round or contoured implant shape. Generally, the larger you want your cup size, the larger the breast implant the surgeon will consider (measured in cubic centimeters, or cc's). Contoured implants that are placed submuscularly (under your chest muscle) may assume a round shape after implantation.

Your surgeon will also evaluate your existing tissue to determine if you have enough to cover the breast implant. If you desire a breast implant size too large for your tissue, the surgeon may warn you that breast implant edges may be apparent or visible post-operatively. You may even risk surgical complications. Also, excessively large breast implants may speed up the effects of gravity and result in earlier droop or sag.

Implant Surface Texturing

Textured surface implants were designed to reduce the chance of capsular contracture. Some information in the literature with small numbers of patients

suggests that surface texturing reduces the chance of severe capsular contracture, but clinical information from studies of a large number of women with INAMED implants shows no difference in the likelihood of developing capsular contracture with textured implants compared to smooth-surfaced implants.

Palpability

The following may cause implants to be more palpable (more easily felt): textured implants, larger implants, subglandular placement, and the amount of skin/tissue available to cover the implant.

WHAT TYPE OF SURGICAL APPROACH IS BEST FOR YOU?

Women with small or medium sized breasts are the best candidates for breast reconstruction. Reconstruction patients commonly undergo additional surgeries to improve breast symmetry and appearance. For example, because the nipple and areola are usually removed with the breast tissue in mastectomy, the nipple is usually reconstructed by using a skin graft from another area of the body or the opposite breast, in addition to tattooing the area. Nipple reconstruction is usually done as a separate outpatient procedure after the initial reconstruction surgery is complete.

Your surgeon will decide whether your health and medical condition makes you an appropriate candidate for breast implant reconstruction. Women with larger breasts may require reconstruction with a combination of a tissue flap and an implant. Your surgeon may recommend breast implantation of the opposite, uninvolved breast in order to make your breasts more alike (maximize symmetry) or he/she may suggest breast reduction (reduction mammoplasty) or a breast lift (mastopexy) to improve symmetry. Mastopexy involves removing a strip of skin from under the breast or around the nipple and using it to lift and tighten the skin over the breast. Reduction mammoplasty involves removal of breast tissue and skin. If it is important to you not to alter the unaffected breast, you should discuss this with your plastic surgeon, as it may affect the breast reconstruction methods considered for your case.

Reconstruction Incision Sites

Most implants in breast reconstruction use the mastectomy scar either immediately (during the mastectomy procedure) or after tissue expansion.

Surgical Setting and Anesthesia

Reconstruction surgery is usually performed on an inpatient basis in an operating room. General anesthesia is most often used.

The Timing of Your Breast Implant Reconstruction

The following description applies to reconstruction following mastectomy, but similar considerations apply to reconstruction following breast trauma or for reconstruction for congenital defects. The breast reconstruction process may begin at the time of your mastectomy (immediate reconstruction) or weeks to years afterwards (delayed reconstruction). Immediate reconstruction may involve placement of a breast implant but typically involves placement of a tissue expander, which will eventually be replaced with a breast implant. It is important to know that any type of surgical breast reconstruction may take several steps to complete.

Two potential advantages to immediate reconstruction are that your breast reconstruction starts at the time of your mastectomy and that there may be cost savings in combining the mastectomy procedure with the first stage of the reconstruction. However, there may be a higher risk of complications such as deflation with immediate reconstruction, and your initial operative time and recuperative time may be longer.

A potential advantage to delayed reconstruction is that you can delay your reconstruction decision and surgery until other treatments, such as radiation therapy and chemotherapy, are completed. Delayed reconstruction may be advisable if your surgeon anticipates healing problems with your mastectomy or if you just need more time to consider your options.

There are medical, financial, and emotional considerations to choosing immediate versus delayed reconstruction. You should discuss with your surgeon, plastic surgeon, and oncologist, the advantages and disadvantages of immediate reconstruction with a breast implant, expander-assisted immediate reconstruction, and delayed reconstruction.

THE BREAST IMPLANT RECONSTRUCTION PROCEDURE

The procedure for reconstruction of a breast utilizing a silicone-filled breast implant differs depending on whether the reconstruction is immediate or delayed and whether it involves a tissue expander.

Immediate or Delayed Breast Implant Reconstruction

Immediate breast reconstruction using only a breast implant may be done at the time of your mastectomy or sometime after. After the general surgeon removes your breast tissue, the plastic surgeon will then implant a breast implant that completes the reconstruction. In reconstruction following mastectomy, a breast implant is most often placed submuscularly.

Expander-Assisted (Immediate or Delayed) Breast Implant Reconstruction

Breast reconstruction usually occurs as a multistage procedure, starting with the placement of a breast tissue expander, which is replaced several months later with a

breast implant. The tissue expander placement may be done immediately, at the time of your mastectomy, or be delayed until months or years later.



**Side View,
Breast
Tissue
Removed**



**Side View,
Expander
Inserted and Filled**

Stage 1: Tissue Expansion

During a mastectomy, the general surgeon removes skin as well as breast tissue, leaving the chest tissues flat and tight. To create a breast shaped space for the breast implant, a tissue expander is placed under the remaining chest tissues.

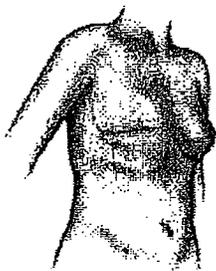
The tissue expander is a balloon-like device made from elastic silicone rubber. It is inserted unfilled, and over time, sterile saline fluid is added by inserting a small needle through the skin to the filling port of the device. As the tissue expander fills, the tissues over the expander begin to stretch, similar to the gradual expansion of a woman's abdomen during pregnancy. The tissue expander creates a new breast-shaped pocket for a breast implant.

Tissue expander placement usually occurs under general anesthesia in an operating room. Operative time is generally 1 to 2 hours. The procedure may require a brief hospital stay, or be done on an outpatient basis. Typically, you can resume normal daily activity after 2 to 3 weeks.

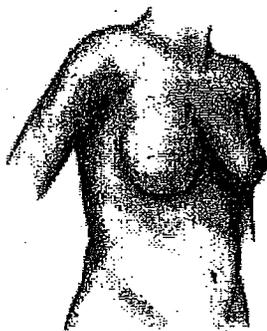
Because the chest skin is usually numb from the mastectomy surgery, it is possible that you may not experience pain from the placement of the tissue expander. However, you may experience feelings of pressure, tightness or discomfort after each filling of the expander, which subsides as the tissue expands but may last for a week or more. Tissue expansion typically lasts four to six months.

Stage 2: Placing the Breast Implant

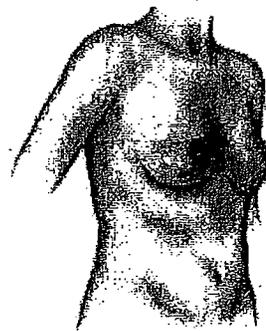
After the tissue expander is removed, the breast implant is placed in the pocket. In reconstruction, following mastectomy, a breast implant is most often placed submuscularly. The surgery to replace the tissue expander with a breast implant (implant exchange) is usually done under general anesthesia in an operating room. It may require a brief hospital stay or be done on an outpatient basis.



Post Mastectomy



**Stage 1: Tissue Expander
Placed and Expansion
Underway**



**Stage 2: Breast Implant
and Nipple/Areola
Reconstruction**

BREAST RECONSTRUCTION WITHOUT IMPLANTS: TISSUE FLAP PROCEDURES

The breast can be reconstructed by surgically moving a section of skin, fat and muscle from one area of your body to another. The section of tissue may be taken from such areas as your abdomen, upper back, upper hip, or buttocks.

The tissue flap may be left attached to the blood supply and moved to the breast area through a tunnel under the skin (a pedicled flap), or it may be removed completely and reattached to the breast area by microsurgical techniques (a free flap). Operating time is generally longer with free flaps, because of the microsurgical requirements.

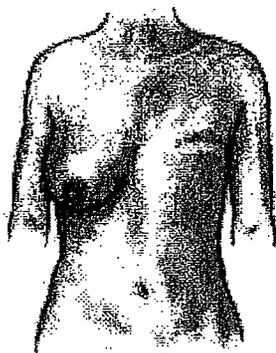
Flap surgery requires a hospital stay of several days and generally a longer recovery time than implant reconstruction. Flap surgery also creates scars at the site where the flap was taken and on the reconstructed breast. However, flap surgery has the advantage of being able to replace tissue in the chest area. This may be useful when the chest tissues have been damaged and are not suitable for tissue expansion. Another advantage of flap procedures over implantation is that alteration of the unaffected breast is generally not needed to improve symmetry.

The most common types of tissue flaps are the TRAM (transverse rectus abdominus musculocutaneous flap) (which uses tissue from the abdomen) and the Latissimus dorsi flap (which uses tissue from the upper back).

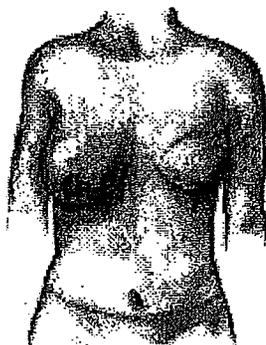
It is important for you to be aware that flap surgery, particularly the TRAM flap, is a major operation, and more extensive than your mastectomy operation. It requires good general health and strong emotional motivation. If you are very overweight, smoke cigarettes, have had previous surgery at the flap site, or have any circulatory problems, you may not be a good candidate for a tissue flap procedure. Also, if you are very thin, you may not have enough tissue in your abdomen or back to create a breast mound with this method.

THE TRAM FLAP (PEDICLE OR FREE)

During a TRAM flap procedure, the surgeon removes a section of tissue from your abdomen and moves it to your chest to reconstruct the breast. The TRAM flap is sometimes referred to as a "tummy tuck" reconstruction, because it may leave the stomach area flatter.

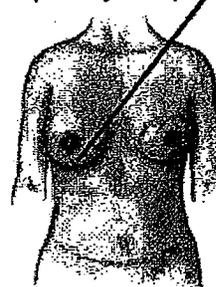


Post Mastectomy



TRAM Flap

This reconstruction includes a Mastopexy to the other breast to improve symmetry



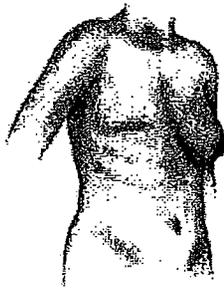
Final Result with Nipple/Areola Reconstruction

A pedicle TRAM flap procedure typically takes three to six hours of surgery under general anesthesia; a free TRAM flap procedure generally takes longer. The TRAM procedure may require a blood transfusion. Typically, the hospital stay is two to five days. You can resume normal daily activity after six to eight weeks. Some women, however, report that it takes up to one year to resume a normal lifestyle. You may have temporary or permanent muscle weakness in the abdominal area. If you are considering pregnancy after your reconstruction, you should discuss this with your surgeon. You will have a large scar on your abdomen and may also have additional scars on your reconstructed breast.

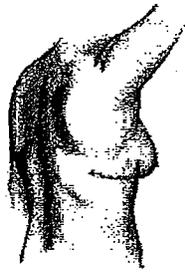
THE LATISSIMUS DORSI FLAP WITH OR WITHOUT BREAST IMPLANTS

During a Latissimus Dorsi flap procedure, the surgeon moves a section of tissue from your back to your chest to reconstruct the breast. Because the Latissimus Dorsi flap is usually thinner and smaller than the TRAM flap, this procedure may be more appropriate for reconstructing a smaller breast.

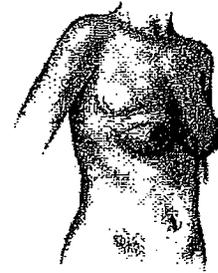
The Latissimus Dorsi flap procedure typically takes two to four hours of surgery under general anesthesia. Typically, the hospital stay is two to three days. You can resume daily activity after two to three weeks. You may have some temporary or permanent muscle weakness and difficulty with movement in your back and shoulder. You will have a scar on your back, which can usually be hidden in the bra line. You may also have additional scars on your reconstructed breast.



Post Mastectomy



View Showing Back Scar



**Latissimus Dorsi Flap and
Nipple/Areola Reconstruction**

REGISTERING YOUR BREAST IMPLANT

INAMED Corporation maintains a device registry to identify patients who have INAMED's silicone-filled breast implants. The registry is designed to collect demographic and contact information for patients who are implanted with INAMED's silicone-filled breast implants. In addition, registration of your device can assist INAMED in handling problems you experience with your implants and in processing ConfidencePlus™ claims.

With patient consent, information collected in the device registry may be provided to assist with national breast implant surveys conducted by, for example, the National Institutes of Health (NIH).

INAMED strongly recommends that all patients receiving silicone-filled breast implants be registered in this database.

Successful device registration begins with the **Medical Device Registration Form** that is supplied with every breast implant. After surgery your doctor should provide you with the Medical Device Registration Form. The top portion of the form will have been completed with device specific information. The rest of the form should be completed by you and returned to INAMED Corporation in the postage paid envelope provided.

Device Identification Card

You will also be given a device identification card with the style and serial number of your breast implant(s). This card is for your permanent record and should be kept in a safe place. In the event you have a concern or problem with your implant you can use this card to describe the implant to your health care provider or to INAMED.

WHAT YOU NEED TO KNOW AFTER THE SURGERY

Once your surgery is complete, there are a few things you can do to minimize the likelihood that you will experience serious complications.

TAKING CARE OF YOUR IMPLANTS AND YOURSELF

You will probably feel somewhat tired and sore for several days following the operation, and your breast may remain swollen and sensitive to physical contact for a month or longer. Depending on the type of surgery you have (i.e., immediate or delayed), the post-operative recovery period will vary.

Post-operative care may involve the use of a post-operative bra, compression bandage, or jogging bra for extra support and positioning while you heal. At your surgeon's recommendation, you will most likely be able to return to work within a few days, although you should avoid any strenuous activities that could raise your pulse and blood pressure for at least a couple of weeks. Your surgeon may also recommend breast massage exercises. If you experience fever, or noticeable swelling and/or redness in your implanted breast(s), you should contact your surgeon immediately.

Once you are healed, you should be routinely monitored for implant ruptures with physical examination by your physician and MRI. Your physician may recommend removal of confirmed or suspected ruptured devices.

IF YOU EXPERIENCE A PROBLEM

You should report any problems that you notice with your implants immediately to your plastic surgeon. If you believe that you have experienced a serious problem(s) related to your breast implants, you should have your health professional report the problem(s) to FDA. You may also report any serious problem directly through the FDA's MedWatch voluntary reporting system. An adverse event is serious and should be reported when it results in an initial or prolonged hospitalization, disability, congenital anomaly, or medical or surgical intervention. This information reported to MedWatch is entered into databases to be used to follow safety trends (patterns) of a device and to determine whether further follow-up of any potential safety issues related to the device is needed.

To report, use MedWatch form 3500 which may be obtained through FDA's website at <http://www.fda.gov/medwatch/index.html>. You may also call 1.888.463.INFO.FDA (1.888.463.6332), from 10:00am-4:00pm Eastern Time, Monday through Friday to receive an additional FDA MedWatch Package. Keep a copy of the MedWatch form completed by your surgeon for your records.

IF YOU NEED TO REPLACE A FAILED IMPLANT

The ConfidencePlus™ Limited Warranties provide lifetime replacement and limited financial reimbursement in the event of loss of shell integrity resulting in implant deflation or rupture, subject to certain conditions as fully discussed in the

002645

ConfidencePlus™ literature. For more information, please contact Product Support at 800.624.4261.

HOW TO RECEIVE MORE INFORMATION

If after reading this booklet, you have additional questions about breast implants or breast implant surgery, there are a number of resources available to you.

TOLL-FREE NUMBER

If you are a patient or a prospective patient and wish to speak to an INAMED Aesthetics product support specialist to inquire about breast implants or discuss any concerns, call toll free at 800.362.4426.

GENERAL RESOURCES ABOUT IMPLANTS

Upon request to INAMED or to your plastic surgeon, you will be provided with a copy of the Directions for Use (package insert). For more detailed information on the preclinical and clinical studies conducted by INAMED, you are referred to the Summary of Safety and Effectiveness Data for this product at <http://www.fda.gov/cdrh/pdf/TBD.html>.

You will also be given a device identification card with the style and serial number of your breast implant(s).

BREAST RECONSTRUCTION RESOURCES

The following list of resources may help you to find more information and support for your breast reconstruction decision.

National Cancer Institute
1-800-4-CANCER
www.cancernet.nci.nih.gov

American Cancer Society (Reach to Recovery)
1-800-ACS-2345
www.cancer.org

Y-ME National Organization for Breast Cancer Information and Support
1-800-221-2141
www.y-me.org

ADDITIONAL RESOURCES

INAMED Aesthetics

1-800-624-4261

www.inamedaesthetics.com

Institute of Medicine Report on the Safety of Silicone Implants

www.nap.edu/catalog/9618.html

Food and Drug Administration

1-888-INFO-FDA or 301-827-3990

www.fda.gov/cdrh/breastimplants/

FDA Breast Implant Consumer Handbook - 2004

<http://www.fda.gov/cdrh/breastimplants/indexbip.html>

<http://www.fda.gov/cdrh/breastimplants/indexbip.PDF>

GLOSSARY OF MEDICAL/TECHNICAL TERMS

Areola	The pigmented or darker colored area of skin surrounding the nipple of the breast.
Asymmetry	A lack of proportion of shape, size and position on opposite sides of the body.
Autoimmune Disease	A disease in which the body mounts an "attack" disease response to its own tissues or cell types. Normally, the body's immune mechanism is able to distinguish clearly between what is a normal substance and what is foreign. In autoimmune diseases, this system becomes defective and produces antibodies against normal parts of the body, causing tissue injury. Certain diseases such as rheumatoid arthritis and scleroderma are considered to be autoimmune diseases.
Axillary	Pertaining to the armpit area.
Bilateral	Pertaining to both the left and right breast.
Biopsy	Removal and examination of sample tissue for diagnosis.
Breast Augmentation	Enlargement of the breast by surgical implantation of a breast implant or patient's own tissue.
Breast Reconstruction	Surgical restoration of natural breast contour and mass following mastectomy, trauma or injury.
Breast Revision	Revision surgery is a plastic surgery procedure to correct or refine the outcome of a previous breast surgery. The revision may involve the replacement of a breast implant.
Capsular Contracture	Tightening of the tissue surrounding a breast implant which results in a firmer breast.
Capsulectomy	Surgical removal of the entire capsule surrounding a breast implant.
Capsulotomy	Closed Capsulotomy: Compression on the outside of the breast to break the capsule and relieve contracture. Open Capsulotomy: Surgically cutting or removing part of the capsule through an incision.
Carcinoma	Invasive malignant tumor.
Congenital Anomaly	Abnormality existing at birth.
Connective Tissue Disease (CTD)	A disease or group of diseases affecting connective tissue. The cause of these diseases are unknown. The diseases are grouped together on the basis of clinical signs, symptoms, and laboratory abnormalities.
Rupture	Refers to loss of saline from a saline-filled breast implant due to a tear or cut in the implant shell or possibly a valve leak.
Displacement	Shifting in the original position.
Epidemiological	Pertaining to the cause, distribution and control of disease in populations.
Extrusion	A breast implant or tissue expander being pressed out of the body.

Fibrous Tissue	Tissue resembling fibers.
Gel Bleed	Gel components passing through the shell.
Hematoma	A swelling or mass of blood (usually clotted) confined to an organ, tissue, or space and caused by a break in a blood vessel.
Immune Response	The reaction of the body to substances that are foreign or are interpreted as being foreign.
Inframammary	Below the breast.
Inframammary Fold	The crease at the base of the breast and the chest wall.
Inframammary Incision	A surgical incision at the inframammary fold.
In-Patient Surgery	Surgery performed in a hospital requiring an overnight stay
Latissimus Dorsi	Two triangular muscles running from the spinal column to the shoulder.
Mammoplasty	Plastic surgery of the breast.
Mammary	Pertaining to the breast.
Mammography	Use of radiography (X-rays) of the breast to detect breast cancer. Recommended as a screening technique for early detection of breast cancer.
Mastectomy	Surgical removal of the breast. Subcutaneous Mastectomy: Removal of breast tissue, preserving the skin and nipple. Partial Mastectomy: Removal of primary tumor and a wide margin of tissue, may include the overlying skin and the muscle fibrous tissue (fascia) underlying the tumor. Total (Simple) Mastectomy: Removal of breast tissue and the nipple; sometimes accompanied by armpit (axillary) node dissection. Modified Radical Mastectomy: Removal of breast tissue, nipple, and fascia of chest (pectoralis) muscle with axillary node dissection.
Mastopexy	Plastic surgery to move sagging (ptotic) breasts into a more elevated position.
Necrosis	Death of tissue. May be caused by insufficient blood supply, trauma, radiation, chemical agents or infectious disease.
Oncologist	A specialist in the branch of medicine dealing with the study and treatment of tumors.
Out-Patient Surgery	Surgery performed in a hospital or surgery center not requiring an overnight stay.
Palpate/Palpability	To feel with the hand.
Pectoralis	The major muscle of the chest.
Plastic Surgery	Surgery intended to improve, restore, repair, or reconstruct portions of the body following trauma, injury or illness.

002649

Prosthesis	An artificial device used to replace or represent a body part.
Ptosis	Sagging of the breast usually due to normal aging, pregnancy or weight loss.
Rectus Abdominus	Major abdominal (stomach) muscle.
Saline	A solution of sodium chloride (salt) and water.
Seroma	Localized collection of serum (the watery portion of blood), that resembles a tumor.
Serratus	Muscle located beneath the chest's pectoralis major and minor muscles and the rib cage.
Silicone Elastomer	A type of silicone that has elastic properties similar to rubber.
Subglandular Placement	Placement of the breast implant behind the skin and mammary gland, but on top of the chest (pectoralis) muscle. Also called prepectoral or retromammary placement.
Submuscular Placement	Placement of the breast implant under the chest (pectoralis) muscle, or under the pectoralis and serratus muscles. Also called retropectoral or subpectoral placement.
Surgical Incision	Cut made in tissue for surgical purposes.
Transaxillary Incision	Incision across the long axis of the armpit (axilla).
Umbilical	Relating to the belly button.
Unilateral	Affecting only left or right breast.

M558 (Draft 27-July-04)

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MAKING AN INFORMED DECISION

SILICONE-FILLED BREAST IMPLANT REVISION

 **INAMED**
AESTHETICS

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INTRODUCTION

TO THE PATIENT

The information contained in this booklet, *Making an Informed Decision, Silicone-Filled Breast Implant Surgery*, is designed to provide you with an understanding of the risks and benefits of surgery with silicone filled breast implants as well as provide an overview of the experience of patients in the INAMED Core Clinical Study.

Please review this information to ensure your preoperative consultation is effective and comprehensive. Make notes about issues that you would like to further discuss with your plastic surgeon, and ask questions. Give yourself time to consider your choices and proceed with surgery only after you are satisfied that the decision is right for you.

TO THE HEALTHCARE PROFESSIONAL

Discussion of the content of this document is an important part of the informed decision making process for the patient. Please take time to familiarize yourself with the information presented here and incorporate it into your pre-operative discussion.

For your convenience a signature block is provided as a means of documenting the preoperative discussion in the patient's file.

After removing the signature block, please give this book to the patient for her records.

Making an Informed Decision

Silicone Filled Breast Implant surgery

Revision

I have reviewed the information presented in *Making an Informed Decision Silicone Filled Breast Implant Surgery, Revision*. My concerns and questions have been addressed by my doctor and I have considered alternatives to augmentation surgery including use of external prostheses or surgery with saline-filled breast implants.

I am choosing to proceed with silicone filled breast implant surgery.

Patient Name

Patient Signature

Date

Surgeon Name

Surgeon Signature

Date

002654

TABLE OF CONTENTS

SO, YOU'RE CONSIDERING SILICONE-FILLED BREAST IMPLANT SURGERY

WHAT GIVES THE BREAST ITS SHAPE?

WHAT IS SILICONE?

WHAT IS A SILICONE-FILLED BREAST IMPLANT?

WHAT TYPES OF SILICONE-FILLED BREAST IMPLANTS ARE AVAILABLE FROM INAMED?

ARE SILICONE-FILLED BREAST IMPLANTS RIGHT FOR YOU?

WHAT ARE THE BENEFITS OF BREAST REVISION SURGERY?

WHAT YOU NEED TO KNOW BEFORE BREAST REVISION SURGERY?

WHAT EVIDENCE IS THERE THAT INAMED SILICONE-FILLED IMPLANTS ARE SAFE AND EFFECTIVE?

SOME PRACTIAL ASPECTS OF BREAST REVISION SURGERY

REGISTERING YOUR BREAST IMPLANT

WHAT YOU NEED TO KNOW AFTER THE SURGERY

HOW TO RECEIVE MORE INFORMATION

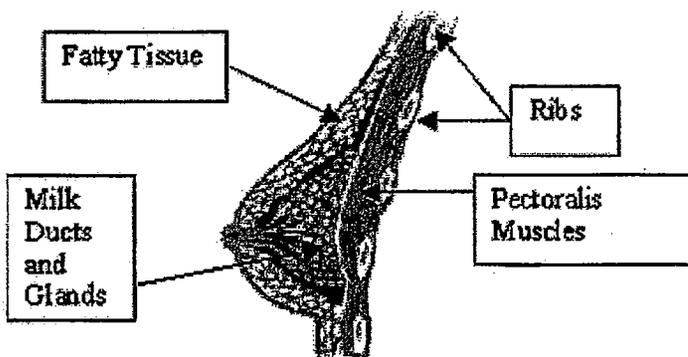
GLOSSARY OF MEDICAL/TECHNICAL TERMS

SO, YOU'RE CONSIDERING SILICONE-FILLED BREAST IMPLANT SURGERY

You may be considering breast implant surgery to correct or re-do (revise) the result of previous breast surgery. The revision may involve the replacement of a breast implant. INAMED has prepared this patient information booklet to help you better understand the breast implant procedure and assist you in making an informed decision about breast revision surgery. It will help to answer some of the questions you may have about the surgery and about breast implants in general. It will also provide you with specific information about the INAMED silicone-filled breast implant product line.

This educational booklet can not and should not take the place of discussing your surgery with your plastic surgeon. Make sure to speak with your surgeon about your expectations of the results, as well as what you can expect regarding the length of the surgery, your recovery, and any potential complications of the surgery. Ask questions. You and your surgeon will work together to help you to achieve the body image you desire.

WHAT GIVES THE BREAST ITS SHAPE?



The breast consists of milk ducts and glands, surrounded by fatty tissue that provides its shape and feel. Beneath the breast is the pectoralis major muscle (chest muscle) of the chest wall.

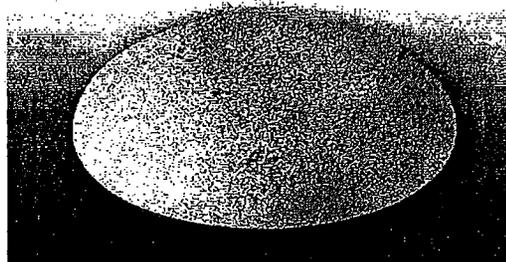
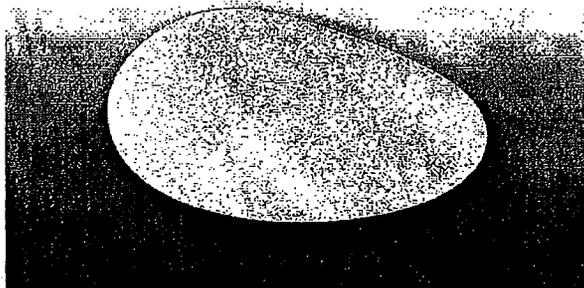
Women may choose breast revision surgery because they wish to correct or refine the result of previous breast surgery.

WHAT IS SILICONE?

Silicones are a family of compounds, made from silicon, a naturally occurring element. Silicones have been part of the consumer industry for over 50 years and because they can be manufactured in various ways, silicones appear in a wide variety of products most of us use everyday. Medical devices utilizing silicone include artificial joints, facial implants, catheters, tissue expanders and breast implants.

WHAT IS A SILICONE-FILLED BREAST IMPLANT?

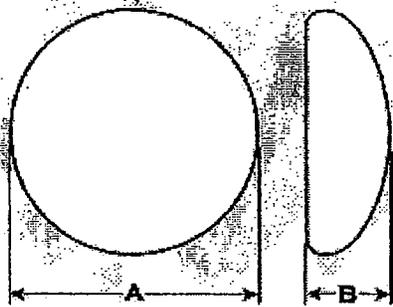
A silicone-filled breast implant is a sac (implant shell) made of silicone elastomer (rubber) and filled with silicone gel. It is surgically implanted either under your breast tissue and above your chest muscle or below your chest muscle. Your plastic surgeon will discuss with you the best positioning for your implants.



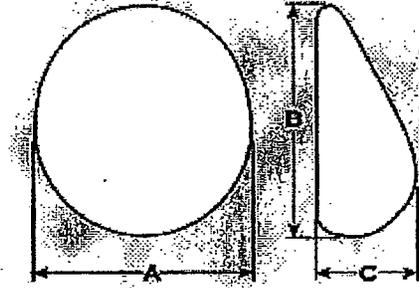
WHAT TYPES OF SILICONE-FILLED BREAST IMPLANTS ARE AVAILABLE FROM INAMED?

Breast implants come in a variety of shapes, surface textures, and sizes. INAMED manufactures several styles of round and one style of shaped silicone-filled breast implant (see below). They are available with smooth shell surfaces or textured shell surfaces. Your plastic surgeon will discuss with you the implant design that will best help you achieve your desired outcome.

Round Breast Implants:	
Style 10:	Smooth shell surface, moderate projection
Style 20:	Smooth shell surface, full projection
Style 40:	Smooth shell surface, standard projection
Style 45:	Smooth shell surface, full projection
Style 110:	BIOCELL® Textured shell surface, moderate projection
Style 120:	BIOCELL® Textured shell surface, full projection
Shaped Breast Implants:	
Style 153:	BIOCELL® Textured shell surface, double lumen, full height, full projection



A = Width; B = Projection
Round Breast Implant



A = Width; B = Height; C = Projection
Shaped Breast Implant

ARE SILICONE-FILLED BREAST IMPLANTS RIGHT FOR YOU?

In order to help you achieve your cosmetic goals safely, silicone-filled implants should not be used in women under the age of 18, in women with existing malignant or pre-malignant cancer of the breast who have not been successfully treated, in women with an active infection anywhere in the body, and in women who are currently pregnant or nursing.

In addition, silicone-filled breast implants have not been clinically testing in women with autoimmune diseases like lupus or scleroderma, in women with conditions that could interfere with wound healing and blood clotting, in women with a weakened immune system (such as women receiving immunosuppressive therapy), and in women with a reduced blood supply to the breast tissue. If you have any of these conditions or other serious health problems you should discuss with your surgeon whether breast revision surgery is appropriate for you.

WHAT ARE THE BENEFITS OF BREAST REVISION SURGERY?

The benefits of breast revision surgery with silicone-filled breast implants are an improved cosmetic appearance, an improved body image, and an increased self esteem.

WHAT YOU NEED TO KNOW BEFORE BREAST REVISION SURGERY

Before you agree to any surgical procedure, you need to fully understand the potential health risks that are associated with the surgery. If you are considering breast revision, you also need to understand the potential health risks that may be associated with the long-term implantation of breast implants. These are described below.

THERE ARE RISKS ASSOCIATED WITH THE IMPLANT SURGERY.

All surgery carries some risk. The most commonly reported surgery-related risks for breast augmentation surgery are infection, bleeding, seroma, scarring, anesthesia, and pain.

Scarring

Most scars following breast augmentation are pale thin lines. However, they may become red, firm, and elevated. Some scars fade with time but scar revision may be desired.

Infection

Infection occurs very rarely following breast implant surgery. Most infections resulting from surgery appear within a few days to weeks after the operation, although infection is possible at any time after surgery. Infections with an implant present are harder to treat than infections in normal body tissues. Infections are typically treated with antibiotics, but if the infection does not respond to antibiotics, the implant may have to be removed. Another implant may be placed after the infection is resolved. In very rare instances, Toxic Shock Syndrome, a potentially life threatening condition, has been noted in women after breast implant surgery. Symptoms include sudden fever, vomiting, diarrhea, fainting, dizziness, and/or sunburn-like rash. You should see your surgeon immediately for diagnosis and treatment for this condition.

Hematoma

Bleeding (hematoma) occurs in 2-4% of breast implant procedures. It is usually seen soon after surgery, however, it can occur at any time after injury to the breast. While the body absorbs small hematomas, large ones will require the placement of surgical drains for proper healing. A small scar can result from surgical draining. Implant rupture can occur from surgical draining if damage to the implant occurs during the draining procedure.

Seroma

Seroma is a collection of the watery portion of the blood (in this case, around the implant or around the incision). While the body absorbs small seromas, large ones will require the placement of surgical drains for proper healing. A small scar can result from surgical draining. Implant rupture can occur from surgical draining if damage to the implant occurs during the draining procedure.

Anesthesia

As with all surgeries, there is a risk that the patient will have an adverse reaction to the anesthesia.

Pain

Pain of varying intensity and duration may occur and persist following breast implant surgery. In addition, improper size, placement, surgical technique, or capsular contracture may result in pain associated with nerve entrapment or interference with muscle motion. You should inform your surgeon if you experience severe pain.

YOU MAY NOT BE PLEASED WITH THE COSMETIC OUTCOME.

Dissatisfying results such as wrinkling, asymmetry (one breast is larger or smaller or a different shape than the other), implant displacement (shifting), incorrect size, unanticipated shape, implant palpability (ability to feel the implant under the skin), scar deformity, and/or hypertrophic (irregular, raised scar) scarring, may occur. Careful surgical planning and technique can minimize but not always prevent such results.

YOU MAY REQUIRE ADDITIONAL SURGERY AND SURGEON VISITS.

Breast implants are not considered lifetime devices. You may undergo implant removal with or without implant replacement during your lifetime.

MANY OF THE CHANGES TO YOUR BREAST FOLLOWING IMPLANTATION ARE IRREVERSIBLE.

If you later choose to have your implant(s) removed, you may experience unacceptable dimpling, puckering, or wrinkling of the skin or other cosmetic changes of the breast.

BREAST IMPLANTS MAY AFFECT YOUR ABILITY TO BREAST FEED.

Breast implant surgery may affect your ability to breast feed because the surgery may sever nerves that stimulate the body to release the hormones that trigger milk release. In addition, an incision around the nipple, which may be done to make the surgical scar less noticeable, also may sever ducts that drain milk from the mammary gland such that even if the mother has an adequate milk supply, it may be difficult for the milk to drain into the nipple. Also, breast implants will not prevent a woman's breasts from sagging after pregnancy.

At this time it is not known if a small amount of silicone may diffuse (pass through) from the silicone-filled breast implant and may find its way into breast milk. If this occurs, it is not known what effect it may have on the nursing infant. Although there are no current methods for detecting silicone levels in breast milk, a study measuring silicon (one component in silicone) levels did not indicate higher levels in breast milk

002660

from women with silicone-filled breast implants when compared to women without implants.

BREAST IMPLANTS MAKE ROUTINE SCREENING MAMMOGRAPHY MORE DIFFICULT.

The presence of breast implants may interfere with finding breast cancer during mammography and also may make it difficult to perform mammography. Therefore, it is essential that you tell your mammography technologist that you have an implant before the procedure. The technologist can use special techniques to minimize the possibility of rupture and to get the best possible views of the breast tissue. You may wish to undergo a preoperative mammogram and another one 6 months to one year after implantation to establish a baseline.

Because the breast is squeezed during mammography, it is possible for an implant to rupture during the procedure. More x-ray views are necessary with these special techniques; therefore, women with breast implants will receive more radiation. However, the benefit of the mammogram in finding cancer outweighs the risk of the additional x-rays.

In addition to routine mammograms, women should perform a breast self-examination monthly on the implanted breast. In order to do this effectively, you should ask your surgeon to help you distinguish the implant from your breast tissue. Any new lumps or an abnormal finding on the mammogram should be evaluated with a biopsy. If a biopsy is performed, care must be taken to avoid puncturing the implant.

YOUR HEALTH INSURANCE PREMIUMS MAY INCREASE, COVERAGE MAY BE DROPPED, AND/OR FUTURE COVERAGE MAY BE DENIED.

Treatment of complications may not be covered as well. You should check with your insurance company regarding these coverage issues.

THE LONG-TERM SAFETY AND EFFECTIVENESS OF BREAST IMPLANTS HAVE NOT BEEN STUDIED.

INAMED is monitoring the long-term (10-year) chance of implant rupture, reoperation, implant removal, and capsular contracture (hardening of the tissues around the implant). INAMED is also conducting mechanical testing to assess the long-term likelihood of implant rupture. As new information becomes available, INAMED will issue an updated version of this brochure.

YOU HAVE OTHER OPTIONS.

There are alternatives to breast revision surgery with a silicone-filled breast implant. You may choose to have no treatment at all and accept your breast as they are. You may choose revision with saline-filled implants.

SOME LOCAL COMPLICATIONS CAN OCCUR IN IMPLANTED BREASTS.

Local complications are sometimes observed in breast of women with silicone-filled implants. These include capsular contracture, rupture, calcification, implant extrusion, wound healing problems or tissue necrosis, visible skin wrinkling and rippling, changes in nipple and skin sensation, pain, malposition, asymmetry, breast tissue atrophy, and re-operation.

Capsular Contracture

The scar tissue or capsule that normally forms around the implant may tighten and squeeze the implant and is called capsular contracture. Capsular contracture may be more common following infection, hematoma, and seroma. It is also more common with subglandular placement (behind the mammary gland and on top of the chest muscle). Symptoms range from mild firmness and mild discomfort to severe pain, distorted shape, palpability of the implant, and/or movement of the implant.

Capsular contracture may occur on one side, both sides, or not at all. In severe cases, the disfigurement or discomfort resulting from capsular contracture may require surgery to remove the scar tissue around the implant and/or implant replacement. In some cases, the contracture may not be correctable and implant removal of the implant and capsule tissue may be necessary. Closed capsulotomy is not recommended due to concerns about implant rupture and localized bleeding. The occurrence of capsular contracture is not predictable, however, the chance of it happening increases with time. Capsular contracture may happen again after these additional surgeries.

Rupture

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 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.

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.

Gel Bleed

There is no evidence from the medical literature or from Inamed's own testing suggesting that gel bleed (gel components passing through the shell) may be associated with local complications in breast implant patients. In addition, clinical study patients in Inamed's Core clinical study for silicone-filled breast implants were at no higher risk of local complications when compared to the risk of local complications reported in Inamed's 1995 saline-filled breast implant clinical study.

Calcium Deposits

Deposits of calcium can be seen on mammograms and although they are benign, they can be mistaken for possible cancer, resulting in additional surgery for biopsy and/or removal of the implant to distinguish the calcium deposits from cancer.

Implant Extrusion

If the skin or breast tissue covering the implant is very thin and/or there is a problem with healing, the implant may break through the skin and become exposed. This will require removal of the implant.

Wound Healing Problems or Tissue Necrosis

Some patients experience delayed healing of the incision site or they may not heal well. This can result in an unattractive scar and if the implant is exposed, further surgery will be required. Tissue breakdown or necrosis (the formation of dead tissue around the implant) will delay wound healing, may cause wound infection, and may require surgical correction and/or implant removal. Permanent scar deformity may occur following necrosis. Factors associated with increased necrosis include infection, use of steroids in the surgical pocket, smoking, chemotherapy/radiation, and excessive heat or cold therapy.

Visible Skin Wrinkling and Rippling

Visible rippling can result when an implant pulls on the overlying tissues or when the natural folds in the implant are visible through the skin. Removal and replacement of the implant may correct this problem.

Change in Nipple and Skin Sensation

Some change in nipple sensation is not unusual right after surgery and after several months, most patients have normal sensation. Only rarely does permanent loss of nipple and skin sensation or hypersensitivity occur. The range of changes varies from intense sensitivity to no feeling in the nipple or breast following surgery. Changes in feeling can be temporary or permanent and may affect your sexual response or your ability to nurse a baby.

Pain

Pain of varying intensity and duration may occur and persist following breast implant surgery. In addition, improper size, placement, surgical technique, or capsular contracture may result in pain associated with nerve entrapment or interference with muscle motion. You should tell your surgeon about severe pain.

Malposition

Breast malposition may result from shifting after initial placement, excessive sagging or stretching of the lower breast, or capsular contracture. Removal and replacement of the implant may correct this problem.

Asymmetry

Asymmetry (differences in size or shape between breasts) can result from some of the above-mentioned complications. Most women's breasts have at least some asymmetry, even without implants. Removal and replacement of the implant may correct this problem.

Breast Tissue Atrophy

Pressure from breast implants may cause the surrounding tissue to thin or shrink and this may result in the implant becoming more visible or palpable. This can occur while implants are still in place or following implant removal without replacement.

Re-operation

Implanted devices do not last forever, and like many other implanted devices may need to be replaced or removed after a period of time. The rates of re-operation reported in the literature for noncosmetic reasons range from 10 to 30%. Patients should expect to have additional surgery at some point to replace or remove the implant. Also, problems such as rupture, capsular contracture, infection, shifting, and calcium deposits can require removal of the implants. Many women decide to have the implants replaced, but some women do not. If you choose not to, you may have cosmetically unacceptable dimpling and/or puckering of the breast following removal of the implant.

THERE IS A CONCERN THAT BREAST IMPLANTS INCREASE THE RISK OF CERTAIN DISEASES OR EVENTS.

There has been discussion in the scientific and regulatory communities regarding the potential for silicone-filled breast implants to be associated with certain systemic diseases or concerns. The strength of these associations between breast implants and connective tissue disease, cancer, nervous system effects, effects on children, and suicide is discussed below.

Connective Tissue Disease

Concern over the association of breast implants to the development of autoimmune or connective tissue diseases, such as lupus, scleroderma, or rheumatoid arthritis, was raised because of cases reported in the literature with small numbers of women with implants. Several large epidemiological studies of women with and without implants indicate that these diseases are no more common in women with implants than those in women without implants.

Some patients in INAMED's Core Clinical Study showed an increase over time in some CTD signs and symptoms and those CTD signs and symptoms specific to fibromyalgia, such as fatigue, swelling, weakness, aches, back and neck pain.

However, patients with INAMED's saline-filled implants showed similar increases in these signs and symptoms. This indicates that the increased signs and symptoms are most likely not caused by the silicone-filled breast implants and may be attributed to other factors such as aging.

Cancer and Benign Breast Disease

The overwhelming majority of epidemiological studies indicate that cancer and benign breast disease are no more common in women with implants than those without implants, thus offering compelling scientific evidence of a lack of association between breast implants and cancers.

Nervous System Effects

Most investigators report no causal relationship between the presence of breast implants and neurological effects including Meniere's disease, hearing loss, and neurological disease, including multiple sclerosis and Guillain-Barre syndrome.

Effects on Children of Women with Breast Implants

The concern that children born to mothers with silicone breast implants are at risk of developing health problems stems from reports of children born to or breastfed by such women who developed swallowing difficulties, irritability, nonspecific skin rashes, fatigue, and other symptoms. However, epidemiological investigations have not found any increased risk of adverse health outcomes, including occurrence of esophageal disorders, connective tissue disease, and congenital malformations in children born to women with breast implants.

Suicide

Some investigators have raised concerns that the risk of suicide is increased in patients with silicone-filled breast implants. However, their studies do not consider other factors that are likely to affect a woman's predisposition for suicidal tendencies and that are widely acknowledged to be more common among women who seek breast implants, such as cigarette smoking, alcohol consumption, weight, parity, low self-esteem, depression, or other psychiatric/emotional disorders.

WHAT EVIDENCE IS THERE THAT INAMED SILICONE-FILLED IMPLANTS ARE SAFE AND EFFECTIVE?

Although you will experience your own risks (complications) and benefits following breast implant surgery, this section describes the specific complications and benefits of INAMED silicone-filled breast implants. INAMED's studies indicate, for example, that about 1 in 3 revision patients (35%) can expect to experience additional breast surgery at some point through 3 years after implant surgery. The information below provides more details about the complications and benefits you may experience.

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.

STUDIES IN WOMEN

INAMED conducted clinical studies testing of its silicone-filled breast implants to determine the short-term and most common complications as well as benefits of its implants. The Core Clinical Study was designed as a 10-year study to assess all complications, as well as patient satisfaction, body image, body esteem, and self concept. Patients were followed annually, and data through 3 years after implantation are currently available. The Core Study enrolled 225 revision patients. Of those revision patients available to be seen at the 3-year follow-up visit, 87% were seen.

Complications Reported in the Core Study

The 3-year complication rates are shown from the most common to the least common in the table below. The rates reflect the number of revision patients out of 100 who experienced the listed complication at least once within the first 3 years after implantation. Some complications occurred more than once for some patients. The two most common complications experienced within the first 3 years of implantation were capsular contracture (14% or 14 patients out of 100) and breast pain (7% or 7 patients out of 100). Some complications required patients to undergo an additional breast surgery in order to address the complication. The following table shows all complications (i.e., those that lead to additional surgery and those that did not.)

Complication	3-Year Complication Rate
Capsular Contracture	14%
Breast Pain	7%
Swelling	6%
Wrinkling, Implant Malposition, Asymmetry, Scarring, Bruising, Infection, Rupture, Seroma/Fluid Accumulation, Implant Palpability/Visibility	2-5%
Hematoma, Tissue or Skin Necrosis, Skin Rash, Other Complications**	1%
Implant Extrusion, Delayed Wound Healing, Irritation, Loss of Skin Sensation, Redness, Ptosis	<1%
Capsule Calcification, Loss of Nipple Sensation, Nipple Hypersensitivity/Paresthesia, Other Nipple Complications, Lymphadenopathy, Lymphedema, Pneumothorax, Skin Hypersensitivity/Paresthesia	0%

*All complications were assessed with severity ratings. Most rates shown in the table include only complications rated moderate, severe, or very severe (excludes mild and very mild ratings). The only complication rates that include all severity ratings are rupture, pneumothorax, and implant extrusion.

** Other complications were described as thinness (n=1) and medial puckering (n=1).

Additional Surgeries

Some of the complications reported in the above table led to an additional surgery, and some additional surgeries involved removal of the implant. A patient's risk of an additional surgery or implant removal is 35% risk of additional surgery through 3 years and 13% risk of implant removal through 3 years.

Through 3 years, 75 augmentation patients had at least one additional surgery, and some patients required multiple surgeries. A total of 115 additional surgeries were performed through 3 years. Although some complications led to an additional surgery, many complications do not require additional surgery and many additional surgeries are performed without removal of the implant. 27 of the 75 patients had an implant removed. For example, a patient's risk of capsular contracture is 11%; however, a patient's risk of a capsular contracture that requires additional surgery is less, at 8.5%, and a patient's risk of having the implant removed to treat the capsular contracture is even lower at 4.0%. The following table describes a patient's risk of having an additional surgery or implant removal for the complications listed in the previous table.

(Because rupture is addressed in the next section, it is not included in the following table.)

002668

Complication	% Risk of Complication Leading to Additional Surgery	% Risk of Complication Leading to Removal/Replacement
Asymmetry	4.0%	1.5%
Breast Pain	2.4%	2.0%
Capsular Contracture	8.5%	4.0%
Hematoma	4.8%	1.1%
Infection	1.4%	0.9%
Implant Malposition	6.3%	3.0%
Implant Palpability	0.5%	0.5%
Loss of Skin Sensation	0%	0%
Nipple Complication	2.5%	0.0%
Ptosis	7.3%	1.5%
Skin Rash	0%	0%
Swelling	0%	0%
Scarring	9.2%	0.0%
Patient Request for Size Change	7.7%	7.7%
Other	5.0%	3.7%
Need for Biopsy	4.1%	1.1%
Delayed Wound Healing	2.9%	0.5%
Breast Tissue Contour Deformity	1.5%	0.5%
Extrusion	1.0%	0.5%
Injury (surgery related or traumatic)	1.0%	0.5%
Wrinkling/Rippling	0.6%	0.0%
Patient Request due to Media Anxiety	0.5%	0.0%
Breast Cancer	0.5%	0.0%

Rupture

Through 3 years, both silent and symptomatic (i.e., non-silent) ruptures have been detected in the augmentation patients. The 3-year rates of these events are described as 5% risk of any rupture, 5% risk of silent rupture, and < 1% risk of symptomatic rupture. The risks presented above are calculated by-implant rather than by-patient because the complication is implant-specific.

Some silent ruptures were discovered using MRI. A portion of the study participants underwent routine screening with MRI. Of the implants that we diagnosed as ruptured and later explanted, the Core Study showed 36-37% of the MRI-diagnosed implants to be intact.

Other Events

Through 3 years, events other than the complications described in the previous tables above were collected in the Core Clinical Study. Some of these events, such as breast cancer and connective tissue disease, can occur in non-implanted patients. Therefore, without a comparison group of women with similar characteristics (such as age, race, etc.) and without breast implants, no conclusions can be made about the relationship between breast implants and some of these other events. These events are described in the following table.

Event	Revision 3-Year Rate
Biopsy Procedure	4%
Malignant Breast Cancer	5%
Benign Breast Cancer	5%
Unknown Breast Cancer (i.e., not yet diagnosed)	5%
CTD - Fibromyalgia	<1%
Implant Removal due to Patient Request for Size/Style Change	0%
Implant Removal due to Patient's Request	8%
Implant Removal due to Implant Damage during Surgery	<1%

Benefits of Implantation

The benefits of silicone-filled breast implants were assessed by a variety of outcomes, including patient satisfaction, body image, body esteem, and self concept. These outcomes were assessed for patients with both original and replacement silicone devices before implantation and at every follow-up visit, except for quality-of-life concepts, which were measured at baseline and at follow-up visit 1, 2, and 4 years.

183 of the original 225 patients were included in an analysis of satisfaction at 3 years. Of these 183 patients, 88% indicated being satisfied with their breast implants at 3 years.

The Quality-of Life patient surveys showed that augmentation patients scored higher (better) than the general U.S. female population on many of the questions measuring general health-related quality of life. However, after 2 years, patients showed a slight worsening in these general scores possibly due to the increase in patient age or other lifestyle changes. Although they did worsen, they continued to remain higher than the U.S. female population. Patient responses to questions regarding overall self-concept and overall self esteem also worsened over the 2

years after receiving implants. However, patient responses to questions regarding overall self esteem related specifically to one's body did not change (improve or worsen); these question may be more informative in measuring the impact of breast implants because it is specific to the patient's body.

SOME PRACTICAL ASPECTS OF BREAST IMPLANTATION SURGERY

When considering breast revision surgery, it is important for you to have confidence in your plastic surgeon and the surgical approach and device design he or she has chosen for you. The following information provides you with some information relating to the more practical aspects of breast implantation surgery.

CHOOSING A PLASTIC SURGEON

When choosing a surgeon who is experienced with breast implantation, you should know the answers to the following questions:

1. How many breast augmentation implantation/revision procedures does he/she perform each year?
2. How many years has he/she performed breast implantation procedures?
3. Is he/she board certified, and if so, with which board?
4. In which states is he/she licensed to practice surgery? (Note that some states provide information on disciplinary action and malpractice claims/settlements to prospective patients either by request or on the worldwide web.)
5. What is the most common complication he/she encounters with breast implantation?
6. What is his/her reoperation rate with breast implantation and what is the most common type of reoperation he/she performs?

QUESTIONS TO ASK THE PLASTIC SURGEON ABOUT BREAST REVISION

The following list of questions may help you to remind you of topics to discuss with your surgeon. You may have additional questions as well.

1. What are the risks and complications associated with having breast implants?
2. How many additional operations on my implanted breast(s) can I expect over my lifetime?
3. How will my breasts look if I decide to have the implants removed without replacement?
4. What shape, size, surface texturing, incision site, and placement site is recommended for me?
5. How will my ability to breast feed be affected?

002671

6. How can I expect my implanted breasts to look over time?
7. How can I expect my implanted breasts to look after pregnancy? After breast feeding?
8. What are my options if I am dissatisfied with the cosmetic outcome of my implanted breasts?
9. What alternate procedures or products are available if I choose not to have breast implants?
10. Do you have before and after photos I can look at for each procedure and what results are reasonable for me?

WHAT SIZE AND DESIGN OF IMPLANT TO CHOOSE

Familiarize yourself with the following options in breast implant surgery and be prepared to discuss with your surgeon the following issues:

Implant Shape and Size

Depending on the desired shape you wish to achieve, you and your surgeon may choose a round or contoured implant shape. Generally, the larger you want your cup size, the larger the breast implant the surgeon will consider (measured in cubic centimeters, or cc's). Contoured implants that are placed submuscularly (under your chest muscle) may assume a round shape after implantation.

Your surgeon will also evaluate your existing tissue to determine if you have enough to cover the breast implant. If you desire a breast implant size too large for your tissue, the surgeon may warn you that breast implant edges may be apparent or visible postoperatively. You may even risk surgical complications. Also, excessively large breast implants may speed up the effects of gravity and result in earlier droop or sag.

Implant Surface Texturing

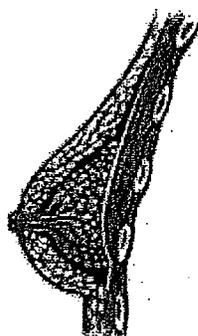
Textured surface implants were designed to reduce the chance of capsular contracture. Some information in the literature with small numbers of patients suggests that surface texturing reduces the chance of severe capsular contracture, but clinical information from studies of a large number of women with INAMED implants shows no difference in the likelihood of developing capsular contracture with textured implants compared to smooth-surfaced implants.

Palpability

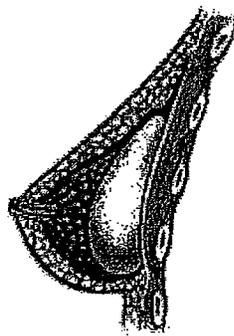
The following may cause implants to be more palpable (more easily felt): textured implants, larger implants, subglandular placement, and the amount of skin/tissue available to cover the implant.

Implant Placement

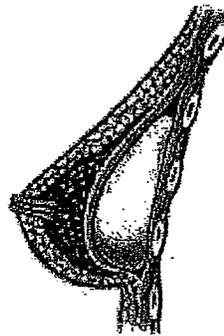
The breast implant can be placed either partially under the pectoralis major muscle (submuscular) or on top of the muscle and under the breast glands (subglandular) depending on the thickness of your breast tissue and its ability to adequately cover the breast implant. You should discuss with your surgeon the pros and cons of the implant placement selected for you.



Breast before
augmentation



Breast after
subglandular
augmentation



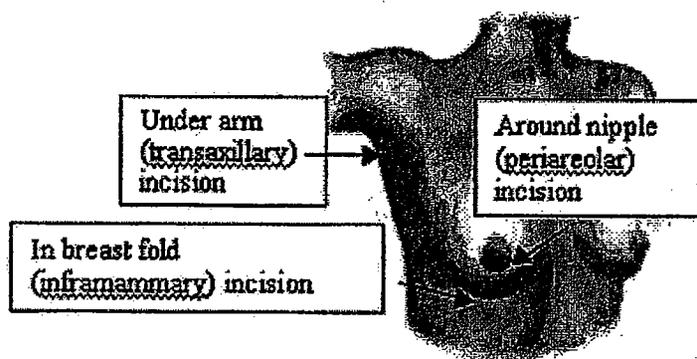
Breast after
submuscular
augmentation

The submuscular placement may make surgery last longer, may make recovery longer, may be more painful, and may make it more difficult to have some reoperation procedures than the subglandular placement. The possible benefits of this placement are that it may result in less palpable implants, less capsular contracture, and easier imaging of the breast with mammography.

The subglandular placement may make surgery and recovery shorter, may be less painful, and may be easier to access for reoperation than the submuscular placement. However, this placement may result in more palpable implants, more capsular contracture, and more difficult imaging of the breast with mammography.

Incision Sites

Breast implant revision surgery is usually accomplished through your existing breast surgery scar. There are three common incision sites: under the arm (axillary), around the nipple (periareolar), or within the breast fold (inframammary). If the incision is made under the arm, the surgeon may use a probe fitted with a miniature camera, along with minimally invasive (very small) instruments, to create a "pocket" for the breast implant.



Periareolar

This incision is most concealed, but is associated with a higher likelihood of inability to successfully breast feed, as compared to the other incision sites.

Inframammary

This incision is less concealed than periareolar and associated with less difficulty than the periareolar incision site when breast feeding.

Axillary

This incision is less concealed than periareolar and associated with less difficulty than the periareolar incision site when breast feeding.

Umbilical/endoscopic

This incision site has not been studied and is not recommended.

Surgical Setting and Anesthesia

Revision surgery is usually performed on an outpatient basis, either in a hospital operating room, surgery center, or surgical suite in the surgeon's office. General anesthesia is commonly used, and local anesthesia is also an option. The surgery usually lasts 1 to 2 hours. Your surgeon will make an incision and remove the existing implant. Your surgeon may also surgically modify the existing breast implant capsule so that it will receive a new breast implant. Then, the breast implant will be placed in the pocket and positioned. Finally, the incision will be closed, usually with stitches, and possibly taped.

Insurance

Insurance does not cover breast augmentation and may not cover reoperation (additional surgery) and additional surgeon's visits following augmentation.

REGISTERING YOUR BREAST IMPLANT

INAMED Corporation maintains a device registry to identify patients who have INAMED's silicone-filled breast implants. The registry is designed to collect

002674

demographic and contact information for patients who are implanted with INAMED's silicone-filled breast implants. In addition, registration of your device can assist INAMED in handling problems you experience with your implants and in processing ConfidencePlus™ claims.

With patient consent, information collected in the device registry may be provided to assist with national breast implant surveys conducted by, for example, the National Institutes of Health (NIH).

INAMED strongly recommends that all patients receiving silicone-filled breast implants be registered in this database.

Successful device registration begins with the **Medical Device Registration Form** that is supplied with every breast implant. After surgery your doctor should provide you with the Medical Device Registration Form. The top portion of the form will have been completed with device specific information. The rest of the form should be completed by you and returned to INAMED Corporation in the postage paid envelope provided.

Device Identification Card

You will also be given a device identification card with the style and serial number of your breast implant(s). This card is for your permanent record and should be kept in a safe place. In the event you have a concern or problem with your implant you can use this card to describe the implant to your health care provider or to INAMED.

WHAT YOU NEED TO KNOW AFTER THE SURGERY

Once your surgery is complete, there are a few things you can do to minimize the likelihood that you will experience serious complications.

TAKING CARE OF YOUR IMPLANTS AND YOURSELF

You will probably feel somewhat tired and sore for several days following the operation, and your breasts may remain swollen and sensitive to physical contact for a month or longer. You may also experience a feeling of tightness in the breast area as your skin adjusts to your new breast size.

Post-operative care may involve the use of a post-operative bra, compression bandage, or jogging bra for extra support and positioning while you heal. At your surgeon's recommendation, you will most likely be able to return to work within a few days, although you should avoid any strenuous activities that could raise your pulse and blood pressure for at least a couple of weeks. Your surgeon may also recommend breast massage exercises. If you experience fever, or noticeable swelling and/or redness in your implanted breast(s), you should contact your surgeon immediately.

Once you are healed, you should be routinely monitored for implant ruptures with physical examination by your physician and MRI. Your physician may recommend removal of confirmed or suspected ruptured devices.

IF YOU EXPERIENCE A PROBLEM

You should report any problems that you notice with your implants immediately to your plastic surgeon. If you believe that you have experienced a serious problem(s) related to your breast implants, you should have your health professional report the problem(s) to FDA. You may also report any serious problem directly through the FDA's MedWatch voluntary reporting system. An adverse event is serious and should be reported when it results in an initial or prolonged hospitalization, disability, congenital anomaly, or medical or surgical intervention. This information reported to MedWatch is entered into databases to be used to follow safety trends (patterns) of a device and to determine whether further follow-up of any potential safety issues related to the device is needed.

To report, use MedWatch form 3500 which may be obtained through FDA's website at <http://www.fda.gov/medwatch/index.html>. You may also call 1.888.463.INFO.FDA (1.888.463.6332), from 10:00am-4:00pm Eastern Time, Monday through Friday to receive an additional FDA MedWatch Package. Keep a copy of the MedWatch form completed by your surgeon for your records.

IF YOU NEED TO REPLACE A FAILED IMPLANT

The ConfidencePlus™ Limited Warranties provide lifetime replacement and limited financial reimbursement in the event of loss of shell integrity resulting in implant deflation or rupture, subject to certain conditions as fully discussed in the ConfidencePlus™ literature. For more information, please contact Product Support at 800.624.4261.

HOW TO RECEIVE MORE INFORMATION

If after reading this booklet, you have additional questions about breast implants or breast implant surgery, there are a number of resources available to you.

TOLL-FREE NUMBER

If you are a patient or a prospective patient and wish to speak to an INAMED Aesthetics product support specialist to inquire about breast implants or discuss any concerns, call toll free at 800.362.4426.

GENERAL RESOURCES ABOUT IMPLANTS

Upon request to INAMED or to your plastic surgeon, you will be provided with a copy of the Directions for Use (package insert). For more detailed information on the preclinical and clinical studies conducted by INAMED, you are referred to the Summary of Safety and Effectiveness Data for this product at <http://www.fda.gov/cdrh/pdf/TBD.html>.

You will also be given a device identification card with the style and serial number of your breast implant(s).

ADDITIONAL RESOURCES

INAMED Aesthetics
1-800-624-4261
www.inamedaesthetics.com

Institute of Medicine Report on the Safety of Silicone Implants
www.nap.edu/catalog/9618.html

Food and Drug Administration
1-888-INFO-FDA or 301-827-3990
www.fda.gov/cdrh/breastimplants/

FDA Breast Implant Consumer Handbook - 2004
<http://www.fda.gov/cdrh/breastimplants/indexbip.html>
<http://www.fda.gov/cdrh/breastimplants/indexbip.PDF>

GLOSSARY OF MEDICAL/TECHNICAL TERMS

Areola	The pigmented or darker colored area of skin surrounding the nipple of the breast.
Asymmetry	A lack of proportion of shape, size and position on opposite sides of the body.
Autoimmune Disease	A disease in which the body mounts an "attack" Disease response to its own tissues or cell types. Normally, the body's immune mechanism is able to distinguish clearly between what is a normal substance and what is foreign. In autoimmune diseases, this system becomes defective and produces antibodies against normal parts of the body, causing tissue injury. Certain diseases such as rheumatoid arthritis and scleroderma are considered to be autoimmune diseases.
Axillary	Pertaining to the armpit area.
Bilateral	Pertaining to both the left and right breast.
Biopsy	Removal and examination of sample tissue for diagnosis.
Breast Augmentation	Enlargement of the breast by surgical implantation of a breast implant or patient's own tissue.
Breast Reconstruction	Surgical restoration of natural breast contour and mass following mastectomy, trauma or injury.
Breast Revision	Revision surgery is a plastic surgery procedure to correct or refine the outcome of a previous breast surgery. The revision may involve the replacement of a breast implant.
Capsular Contracture	Tightening of the tissue surrounding a breast implant which results in a firmer breast.
Capsulectomy	Surgical removal of the entire capsule surrounding a breast implant.
Capsulotomy	Closed Capsulotomy: Compression on the outside of the breast to break the capsule and relieve contracture. Open Capsulotomy: Surgically cutting or removing part of the capsule through an incision.
Carcinoma	Invasive malignant tumor.
Congenital Anomaly	Abnormality existing at birth.
Connective Tissue Disease (CTD)	A disease or group of diseases affecting connective tissue. The cause of these diseases are unknown. The diseases are grouped together on the basis of clinical signs, symptoms, and laboratory abnormalities.
Rupture	Refers to loss of saline from a saline-filled breast implant due to a tear or cut in the implant shell or possibly a valve leak.
Displacement	Shifting in the original position.
Epidemiological	Pertaining to the cause, distribution and control of disease in populations.
Extrusion	A breast implant or tissue expander being pressed out of the body.

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Fibrous Tissue	Tissue resembling fibers.
Gel Bleed	Gel components passing through the shell.
Hematoma	A swelling or mass of blood (usually clotted) confined to an organ, tissue, or space and caused by a break in a blood vessel.
Immune Response	The reaction of the body to substances that are foreign or are interpreted as being foreign.
Inframammary	Below the breast.
Inframammary Fold	The crease at the base of the breast and the chest wall.
Inframammary Incision	A surgical incision at the inframammary fold.
In-Patient Surgery	Surgery performed in a hospital requiring an overnight stay
Latissimus Dorsi	Two triangular muscles running from the spinal column to the shoulder.
Mammoplasty	Plastic surgery of the breast.
Mammary	Pertaining to the breast.
Mammography	Use of radiography (X-rays) of the breast to detect breast cancer. Recommended as a screening technique for early detection of breast cancer.
Mastectomy	Surgical removal of the breast. Subcutaneous Mastectomy: Removal of breast tissue, preserving the skin and nipple. Partial Mastectomy: Removal of primary tumor and a wide margin of tissue, may include the overlying skin and the muscle fibrous tissue (fascia) underlying the tumor. Total (Simple) Mastectomy: Removal of breast tissue and the nipple; sometimes accompanied by armpit (axillary) node dissection. Modified Radical Mastectomy: Removal of breast tissue, nipple, and fascia of chest (pectoralis) muscle with axillary node dissection.
Mastopexy	Plastic surgery to move sagging (ptotic) breasts into a more elevated position.
Necrosis	Death of tissue. May be caused by insufficient blood supply, trauma, radiation, chemical agents or infectious disease.
Oncologist	A specialist in the branch of medicine dealing with the study and treatment of tumors.
Out-Patient Surgery	Surgery performed in a hospital or surgery center not requiring an overnight stay.
Palpate/Palpability	To feel with the hand.
Pectoralis	The major muscle of the chest.
Plastic Surgery	Surgery intended to improve, restore, repair, or reconstruct portions of the body following trauma, injury or illness.

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Prosthesis	An artificial device used to replace or represent a body part.
Ptois	Sagging of the breast usually due to normal aging, pregnancy or weight loss..
Rectus Abdominus	Major abdominal (stomach) muscle.
Saline	A solution of sodium chloride (salt) and water.
Seroma	Localized collection of serum (the watery portion of blood), that resembles a tumor.
Serratus	Muscle located beneath the chest's pectoralis major and minor muscles and the rib cage.
Silicone Elastomer	A type of silicone that has elastic properties similar to rubber.
Subglandular Placement	Placement of the breast implant behind the skin and mammary gland, but on top of the chest (pectoralis) muscle. Also called prepectoral or retromammary placement.
Submuscular Placement	Placement of the breast implant under the chest (pectoralis) muscle, or under the pectoralis and serratus muscles. Also called retropectoral or subpectoral placement.
Surgical Incision	Cut made in tissue for surgical purposes.
Transaxillary Incision	Incision across the long axis of the armpit (axilla).
Umbilical	Relating to the belly button.
Unilateral	Affecting only left or right breast.

M558 (Draft 27-July-04)

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RESPONSE TO DEFICIENCY 10

POSTAPPROVAL STUDY PLAN

The postapproval study plan has been revised to require annual follow-up visits by physical examinations for all Core Study patients for the full 10-years of the study. Instead of patients being followed via survey form following PMA approval as Inamed originally proposed, patients will now be required to continue returning to their physician annually at the anniversary of their enrollment into the study. Additionally, patients who are explanted without receiving replacement implants will be followed via telephone survey instead of being discontinued from the study.

Attachment 10-1, *Revised Investigator Brochure*, includes a revised study protocol reflecting the changes listed below and identifying all the data points that will be collected. The revised protocol (dated 8/1/04) and associated appendices are based on the current FDA approved study Investigator Brochure for IDE [REDACTED]

Since Inamed Corporation no longer intends to use the "McGhan" brand name, all references to McGhan have either been removed, if appropriate, or changed to Inamed.

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RESPONSE TO DEFICIENCY 11

The purpose of Inamed's current Registry is to provide a database that identifies and tracks patients who use Inamed Corporation's silicone-filled breast implants. It is not designed to collect prospective outcome data, but rather to collect demographic and contact information for patients who are implanted with Inamed's silicone-filled implants.

Inamed acknowledges that certain Panel members recommended tracking data elements such as CTD in a registry; however, development of a comprehensive outcomes driven registry in the United States is not feasible. In order to yield accurate and complete results, women enrolled in the registry would be required to consent to participation in the registry and would have to allow Inamed access to their medical records. Not only would this require the women's consent, but in order to review and/or obtain the necessary medical records for adequate conduct of the registry, full cooperation would also be required from the health care facilities where the women have received treatment. Comprehensive and linked medical registries do not exist in the U.S., as they do in some countries that are governed by different health care systems. The resources required to operate and maintain such a large registry, coupled with the restrictions of the current patient privacy laws (e.g., HIPAA) render development of such a registry in this country impossible at this time. Another limitation to registries is the difficulty in detecting events with a low rate of occurrence such as CTD. For example, in a study of pregnancy registries, Reiff-Eldridge et al. (2000)² (Attachment 11-1) examined several registries, identifying weaknesses in the registry concept such as lack of a control group not exposed to the drug, reliance on voluntary reporting, possible bias in underreporting patients with positive outcomes, high rates of patients lost to follow-up and generally small sample sizes. In the largest registry studied, the Acyclovir pregnancy registry enrolled women over a 14 year period. With 26% loss to follow up, outcomes were available for over 1,200 women. However, for a specific birth defect occurring for 1 in 100 live births, the Acyclovir registry would have the ability to detect with 80% power a doubling in that birth defect; all smaller increases would go undetected. Also undetected

² Reiff-Eldridge, R., Heffner, C.R., Ephross, S.A., Tennis, P.S., White, A.D., and Andrews, E.B. 2000. Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: A pharmaceutical company commitment, *Am. J. Obstet. Gynecol.* 182:159-163.

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would be a doubling in a specific defect that occurs less frequently than 1 in 100 births for the general population. The above examples reinforce why registries are not very useful in identifying health outcomes that typically occur at low rates. This further illustrates why a stand-alone registry is indeed not the best method for obtaining the comprehensive clinical data to evaluate the long-term health outcomes in women with silicone-filled breast implants.

Although a registry to track clinical outcomes for all implanted women is not feasible, Inamed does have the ability to provide the requested information on a subset of women, namely those enrolled in the Core Study and those enrolled in the Danish Breast Implant Registry. Clinical outcome data are collected under the Core Study, and per the existing protocol, patients have already agreed to be followed for 10 years. As described in our response to Deficiency 10, the postapproval follow-up for Core Study patients will include a yearly physician visit during which clinical outcome data, such as that recommended by the Panel, will be collected. During these annual exams, physicians will continue to collect data on all of the clinical endpoints specified in the protocol, including local complications, rupture, CTD, breast cancer, reproduction and lactation problems, and patient quality of life. In addition, patients enrolled in the MRI cohort will continue to undergo MRI screening for silent rupture every 2 years. Furthermore, patients who are explanted of all study devices without receiving replacement implants will be followed annually through telephone follow-up with their physician to assure that complications occurring after explantation are captured. Inamed provides financial incentives to assure a high level of compliance with the follow-up requirements, thus allowing for complete and accurate data collection.

The Danish Breast Implant Registry is an established registry that utilizes electronically linked medical records of patients receiving breast implants, including Inamed silicone-filled implants. Information collected in the Danish Breast Implant Registry includes:

- **Pre-operative data:** Patient Identification (Personal Identification Number [PIN] assigned at birth), previous breast surgery information, health status (history of diseases, etc.) and lifestyle factors (use of cigarettes, alcohol, etc.);
- **Peri-operative data:** patient PIN, date of surgery, location of surgery (clinic or hospital), surgical procedure information and implant characterization (filler material, surface, size, manufacturer, serial number, etc.);
- **Post-operative data** (at each post-operative examination): patient PIN, date of visit, clinic identity, adverse event information and type of treatment.

Inamed provides financial support to the Danish Breast Implant Registry and has access to the data, including the ability to link the data from women with breast implants to Danish registries that track CTDs, cancer and other conditions. The patients enrolled in Inamed's Core Study and the Danish Breast Implant Registry are representative of women who would be receiving Inamed silicone-filled implants in the U.S., should they become commercially available. As such, the data obtained through these sources is

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sufficient to provide a reasonable assessment of the long-term clinical outcome of patients implanted with Inamed devices.

Further, Inamed believes that large epidemiological studies, incorporating appropriate control groups, are the only means of yielding meaningful conclusions regarding the clinical outcome data requested by the Panel. Without an appropriate control group, comparisons against the general population cannot be conducted. Third-party organizations, such as the National Institutes of Health (NIH), are better suited and may have the resources and access to comprehensive medical data for conducting these types of studies. Therefore, in addition to collecting the requested information under the Core Study and Danish Breast Implant Registry, the Inamed Registry form (Attachment 11-2) will be modified to query the patient as to whether she would be willing to participate in an epidemiological study. The modified registration form will allow the patient to use a "yes" check box and her initials to indicate her willingness to participate. The contact information for the positive responders could then be provided to third party organizations for inclusion in a national breast implant study.

Regarding the collection of rupture data, Inamed will link the registry system with our warranty programs that provide substantial financial incentives to report such events. Linking the two systems electronically will allow Inamed to potentially contact patients who have reported a device rupture in an effort to collect additional clinical outcome data, as well as conduct analyses on the demographic information. These warranties supply between \$1,200 and \$2,400 toward surgical costs and free replacement product, which provides an excellent incentive for patients and physicians to report implant ruptures. Linking the two systems will be a more effective tool in gathering data than attempting to develop a stand-alone registry as recommended by the Panel.

In summary, Inamed will address the Panel's concerns for long term data by collecting clinical outcomes on Core Study patients through 10 years, obtaining Danish Breast Implant Registry data for women with Inamed's silicone-filled breast implants, linking Inamed's registry with its rupture warranty programs and requesting authorization from implanted patients to forward their information to third-party organizations who might have the ability to conduct large epidemiological studies.

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BREAST IMPLANT REGISTRATION FORM

THIS PORTION TO BE COMPLETED BY THE HEALTHCARE PROFESSIONAL. PLEASE PRINT.

DEVICE AND SURGERY INFORMATION	
<p>AFFIX LEFT DEVICE LABEL or fill in the device data</p> <p>LEFT SIDE SERIAL NUMBER</p> <p>LEFT SIDE CATALOG NUMBER</p>	<p>AFFIX RIGHT DEVICE LABEL or fill in the device data</p> <p>RIGHT SIDE SERIAL NUMBER</p> <p>RIGHT SIDE CATALOG NUMBER</p>
<p><input type="checkbox"/> Reconstruction <input type="checkbox"/> Augmentation <input type="checkbox"/> Revision <input type="checkbox"/> Reconstruction <input type="checkbox"/> Augmentation <input type="checkbox"/> Revision</p>	
<p>DATE OF IMPLANTATION mm _____ / dd _____ / yy _____</p>	

PHYSICIAN INFORMATION		
LAST NAME (INCLUDE SUFFIX: SR, JR, ETC.)	FIRST NAME	ACCOUNT NUMBER
CITY	STATE/PROVINCE	ZIP/POSTAL CODE
E-MAIL	TELEPHONE	FAX

THIS PORTION TO BE COMPLETED BY THE PATIENT	
LAST NAME	FIRST NAME
STREET ADDRESS	AGE (CHECK ONE) <input type="checkbox"/> 18-25 <input type="checkbox"/> 26-33 <input type="checkbox"/> 34-41 <input type="checkbox"/> 42-49 <input type="checkbox"/> 50+
CITY, STATE/PROVINCE ZIP/POSTAL CODE	
E-MAIL	
Would you like to receive information from INAMED on upcoming promotions or new product introductions? <input type="checkbox"/> Yes <input type="checkbox"/> No Please initial and date here _____	

Please review INAMED's ConfidencePlus™ document for information on our breast implant limited warranties and your options for coverage

<p>INAMED will not disclose your information without your express permission. Please consider the question below and indicate your preference.</p>
Would you be willing to participate in a national breast implant survey or other study conducted by, for example, the National Institutes of Health (NIH)? <input type="checkbox"/> Yes <input type="checkbox"/> No Please initial and date here _____

RETURN THIS COPY TO INAMED IN THE ENVELOPE PROVIDED
 INAMED Corporation
 5540 Ekwil Street, Santa Barbara, CA 93111
 800.624.4261

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Email Subject: P020056 (Deficiency 11)

Sent to FDA: Wednesday, December 8, 2004

Attached is our response to Item 1

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RESPONSE TO ISSUE 1

The types of AEs (complications) collected in the “Danish Registry for Plastic Surgery of the Breast” (Danish BI Registry) include: “infection in the scar”, “periprosthetic infection (deep infection)”, “wound rupture”, “perforation to the skin”, hematoma, seroma, “wrinkles of the skin”, implant palpability, “displacement of the implant (including asymmetry)”, capsular contracture, change of tactile sense, implant rupture (suspicion of), prolonged pain in the breast (minimum 3 months), and “other” complications (to be specified on the follow up form). If surgical treatment of any of the reported complications is required additional operative information is also obtained.

No CTD or other type of systemic information is collected postoperatively as part of the Danish BI Registry. However, this information is accessible via links from the Danish BI Registry to other National (Danish) registries, e.g. Cancer Registry, Mortality Registry, Birth Outcomes Registry, Psychiatric Registry, Outpatient Registry and Hospital Discharge Registry. 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.

No patient satisfaction information is collected postoperatively in the Danish BI Registry. This registry was designed to primarily examine complications and other health effects in women who have received breast implants or undergone other types of breast surgery not involving breast implantation.

For your reference and for additional information the following article is attached: *The Danish Registry for Plastic Surgery of the Breast: Establishment of a Nationwide Registry for Prospective Follow-Up, Quality Assessment, and Investigation of Breast Surgery* by Henriksen, et al.

Email Subject: P020056 (Deficiency 11)

Sent to FDA: Monday, December 13, 2004

I have been able to obtain a complete set of the CRFs for the Danish Registry, i.e. "Enrollment" Questionnaire, Operative Form and Follow-up Form. Please note that that the Operative Form includes handwritten notations and data entry codes, and the shaded portions of the Follow-up Form may be difficult to read; however, these are the best available copies.

The Danish Registry for Plastic Surgery of the Breast

**Questionnaire for women,
who are to have a breast implantation
or have previously had one**

Date of questionnaire fill-in:

day

month

Year

We are pleased that you have chosen to participate in "The Danish Registry for Plastic Surgery of the Breast".

This questionnaire is to be filled in by all patients participating in "The Danish Registry for Plastic Surgery of the Breast".

The questionnaire contains questions concerning height, weight, former and present symptoms/diseases, menstruation/pregnancy, medicine, tobacco and alcohol.

It is optional whether you want to answer all the questions. An optimal register, though, is conditioned by the questionnaire being filled in as properly as possible

Some of the questions concern dates of treatment and what kind of medication you received years ago. Such questions can be difficult to answer accurately. Some answers might therefore be somewhat imprecise, but it does not have decisive influence on the study.

As soon as your questionnaire has been received in the database your civil registration number will be replaced by a random study number before the questionnaire is fed into the computer. All information of the database is therefore anonymous. The information we receive from you will only be used for statistical tables in which it cannot be read what single persons have answered. The personal identification number is only to be used for tracking down missing questionnaires.

Before filling out the questionnaire please sign the declaration of consent on the next page.

If you during the answering of the questionnaire have any doubts about how to understand a question – or do you have any other question on the questionnaire, please feel free to contact me :

On Wednesday and Thursday 10⁰⁰-12⁰⁰ on telephone 35 25 76 88

**Please fill in the questionnaire before the operation
and return it in the enclosed envelope to the registry.**

Beforehand we wish to thank you for your help

Best regards


Registry responsible doctor

Please state your civil registration number:

day

month

year

-

Serial number

Height and weight

At first we would like you to answer some questions concerning your height and weight and whether you have previously had a breast operation

1. How tall are you? cm
- What is your weight? kg

2. This question is supposed to enlighten changes in your weight.

The cause of any changes in weight is to be written on the empty lines.

(Try to answer as precisely as possible. We know it may be difficult to remember facts of several years ago).

What was your weight approx.:

When 20-year old	<input type="text"/>	kg	<input type="text"/>
When 30-year old	<input type="text"/>	kg	<input type="text"/>
When 40-year old	<input type="text"/>	kg	<input type="text"/>
When 50-year old	<input type="text"/>	kg	<input type="text"/>
When 60 year old	<input type="text"/>	kg	<input type="text"/>

Breast operations

Have you had a previous :

	No	Yes	Year of operation				
1. Removal of a tumour in your breast	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1" style="width: 100%; height: 20px;"> <tr> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> </tr> </table>				
- removal of benign tumour	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1" style="width: 100%; height: 20px;"> <tr> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> </tr> </table>				
- removal of malignant tumour	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1" style="width: 100%; height: 20px;"> <tr> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> </tr> </table>				
- removal of breast due to breast cancer	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1" style="width: 100%; height: 20px;"> <tr> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> </tr> </table>				
2. Breast implantation	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1" style="width: 100%; height: 20px;"> <tr> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> </tr> </table>				
3. Breast lift	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1" style="width: 100%; height: 20px;"> <tr> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> </tr> </table>				
4. Breast reduction	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1" style="width: 100%; height: 20px;"> <tr> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> </tr> </table>				
5. Other breast operations	<input type="checkbox"/>	<input type="checkbox"/>	<table border="1" style="width: 100%; height: 20px;"> <tr> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> </tr> </table>				
If yes, please state which	<table border="1" style="width: 100%; height: 30px;"> <tr> <td style="width: 100%;"></td> </tr> </table>						

Information on health - symptoms

The following questions concern various kinds of pain or discomfort (symptoms).

Start by marking whether you have/have had any of the symptoms mentioned below. If confirmative, please state the date of diagnosis, whether you have received any treatment and where this treatment took place.

Have you had any of the following for **more than 3 months**:

	Start of symptoms		Have you received any treatment?		Please state place of treatment				
	No	Yes	(year)	No	Yes	Hospital	Own physician	Specialist	Other
1. Pain in your									
Back	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Finger joints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Knee joints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hip joints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ankle joints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
All joints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Swelling of your									
Back	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Finger joints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Knee joints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hip joints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ankle joints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
All joints	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Joint stiffness in the morning									
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Distinct weakness of the muscles									
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Muscle pain									
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- if yes, please state in which part of your body: <input style="width: 400px; height: 20px;" type="text"/>									

Have you had any of the following symptoms for more than 3 months :

	Start of symptoms		Have you received any treatment?		Please state place of treatment				
	No	Yes	(year)	No	Yes	Hospital	Own physician	Specialist	Other
6. Frequent eye burn	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Eye gravel sensation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Mouth dryness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Oral ulceration	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Troubled swallowing (e.g. needing to drink when swallowing dry food)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Swelling of salivary glands	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Swelling of lymph nodes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Have you had:

	Start of symptoms		Have you received any treatment?		Please state place of treatment				
	No	Yes	(year)	No	Yes	Hospital	Own physician	Specialist	Other
13. Fever with no obvious cause for <u>more than 2 weeks</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Night sweat for <u>more than 2 weeks</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Widespread skin rash	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Skin rash on both cheeks for <u>more than 2 weeks</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Abnormal skin tightness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Skin changes that are worsened by sunlight?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- If confirmative, please state in which part of your body	<input type="text"/>								
- If confirmative, please state the appearance of skin changes	<input type="text"/>								
19. Other skin changes?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- If confirmative, please state in which part of your body	<input type="text"/>								
- If confirmative, please state the appearance of skin changes	<input type="text"/>								

Have you had:

	Start of symptoms		Have you received any treatment?		Please state place of treatment				
	No	Yes	(year)	No	Yes	Hospital	Own Physician	Specialist	Other
20. Skinrash after exposure to sunlight	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. Reduced blood circulation followed by finger pain (white fingers) or toe pain due to cold or excitement	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Chestpain on deep inspiration (for more than one week)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. Neck pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24. Shoulder pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. Back pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. Abnormal loss of hair	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. Abnormal fatigue	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
28. Sleep disturbances	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29. Depression/Low spirit	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30. Memory impairment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31. Difficulties in finding the right words	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32. Lack of concentration when solving simple tasks	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
33. Difficulties in traffic orientation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34. Difficulties in understanding written instructions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
35. Difficulties in adding figures	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments to question concerning symptoms:

Information on health - diseases

The following is a list of diseases, some of which are so rare that only a few will know of their existence. Those suffering from these diseases usually know their names, though.

Start by marking (No/Yes) whether you have or have had one or more of these diseases. If confirmative, please state the date of diagnosis, whether you have received any treatment and where that treatment took place.

Have you or have you ever had :

	Start of symptoms		Have you received any treatment?		Please state place of treatment				
	No	Yes	(year)	No	Yes	Hospital	Own Physician	Specialist	Other
1. Hypertension	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Diabetes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Allergy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
- If confirmative, which symptoms have you had/ do you have? <input type="checkbox"/> asthma <input type="checkbox"/> skinrash <input type="checkbox"/> eye symptoms <input type="checkbox"/> nasal symptoms <input type="checkbox"/> other, state which <input style="width: 150px;" type="text"/>									
4. Rheumatoid arthritis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Osteoarthritis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Gout (podagra)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Sjögrens Syndrome	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Dermatomyositis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Polymyalgia rheumatica or Arteritis temporalis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Psoriatic arthritis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Enlarged thyroid gland (struma)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Anaemia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments :

5. Please state for each child you have birth to the date and time of birth in relation to term.
(If you have not given birth please go to question 9)

Child no.	Time of birth			Time of birth in relation to expected time of birth (term)	
	day	month	year	(Whole weeks)	Cannot remember
1	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> weeks	<input type="checkbox"/>
2	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> weeks	<input type="checkbox"/>
3	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> weeks	<input type="checkbox"/>
4	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> weeks	<input type="checkbox"/>
5	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> weeks	<input type="checkbox"/>

6. Please state for each child you have given birth to the following data

Child no.	Birth weight	Birth length
1	<input type="text"/> gram	<input type="text"/> cm
2	<input type="text"/> gram	<input type="text"/> cm
3	<input type="text"/> gram	<input type="text"/> cm
4	<input type="text"/> gram	<input type="text"/> cm
5	<input type="text"/> gram	<input type="text"/> cm

7. Have you breast-fed all your children ?

- No Yes

If no, please state reason :

If you have breast-fed, please state problems, if any, experienced by you or your child/children concerning breast-feeding :

- No problems
 Yes, there were problems (please state which):

8. If you have breast-fed, please state for how long you breast-fed each child (in whole months)

Child no		Cannot remember
1	<input type="checkbox"/> months	<input type="checkbox"/>
2	<input type="checkbox"/> months	<input type="checkbox"/>
3	<input type="checkbox"/> months	<input type="checkbox"/>
4	<input type="checkbox"/> months	<input type="checkbox"/>
5	<input type="checkbox"/> months	<input type="checkbox"/>

9. Have you ever taken oral contraceptives ("The Pill") ?

Yes No (please go to question 10)

Are you taking oral contraceptives ("The Pill") now ?

Yes No

How old were you when you originally started taking oral contraceptives ("The Pill") ?

--	--

 Years
 Age

Please state in which period(s) you have been taking oral contraceptives ("The Pill") :

	month	year		month	year
I started taking The Pill			and stopped		
I started taking The Pill again			and stopped		
I started taking The Pill again			and stopped		
I started taking The Pill again			and stopped		

10. Have you ever taken the Mini Pill ?

Yes No (please go to questions concerning breast)

Do you take the Mini Pill now ? Yes No

How old were you when you originally started taking the Mini Pill ?

--	--

 years
 age

Please state in which period(s) you have been taking the Mini Pill :

	month	year		month	year
I started taking the Mini Pill			and stopped		
I started taking the Mini Pill again			and stopped		
I started taking the Mini Pill again			and stopped		
I started taking the Mini Pill again			and stopped		

Breast

1. How often (approximately) do you undertake a self examination of your breasts ?

Times a month

Times a year

Less than once a year

2. What size of bra do you take at present (e.g. 75A, 85A, 80B)

Width of
breast Cup:

Do not use a bra

Medication

1. Do you use or have you ever used any kind of medication regularly (besides oral contraceptives) – (i.e. at least every second day for a period of least 3 months)

No Yes

If confirmative, please state which kind of medication. Besides, state the period in which you used the medication.

Type of medication and/or name of it	Started year	Stopped year
	_ _ _	_ _ _
	_ _ _	_ _ _
	_ _ _	_ _ _
	_ _ _	_ _ _
	_ _ _	_ _ _

2. Do you use or have you ever used any kind of dietary supplement or naturopathic medication regularly (i.e. at least every second day for at least 3 months)

No Yes

If confirmative, please state what kind of naturopathic medicine or dietary supplement. Besides, state the period in which you used it.

Type of medication and/or name of it	Started year	Stopped year
	_ _ _	_ _ _
	_ _ _	_ _ _
	_ _ _	_ _ _
	_ _ _	_ _ _
	_ _ _	_ _ _

3. How often do you use non-prescriptive drugs as painkillers, e.g Magnyl, Treo, Iprem, Panodil, Pinex or a similar medication ?

- Never or less than once or twice a year
- Up to once a month on average
- Several times a month on average, but less than once a week
- Several times a week but not every day
- Daily

Comments:

Tobacco and alcohol

The next questions concern your consumption of tobacco and alcohol

1. Do you smoke ?
(only mark once)

- Yes
- Yes, at parties only
- No, but I did earlier
- No, I have never been smoking (go to question 3)

2. How much do you smoke during the day (if there are any type of tobacco you do not smoke, please answer 0)

Cigarettes	<input type="text"/>	Number a day
Cheroots	<input type="text"/>	Number a day
Cigars	<input type="text"/>	Number a day
Pipe (no. of fillings)	<input type="text"/>	Number a day

How old were you when you started smoking ?

years
age

How many years have you been smoking regularly ?

år

If you have been smoking
- how many years ago did you quit?

år

3. How many hours a day have you on average been exposed to tobacco smoke from other people at your workplace in the following period of your life ?

	Did not work outside of home	No. of hours			
		0	1-3	4-7	8 or more
Younger than 20 Years old	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20-29 years old	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30-39 years old	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
40-49 years old	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
50 years or older	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Comments:

4. How often do you usually consume alcohol ?

Do not drink beer, wine, dessert wine or spirits	<input type="checkbox"/>
Less than once a week	<input type="checkbox"/>
1 - 3 times a month	<input type="checkbox"/>
Once a week	<input type="checkbox"/>
2 - 4 times a week	<input type="checkbox"/>
5 - 6 times a week	<input type="checkbox"/>
Every day	<input type="checkbox"/>

5. How many units of alcohol (beer, wine, dessert wine or spirits) do you usually consume a week?

Units of alcohol

The next 3 pages are only to be filled in if you have had a previous implantation

The following questions concern the period from your last breast implantation until today.

1. Do you know what kind of implants you are/want to have ?

- No Yes

If confirmative, please mark the type ?

- Silicone implant
 Saline implant
 Combined silicone and saline implant
 Implant with a different content (please state which if you know it):

- Other:

2. How do you overall estimate the final results after your last breast implantation

- Very satisfying
 Satisfying
 Neither satisfying nor dissatisfying
 Dissatisfying
 Very dissatisfying

3. Has your satisfaction of having breasts implants changed from the year of your operation and until today ?

- No, I am still as dissatisfied with the result
- No, I am still equally satisfied with the result
- Yes, I have become dissatisfied with the result
- Yes, I have become satisfied with the result
- I am still neither satisfied nor dissatisfied with the result

Comments:

4. Have you been bothered by capsular contracture around the implantation (has the implantation been very hard) ?

- Have not had capsular contracture at all
- Have not had capsular contracture of any importance
- Have had some capsular contracture
- Have had huge capsular contracture

5. Have you had breast pain ?

- No
- Hardly any pain
- Yes, moderate pain
- Yes, fierce pain

6. Can you sleep lying on your stomach ?

- No
- Yes

7. How does your scar look ?

- Invisible
- Hardly visible
- Visible, but not disfiguring
- Somewhat disfiguring
- Very disfiguring

8. If you have given birth after you had the breast implantation, then how was breast-feeding ?

- I did not breast-feed
- The breast-feeding was without problems
- I tried to breast-feed, but did not have enough milk
- I breast-fed, but had to give up due to inflammation of the breast.
- I breast-fed, but had to give up due to rawness and pain around the nipple.
- I breast-fed but had to give up due to diffuse pains within the breast

Other:

9. Have you had any doubts whether you wanted a new breast implantation ?

- No Yes

If confirmative, please explain the nature of your doubt :

Please look through the questionnaire again

DID YOU REMEMBER ALL THE QUESTIONS ?

If you have any comments or suggestions to the questionnaire, please feel free to write these below.

Do you think that any of the questions are difficult to understand or ought to be reworded ? Please state the number of the question and your comments:

Do you think any of the questions were too personal ? Please state number of the question and your comment:

Are there any subjects that need to be dealt with in the questionnaire or do you have any other comments ?

THANK YOU VERY MUCH FOR YOUR HELP

	Terminated expansion		Removal of sutures		Three-monthly control		Day case surgery		Other occasions	
	Mamma Dxt.	Mamma Sin.								
Wrinkles of the skin (because of textured implant surface and thin covering of skin)			<input type="checkbox"/>							
Implantat wrinkle (palpable) - requiring surgical treatment - no treatment			<input type="checkbox"/>							
Displacement of the implant (including. asymmetry) - requiring bandaging - requiring surgical treatment - no treatment			<input type="checkbox"/>							
Capsular contraction - Baker II - Baker III - Baker IV)					<input type="checkbox"/>					
Change of tactile sense (only at augmentation) - paraesthesia (no tactile sense) - dysaesthesia (unpleasant sense)					<input type="checkbox"/>					
Implant ruptur (suspicion of)					<input type="checkbox"/>					
Prolonged pain in the breast (min. 3 month.)					<input type="checkbox"/>					
Other complains, which are assigned to the implant by the patient (Please specify below)	<input type="checkbox"/>									

If a complications require **surgical treatment**: Please complete a new operation form.
(The patient is not supposed to complete a new questionnaire, if she has completed a prior questionnaire within one year.)

Notes, incl. date and results of adjuvant paraclinical analysis

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RESPONSE TO DEFICIENCY 12

A. PHYSICIAN EDUCATION INITIATIVES

Inamed acknowledges the importance of educating physicians on issues relevant to Inamed's breast implants, and is committed to this endeavor. To that end Inamed had already developed educational initiatives for physicians, some of which have been ongoing. These consist of the INAMED Academy, INAMED Scholarship Program and INAMED Continuing Education Series. Through their participation in these initiatives physicians have the opportunity to learn more about Inamed's breast

002883

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implants from Inamed representatives, from their surgeon colleagues and from other medical experts in the field of plastic surgery. There are three overarching goals of these initiatives: 1) to provide a forum for Inamed to convey important information to physicians from our multicenter clinical studies and implant retrieval analyses, 2) to ensure that physicians are equipped with the most current clinical outcome and risk information to provide to their patients, and 3) to provide a structured opportunity for surgeons to share their experiences with each other in an ongoing effort to develop "best practices". Details of these physician educational initiatives are provided below.

INAMED Academy

Prior to the proceedings at FDA's General and Plastic Surgery Devices Advisory Panel meeting, Inamed Corporation embarked on development of an educational program for surgeons that would provide for the exchange of information and best practice ideas. As the manifestation of that initiative, the INAMED Academy has been in development for almost two years. Through discussion with key surgeon customers and internal corporate personnel, initial Academy curriculum was planned, faculty identified and locations for a mid-year 2003 calendar developed. Coincident with this ongoing discussion and program development, Inamed was pleased to receive notice of the General and Plastic Surgery Devices Advisory Panel convened to review Inamed's premarket approval (PMA) application for silicone-filled breast implants.

In the interest of resource allocation and to allow for all involved parties to concentrate on this most important project, the INAMED Academy launch was postponed. The timing of the postponement also gave the company a chance to consider the impact of the pending Panel meeting and possible subsequent FDA communication on the form and function of INAMED Academy content. A formal surgeon education/training program became the subject of extensive Panel debate with respect to conditions of approval. The INAMED Academy is poised to address the objective of surgeon education and training.

INAMED Academy content is developed under the guidance of our course directors:

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002884

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Additional input and validation of content is provided by the current 2004 faculty:

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All of the INAMED Academy directors and faculty members are respected by their colleagues and honored by their societies. Their collective experience in plastic surgery, implant evolution and rendering of informed consent lends depth to the Academy program and provides the sounding board needed to ensure that program content is timely and relevant to the attendees at each Academy.

Academy Implementation

Through July 2004 approximately 300 surgeons have attended twelve INAMED Academy events. Held at convenient locations across the nation, surgeons have the opportunity to avail themselves of this unique peer-to-peer educational experience. Records of surgeon attendance are maintained by Inamed, and therefore, as described at Panel, the company is able to certify or verify which surgeons have attended the program. At the conclusion of the Academy, sign-in sheets are collected and the attendee information is entered into a database connecting the attendee with the curriculum for the particular event. Each attendee is asked to complete a post event survey to ensure his/her comments and suggestions for improvement are captured and forwarded to the faculty for continuous improvement opportunities.

Academy Content

Inamed intends to use the INAMED Academy as one avenue to report on device specific information gleaned from sources such as our retrieval evaluations, multicenter clinical trials and complaint database. Current content of INAMED Academy includes discussion of local risks and complications associated with breast implant surgery. Specific complications discussed include rupture (both symptomatic and asymptomatic), leakage, gel bleed, gel migration and capsular contracture. These risks are presented in the context of literature review as well as the experience from

002885

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Inamed Corporation's multicenter clinical studies. Systemic effects considered in association with silicone breast implants are also covered, with a review of published literature and a discussion of the types of studies that examine the association between breast implants and systemic complications. This provides a better understanding of the frequency of these effects and the strength of the associations.

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

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

While some members of the Panel suggested that certification of training be a condition of access to our device, Inamed does not agree with this proposed requirement. The education of physicians, and particularly surgeons, in the United States is lengthy. It not only involves successfully completing medical school, but it also involves graduate medical education (GME) in the form of specialized residency and fellowship training. After completing medical school and graduate medical education, physicians still must obtain licensure to practice medicine from a state or jurisdiction of the United States in which they are planning to practice. They apply for permanent licensure after completing a series of exams and completing a minimum number of years of graduate medical education.

Learning does not end when physicians complete their residency or fellowship training. Doctors continue to receive credits for continuing medical education (CME), and some states require a certain number of CME credits per year to ensure the doctor's knowledge and skills remain current.

At the conclusion of this rigorous training and testing, and assuming his/her license remains in good standing it is recognized that the physician is capable of rendering patient care. It is the position of Inamed that no device manufacturer is knowledgeable to dictate or oversee medical practice for licensed physicians; however, as stated above we do agree that providing a forum such as the INAMED Academy that reinforces product knowledge, allows for Inamed to deliver important

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device related information and allows for the exchange of new ideas in a peer-to-peer setting, encourages practice innovation and is in the best interest of practicing breast implant surgeons and their patients.

RELATED EDUCATIONAL INITIATIVES

INAMED Scholarship program

The INAMED Scholarship is specifically aimed at those surgeons who may be less experienced in breast implant surgery, and is designed to underwrite the expense associated with physician travel. It allows selected physicians to learn from recognized experts in the field of plastic and reconstructive surgery and provides them with an accelerated learning opportunity through discussion of surgical technique as it relates to physical/mechanical product properties and overall patient outcomes and satisfaction, without incurring travel expenses normally associated with such endeavors.

Inamed is continually striving to identify surgeon affiliates across the nation with the experience and product awareness necessary to impart key learning to other physicians. In 2004 funding has been approved for approximately 18 scholarships. These scholarships will be awarded based on an application process that includes a review by key surgeon leadership.

INAMED Continuing Education Series

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

In summary, Inamed believes the educational initiatives outlined above are essential in providing information that is of interest to the surgeon, might affect clinical outcomes when using Inamed silicone-filled breast implants and is timely with respect to the current literature review. To that end Inamed is committed to the physician educational initiatives program and will continue to focus significant efforts to ensure it lives up to its charter.

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B. INFORMED CONSENT

Inamed apologizes for the confusion on this topic. Our plan for a model surgical informed consent form will in fact be incorporated into the "Making an Informed Decision" brochure. This is the document alluded to in Item 12.c. This single document will be inclusive of all information relevant to the patient who is contemplating silicone breast implant surgery.

C. PATIENT EDUCATION BOOKLET "MAKING AN INFORMED DECISION"

Again, Inamed apologizes for any confusion created around information to be supplied to the patient as part of the informed decision process. To reiterate, Inamed intends to supply a single patient informed decision booklet, "Making an Informed Decision". This booklet will include all information necessary for a patient to evaluate the risk and benefits of breast implant surgery. In addition to an overview of surgery, and a summary of long term and systemic risks based on literature review and presentation of the results of Inamed's clinical study, this booklet will include recommendations to patients for monitoring their breast implants following surgery, as well as the toll-free number to use in the event they wish to discuss issues related to their breast implant(s) with company representatives.

In order to make information readily available to patients, distribution of the "Making an Informed Decision" brochure will be as follows:

- Upon FDA approval of the labeling, the document will be finalized and all physician customers will receive an inventory of brochures at no charge; further copies will be available to physicians at no charge upon request by phone, mail or email;
- The brochure will be available to patients from our physician customers via a personal visit to the physician's office;
- The brochure will be available to the public directly from Inamed via a patient request by phone, mail or email;
- The brochure will be available via internet access to our web site; and
- The brochure may be available via internet access to FDA's web site.

Please see the response to Deficiency 9 for more details on the revised draft patient labeling, "Making an Informed Decision". The drafts of the "Making an Informed Decision" brochure are provided in Attachments 9-2, 9-3, and 9-4.

002888

Email Subject: P020056 (Deficiency 12)

Sent to FDA: Wednesday, December 8, 2004

Attached is our response to your request below. Please let me know if you have any further questions re: this topic.

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INAMED RESPONSE

Introduction

As described in our response to Deficiency #12 in Amendment 8, Inamed's Continuing Education Series will include the periodic publication and direct mailing to physicians of the most current relevant information, including the dissemination of information regarding specific findings related to modes and causes of rupture from our ongoing retrieval program. Furthermore, this Series will include information regarding the frequency and method of rupture screening. The INAMED Academy is also a venue that will be used for conveying information on the modes and causes of rupture and methods and frequency of rupture screening.

The specific modes and causes of rupture identified for Inamed's silicone-filled breast implants and information on rupture screening are currently described in the draft Directions for Use (DFU) document. Inamed considers the DFU document to be an inherent part of physician education. The latest information on rupture and other topics included in the DFU will, therefore, also be communicated directly to physicians via Inamed's education initiatives. The Continuing Education Series publication and the INAMED Academy will draw on the specific latest information provided in the DFU, including specific information on Inamed's findings regarding the modes and causes of rupture and Inamed's recommendations regarding the frequency and method of rupture screening. As new information becomes available it will be incorporated into the DFU and into the ongoing physician education initiatives, as described above.

In order to make this information more readily available to surgeons, all Inamed surgeon customers will receive an inventory of the DFU at no charge and additional copies will be available to physicians at no charge upon request. The DFU will also continue to be available via our web site. Inamed's Continuing Education Series publications will also be provided to physicians at no charge.

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Specific Instructions/Information

Based on the findings of our retrieval analysis, Inamed has provided specific instructions and warnings in the DFU regarding surgical techniques and implant handling that may potentially damage the implants and result in subsequent implant rupture.

These instructions in the current draft DFU are in the section titled **INTRODUCTION**. The surgeon is alerted to the fact that the information supplied in the document includes "...warnings, including surgical technique that should be avoided as it may compromise implant integrity..." The DFU states:

- ***DIRECTIONS TO THE SURGEON***

This document contains information that is essential to the patient consultation process. Please familiarize yourself with the content of this document and resolve any questions or concerns prior to proceeding with use of the device.

The information supplied in this Direction for Use document is intended to provide an overview of the appropriate use of Inamed silicone-filled breast implants, contraindications for use, warnings, including surgical techniques that should be avoided as it may compromise implant integrity, precautions, adverse and potential adverse events, as well as a clinical study summary.

Additionally in the section titled **WARNINGS**, the following instructions are provided:

AVOID DAMAGE DURING SURGERY

- ***Care should be taken to avoid the use of excessive force and to minimize handling of the implant during surgical insertion.***

Based on analyses of explanted ruptured silicone-filled breast implants, observations of surgeries, and a review of the published literature, INAMED believes that the forcing of implants through small incisions may result in localized weakening of the breast implant shell potentially leading to shell damage and possible implant rupture.

- ***Care should be taken when using surgical instruments in proximity with the breast implant, including scalpel, sutures, and dissection instrumentation.***

Silicone-filled breast implants are prone to unintended instrument trauma during implantation or during explantation (Brandon et al. 2001, Young and Watson 2001). Failure can result from damage by scalpels, suture needles, hypodermic needles, hemostats, and Adson forceps and has been observed in explanted device shells using scanning electron microscopy (Brandon et al. 2001).

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Use care in subsequent procedures such as open capsulotomy, breast pocket revision, hematoma/seroma aspiration, and biopsy/lumpectomy to avoid damage to the implant.

Re-positioning of the implant during subsequent procedures should be carefully evaluated by the medical team and care taken to avoid contamination of the implant before placement back in the pocket. Use of excessive force during removal and replacement can contribute to localized weakening of the breast implant shell potentially leading to decreased device performance.

In the section titled **INSTRUCTIONS FOR USE** the following directions are provided:

***Surgical Procedure
Placement***

Ensure incision is sufficiently large to facilitate insertion without excessive manipulation and handling of the device and to avoid damage to the device. Inadequate pocket dissection increases the risk of rupture and implant malposition.

DO NOT damage the breast implant with sharp surgical instruments such as needles and scalpels, blunt instruments such as clamps and forceps, or by overhandling and manipulation during introduction into the surgical pocket.

DO NOT use excessive force during breast implant placement.

DO NOT manipulate the implant for either radial expansion, compression or dissection of the pocket.

Rupture screening methods and frequency recommendations are outlined in Inamed's response to Deficiency 9 in Amendment 8. Inamed stated: "Specific labeling instructions to physicians and patients, regarding recommendations for the method(s) and frequency of screening for rupture, have been added to the draft product insert (DFU)..."

The text of this addition in the draft DFU is:

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, Holmich 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*

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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."

Summary

To summarize, the specific instructions/information for physicians related to specific modes and causes of rupture, and rupture screening method and frequency are currently included in Inamed's draft DFU. This information will also be reinforced to physicians as part of Inamed's Continuing Education Series and via the INAMED Academy. As new information becomes available as part of Inamed's ongoing retrieval program or via new information gleaned from Inamed's clinical trial and other sources, this information will be incorporated into physician labeling, e.g. the DFU, as well into other Inamed physician training and education initiatives.