

Modes and Causes of Rupture

3. The rupture rate is a critical safety parameter for your device. The preclinical, mechanical testing on your device indicates that the device should not rupture even when subjected to loads much greater than that predicted during normal daily activities. However, clinical information provided in your PMA included reports of rupture of your device. You proposed to work with an independent laboratory to perform analysis and testing of explanted devices as a postapproval condition. However, FDA believes that, to establish reasonable assurance of safety for your device, it is critical that the modes and causes of rupture are characterized to predict or estimate the long-term rate of rupture and, therefore, we believe that this information should be obtained pre-market. In addition, if the modes and causes of rupture are known, steps may be taken to minimize the rupture rate and, thus, improve patient safety.

Your retrieval study was specifically designed to characterize the failure modes of explanted devices from your Core Study. The results were inconclusive. The sample size was very low, with only approximately half of the explanted devices from the Core Study being included. Of the 42 explanted devices that were part of your retrieval study, none were deemed ruptured by the physician and 34 of 42 were not ruptured as evidenced by the laboratory analyses. Thus, the modes and causes of the clinical rupture of your device remain unknown.

Your literature review discussed breast implant rupture, but your discussion of the causes of rupture was inadequate. Your literature review considered only the factors of implant generation (1st, 2nd, or 3rd) and iatrogenic damage, which are only some of the factors that may contribute to implant rupture. As reported in literature, factors to consider in explaining implant rupture include implant type/model, implant size, implant shell thickness, implant surface (smooth versus textured), implant lot (lot-to-lot variability in initial gel and shell crosslinking and mechanical properties), length of implantation, implant handling prior to insertion, implant position, implantation technique (scalpel nicks, suture punctures, surgeon's finger imprints, clamp grip marks), in-vivo material property and chemistry changes/degradation, in-vivo cyclic stress, in-vivo trauma (accident, mammography), procedures performed while device is in-situ (biopsies, cyst aspirations), and explantation technique. Some of these factors are directly related to the device or its use, others are not. Nevertheless, all of these factors should be considered in designing a future test plan to evaluate the modes and causes of rupture for your device.

Please provide adequate data to explain the modes and causes of clinical rupture of your device. To address this item, you should consider:

- a. an independent re-analysis of the 8 devices deemed ruptured by your laboratory from your current retrieval study to determine if any new information regarding the modes and causes of rupture can be gained;

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- b. a new retrieval study of your device by an independent party. To increase the number of explanted devices that were deemed to have been ruptured by the physician, we recommend that you include explanted devices from other sources (e.g., Adjunct Study). FDA also recommends that you review the article by Brandon, et al^{1/} for the type of information to consider during the development of your protocol (e.g., control group of unimplanted devices, detailed chemical analyses of materials, detailed mechanical testing, scanning electron microscopy, analysis of local tissues/capsule);

3a and 3b Response:

In response to Deficiencies 3a and 3b, and prior to PMA approval, per FDA's recommendations, Mentor expanded its explant retrieval study to re-evaluate the seven devices deemed ruptured of unknown origin and to include a sampling of ruptured explanted devices from the Adjunct study. (One sample of the original eight samples was determined to be unsuitable for testing after the initial microscopic examination at Mentor.) The modes and causes of rupture for these seven devices have been determined to be sharp instrument damage in five cases, and suspected instrument damage for two cases (holes in one case, and tear in one case), as discussed below in detail. In addition to evaluating and characterizing the modes of failure for these seven devices, Dr. Harold Brandon of Washington University evaluated and characterized the modes of failure for devices from the Adjunct Study, as well as control samples.

In Dr. Brandon's study, a sampling of devices implanted up to 9.4 years was examined microscopically and with scanning electron microscopy ("SEM"), including inspection for voids, microbubbles, and foreign material, to better characterize the modes and causes of rupture. Dr. Brandon also determined crosslink density on a limited number of devices to determine if there were any physical property changes or chemical bond disruptions resulting from implantation. Physical testing also was performed on explanted devices to assess any changes in physical properties of shell materials (i.e., shell tensile, break force, elongation, tension set, and joint strength) resulting from exposure to the physiological environment.

1/ Brandon, et. al, "Protocol for Retrieval and Analysis of Breast Implants." *Journal of Long-Term Effects of Medical Implants*. 13(1): 49-61. 2003.

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SEM Analysis (Report MP 050 in Attachment 3 and Report MP 051 in Attachment 4)

In the initial phase of the project 39 samples, most from the Adjunct Study, were provided to Dr. Brandon. The explanted devices were chosen to represent all of the different failure characteristics that have been identified by Product Evaluation personnel in Mentor Texas operations. Included in this set of samples were eight control samples. Implantation times for the sample devices ranged from 0 (intraoperative failure) to 9.4 years. The explant sample population included both smooth and textured devices. Examples of smooth and textured round and high profiles were included.

In an effort to establish a preliminary mode of failure, Mentor personnel examined the failed explanted devices with an optical microscope before submitting them for analysis at Washington University.

Not all submitted samples were examined by SEM. Dr. Brandon and his staff did a preliminary screening and selected samples to insure that all failure modes were examined. Twenty-two samples were examined with SEM. These included three control samples (blade damage, needle puncture and tear) and 19 explanted devices.

Analysis of the resulting pictographs resulted in a classification of failures as follows:

- Sharp Instrument Damage (5 devices)
 - Blade Damage
 - Needle Puncture
- Localized Shell Fatigue Failure (11 devices)
- Long Failure Lines with Un-assignable Cause (3 devices)
- Miscellaneous (3 devices)
 - Failure at Shell/Patch Junction (periphery of patch)
 - Layer Delamination
 - Surface Defect

The mode of failure was identified for nine failed devices that Mentor had initially categorized as "unknown." The modes of failure for four other devices were refined from a general description of the failure to a more specific designation for the failures. According to the results of the SEM analyses, one device had been misclassified by Mentor personnel. There was agreement for the categorization of the modes of failure for the remaining 8 devices. The foregoing sample count (22) includes the control samples.

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Thin line failures can occur as the result of iatrogenic damage (sharp blade cut or needle puncture), fatigue failure in an area of the shell weakened by localized stress during implantation or long term fatigue failure of the shell. As was noted in the Brandon SEM studies, long thin line failures are problematic in terms of assigning a cause of failure because the failure initiation of the long rent may be an extremely small portion of that rent, i. e., a very short scalpel cut or a needle puncture. These can be extremely difficult to locate and identify. In the case of fatigue failure resulting from local stress applied during implantation, the initiation point looks precisely identical to the propagation section of the failure line. In many of the foregoing examples, the cause can not be identified and will ultimately be classified as "unknown."

Localized shell fatigue failure is a uniquely distinctive mode of failure. These failures result from folding of the shell followed by cyclic fatigue that eventually leads to failure. The appearance of the failure area is distinctive. It is characterized by a fishbone pattern in the elastomer radiating out from the failure. Abrasion lines on the exterior of the shell are frequently, but not always, located in the proximity of the failure area. Inner or outer shell layer delamination sometimes occurs in the proximity of the failure area. Delamination of the inner layer is more frequent than the outer layer. The preponderance of these failures occur with textured devices. This is to be expected since the stress related to the folding of the shell is increased with the thickness of the shell. Textured shells are thicker than smooth shells. Thus, the stress and the ultimate fatigue related to the cycling of the fold will be exacerbated in the textured device.

The Brandon report characterizes Localized Shell Fatigue mode and cause of failure as follows:

"Localized shell fatigue damage is the result of localized flex fatigue or fold flaw mechanisms. The damage is characterized as a tapered or feathered opening, material cracking, parallel feathering lines, and in some cases, shell layer delamination. In some cases, there was evidence of exterior surface abrasive wear due to abutment, folding and rubbing contact of the exterior surface. When it is present, this failure mode is quite distinctive and easily identifiable in the explant samples."

Shell/patch delamination is the failure of the bond between the shell and patch of the device. The preponderance of these failures occurs with textured devices. These failures could result from (1) cyclic fatigue of the bond area due to the fact that on textured devices this bond lies close to the radius of the device (it is postulated that this area could be subject to cyclic stress) or (2) lower than normal bond strength resulting from the manufacturing process. It should be noted that joint strength of the shell/patch bond is verified as meeting an internal specification limit during finished device testing. Shell/patch delaminations represent a small portion of the overall device failure populations that were investigated.

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As a follow-up to the larger investigation into the modes and causes of failures of Mentor gel-filled implants, seven samples of surgical placement failures from the Core Gel Clinical Study were provided to Dr. Brandon. After three years of follow-up, a total of 10 implants were suspected ruptures, of which two were confirmed to be intact and two were confirmed ruptures. The remaining six implants failed intraoperatively. Therefore, eight samples had failed either *in vivo* or intraoperatively. One sample was determined to be unsuitable for testing after the initial microscopic examination at Mentor. Thus, seven samples were provided to Dr. Brandon's group for examination. All devices had smooth surfaces. *In vivo* residence time for the devices ranged from 0 (intraoperative failure, 2 devices) to 1.1 years.

The samples were examined at the Mentor Texas facility before being transferred to Dr. Brandon for examination with SEM. The failure mode assigned by Mentor to all seven samples was "Instrument Damage-Shell." Failure mode designation resulting from SEM examination agreed on five of the seven failure samples. No parallel striations were found along the failure lines for the other two devices and there was no clear evidence that needle punctures were involved. For these reasons, these failures were classified as "Unknown Cause" (see table below for details).

Sample Number	Failure Mode-Mentor Determination	Failure Mode from SEM Analysis	Observations from Brandon Report
14185 L	Instrument Damage - Shell	Sharp Instrument Damage	Tear propagation from 3 small holes. Striation lines at each hole.
200010-0202	Instrument Damage - Shell	Sharp Instrument Damage	3.5-inch tear that propagated from needle puncture.
200101-0655	Instrument Damage - Shell	Sharp Instrument Damage	2 holes ~ 1/2 inch apart. Staple punctures. Parallel striations on edge of hole.
200107-0413	Instrument Damage - Shell	Sharp Instrument Damage	Failure line ~ 1 inch long. Striation along failure line.
200205-0417	Instrument Damage - Shell	Sharp Instrument Damage	Two small holes in test sample. Surgical instrument damage.
14185 R	Instrument Damage - Shell	Unknown Cause	Two small holes, 2 mm apart. No parallel striations.
200102-0308	Instrument Damage - Shell	Unknown Cause	Unremarkable tear with no striation marks.

In his report Dr. Brandon speculates the following with regard to the possible initiating sources of the two failures that were categorized as "Unknown Cause."

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“ Conversely, with short failure lines a thorough examination could be and was made via SEM and no initiation point was identified. This examination almost certainly eliminates iatrogenic failures (sharp blade cuts or needle punctures) since these would have been identified with a high degree of certainty, through the view of SEM micrographs. It is reasonable to speculate that the unknown failures could have resulted from localized stress introduced during the implantation procedure, a micro-flaw from a surgical instrument, or from an unobservable manufacturing defect that resulted in a weakened area of shell. None of these would necessarily result in an observable physical signature along the failure line. Because of the lack of any specific identifying characteristic, a precise designation of cause of failure was not possible.”

The obvious conclusion from the analysis is that the preponderance (5 devices out of 7, 71%) of device failures through the early stages (approximately 1 year) of the Core Gel Clinical Study result from instrument damage. The cause of failure of the remaining 2 devices could not be confirmed as instrument damage.

Crosslink density was determined on five devices. Four of these had textured surfaces and one was smooth. Test samples for the determination of crosslink density were cut at the failure line and at a point in the proximity and adjacent to the failure line of each device. The sample cut from an area away from the failure line provides a control reference for the sample from the failure site. The results of this determination along with the failure mode for each device are included in the table below.

Sample Number	Shell Surface	Failure Mode	Years <i>In vivo</i>	Percent Difference between Crosslink Density of Damaged and Undamaged Regions
200206-0061	Textured	Localized Shell Fatigue	3.5	5%
200202-0538	Smooth	Instrument Damage	0.7	1%
200205-0725	Textured	Miscellaneous--Surface Defect	8.0	9%
200201-0204B	Textured	Fatigue	7.8	4%
200207-0302	Textured	Miscellaneous—Shell Patch	7.4	6%

After personnel from Mentor Corporate Laboratories reviewed the results on crosslinking, their comment was that the 4 to 9% range of differences in crosslink density between damaged and undamaged sites falls within the experimental error for such measurements.

One final observation on the crosslink density results needs to be made. One would assume that failures occur at the weakest point within the silicone shell elastomer. This should be the point of lowest crosslink density. The results

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shown above suggest the opposite. Also, crosslink density can be reduced by two different mechanisms: (1) breaking of bonds through chemical action or (2) breaking of bonds through mechanical fatigue.

Device Re-examination and Optical Microscopy Study (Report M 052 in Attachment 5)

The objective of this investigation was to determine the modes of failure of gel implant devices, to propose mechanisms and causes of failure, and to test those proposed mechanisms against characteristics of failed devices. The study was based upon devices that were sold in the domestic U.S. market, and the vast majority of devices examined were representative of PMA product lines.

Gel-filled breast implant devices that have been explanted because of complaints are returned to the Mentor facility in Irving, Texas for evaluation and classification with regard to mode of failure. The results of this investigation, including the assigned modes of failure, are recorded in the Product Evaluation (PE) database. Two specific segments of that database, sub-populations entitled, "Rent—Unknown Cause" (RUC) and "Not Apparent—Etiology Unknown," (NAEU) contain the records of devices for which a specific mode of failure was not identified during this initial inspection of complaint devices that had been returned by physicians. With improved capabilities for microscopic evaluation and improved understanding of the characteristics learned with the assistance of Dr. Brandon that signify certain types of failures, Mentor concluded that there was a reasonable likelihood of being able to reliably assign modes of failure to some of these devices by a close re-examination of those devices.

The table below provides a direct comparison of the classifications of modes of device failure specified by Dr. Brandon in his SEM investigation of Mentor devices and those used in this study (see Reports MP 050 and MP 051). In the Mentor study, thin line failures are defined as those failure lines that, if the opposing sides of the failure are placed back together, will match precisely. In other words, the failure line will resemble a tear in the silicone elastomer. The thin line failures were segregated by location on the surface of the device because the cause of each mode of failure could be different.^{2/}

2/ Patch Internal is a special classification that relates specifically to the area on the patch of textured devices that lies inside the periphery of the patch radius. This area is very similar to the shell of the device, and, therefore, could be expected to fail in a manner similar to the shell area. The Patch Internal failure mode was established to ensure that, if this mode of failure was significant, it would be clearly identified and not lost in a more general classification. In fact, very few cases of this mode of failure were found.

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Failure Modes Characterization	
Mentor Investigation	Brandon Investigation
Thin Line <ul style="list-style-type: none"> • Shell Only • Patch Internal • Patch/Shell Junction 	Sharp Instrument Damage <ul style="list-style-type: none"> • Blade Damage • Needle Puncture Long Failure Lines with Un-assignable Cause
Localized Shell Fatigue	Localized Shell Fatigue Failure
Shell/Patch Delamination	Miscellaneous—Layer Delamination

The table below shows the percent of failures attributed to each mode of failure for the populations investigated and for the combined populations.

Failure Characterization	Rent-Unknown Cause (RUC)		Not Apparent-Etiology Unknown (NAEU)		Combination of RUC and NAEU	
	No. of Failures	Percent of Actual Failures	No. of Failures	Percent of Actual Failures	No. of Failures	Percent of Actual Failures
Thin Line (Shell)	72	60%	60	73%	132	65%
Patch Internal (Thin Line)	3	3%	0	0.0%	3	2%
Shell/Patch Junction (Thin Line)	21	17%	2	2%	23	11%
Localized Shell Fatigue	17	14%	3	4%	20	10%
Shell/Patch Delamination	4	3%	8	10%	12	6%
Combination Failures	4	3%	9	11%	13	6%
Total Failed Device Population	121	100%	82	100%	203	100%

After the first year of implantation, the total failure populations of RUC and NAEU displayed a very similar profile of failures over time. In year 0 (intraoperative failures) and up through year 1, the number of failures was elevated over the ensuing years. In year 2 through the period ranging from 8 to 10 years, the number of failures was less than the initial period of intraoperative failures through year 1. There were no failures after year 10 for these sample populations.

There were no intraoperative failures associated with either the thin line shell/patch junction or the localized shell fatigue modes of failure. In fact, there was only 1 (out of a total population of 23) of thin line shell/patch junction failures and 0 localized shell fatigue failures (total population of 20) in the 0-1 time interval. The obvious conclusion is that failures from thin line shell/patch junction or localized shell fatigue take time to develop. Proposed mechanisms for

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these failure modes are presented in the Mentor report (M 053). Both of these mechanisms involve cyclic fatigue. Cyclic fatigue requires time to produce failures in the silicone shell elastomer.

Analyses of the location of failures were performed on the RUC and NAEU overall populations and the subset modes of failure of these populations. These analyses indicate that initial failures cluster in a circumferential area circumscribed by the anterior region of the device just above the radius and the radius area itself. This region is most susceptible to instrument damage either during the implantation and closure procedure or the removal of an implant (e. g., for resolution of capsular contracture problems). It is hypothesized that this same region is more susceptible to wrinkling and subsequent cyclic fatigue than the anterior and posterior regions of a device that are remote from the radius area. The shell wear patterns associated with localized fatigue failure terminate within this same region. It is certain that these failures result from fatigue. This physical evidence provides strong support for the hypothesis that wrinkling does occur and that this may ultimately result in cyclic fatigue failure in this region.

The ---- devices from the NAEU category include the subpopulation of 82 failed devices that were re-examined during this study. However, the devices that were not re-examined will not have the specific computer searchable information, such as failure mode, failure location, length of failure line, etc., that is available on the devices that were inspected during this investigation. Nevertheless, those devices that were not re-examined will have enough information to yield a time to failure plot.

When the number of complaint devices is plotted against the time interval to explantation, the following observations can be made.

- There are 6 intraoperative (*in vivo* time equal to 0) failures, and 120 and 57 in two time intervals >0 to ≤ 1 and >1 to ≤ 2 years, respectively.
- For the time interval from 3 through 7 years the number of observed plus assumed failures per year is relatively constant at approximately 20-25 devices.
- Beyond 8 years the rate falls to 1-4 per year with no failures beyond 14 years.

The elevated populations in the 0-1 and 1-2 year time intervals most likely represents failures related to instrument damage (scalpel cuts or needle punctures) or application of localized stress during implantation that resulted in a weakened area on the shell. The overall profile of the number of devices versus implantation time is very similar to the profiles of the RUC and NAEU smaller populations of re-examined failed devices. It is concluded that the smaller populations are, in fact, representative of the larger failure populations.

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Of significance is the fact that the failure rate after 8 to 10 years falls to a very low rate and after 14 years there are no more failures for the overall NAEU population. The overall exposure population of devices that could fail, devices sold greater than 10 years ago (approximately ----- sold devices), is significant. The number of actual observed failures is low, however, as shown in the populations of the re-examined devices as well as the more liberal estimate made from the overall NAEU population.

It is a given that these devices will have a finite life. The fact that the rate of observed failures decreases dramatically after about 10 years indicates that these devices will ultimately fail in a bimodal distribution. This initial failure population has been characterized in terms of modes and causes of failure and time to failure in the report on this investigation. The size of this failure (rupture) population based upon customer complaints and sales data has been reported to the FDA as ----- of the total devices sold.^{3/} If there is only a ---- observed failure rate, then the rest of the devices remain as potential future failures.

Simple logic can lead to a gross estimation of device life. It is likely that the bulk of these devices will ultimately fail through cyclic fatigue. It is believed that mechanisms that result in early failures, e. g., iatrogenic damage, have already exhausted those devices that will fail from those mechanisms. This would leave only mechanisms that involve elastomer fatigue, except for catastrophic events, such as automobile accidents. Catastrophic events will be infrequent. Cyclic fatigue testing on these devices has demonstrated that cycles to failure over several test samples will vary, i. e., as expected not all devices will fail at the same time. There will be a distribution of cycles to failure for a population of test devices. This failure distribution *in vivo* will become more diverse, because the stress values will vary and will be a function of the lifestyle of the implanted individual.

The failure distribution of the final bulk of these devices will follow some distribution. For simplicity sake, let us assume that the distribution is normal. If we also assume that the normal distribution is broad with a relatively large standard deviation (i. e., is not a very narrow distribution) and that an increased rate of failure starts now at the 18th-19th year in the age of the oldest implanted devices recorded in the PE database, then it is almost a certainty that the median life of the devices will be greater than 25 years.

It is clearly recognized that uncertainty is added to this very rough estimate by the possibility of silent rupture or unreported failures. As explained in the report, it is believed that most failures are reported for financial, legal, and regulatory reasons.

3/ Mentor PMA Submission, PMA P030053, Section 8.2, Volume 13, December 11, 2003.

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A detailed discussion of this study is provided in Report M 052 in Attachment 5. Additionally, we have updated the Core Retrieval report to include the analyses of any explanted devices received since the original PMA submission. This report, HS222.020819.02AdA can be found in Attachment 6.

Explant Physical Testing Summary (Report M 048 in Attachment 7)

This report analyzes changes in Mentor Gel-filled Mammary Prostheses shell physical properties over time implanted by looking at the shell properties of primarily ruptured explanted devices from Mentor's Texas Product Evaluation Department ("PE") database, most from the Adjunct study, and explanted devices (ruptured and intact) from Mentor's Core Gel-filled Mammary Prosthesis Clinical Study. Since ASTM F 703 Standard Specification for Implantable Breast Prostheses contains tests appropriate for assessing the physical properties of unimplanted finished devices, it was used as a reference for selecting appropriate tests for the explants. The following physical tests were performed on explanted devices:

- Shell Stress at Ultimate
- Shell Break Force
- Shell Elongation
- Shell Tension Set
- Patch-to-shell Joint Strength

While shell stress at ultimate is not mentioned in the ASTM standard, it is a property based upon the shell breaking force and the cross sectional area of the sample and provides a normalized (i.e., unit area) measure of a shell's ability to resist force. This provides a more direct assessment of any shell silicone material changes since it takes into account shell thickness.

Ruptured devices were primarily chosen from the PE database because they represented devices which were expected to have been stressed the most. Iatrogenic ruptures were not selected since they usually are not in the body long enough for the shell physical properties to change. Explanted devices from Mentor's Core Clinical Study were tested as requested by FDA (see Report M 048 in Attachment 7).

The results of the PE explant physical testing indicate that, in general, the device shell properties remain either fairly constant during their time implanted, or experience a slight reduction in their physical properties during an initial implantation period, but then usually level off and remain fairly constant out to 9.5 years of implant time. The Mentor Core Gel Mammary Study smooth explant physical testing data demonstrate that physical properties are mostly unchanged

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over about three years of implantation. For several properties, Siltex devices show a decrease in property over an initial early time period but then become fairly constant for much of the rest of the time *in vivo*.

A detailed discussion of this study is provided in Report M 048 in Attachment 7.

Explant Rupture Failure Rate Analysis (Report M 049 in Attachment 8)

This analysis of explanted devices in the records of the PE database was performed to better understand the rates of rupture failure of Mentor's Low Bleed Gel-filled Mammary Prostheses based upon examination of returned devices (see Report M 049). Rates of failure (calculated based upon the number of domestically distributed returned ruptured devices and domestic sales of gel-filled devices from 1985 through 2003) and numbers of returned ruptured devices per individual device lot were determined to understand whether failure rates differed due to device size, surface type, or product line. These factors were also examined for iatrogenic and non-iatrogenic device failure groups. Numbers of device failures within device manufacturing lots, or by year manufactured, were used to examine whether manufacturing changes could have affected failure rates over time. All device failures analyzed had been verified by PE personnel.

Using Mentor's Texas PE database of complaints and verified failure data from those complaints, the overall rupture failure rate for gel-filled devices is much less than one percent of the devices sold. No differences were seen in the overall failure rate between Mentor's Smooth and Siltex Gel-filled devices. Similarly, there were no differences in failure modes (*i.e.*, iatrogenic versus non-iatrogenic) between surface types. This conclusion, and others that follow, are tentative because of the large number of explanted devices that could not be examined in a detailed manner because they are part of Mentor's class action lawsuit settlement or were not returned.

Iatrogenic failure rates are low for all product lines (mostly less than 0.25% of products sold). As one might expect, these rates do not appear to be influenced by product size, do not appear to be associated with any historical manufacturing changes, and appear to be a random occurrence in individual product lots.

Non-iatrogenic rupture rates are low for gel-filled product lines (generally about 0.30%). Device size may have some effect on the non-iatrogenic failure rates of some product lines, but the effect is not consistent within sizes of a product line and involves different sizes in different product lines. Non-iatrogenic ruptures do not appear to be related to any historical manufacturing changes and are not noticeably concentrated in any product lot(s).

A detailed discussion of this analysis is provided in Report M 049 in Attachment 8.

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***In Vitro* Biodegradation (Report M 044 in Attachment 9)**

Following discussions with FDA on April 28, 2004, in which the Agency suggested that shell integrity might be adversely affected by exposure to the physiological environment *in vivo*, Mentor undertook studies to determine whether exposure of the silicone gel-filled breast implant to a simulated physiological environment affected shell properties. Porcine serum was chosen to simulate the composition, including lipid content, of the extracellular fluid within the fibrous capsule that is in direct contact with the implant in the patient. This report presents results of a study of *in vitro* biodegradation of Siltex® Round Moderate Profile Gel-Filled Mammary Implants. Whole devices were immersed in saline (the control solution) or porcine serum (the test solution), and incubated at 37 °C for 60 days. Devices periodically were sampled and weighed, dissected, and gel and shell were subjected to rheological and tensile testing, respectively.

The study was intended to determine the effects of porcine serum immersion on gravimetric and mechanical properties of mammary implants. Weight measurements allowed for monitoring of changes associated with potential gel bleed and lipid infiltration. Mechanical testing of gel and shell facilitated assessment of the extent of crosslinking and potential degradation. Results indicate that no weight change was observed for either saline or porcine serum. In addition, the tensile strength of shells and crossover modulus of gel showed no effects for either saline or porcine serum. Accordingly, *in vitro* biodegradation of gel mammary implants was not observed under the conditions tested. Details of this study are provided in Report M 044 in Attachment 9.

Fatigue Testing

Currently, mechanical testing is not predictive of clinical experience, but may be used to establish baseline parameters for fatigue and physical characteristics of materials. However, models that utilize *in vitro* fatigue data, combined with assumptions about patients' lifestyle, may yield device life predictions. Since fatigue data historically have been generated under stringent and exaggerated stress conditions, these product life predictions in the past have represented highly exaggerated worst case scenarios. As described below, Mentor estimated product life predictions based on data from fatigue tests using the hemispherical cage and parallel plate methodologies, combined with assumptions that more closely correlate to patient lifestyle conditions.

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Biaxial Cyclic Fatigue Analysis of Gel Mammary Implant (Report M 016 in Attachment 10)

Mentor has generated cage fatigue data that was utilized in a model to provide a device fatigue lifetime prediction. The hemispherical cage fixture exposes the implant to biaxial stresses that are more representative of *in vivo* conditions than the parallel plate (uniaxial) fixture described below. The modeling approach utilized a combination of *in vitro* stress on the implant shell that was derived from the experimental measurements and assumptions of *in vivo* stress using published literature-based estimates of likely daily physical activity. Environmental testing conditions were controlled to mimic *in vivo* conditions. Cycles-to-failure was experimentally determined at several loads and endurance limit load (no failure at 10^7 cycles) was determined. The *in vivo* stress on a device was determined by analyzing the loading resulting from physical activities such as walking and running and is modeled with a free body diagram at rest and in motion. Estimation of implant lifetime combines the *in vitro* and *in vivo* stresses with application of Basquin and Gerber relations^{4/} and incorporation of the frequency of physical activities. Details of this study are provided in Report M016 in Attachment 10.

Cyclic fatigue analysis of Siltex[®] Round Moderate Profile Gel-Filled Mammary Implants has been conducted using a servohydraulic tester equipped with *in vitro* test chamber and fixture.

Experimentation included monotonic servohydraulic testing and cyclic servohydraulic testing of devices, electromechanical testing of the device shell, and rheological characterization of the device gel. Monotonic servohydraulic testing was conducted to identify the appropriate conditions for cyclic testing. Cyclic servohydraulic testing was conducted to evaluate fatigue behavior used for estimation of a device fatigue lifetime. Electromechanical testing of the device shell was undertaken to provide data necessary for the fatigue lifetime calculations and to determine tensile properties prior to and following fatigue. Rheological characterization of device gel was also measured prior to and following fatigue to assess whether changes occurred.

Cyclic fatigue testing was performed under load control at several stress levels to define the cycles-to-failure behavior. The test fixtures and chamber used for cyclic fatigue testing were designed to provide *in vitro* uniform stress conditions at 37 °C. A uniaxial and a biaxial test fixture were used to stress the radius (*i.e.*, the area at the circumference of the device that consists of a strip of the surface around the device at the circumference) and radius plus anterior regions of the device respectively. Cyclic testing was performed at frequency $f= 1$ Hz with the exception of testing to 10^7 cycles without failure, which was performed at accelerated frequency ($f= 5$ Hz) to minimize experimental time requirements.

4/ Suresh, S. 1998. Fatigue Materials, 2nd Edition, Cambridge University Press, Cambridge, UK.

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Comparison of $f=1$ Hz and $f=5$ Hz frequencies was undertaken at a moderate stress level for validation of accelerated frequency condition. Comparison of the uniaxial and biaxial test fixtures was undertaken at a moderate stress level for validation of the fixture design. Upon validation fixtures were used interchangeably for cycles-to-failure testing.

Comparison of $f=1$ Hz and $f=5$ Hz data showed no frequency dependence. Comparison of the fixture design indicated no significant difference for cycles-to-failure results. Device shell tensile testing prior to and following fatigue showed no significant differences. Gel rheological properties measured prior to and following fatigue showed no significant differences. The fatigue lifetime estimate obtained using the biaxial fixture is similar to the results presented below for the uniaxial testing (see Report M 028).

Uniaxial (Parallel Plate) Cyclic Fatigue Analysis of Gel Mammary Implant (Report M 028 in Attachment 11)

The process for the prediction of device life resulting from parallel plate test data was identical to the approach described above for the data from the hemispherical test fixture. During the parallel plate test, the devices were maintained at normal body temperature (37°C) and were cushioned so that the metal fixture did not contact the device directly. These environmental conditions were maintained to more closely simulate *in vivo* conditions. Cycles-to-failure were experimentally determined at several loads. Endurance limit load (no failure at 10^7 cycles) was also measured.

Using these test data, the same patient lifestyle assumptions as were applied in the model for the hemispherical fixture to provide a prediction of device fatigue life were used. Details of this study are provided in Report M 028 in Attachment 11.

Cyclic fatigue analysis of Siltex[®] and Smooth Round Moderate Profile Gel-Filled Mammary Implants was conducted using a servohydraulic tester equipped with *in vitro* test chamber and fixture. The resulting data were used to estimate a fatigue lifetime for these devices related to *in vivo* load and stress associated with physical activity.

Experimentation included monotonic servohydraulic testing and cyclic servohydraulic testing of devices and electromechanical stress-strain testing of the material composing the device shell. Monotonic servohydraulic testing of devices was conducted to identify the appropriate conditions for cyclic testing. In addition, the monotonic servohydraulic testing provides calibration data that are needed for interpreting the results of the cyclic tests. Cyclic servohydraulic testing was conducted to evaluate the fatigue behavior of devices and the results are used for estimation of a device fatigue lifetime. Electromechanical testing of the material composing the device shell was undertaken to provide data on its stress-strain behavior.

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Cyclic fatigue testing of devices was performed under load control at several load levels to define the cycles-to-failure behavior. These tests were continued until the device failed by rupture or until 10^7 cycles of load have elapsed. The test fixture and chamber used for cyclic fatigue testing was designed to provide *in vitro* stressing of the devices at 37 °C. A uniaxial compression parallel plate test fixture was used to compress the device and therefore cause tensile stress at the outer radius of the device. Cyclic testing was performed in most cases at a frequency of $f= 1$ Hz, considered to be representative of *in vivo* loading of devices. In addition, some tests were performed at an accelerated frequency ($f= 5$ Hz) to minimize experimental time requirements. Comparison of the results from testing at $f= 1$ Hz and $f= 5$ Hz was undertaken at a moderate stress level for validation of the accelerated frequency condition.

Monotonic servohydraulic testing revealed that cyclic testing is performed in the regime of prosthesis behavior involving limited nonlinear response. Cyclic results indicate that cyclic fatigue data for mammary implants can be used to estimate a fatigue lifetime for devices *in vivo*. Comparison of $f= 1$ Hz and $f= 5$ Hz data showed no frequency dependence.

The *in vivo* stress amplitude in device shells associated with the most common physical activity of walking, jogging, and running is estimated to be as high as 8.6 psi. Load amplitudes associated with activities such as lying face down, embracing another person, *etc.* are estimated to cause compressive loads of 5 lb *in vivo*. The possibility of wrinkles forming at the outer radius of the prosthesis was considered and the action of such wrinkles appearing and disappearing was estimated to cause tensile stress amplitudes of 20 psi. Wrinkling and unwrinkling were considered to accompany other physical activities such as walking.

A Basquin-Gerber equation, a log-log relationship between the load or stress amplitude during cycling and the number of cycles to failure, was established for the implants and the material composing their shells. This relationship can be used to determine the fatigue lifetime at any specified level of device loading or stressing. It was found that the fatigue lifetime of the devices is 8.07×10^8 to 1.44×10^9 cycles of loading by walking, jogging, and running and 4.87×10^9 to 1.25×10^{11} cycles of lying face down, embracing and similar activities. On the assumption that an implant recipient walks at most 10 hours per day at 1 pace per second and goes through no more than 1,000 actions per day of lying face down, embracing and related activities, it was determined that the fatigue life of an implant *in vivo* based on these assumptions might range from 61 to 109 years. Mentor acknowledges that this lifetime prediction exceeds actual device lifetimes observed clinically, as reported in the Sharpe and Collis study of women implanted for up to 12 years, and in the literature. However, this lifetime prediction is derived from *in vitro* data that does not incorporate damage that may occur prior to or during implantation. Such damage (see Response 3e below) is known to shorten device life.

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- c. an assessment of your manufacturing processes related to release specifications of your shell to determine whether any allowances for imperfections, such as bubbles and contaminants, may be related to device rupture;**

3c Response:

Mentor has assessed whether several aspects related to manufacturing processes (i.e., release specifications, process changes, and lot-to-lot variances) have influenced device rupture and rupture rates of Mentor's Gel-filled Mammary Prostheses. Physical testing and product evaluation rupture analysis data are provided to show that the manufacturing process and release specifications are not related to device rupture.

A review of the device specifications was performed from dipping, rubber processing, main assembly and finished device inspection. The primary allowances for imperfections identified in these specifications relate to the acceptance of embedded particles and bubbles of a certain size. Tensile strength and elongation testing of device shells with particulates and bubbles slightly exceeding the maximum specification limit of 0.015" for each type of imperfection still met the stipulated acceptance criteria for finished products (see report HS33.000111.01 HTV Particle Specification Analysis in Attachment 12 and HS222.040719.01 HTV Bubble Specification Analysis in Attachment 13). In addition, a review of the product complaint database for silicone device ruptures showed that the assignable cause of any rupture, rent, or cut in a device could not be attributed to the presence of an embedded particle or bubble.

In addition to the above, a review of the major manufacturing process changes from 1991 through 2003 (see Mentor's response to PMA deficiency letter question 27 in this submission) shows that the number of ruptures per device lot received as a complaint in Mentor's Texas Product Evaluation Department did not noticeably change after any of the historical process changes. Finally, the rupture analysis by manufacturing lot also shows that almost all lots with ruptures returned to Mentor have two or less ruptured devices per lot with only three lots having three ruptures each. In total, all of the above manufacturing process analyses suggest that Mentor's manufacturing processes and release specifications do not appear to have a contributory role in the cause of gel-filled mammary ruptures.

- d. an assessment of the surgical techniques that increase the risk of rupture; and**

Effects of Surgical Insertion on Mechanical Properties (Report M 041 in Attachment 14)

Mentor performed fatigue analyses on Smooth Round Moderate Profile Silicone Gel-Filled breast implants that were subjected to simulated surgical and diagnostic procedures to determine the affect upon cyclic fatigue lifetime. Iatrogenic procedures included mammary surgical insertion procedure, inadvertent scalpel damage, suture needle puncture, and mammography-induced compression. Devices were subsequently tested

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with servohydraulic instrumentation to measure cycles-to-failure for comparison to control devices that had not been subjected to iatrogenic events. Simulated surgical insertion procedure and mammography diagnostic procedure did not affect the device fatigue lifetime. Induced suture needle puncture damage through the device shell resulted in immediate failure of the implant or a loss of ~99 % of fatigue lifetime. Induced scalpel damage of the device shell with and without penetration through the shell also resulted in a variety of failures of the implant yielding no effect on fatigue lifetime to a loss of ~99 % of the fatigue lifetime. These results indicate that minimal scalpel damage achieved with a surface scratch has no apparent effect on fatigue lifetime. Major scalpel damage achieved with an incision through the shell has a dramatic effect on fatigue lifetime (*i.e.*, 99% reduction). Details of this study are provided in Report M 041 in Attachment 14.

Relationships Between Rupture Rates and Surgical and Product Parameters From Mentor's Adjunct Clinical Study (Report M 053 in Attachment 15)

In an attempt to further characterize modes and causes of rupture for Mentor's silicone gel-filled breast implants, a statistical analysis of the relationships between rupture rate and parameters associated with device implantation, as well as device characteristics, was undertaken using data derived from the Adjunct Clinical Study database. For the purposes of this analysis, only ruptures that occurred after the date of implant surgery, *i.e.*, ruptures that occurred in devices that were implanted without apparent damage were considered. Out of ----- implanted devices recorded in the database (from 1985 through the present), only 159 met this definition of failure. Details of this study are provided in Report M 053 in Attachment 15.

The following populations were analyzed:

- (1) Total population (TP) of the Adjunct Study database
- (2) Smooth devices within the TP
- (3) Textured devices within the TP
- (4) Revision Augmentation Subpopulation (RAS) of the total Adjunct database population
- (5) Smooth devices within the RAS
- (6) Textured devices within the RAS
- (7) Total Reconstruction Subpopulation.

The following parameters were assessed:

- Surgical approach
 - Inframammary

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- Transaxillary
- Periareolar
- Device placement
 - Subglandular
 - Submuscular
- Incision size
 - Small (3 cm)
 - Medium (3-6 cm)
 - Large (6-9 cm)
- Device size (150-800 cc)
- Interaction of device size and incision size
- Surface characteristic (smooth versus textured)

Since the rates of device rupture in the Adjunct Study were very low, the parameter for analysis (rupture rate, "RR") was defined as the rate of rupture per 10,000 implant years. Relationships between RR and the factors listed above were analyzed using Poisson regression methods. A complete discussion of the statistical methodology employed, and the factors considered in deriving the relationships, is provided in the full study report (Report M 053).

The results of this analysis are summarized below and in the table that follows.

- Device placement has a statistically significant influence on rupture rates, with submuscular placement being associated with a 2-3.3-fold higher rupture rate than subglandular placement, in populations (1), (3), (4) and (6) above. Device placement appears not to influence rupture rate for smooth devices (any indication) or devices implanted for reconstruction.

Submuscular placement can provide greater cyclic stress on a device as the muscle contracts and relaxes. Probably of greater significance in producing failures is the fact that the device is more closely confined in the submuscular position. This makes folding and wrinkling of the device more likely. This folding exacerbates cyclic fatigue that can lead to failures classified as localized shell fatigue failures. Textured devices are more prone to this mode of fatigue failure due to their thicker shells. Thickness of shells is a direct determinant of the stress applied to the surface of the shell on the outside of the shell; the thicker the shell the greater the stress. Conversely, smooth devices have thinner shells

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and are less susceptible, but not immune, from this type of failure. Thus, the higher rupture rate seen with submuscular implantation of textured devices is not an unexpected finding.

- Smooth implants tend to have 1.5–1.8-times higher rupture rates than textured devices (except in the reconstruction subpopulation).

When the question is asked whether textured or smooth devices fail with the greatest frequency as a result of device placement, the answer is textured devices, as explained in the above response. However, when the broader question is asked as to which type of device fails in general after implantation, the answer is just the opposite. In general, smooth devices fail more frequently. This apparent dichotomy can be reconciled. The graphs and statistics in the Mentor report on modes and causes of gel implant failures show that there is an elevated frequency of failure of devices intraoperatively and in the 0-1 and 1-2 year time intervals for both the “Rupture-Unknown Cause” (RUC) and “Not Apparent-Etiology Unknown” (NAEU) populations of failed gel-filled devices. Further, comparison of the plots for total population of failures to those for thin line failures of the shell for each of the two (RUC and NAEU) populations separately, reveals that thin line shell failures account for essentially all failures in those time intervals. See the table below for those comparisons.

Failure Populations	Failures in Different Time Intervals			A: Total Failures from 0 to 2 years	B: Total Population of Failures	Ratio of A to B
	Intraoperative Failures (Time =0)	0-1 years	1-2 Years			
Rupture-Unknown Cause (RUC)	31	3	13	47	121	
Thin Line Shell-RUC	30	2	10	42		35%
Not Apparent-Etiology Unknown (NAEU)	3	13	6	22	45	
Thin Line Shell-NAEU	3	13	6	22		49%

The thin line shell device failures in the 0 to 2 years period for the RUC and NAEU populations account for 35% and 49% of the total failures in those populations, respectively. These failures are a large portion of each of the respective populations.

In the Mentor report on modes and causes of failures (Report M 053), it is postulated that the failures during the 0 to 2 year timeframe result from damage to the devices during implantation. These thin line failures will most likely result from instrument damage (scalpel nicks or needle punctures) or localized stress that weakens the shell in a small area. Smooth devices have thinner shells than textured devices, because the texturing process adds an additional layer to the device. A rough estimate of the thickness of thin shells is 0.010 to 0.012 inches; for textured devices this measurement is approximately 0.018 to 0.020 inches. The thinner shells of the smooth devices may be more susceptible to localized stress damage, i. e., thinner sections of any elastomer require less stress to

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elongate the elastomer to its ultimate elongation. Also, it is logical that any sharp instrument damage that is done to a thinner shell may propagate to a larger opening in less time than with a thicker shell.

Thus, we see that the underlying mechanism governing the frequency of failures for textured devices over smooth ones when only placement is considered, and that the mechanisms responsible for the failure of devices with smooth shells over those with textured surfaces in the overall populations are different and understood.

- Surgical approach has no influence on rupture rate for all populations and subpopulations.

This result is not surprising. Where the incision is made on the breast to insert an implant should be of little consequence on the stress that is applied to the device to place it into the surgical pocket. Any stress would be more dependent upon the surgical technique than the location of the incision on the breast.

- An analysis was performed to determine if size of device (volume) had an influence on frequency of rupture. For this analysis devices were categorized into the following categories:

Category	Device Size (cc)
1	≤ 300
2	> 300 and ≤ 375
3	> 375 and ≤ 500
4	> 500

First, the rates of rupture were compared across these four categories. If statistical significance was found, then the categories were compared pairwise. The results of this analysis are summarized below:

- Total Adjunct Study population
 - Statistically significant difference ($p = 0.025$) across all categories
 - Statistically significant difference between categories 1 and 4 ($p = 0.05$) and 2 and 4 ($p = 0.02$). The ratio of rupture rate for categories 4 to 1 is 1.7 and that for 4 to 2 is 2.1.
- Textured Devices in Adjunct Study population
 - There is a weak statistically significant difference when all categories of textured device sizes are compared ($p = 0.054$).
 - There is a statistically significant difference between categories 2 and 3 and 2 and 4. The ratio of rupture rates for categories 3 to 2 is 1.9, and for 4 to 2 the ratio is 2.6.

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- There is no statistically significant difference across the device size categories for (a) the total Revision Augmentation subpopulation or the Total Reconstruction Subpopulation, (b) smooth devices in the Adjunct Study population or in the Revision Augmentation subpopulation or (c) textured devices in the Revision Augmentation subpopulation.
- An analysis of the Total Reconstruction Subpopulation was done. No statistically significant results were obtained. Within this subpopulation, the numbers of implant-years of exposure to textured and smooth devices were, when viewed separately, too small to perform a meaningful statistical analysis on them.

The above results indicate that there is a higher failure rate for larger devices, but the trend is not strong. In most cases, the difference in rates can only be established for non-adjacent categories of implants, e. g., when the <300 cc or >300 to <=375 cc categories are compared to >500 cc devices. This may indicate that the limitation of incision size imposed for the sake of aesthetics is of a marginal size to accommodate larger size devices. Another contributing factor is likely to be that larger devices may have a greater tendency to fold or wrinkle. Folding and wrinkling can contribute to cyclic fatigue failure in those areas. It should be emphasized that the tendency of larger size devices to fail is weak and hard to detect.

- Incision size has no influence on rupture rate for all populations and subpopulations.

At first review, this result seems surprising. Logic dictates that, for a given size of incision, one would expect that, as the volume of an implant increases, more stress would be required in the implantation procedure, more damage would be done to the implant shell and, consequently, a higher frequency of failures would result. The key phrase is "for a given size of incision." Surgeons are apparently making the logical adjustment, i. e., with larger implants they are making larger incisions. If this is true, then the relationship of incision size to implant volume remains in a range that results in no correlation between incision size and frequency of failure across all populations and subpopulations.

A more detailed analysis was performed in which the influences of both device size and incision size on frequency of failures were considered, in a factorial ANOVA-like manner. The analysis was aimed at determining if these two factors interact; *i.e.*, whether the RR changed differently, with respect to increasing device size, for different incision sizes. The results of this analysis are:

Regardless of the population or subpopulation, there is no interaction between device size and incision size in influencing the RR. Thus, although the RR does increase slightly with increasing device size, the increase seems to be the same for all the incision sizes. One cautionary note: the power of this test for interaction is not as high as that for the one-factor tests, so it is possible that a subtle interaction has been missed in this analysis.

The mechanisms for failure as proposed in the Mentor report on modes and causes of failure in gel-filled devices provide credible explanations for the trends that were

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identified by this statistical analysis of the Adjunct Clinical Study database. The total number of postoperative failures (159) identified in the Adjunct database was small in comparison to the total number of individual devices ----- included in the database. The small numbers of implant-years of exposure and of failed devices limited the possible analyses of some subpopulations for the effects of certain parameters on rupture rates. This was especially true in the Total Reconstruction Subpopulation.

SUMMARY OF RELATIONSHIPS BETWEEN RUPTURE RATES AND SURGICAL AND PRODUCT PARAMETERS FROM MENTOR'S ADJUNCT STUDY

	Surgical Approach	Device Placement	Device Size	Incision Size	Device Size + Incision Size	Surface Characteristic (Smooth vs. Textured)
Total Population^a (TP)	NS ^b	<i>p=0.0008</i> (all categories) <i>p=0.000019</i> (subglandular vs. submuscular; rupture rate for submuscular placement is 2.09 times greater than subglandular placement)	<i>p=0.02</i> across all categories <i>p=0.05 and 0.17</i> for devices >500 cc compared to ≤300 cc and devices 500 cc compared to 300-375 cc, respectively	NS	The rupture rate as device size increases is not influenced by incision size.	<i>p=0.049</i> rupture rate for smooth is 1.50 times greater than textured)
Smooth (TP)	NS	NS	NS	NS	The rupture rate as device size increases is not influenced by incision size.	
Textured (TP)	NS	<i>p=0.000028</i> (subglandular vs. submuscular; rupture rate for submuscular placement is 2.42 times greater than subglandular placement)	Nearly significant difference (<i>p = 0.054</i>) across all categories <i>p=0.04 and 0.015</i> for devices 300-375 cc compared to 375-500 and devices 300-375 compared to >500 cc, respectively	NS	The rupture rate as device size increases is not influenced by incision size.	

	Surgical Approach	Device Placement	Device Size	Incision Size	Device Size + Incision Size	Surface Characteristic (Smooth vs. Textured)
Revision Augmentation Subpopulation^a (RAS)	NS	<i>p</i> =0.0003 (subglandular vs. submuscular; rupture rate for submuscular placement is 2.39 times greater than subglandular placement)	NS	NS	NS	<i>p</i> =0.04 (rupture rate for smooth is 1.84 times greater than textured)
Smooth (RAS)	NS	NS	NS	NS		
Textured (RAS)	NS	<i>p</i> =0.0002 (subglandular vs. submuscular; rupture rate for submuscular placement is 3.28 times greater than subglandular placement)	NS	NS		
Total Reconstruction Subpopulation	NS	NS	NS	NS		NS

^aIncludes both smooth and textured devices

^bNot statistically significant

Gray shading indicates that either the analysis was not relevant, e. g., surface characteristic analysis in a subpopulation of either smooth or textured device, or that the implant-years of exposure for a population were so small that the analysis would not be meaningful.

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- e. a comprehensive literature review of durability/explant studies that involves all potential factors that may contribute to rupture, not just implant generation and iatrogenic damage. Please include a summary table of the causes and modes of rupture detailed in the literature.

3e Response:

A summary of the causes and modes of rupture detailed in the literature is provided in the table below. Additionally, a detailed literature review and analysis concerning causes and modes of implant rupture was performed by Dr. Harold Brandon, and is provided as an attachment to this amendment (see Attachment 16).

As described below, there are several factors that may contribute to implant failure, including: implant handling before the surgical procedures; the implantation procedure (e.g., stress and deformation during insertion, local weakening of the shell where the surgeon's fingers force the implant through the breast incision); *in vivo* processes (e.g., abrasion); trauma to the breast (e.g., breast massage, closed capsulotomy, patient injuries in the chest area, surgical revisions, multiple mammograms); other surgically induced damage (e.g., breast biopsies, needle localization procedures, cyst aspirations); manufacturing defects; increasing length of implantation; implant type; and the explantation procedure.

Bostwick (2000), in a well-respected treatise concerning augmentation mammoplasty techniques and failure mode results, provided the following commentary on expected modes/causes of rupture:

“Although breast implants are manufactured to specific standards requiring that they withstand breast compression as well as multiple and long-term physical stress, these devices are not indestructible. The outer shell of the implant can break if subjected to severe trauma such as pressure from a seat belt during a car accident, and certainly from a needle stick. Compression views taken during mammography are calibrated to avoid undue pressure that could rupture or deflate a breast implant.

The chance for rupture or deflation may increase with normal wear and tear and the length of time the device has been implanted. The incidence of rupture increases when the implant develops folds or rippling on the outer surface. Implants with thicker elastomer envelopes can develop more distinct folds and leak at a fold flaw point. Trauma or injury to the breast also increases the chance of rupture as may closed capsulotomy (a technique to correct capsular contracture in which strong pressure is applied to the breast to break up the scar tissue around the implant). This technique is less frequently used today and is not recommended by the manufacturers.”^{5/}

5/ Bostwick, J., III. 2000. *Plastic and Reconstructive Breast Surgery, 2nd Edition*. St. Louis: Quality Medical Publishing. Dr. Bostwick authored approximately 100 publications and two textbooks on breast surgery (Finishing Touches in Breast Reconstruction (1995), Plastic & Reconstructive Breast Surgery

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Brandon et al. (2001)^{6/} provided further findings to supplement the modes of failure characterized by Bostwick. In particular, Brandon et al. focused on breast implant ruptures attributable to iatrogenic damage that may occur during the implantation and explantation procedures. Because "damage at explantation [or implantation] may be erroneously diagnosed as an *in vivo* rupture," Brandon et al. provided a detailed characterization of the appearance of damage to the elastomer shell from a range of surgical instruments (*e.g.*, forceps, suture scissors, scalpels, suture needles, hemostats) using scanning electron microscopy ("SEM"). This method allows characterization of morphological features not easily visualized with the unaided eye. Characteristic surface features detected by SEM can be used to distinguish between wear and fatigue in fold-flaw, and damage by surgical instruments. The unaided eye, *i.e.*, visual inspection at the time of explant, can not discriminate between a pinhole caused by abrasion versus instrument damage. Therefore, Brandon et al. demonstrated that some explants considered ruptured or having defects at the time of removal did not fail *in vivo*, but rather, suffered instrument damage.

Based on their results, Brandon et al. concluded that manipulation of a breast implant with a surgical instrument at the time of insertion could predispose the device to fail at a later date. Additional support for this conclusion has come from this group's studies on saline-filled implants that have been returned to the manufacturer (Young V.L. et al., 2000).^{7/} An examination of these "failed" implants demonstrated that needle damage caused 7% of the implants to deflate. Because silicone gel implants are prefilled and typically inserted through small incisions, these investigators believe that silicone gel implants are more prone to damage during implantation. Failures would not be detected because, in contrast to saline filled implants, the gel would not leak out. Slavin and Goldwyn (1995)^{8/} also have found that 24% of consecutively removed gel implants were damaged when explanted, which further demonstrates that some explants considered ruptured or having defects at the time of removal did not fail *in vivo*.

In addition to surgical instrument damage during insertion, stress applied by the surgeon handling the implants during the procedure can contribute to implant failure. Wolf et al. (2000)^{9/} studied the mechanical properties of 14 implants inserted into a cadaver and compared them with lot-matched control implants. They found that the average mechanical properties of the implanted shells were slightly lower than the unimplanted controls. Local areas of the shell at the point where the surgeon's fingers forced the

(1999), and A Woman's Decision: Breast Care Treatment & Reconstruction).

- 6/ Brandon, H.J., et al. 2001. Scanning electron microscopy characterization of surgical instrument damage to breast implants. *Plast. Reconstr. Surg.* 108:52-61.
- 7/ Young, V.L., et al. 1998. Determining the frequency of breast implant failure requires sound scientific principles. *Plast. Reconstr. Surg.* 102(4):1295-9.
- 8/ Slavin, S.A., and Goldwyn, R.M. 1995. Silicone gel implant explantation: Reasons, results, and admonitions. *Plast. Reconstr. Surg.* 95(1):63-9
- 9/ Wolf, C.J., et al. 2000. Effect of surgical insertion on the local shell properties of Silastic® II silicone gel breast implants. *J. Biomater. Sci. Polymer Edn.* 11(10):1007-21.

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implant through the breast incision exhibited degradation in the barrier coating and a small, but detectable decrease in average tensile strength, breaking energy, and moduli. The authors hypothesized that "the local degradation of the barrier coating is probably accompanied by enhanced diffusion and solubility of low molecular weight linear and cyclic silicone components of the gel into the shell at the damage site with an overall reduction in mechanical properties."^{10/}

A number of investigators have proposed that increasing time *in vivo* results in a degradation of mechanical strength properties of the silicone elastomer over time, leading to failure. For example, Marotta and colleagues have constructed a "master curve" using data from over 40 studies that suggests that implant duration correlates with increased failure rates.^{11/} These investigators hypothesized that the degradation in mechanical strength over time is the result of progressive cyclic mechanical stress, which creates and exacerbates tears at the sites of thin areas, folds, and/or defects where stress is concentrated in silicone elastomer shells that have been weakened by the infiltration of silicone fluid over time *in vivo*.

Marotta's group's analyses and subsequent conclusions have come under considerable scrutiny and criticism, however, for the following reasons. First, Marotta's analyses were conducted without proper comparison to type, generation, manufacturer, or lot-matched controls. Investigators have shown that there is considerable variability in shell strength properties across implant generation, type, manufacturer, and lot.^{12/} Conclusions drawn concerning the shell strength properties of explanted devices without comparison to appropriate virgin controls could lead to erroneous hypotheses concerning mechanisms of failure. Second, Marotta's proposed causes of failure are not based on careful examination of the explants, and unless explants are carefully examined, the precise cause of failure might not be readily apparent. As noted by Young et al. (1998), "[w]e have learned that a careful microscopic examination, such as that conducted with a scanning electron microscope, is needed to evaluate the actual cause of failure. Unless explants with defects that could have been caused by instruments such as scalpels, needles, or clamps are examined with an instrument like the scanning electron microscope, it is nearly impossible to determine whether a loss of shell integrity resulted from surgically induced flaws."^{13/}

10/ *Id.*

11/ Goldberg, E.P. 1997. Failure of silicone gel breast implants: Analysis of literature data for 1652 explanted prostheses. *Plast. Reconstr. Surg.* 100(1):281-3; Marotta, J.S., et al. 1999. Silicone gel breast implant failure and frequency of additional surgeries: Analysis of 35 studies reporting examination of more than 8000 implants. *J. Biomed. Mater. Res. (Appl. Biomater.)* 48:354-64; Marotta, J.S., et al. 2002. Silicone gel breast implant failure: Evaluation of properties of shells and gels for explanted prostheses and meta-analysis of literature rupture data. *Ann. Plast. Surg.* 49:227-47

12/ See, e.g., Brandon, H.J., et al. 1999b. Ultimate strength properties of control and explanted Silastic) and Silastic I silicone gel-filled breast implant shells. *Aesth. Surg. J.* 19(5):381-7; Brandon, H.J., et al. 2001. Variability in the properties of silicone gel breast implants. *Plast. Reconstr. Surg.* 108:647-55; Young, V.L., et al. 1998. Determining the frequency of breast implant failure requires sound scientific principles. *Plast. Reconstr. Surg.* 102(4):1295-9.

13/ Young, V.L., et al. 1998. Determining the frequency of breast implant failure requires sound scientific principles. *Plast. Reconstr. Surg.* 102(4):1295-9.

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In fact, Brandon et al. and others^{14/} have demonstrated that implant failure does not result from *in vivo* degradation of shell mechanical properties. In an analysis of biodurability, shell properties measured for controls and explants of devices implanted from 3 months to 32 years included: stress-strain relationships, tensile strength, elongation, tear resistance, moduli, cross-link density, and amount of extractable material in the shell. Brandon et al. showed that these properties were essentially independent of implantation time. Furthermore, the silicone polymer used to fabricate the implant shells does not undergo appreciable degradation for up to 13 years *in vivo* for those third generation implants studied (Brandon et al., 2002).^{15/} Based on these studies, Brandon and colleagues have concluded that "degradation of shell mechanical and chemical properties is not a primary mechanism for implant failure."^{16/}

Peters (2000)^{17/} has proposed a failure mechanism referred to as the "fold flaw" theory. According to this theory, an internal abrasion of the implant shell can develop over time at the site of a fold in the shell, ultimately leading to shell failure.

In a study conducted by Feng and colleagues,^{18/} univariate and/or multivariate analyses of 1619 explants from a single surgeon's practice revealed the following statistically significant risk factors for implant rupture: increasing length of implantation; retroglanular implant location; Baker capsular contracture Grade III or IV; presence of local symptoms (e.g., breast tenderness, burning pain); implant type; and implant manufacturer. Interestingly, in this study, the following factors were found not to be significantly associated with rupture in this study: compression mammogram; closed capsulotomy; reason for implantation; history of radiation; and calcification of the capsule.

Thus, Brandon et al. and other investigators have identified potential sources of implant failure in addition to implant generation. Implant failure has been demonstrated to be

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- 14/ Brandon, H.J., et al. 1999a. Analysis of two Dow Corning breast implants removed after 28 years of implantation. *Aesth. Surg. J.* 19(1):40-8; Brandon, H.J., et al. 1999b. Ultimate strength properties of control and explanted Silastic) and Silastic I silicone gel-filled breast implant shells. *Aesth. Surg. J.* 19(5):381-7; Brandon, H.J., et al. 2000. Ultimate strength properties of explanted and control Silastic II and silicone gel-filled breast implant shells. *Aesth. Surg. J.* 20(2):122-32; Brandon, H.J., et al. 2002. In vivo aging characteristics of silicone gel breast implants compared to lot-matched controls. *Plast. Reconstr. Surg.* 109:1927-33; Brandon, H.J., et al. 2003. Biodurability of retrieved silicone gel breast implants. *Plast. Reconstr. Surg.* 111:2295-306; Peters, W. 2000. Current status of breast implant *survival properties and the management of the woman with silicone gel breast implants.* *Can. J. Plast. Surg.* 8(2):54-67.
- 15/ Brandon, H.J., et al. 2002. In vivo aging characteristics of silicone gel breast implants compared to lot-matched controls. *Plast. Reconstr. Surg.* 109:1927-33.
- 16/ Brandon, H.J., et al. 2002. In vivo aging characteristics of silicone gel breast implants compared to lot-matched controls. *Plast. Reconstr. Surg.* 109:1927-33
- 17/ Peters, W. 2000. Current status of breast implant *survival properties and the management of the woman with silicone gel breast implants.* *Can. J. Plast. Surg.* 8(2):54-67.
- 18/ Feng, L.-J., et al. 1999. Analysis of risk factors associated with rupture of silicone gel breast implants. *Plast. Reconstr. Surg.* 104(4):955-63.

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associated with several failure mechanisms that have been documented with scanning electron microscopy. Failure can be attributed to: implant handling before the surgical procedure; the implantation procedure (e.g., stress and deformation during insertion, local weakening of the shell where the surgeon's fingers force the implant through the breast incision); *in vivo* processes (e.g., abrasion); trauma to the breast (e.g., breast massage, closed capsulotomy, patient injuries in the chest area, surgical revisions, multiple mammograms); other surgically induced damage (e.g., breast biopsies, needle localization procedures, cyst aspirations); increasing length of implantation; implant type; manufacturing defects; and the explantation procedure.^{19/}

Depending on the information learned regarding the modes and causes of failure for your device, new fatigue testing may be necessary.

In addition to the cyclic fatigue analysis of unimplanted devices, Mentor performed fatigue analyses on devices subjected to iatrogenic effects (see description of "Effects of Surgical Insertion on Mechanical Properties" above).

Crease Fold Failure Test (HS 222.040823.002 in Attachment 17)

Mammary prostheses experience various forms of mechanical stresses during their *in vivo* life. These stresses are both compressive and cyclic. Normal everyday movements like walking, running, flexing, and bending cause these stresses, which may result in shell fatigue. Mentor has been studying the fatigue life of gel mammary implants by identifying the failure modes of shell fatigue. A comprehensive study was conducted on explanted gel implants returned to the Product Evaluation Department (PE) for evaluation (see Report HS 222.040823.002 in Attachment 17). This study indicated that, of the returned explanted devices classified as "Rent-Unknown Cause," 14% of the actual failures were attributed to shell fatigue. This type of failure results from folding (creasing) of the shell. This failure mechanism was initially identified in Siltex Saline devices as a crease fold or fold flaw failure.

Previous laboratory efforts to simulate crease fold failure of Siltex saline devices *in vitro* have resulted in new equipment designs and test methods that produce crease fold failures in that they imitate the *in vivo* crease fold failures seen in returned Siltex saline device. Applying this equipment and test method to gel devices allows evaluation, under similar test conditions, of fatigue failures that imitate the *in vivo* crease fold failures seen in returned Siltex gel devices.

To date, none of the test samples has failed. All test devices have endured over 12M cycles with no visible signs of fatigue stress. Because no failures occurred in the test samples, no conclusions can be made. All tests will be fatigue cycled until failure, at which point the cycles to failure will be analyzed and used for a comparison to PE data. Therefore, based on the fatigue and other testing performed, Mentor believes that no new

19/ Young, V.L., et al. 1998. Determining the frequency of breast implant failure requires sound scientific principles. *Plast. Reconstr. Surg.* 102(4):1295-9; Feng, L.-J., et al. 1999. Analysis of risk factors associated with rupture of silicone gel breast implants. *Plast. Reconstr. Surg.* 104(4):955-63.

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fatigue testing is necessary, and that long-term safety information with respect to rupture,
is best provided through clinical support.

**CAUSES AND MODES OF SILICONE GEL-FILLED BREAST IMPLANT RUPTURE
EXPLANT LITERATURE SUMMARY**

Reference	Manufacturer	Generation	Mode/Cause of Failure
Slavin and Goldwyn (1995)	No data	No data	Analysis of 74 explanted devices revealed that 11 of 46 consecutive devices ruptured during removal, providing evidence that some explants considered ruptured or having defects at the time of removal did not fail <i>in vivo</i> .
Peters et al. (1996)	Multiple (Dow Corning, Heyer-Schulte, Surgitek)	First, Second, Third	<p>Evaluation of 352 explants revealed the following relationships:</p> <ul style="list-style-type: none"> • Rupture rate was dependent on implant generation (second generation implants had the highest rates). • Rupture rate was dependent on implant duration for second generation implants only. <p>Authors also noted that closed capsulotomy might be a cause of implant failure.</p>
Goldberg et al. (1997)	Multiple	First, Second, Third	“Master curve” constructed from the results of 11 studies (1652 implants) suggests that increased implantation duration correlates with increased failure rates, and the authors explain this relationship as likely being the result of the degradation of mechanical properties of the silicone elastomer shell over time.

Reference	Manufacturer	Generation	Mode/Cause of Failure
Feng et al. (1999)	Multiple (Dow Corning, Surgitek, McGhan, Heyer Schulte, Naturaly Y, Mentor, Cox Uphoff, Bristol Meyers)	First, Second, Third	<p>Univariate and/or multivariate analysis of 1619 explants (implant duration = 11±6 years, range 1-30 years) from a single surgeon's practice revealed the following statistically significant risk factors for rupture:</p> <ul style="list-style-type: none"> • increasing length of implantation; • retroglandular implant location; • Baker capsular contracture Grade III or IV; • presence of local symptoms (e.g., breast tenderness, burning pain); • implant type (double-lumen and polyurethane implants had lower rupture rates than smooth gel implants); and • implant manufacturer Surgitek had the highest rupture rates, and McGhan, Mentor, and Cox Uphoff had significantly lower rupture rates). <p>Factors found not to be significantly associated with rupture included:</p> <ul style="list-style-type: none"> • compression mammogram; • closed capsulotomy; • reason for implantation; • history of radiation; and • calcification of the capsule. <p>The authors suggested that progressive lipid infiltration of the silicone shell in older implants, and thinner shells (such as those used in second generation implants) might be a cause for rupture in older implants.</p>
Marotta et al. (1999)	Multiple	First, Second, Third	<p>Curve constructed using data from 35 studies including more than 8000 implants suggests that implantation duration correlates with increased failure rates.</p> <p>Authors suggest that mechanical strength properties degrade with time, and that "progressive (time dependent) cyclic mechanical stress induced creation and enlargement of tears in weakened silicone fluid swollen silicone elastomer shells at sites of folds and/or defects where stress is concentrated" is a "primary mechanism for rupture."</p>

Reference	Manufacturer	Generation	Mode/Cause of Failure
Brandon et al. (1999a)	Dow Corning (Silastic 0)	First (implanted in 1969)	<p>Mechanical testing (tensile strength, elongation, tear resistance, 200% modulus, 400% modulus, and cross-link density) of two intact implants after 28 years <i>in vivo</i> revealed little to no meaningful degradation in shell properties as compared to unimplanted control devices, and all results were within ASTM recommended values.</p> <p>The authors concluded that, based on the results of this study, time <i>in vivo</i> does not contribute to degradation of shell integrity that might lead to implant failure.</p>
Brandon et al. (1999b)	Dow Corning (Silastic 0 and Silastic I)	First and Second	<p>Mechanical testing (tensile strength, elongation-to-failure, and tear resistance) of 18 explants (implant duration 6-28 years) compared to 7 control devices indicates that shell mechanical properties are not a function of time <i>in vivo</i> (<i>i.e.</i>, there is no significant degradation of shell mechanical properties over time).</p> <p>There were no significant differences between ruptured explants and intact explants with regard to shell tensile strength or elongation</p> <p>Based on these results, the authors concluded that “implant failure is not the result of <i>in vivo</i> degradation of shell mechanical properties.”</p>
Brandon et al. (2000)	Dow Corning (Silastic II)	Third	<p>Mechanical testing (tensile strength, elongation-to-failure, and tear resistance) of 22 explants (implant duration 0.3-13.2 years) compared to 43 lot-matched control devices indicates that, with the exception of an initial decrease in the shell's ultimate strength properties after implantation, likely due to diffusion of the non-cross-linked silicones from the gel into the shell, shell mechanical properties are not a function of time <i>in vivo</i> (<i>i.e.</i>, after the initial decrease, there is no significant degradation of shell mechanical properties over time).</p> <p>There were no significant differences between ruptured explants and intact explants with regard to shell tensile strength or elongation.</p> <p>Based on these results, the authors concluded that “implant failure is not due to mechanical property degradation during long-term implantation.”</p>

Reference	Manufacturer	Generation	Mode/Cause of Failure
Collis and Sharpe (2000)	Multiple (Nagor; Mème; Dow Corning; Surgitek; Medasil; Misti; Mentor (gel and saline); McGhan; Lipomatrix)	First, Second, and Third Total No. of explants: 478 (256 women)	<p>The authors proposed the following mechanisms of failure based on their explant analysis:</p> <ul style="list-style-type: none"> • <u>Generation</u>: First: 44% rupture Second: 65% rupture Third: 9% rupture • <u>Years <i>in vivo</i></u> • <u>Position</u>: Subpectoral implants had significantly higher rate of rupture than subglandular implants (p<0.001). • <u>Trauma</u> <p>NOTE: capsular contracture was not associated with an excess of implant ruptures.</p> <p>Additional information: 15 breasts (11 patients) had pericapsular silicone granulomas; 13 of these were associated with ruptured implants (all second generation); 4 of these were extracapsular ruptures. One patient with severe bilateral silicone granulomas and bilateral extracapsular ruptures suffered a fractured sternum in a traffic accident.</p>

Reference	Manufacturer	Generation	Mode/Cause of Failure
Peters (2000)	Multiple (Dow Corning, Heyer-Schulte, Surgitek)	First, Second, Third	<p>Evaluation of 527 explants revealed the following relationships:</p> <ul style="list-style-type: none"> • Rupture rate was dependent on implant generation (second generation implants had the highest rates); differences likely related to differences in shell thickness. • Rupture rate was dependent on implant duration. • Rupture rate was dependent on manufacturer. <p>Author noted that mechanical strength analyses of explant shells revealed little or no large scale degradation in properties after up to 28 years <i>in vivo</i>.</p> <p>Author suggested that “the mechanism of implant disruption likely involves the ‘fold flaw’ theory, whereby an internal abrasion can develop over time at the site of a fold in the implant wall.” Other suggested failure mechanisms include closed capsulotomy, trauma, general wear and tear, lipid infiltration of the elastomeric shell leading to weakening, mammography, and manufacturing defects.</p> <p>Additional information: Extracapsular rupture/presence of gel in breast tissue observed in 4.2% of second generation implants and none of the first or third generation implants.</p>
Wolf et al. (2000)	Dow Corning (Silastic II)	Third	<p>Results from a study of the mechanical properties of 14 implants inserted into a cadaver and compared with lot-matched control implants revealed that the average mechanical properties of the implanted shells were slightly lower than the unimplanted controls. Local areas of the shell at the point where the surgeon’s fingers forced the implant through the breast incision exhibited damage (degradation in the barrier coating) and a small, but detectable decrease in average tensile strength, breaking energy, and moduli. The authors hypothesized that “the local degradation of the barrier coating is probably accompanied by enhanced diffusion and solubility of low molecular weight linear and cyclic silicone components of the gel into the shell at the damage site with an overall reduction in mechanical properties.” Thus, a potential cause of failure is stress applied during the insertion procedure.</p>

Reference	Manufacturer	Generation	Mode/Cause of Failure
Young et al. (2000)	NA	NA	<p>The following potential modes/causes of rupture were suggested in this article commenting on Collis and Sharpe (2000):</p> <ul style="list-style-type: none"> • Iatrogenic damage during implantation or explantation; • Other surgically induced damage, including: breast biopsies, needle localization procedures, and cyst aspirations; • Implant trauma, including: use of breast massage, closed capsulotomy, patient injuries in the chest area, surgical revisions, multiple mammograms. <p>The authors also suggest that 80-93% of ruptures are intracapsular.</p>
Brandon et al. (2001)	Dow Corning (Silastic II)	Third	<p>Failure was artificially induced by surgical instrument damage (scalpels, suture needles, hypodermic needles, hemostats, forceps).</p>
Brandon et al. (2002)	Dow Corning (Silastic II)	Third	<p>Mechanical and chemical testing (tensile strength, elongation, moduli, tear resistance, cross-link density, and percent extractables) of 16 explants (implant duration 0.3-13 years) compared to 17 lot-matched control devices indicates that, for unextracted explant shells, with the ultimate properties of tensile strength, elongation, and tear resistance were 18-27% below lot-matched control values; there was a 2-times greater amount of extractables in the explants; and there was no difference in 200 and 400% moduli or cross-link density between explants and lot-matched controls. Elongation values in the explants, even though lower than in controls, still were within ASTM acceptable values. Extracted explant shells exhibited very similar properties to the lot-matched controls.</p> <p>Based on these results, the authors concluded that "the silicone polymer used to fabricate the shells does not undergo appreciable degradation for up to 13 years <i>in vivo</i>."</p>
Marotta et al. (2002)	Multiple (Dow Corning, McGhan, Surgitek, Mentor)	First, Second, Third	<p>Update of 1999 analysis to include a total of 9770 implants from 42 studies continues to suggest a correlation between rupture rate and implant duration.</p> <p>Mechanical and chemical testing analysis of 74 explants as compared to reported properties of unimplanted devices (with no effort to match manufacturer, generation, or lot) revealed no significant correlation between implant duration and degradation of implant strength.</p> <p>Authors conclude that "after early weakening of shells as a result of swelling of the shell elastomer by diffusion of silicone oil from the gel, SGBI failure can occur in a time-dependent manner as a result of continuing implant motion and cyclic stresses that are exacerbated by stress concentration in thin areas, defects, and folds in the shell."</p>
Brandon et al. (2003)	Dow Corning (Cronin seamed,	First, Second, Third	<p>Mechanical and chemical testing (stress-strain relationship, tensile strength, elongation, tear resistance, moduli, cross-link density, and amount of extractable material in the shell) of two Cronin seamed explants and one control; 18 Silastic 0 and Silastic I explants and seven controls; and 22 Silastic II explants and 43 controls implanted for 3 months to 32 years</p>

Reference	Manufacturer	Generation	Mode/Cause of Failure
	Silastic 0, Silastic I, and Silastic II)		<p>revealed that there is no catastrophic decrease in the ultimate properties in shells implanted up to 32 years as compared to control values.</p> <p>A large degree of swelling (18.7-39.5%) in the explants due to diffusion of non-cross-linked silicones from the gel into the shell did not cause failure in implants for up to 32 years <i>in vivo</i>.</p> <p>Based on these results, the authors concluded that “degradation of shell mechanical and chemical properties is not a primary mechanism for implant failure.”</p> <p>The authors proposed the following mechanisms of implant failure:</p> <ul style="list-style-type: none"> • Implant handling before the surgical procedure; • Implantation procedure (e.g., stress and deformation during insertion; local weakening of the shell where the surgeon’s fingers force the implant through the breast incision); • <i>In vivo</i> processes (e.g., abrasion or breast biopsy); and • Explantation procedure.

NA = Not applicable

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