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Deficiency Letter Responses:

Local Complication Data from Core Study

1. The data in the PMA are not adequate to describe the rate and rate of change of local complications over time, to describe the frequency of ruptures observed (intracapsular, extracapsular, and migrated gel), and to characterize the potential local health consequences of ruptured implants. These data are necessary to provide a reasonable assurance of safety for your device.

Although you provided three sources of data regarding rupture rates (i.e., Core Study, Adjunct Study, and Complaint Analysis), the rupture rate of your device remains unknown. The Core Study data were not adequate because they were not collected for a sufficient duration to characterize the rate of rupture and how it changes over time. (Please note that FDA has issues related to your diagnosis of rupture in item 4 below.) The Adjunct Study data are inadequate because of the low follow-up rates (ranging from 7-13%) and because silent rupture was not assessed. The complaint analysis data are inadequate because it is impossible to determine an accurate rupture rate without knowing the total number of devices implanted at each timepoint, the complaint data include devices not the subject of this PMA, and these data do not include an assessment of silent rupture.

Furthermore, you have not provided information from your Core Study that describes whether and how often a ruptured implant may lead to intracapsular, extracapsular, and migrated gel, nor have you characterized the potential associated health consequences of ruptured implants and subsequent release of silicone (also addressed by item 2 below). This safety concern is addressed in our breast implant guidance document. When a silicone gel-filled breast implant ruptures, the patient and the physician may be unaware of it, the body does not have a mechanism for eliminating the silicone gel, and the gel can migrate outside of the capsule into the breast area, the lymph nodes, and distant locations.

Therefore, to further evaluate the safety of your device, please provide data from your Core Study (including the MRI cohort) with follow-up of sufficient duration to adequately describe the rate and rate of change of local complications over time, as well as the specific rupture issues below. The study duration should be, for example, sufficient to measure or reasonably estimate how the shape of the curve for the percentage of ruptured implants versus time changes over the expected lifetime of the device. With respect to follow-up rates, FDA is concerned that the current follow-up rates for the MRI cohort in your Core Study were only 69% at 1 year and 67% at 2 years. The updated data should provide adequate follow-up (i.e., 80%) at each timepoint for all patients enrolled, including the MRI cohort.

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You should continue to collect all data described in the current protocol but modify the protocol, as necessary, to address the specific rupture issues below.

Mentor is responding to FDA's request for additional information on the rate and rate of change of local complications over time, frequency of intracapsular and extracapsular ruptures and migrated gel, and potential health consequences of rupture, through three sources of information: (1) Mentor's Core Gel study MRI follow-up cohort (see Response 1 below); (2) a clinical study on long-term silent and overt rupture rates for Mentor implants, as evaluated by Dr. David T. Sharpe and Dr. Nicholas Collis of the Bradford Royal Infirmary in the U.K. (see Response 2); and (3) the published literature, which provides important information from explant studies and recent well-controlled epidemiological reports concerning rupture of third generation silicone gel-filled breast implants generally (see Responses 2, 32, and 33). Mentor has reported, and will continue to report, rupture rates for its devices over time, as well as rupture rates reported in the long-term epidemiology studies discussed above, in the labeling for its silicone gel-filled breast implants (see attached proposed labeling). Mentor's attached proposed labeling contains a summary narrative of rupture rates from the Core Gel study, the new Sharpe and Collis findings described in Response 2, the updated literature, and (as relevant) Mentor's bench testing, to further educate physicians and their patients on these areas. This information should provide women with the necessary information to determine how long to expect their implants to remain intact as well as rupture-related risk factors.

- a. To increase your sample size of women with ruptured implants and, thereby, provide sufficient information to address the issues in items 1(b-f) below, please enroll additional women from the Core Study into the MRI cohort.**

1a Response:

Based on the design and objective of the MRI substudy to determine the rupture rate, Mentor does not believe that an increase in the substudy population is warranted. As discussed below, the current sample size of 420 women exceeds the sample size required to detect a conservative rupture rate of 5%, which is greater than the 0.7% rupture rate (per patient) observed at three years.

The objective of the MRI substudy is to determine the incidence and prevalence of silicone gel-filled breast implant rupture, using a standardized MRI-based protocol. The rate of silent rupture (*i.e.*, ruptures that are not clinically evident to the patient or physician without the use of imaging techniques, such as MRI) has been reported in a number of recent studies to be between 5.0% to 10.0%.^{1/} Based on estimates of rupture incidence in FDA sponsored trials,^{2/} a rate of 5% at two years was chosen.

^{1/} Brown, S.L., et al. 2000. Prevalence of rupture of silicone gel breast implants revealed on MR imaging in a population of women in Birmingham, Alabama. *AJR*. 175:1057-64; Hölmich, L.R., et al. 2003. Incidence of silicone breast implant rupture. *Arch. Surg.* 138 801-6; Gabriel, S.E., et al. 1997. Complications leading to surgery after breast implantation. *N Engl J. Med* 336(10):677-682.

^{2/} *Id.*

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If the silent rupture rate is 5% at 2 years, then a sample size of 324 yields an estimate of 4.9% with an upper 95% one-sided confidence limit of 7.4 and an interval half-width of 2.5%. If the silent rupture rate is 7.5%, then a sample of 210 subjects produces an estimate of 7.6% with an upper 95% one-sided confidence limit of 11.3 and an interval half-width of 3.7.

If the silent rupture rate were 10%, then a sample of 150 patients would yield a rate of 10% with a 95% one-sided upper confidence limit of 15% and an interval half-width of 5%. To be conservative, a rate of 5% was chosen by Mentor, resulting in an MRI sample size of 324. To assure a sample size of 324 at two years, allowing for 20% lost to follow-up, 405 patients must be enrolled in the MRI substudy. Mentor enrolled more than 405 patients to ensure an adequate follow-up rate. Thus, adding patients will not result in a more meaningful rupture rate. In fact, the sample size has been adequate to detect Mentor's low rupture rate of 0.7%, with a 95% upper bound confidence interval of 1.4%. Therefore, the study is adequately powered to show that patients face a risk of rupture of 1.4% or less at three years, and the inclusion of additional patients will not change the overall rupture rate.

A subset of 420 women participating in the Mentor Core Gel Study was selected by random number generation to participate in the substudy based on an anticipated conservative rupture rate of 5% at two years. Mentor considered a 5% rupture rate to be conservative, given that information in the published literature suggests that silent rupture rates of third generation implants are less than 5% through 5-6 years *in vivo*.³ Additionally, in the MRI study conducted by Drs. Sharpe and Collis described in Response 2, no ruptures of third generation implants were seen until 6 years *in vivo*. Any patient, regardless of their participation in the substudy, is directed to see their physician whenever the patient believes a rupture has occurred. These patients will undergo a MRI scan and the scans will be sent to a central reviewer for confirmation of the local radiologist's assessment.

As a point of clarification, the actual follow-up rate for the MRI substudy is 78% and 89% for 1 and 2 years, respectively. These rates are based on a total MRI substudy population of 420 patients participating in this MRI substudy. FDA calculated the follow-up rate using an "n" of 496. A denominator of 496 is not appropriate for this substudy, as it does not reflect the true patient accounting. A total of 496 patient numbers were initially randomized to ensure a final study cohort population greater than or equal to 405 participants. A total of 472 patients were contacted, of which 420 agreed to participate and the remaining 52 declined to participate. Table 13.3 in the attached 3-Year Core Gel Clinical Study Update has been corrected to reflect the true patient accounting of the 420 MRI substudy participants.

3/ Brown, S.L., et al. 2000. Prevalence of rupture of silicone gel breast implants revealed on MR imaging in a population of women in Birmingham, Alabama. *AJR*. 175:1057-64; Hölmich, L.R., et al. 2003. Incidence of silicone breast implant rupture. *Arch. Surg*. 138:801-6.

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The entire updated 3-Year Core Gel Clinical Study Report, including appendices with tables, is provided in Attachment 1.

As noted above, in addition to the MRI Core Gel substudy data, Mentor also is providing in this PMA amendment important new silent and overt rupture data from an MRI study in a cohort of augmentation patients implanted for up to 12 years (see summary of Sharpe and Collis study provided in Response 2).

- b. For all patients with ruptured implants who are being explanted, please provide the results of tissue sampling analysis of the surrounding breast tissue and capsule. The analysis should confirm whether or not gel implant constituents are present. This will help determine whether the ruptured implants led to the presence of extracapsular gel (outside the capsule but in the breast tissue area) or migrated gel (outside the breast tissue area).**

1b Response:

It has already been established that gel implant constituents are detectable at very low levels in the surrounding capsule and significantly lower levels in adjacent breast tissue, whether the implants are ruptured or intact. There is very substantial existing evidence from published literature that: 1) silicone gel is predominantly restricted to the surrounding capsule (even in women with ruptured implants); 2) except under very rare circumstances silicone gel does not tend to migrate to remote sites in the body; and 3) there is a lack of association between implant rupture and systemic disease (discussed further in response to #32). Furthermore, available information, to date, from Mentor's Core Gel Study and a long-term MRI study by Drs. Sharpe and Collis (with up to 12 year follow-up of Mentor gel filled implants) include no confirmed cases of extracapsular rupture. Based on these factors, Mentor believes that further collection and analysis of surrounding breast tissue and capsule would not provide any new information that would meaningfully inform the safety assessment of these devices.

Release of silicone from gel-filled breast implants can occur as a result of either rupture of the envelope or diffusion of minute quantities of silicone through the intact elastomer envelope ("bleed"). As discussed below, a substantial body of data exists demonstrating that the released silicone remains almost entirely within the confines of the fibrous capsule surrounding the implant, and does not migrate away from the breast tissue. This was noted by the IOM expert Panel⁴ report in its conclusions regarding the animal toxicology studies of silicone and silicone breast implants:

⁴ Bondurant, S., Enrster, V., and Herdman, R., Eds. 2000. *Safety of Silicone Breast Implants*. Committee on the Safety of Silicone Breast Implants, Division of Health Promotion and Disease Prevention, Institute of Medicine (Washington, D.C., National Academy Press).

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"depots of gel, whether free or in implants, remain almost entirely where injected or implanted. Even low molecular weight cyclic and linear silicone fluids appear to have low mobility" (Chapter 4).

Animal Studies

Studies investigating the metabolic fate and tissue distribution of subcutaneously implanted ^{14}C -polydimethylsiloxane ("PDMS") over 90 days in mice were conducted by Dow Corning in the 1960s. The data from these studies were reevaluated by Young in 1991,^{5/} who found that minute fractions of the radiolabel appeared in the urine (0.008% of total injected radioactivity) and feces (0.019% of total radioactivity), with the vast majority of radiolabel remaining stable at the point of injection (99.97% of total injected radioactivity). These studies support the conclusion that every little of the silicone gel used in Mentor's implants leave the site of deposition.

Results of chronic toxicity/carcinogenicity studies of silicone gels in rats conducted by Dow Corning and ASC (see PMA M020018 Module #1) indicate no evidence of systemic toxicity attributable to the implant material. The only abnormal finding was the occurrence of implant site fibrosarcomas (solid state tumorigenesis). The lack of systemic findings in these long-term studies provides evidence that implanted gel does not migrate and does not cause adverse systemic effects.

Published Clinical Literature

Measurement of Tissue Silicon Levels

There are numerous published reports describing the analysis of silicon (as a marker for the organosilicones contained in silicone gel and elastomer) in breast implant capsules, breast tissue, and remote locations in the body. These studies indicate that, while silicon is ubiquitous, its presence can be measured in capsules surrounding silicone gel-filled breast implants, and the levels of silicon in these tissues can be distinguished from the levels found in tissues from women without implants and/or tissues at remote sites. Thus, carefully conducted experiments analyzing silicon levels, as summarized below, provide a sensitive measure of silicon, and ample evidence of the disposition of silicone gel from silicone gel-filled breast implants. Additional tissue sampling from women with ruptured implants is therefore, neither necessary nor will it likely provide any new information on the fate of silicone gel.

A number of studies have demonstrated that silicon levels in the fibrous implant capsules and surrounding breast tissue from women with silicone gel-filled breast implants, as measured using a variety of techniques, are elevated when compared to breast tissue from

5/ Young, J.F. 1991. Disposition, storage, degradation, removal and excretion of the different silicones. Silicone in Medical Devices, Proceedings of a Conference. U.S. Department of Health and Human Services, February 1-2, 1991.

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women without breast implants, women with saline breast implants, and/or men with silicone inflatable penile prostheses. For example, Peters et al.⁶ report that the median level of silicon in 58 capsules from patients with silicone gel-filled breast implants was approximately 10,000 times greater than that found in breast tissue taken from women without breast implants. Comparable levels of silicon in capsules from women with silicone gel-filled implants have been reported by several other investigators.⁷ Importantly, these studies have all demonstrated that there is no meaningful difference between the silicon levels measured in capsules from intact implants and capsules from ruptured implants.⁸ Moreover, Evans and Baldwin⁹ found that tissue levels from distant sites in women with silicone gel-filled breast implants were similar to levels found in cadavers of women who did not have breast implants, and Barnard et al.¹⁰ observed no difference in the concentration of organosilicon polymer in liver, lung, or spleen tissues taken from cadavers with or without breast implants. These studies demonstrate that silicone released from implants, ruptured or intact, is retained primarily within the capsule, with only very small amounts detected in surrounding breast tissue and no distant migration.

Determination of silicone in tissues of women with ruptured breast implants will not provide any meaningful information on the potential health consequences of ruptured implants. McConnell et al.¹¹ found no correlation between tissue silicon concentration

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6. Peters, W., et al. 1996. Silicon and silicone levels in patients with silicone implants. In: Current Topics in Microbiology and Immunology. Vol. 210. Immunology of Silicones. Potter, M., and Rose, N.R., Eds. Springer. pp. 39-48; Peters, W., et al. 1999. Silicon assays in women with and without silicone breast implants -- A review. *Ann Plast Surg.* 43:324-30.
 7. See, e.g., Evans, G.R.D., and Baldwin, B.J. 1997. From cadavers to implants: Silicon tissue assays of medical devices. *Plast. Reconstr Surg.* 100:1459-65; Schnur, P.L., et al. 1996. Silicon analysis of breast and periprosthetic capsular tissue from patients with saline or silicone gel breast implants. *Plast. Reconstr Surg* 98:798-803; Lugowski, S.J., et al. 2000. Analysis of silicon in human tissues with special reference to silicone breast implants. *J. Trace Elements Med Biol.* 14:31.
 8. Peters, W., et al. 1996. Silicon and silicone levels in patients with silicone implants. In: Current Topics in Microbiology and Immunology. Vol. 210. Immunology of Silicones. Potter, M., and Rose, N.R., Eds. Springer. pp. 39-48; Peters, W., et al. 1999. Silicon assays in women with and without silicone breast implants -- A review. *Ann. Plast Surg* 43:324-30; Evans, G.R.D., and Baldwin, B.J. 1997. From cadavers to implants: Silicon tissue assays of medical devices. *Plast. Reconstr. Surg.* 100:1459-65; Schnur, P.L., et al. 1996. Silicon analysis of breast and periprosthetic capsular tissue from patients with saline or silicone gel breast implants *Plast. Reconstr Surg* 98:798-803; Lugowski, S.J., et al. 2000. Analysis of silicon in human tissues with special reference to silicone breast implants. *J. Trace Elements Med. Biol.* 14:31.
 9. Evans, G.R.D., and Baldwin, B.J. 1997. From cadavers to implants: Silicon tissue assays of medical devices. *Plast Reconstr Surg* 100:1459-65.
 10. Barnard, J.J., et al. 1997. Distribution of organosilicon polymers in augmentation mammoplasties at autopsy. *Plast. Reconstr Surg.* 100(1):197-203.
 11. McConnell, J.P., et al. 1997. Determination of silicon in breast and capsular tissue from patients with breast implants performed by inductively coupled plasma emission spectroscopy. Comparison with tissue histology. *Am. J. Clin. Pathol* 107(2):236-46.

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and various parameters of inflammation and calcification in breast tissue, nor was there any correlation between tissue silicon concentration and the presence of signs and symptoms of morbidity. A later study by the same group reported no correlation between symptoms in women with silicone gel-filled implants.¹²

Because tissue silicon levels appear not to provide any relevant information concerning breast implant status or health status, the College of American Pathologists stated that

“It is the position of the College of American Pathologists that laboratory tests measuring blood, urine, or tissue silicon, silicone, toluene diamines, or related substances are not currently indicated or useful for purposes of medical management of individual breast implant recipients.”^{13/}

Similarly, the American Medical Association Council on Scientific Affairs issued the following policy statement:

“The AMA condemns the inappropriate use of laboratory tests that purport to measure the dissemination of silicone through a patient's body and which are used to make unsubstantiated diagnoses of silicone-related illness.”^{14/}

Recent Determination of Silicone Gel Components by Other Methods

Flassbeck et al.^{15/} analyzed D₄ through D₆ and platinum in the fat and/or muscle tissue immediately adjacent to the capsule in a total of three women with silicone gel-filled breast implants and three women with no prior silicone breast implant exposure. Based on this very limited sampling, the authors asserted that “the use of elemental silicon as an indicator of migration of siloxane species from breast implants to the surrounding tissue is not appropriate” and based their argument largely on the D₄-D₆ cyclics accounting for only a small portion of total silicon (3.6% in the particular example cited). Such an argument appears invalid, however, in light of the earlier reported findings of Schnur et al.^{16/} and Evans and Baldwin.^{17/} In the Schnur et al.

12/ Weinzwerg, J., et al. 1998. Silicon analysis of breast and capsular tissue from patients with saline or silicone gel breast implants: I. Correlation with connective-tissue disease. *Plast. Reconstr. Surg* 101(7):1836-41.

13/ Cited in : Silicone Breast Implants and Disease. Report of the AMA Council on Scientific Affairs (CSA Report 8, I-96), Adopted by the American Medical Association House of Delegates, December 1996. Available at: <http://www.ama-assn.org/ama/pub/article/2036-2536.html>.

14/ H-525-979. Silicone Breast Implants and Disease. Available at: <http://www.ama-assn.org/ama/pub/article/2036-2536.html>.

15/ Flassbeck, D., B. Pfeleiderer, P. Klemens, K.G. Heumann, E. Eltze and A.V. Hirner. 2003. Determination of siloxanes, silicon, and platinum in tissues of women with silicone gel-filled implants. *Anal. Bioanal. Chem* 375(3):356-362.

16/ Schnur, P.L., et al. 1996. Silicon analysis of breast and periprosthetic capsular tissue from patients with saline or silicone gel breast implants. *Plast Reconstr. Surg* 98:798-803

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study, average baseline silicon levels in breast tissue from patients with no implants (n=17) were 60 µg Si/g tissue and represented only 0.4% of silicon levels in periprosthetic capsular tissue of patients with either intact (n=63) or ruptured (n=47) silicone gel implants. Similarly, in the Evans and Baldwin study, the average baseline silicon level in tissue samples (including breast) from cadavers (n=120, from 20 pts) was 2.2 µg Si/g tissue and represented only 0.2% of silicon levels in periprosthetic capsular tissue of patients undergoing explantation of silicone gel-filled breast implants (n=58, from 31 patients). Given the very low detection limits for elemental silicon in these studies (as low as 0.5 µg/g in the Evans and Baldwin study), these methods appear fully capable of providing valid information on the distribution of silicone materials, including cyclics in these patients. As noted above, such studies have shown that silicone materials released from the silicone gel-filled breast implants, both ruptured and intact, remain almost entirely within the confines of the fibrous capsule surrounding the implant, and does not migrate away from the breast tissue.

With respect to potential quantitative information for specific breast implant constituents that potentially might be acquired through additional sampling and analysis of explanted breast and capsular tissue, the existing data indicates that toxicologically significant levels would not be present. For example, the extent of cyclics exposure represented by Flassbeck's analysis would amount to essentially the entire amount of D₄ present in two maximum size Mentor implants, and also appears to be significantly below typical quantities absorbed on a daily basis from consumer products. The highest D₄ measurements reported by Flassbeck were from their only two fat tissue samples and were 0.083 µg/g and 1.3 µg/g. Assuming the average body composition of 27% fat in a 60 kg woman, and that breasts account for 3.5% of the total weight of body fat (Katch et al.¹⁸), the total quantity of breast fat would be approximately 567 grams. Applying Flassbeck's D₄ measurements to this quantity would equate to total D₄ levels in breast tissue fat of 0.05 to 0.7 mg D₄ (conservatively assuming that the level is as high throughout the breast as it was in the sampled tissue immediately adjacent to the implant capsule). Importantly, the total quantity of D₄ present in two maximum-size Mentor 800 cc implants is 0.78 mg D₄ (based on validated exhaustive analysis of extractable D₄). Furthermore, Meeks et al.¹⁹ notes that current daily intake of D₄ from consumer products amounts to 4.7 mg D₄/day, an amount substantially greater than either the total amount of D₄ present in current Mentor silicone gel-filled breast implants or in the breast fat tissue analyzed by Flassbeck and colleagues.

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- 17/ Evans, G.R.D., and Baldwin, B.J. 1997. From cadavers to implants: Silicon tissue assays of medical devices. *Plast Reconstr Surg* 100:1459-65.
- 18/ Katch, V.L., B. Campaigne, P. Freedson, S. Sady, F.I. Katch and A.R. Behnke. 1980. Contribution of breast volume and weight to body fat distribution in females. *Am. J Phys. Anthropol* 53(1):93-100.
- 19/ Meeks, R.G. 2002. Bioavailability of D₄ after inhalation and implantation exposure to silicones. *Environ. Health Perspect.* 110:A442-A443.

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For the many reasons discussed above, there appears to be no significant information to be gained from further breast and capsular tissue analysis.

- c. For all patients with ruptured implants, please provide the frequency of observed intracapsular gel, extracapsular gel, and migrated gel, as well as the destination of the migrated gel. This information will be supplemented by your response to item 2 below.**

1c Response:

There was only one patient (404-015) out of a total of 1,007 Core study patients with confirmed (bilateral) ruptured implants. The rupture confirmation in this patient is based on inspection of the explanted devices. This patient did not have any reports of intracapsular gel, extracapsular gel, or migrated gel, as determined by MRI evaluation.

Please see the response to question 2 for supplemental information from the Sharpe and Collis study and the literature on the frequency of patients with observed intracapsular gel, extracapsular gel, and migrated gel, as well as the destination of the migrated gel. Please also see the response to question 1b above concerning the issue of migrated gel.

- d. The potential local health consequences of rupture (intracapsular, extracapsular, or migrated gel) have not been fully determined clinically. Therefore, please provide a detailed description, including the severity, of the local health consequences experienced by all patients with ruptured devices and their clinical course. This information will be supplemented by your response to item 2 below.**

1d Response:

There was only one patient (404-015) with confirmed (bilateral) ruptured implants. This patient did not report any local health consequences.

Please note that there were three Revision patients (421-005, 435-014, 418-010) who had non-study ruptured devices replaced with Core Study devices. While the extracapsular silicone observed in these patients was not from the Core devices, review of these patients' local health consequences revealed that their complications were limited to nipple sensation changes.

Additionally, Cox regression analysis showed no correlation between local health consequences – confirmed or suspected rupture did not increase the risk of having a complication.

As described in Response 2, Mentor also has provided additional clinical data evaluating the local health consequences of rupture from the Sharpe and Collis study, as well as the literature.

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- e. **For patients with ruptured devices, please provide the results of patient satisfaction, local complications, and connective tissue disease (CTD) signs/symptoms, analyzed separately from patients with intact implants.**

1e Response:

There was only one patient (404-015) with confirmed (bilateral) ruptured implants. This patient did not have any reports of local health consequences or reports of connective tissue disease (CTD) signs/symptoms. As there was only one patient with a confirmed rupture, analysis comparing this single patient to the non-ruptured cohort is not meaningful. However, in terms of patient satisfaction, this patient reported that she would have the surgery again.

Mentor also provides important new clinical data, along with literature, on local and systemic health consequences of ruptured implants in Response 2.

- f. **Please collect data on the clinical course of all patients who have your device removed and do not receive a replacement breast implant.**

1f Response:

In Mentor's protocol, approved by FDA, we specify that all patients with study implants will be followed for the entire duration (10 years) of the study. In addition, the protocol stipulates that patients whose implants are explanted and not reimplanted with a study device will be discontinued from the study. Mentor does not believe that it is necessary to follow these patients after the study device has been removed, as available data indicate that there are no health consequences associated with intact or ruptured implants. (see Response 2). Moreover, it is unlikely that patients who no longer are implanted with Mentor devices would be willing to return for follow-up visits.

Supplemental Clinical Information Regarding Rupture

- 2. The Core Study is not adequate to fully address implant rupture due to its limited sample size. You provided literature information in Sections 5.1 and 8.6 of your PMA to further address rupture and its health consequences. However, that information was not adequate to address the specific issues below related to the potential health consequences of rupture. Therefore, please provide additional clinical information on your device from sources other than the Core Study (e.g., retrospective or prospective data from Adjunct Study and/or European studies), as well as relevant information from the published literature, for the items below.**

In response to FDA's request for supplemental clinical information regarding implant rupture and potential health consequences of rupture, provided below is a summary of a clinical MRI study on long-term silent and overt rupture rates (as well as other complications), and potential related health consequences of rupture in a total of 190 women with Mentor silicone gel-filled devices after up to 12 years of implantation. This study was undertaken by Dr. David T. Sharpe and Dr. Nicholas Collis of the Bradford Royal Infirmary in the U.K. In addition, a review of relevant published literature is included in this response, which provides important information from explant studies and recent well-controlled epidemiological reports concerning rupture, and the health consequences of rupture, of third generation silicone gel-filled breast implants generally and Mentor implants specifically. The published epidemiological reports presented in this response, together with the rate of silent ruptures collected by Drs. Sharpe and Collis, provide reasonable assurance of safety with respect to intra- and extracapsular ruptures, the destination of migrated gel, and the health consequences of rupture, and sufficient information to inform doctors and their patients about these issues.

Investigation of Long-Term Silicone Gel-Filled Implant Integrity and Observational Analysis of Potential Health Consequences of Rupture

A study was designed and conducted by Dr. David T. Sharpe, and Dr. Nicholas Collis, Bradford Royal Infirmary, U.K., to evaluate Mentor silicone gel-filled breast implant integrity in implants that have been in place for 4-12 years, as determined by Magnetic Resonance Imaging ("MRI") and confirmed at explantation. An observational analysis of the potential health consequences of implant rupture was included in this study. The study methods, results, and conclusions are summarized below.

Study Design and Methods

MRI to Assess Implant Integrity

A database was compiled detailing all patients in Dr. Sharpe's practice who received, or were treated for complications arising from, the use of silicone breast implants for both cosmetic and reconstructive purposes. Patients were included from both the U.K. National Health Service ("NHS") and the private sector. The database was started in February 1997 and

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updated continuously, so that by December 1998 it contained the details of the 1,140 patients who had surgery since 1986, as well as information on the use of silicone breast implants since 1971. The largest cohort of patients in the database was those who had received subglandular Mentor textured silicone gel breast implants for cosmetic reasons. Excluding revisional procedures,²⁰ there were 179 NHS and 129 private patients who had no further interventions since their original breast augmentation. Drs. Sharpe and Collis initially decided to limit the study to the NHS patients, since explantation could be offered, without cost, to any patient with radiologically ruptured implants. Thus, this study pertains to the NHS cosmetic patients in their database only.

The study design was approved by the Institutional Ethics Committee. NHS women with cosmetic implants who had no further interventions since their original surgery and who met the pre-specified inclusion criteria (including asymptomatic and implant duration of at least 4 years), and exclusion criteria (including Baker Grade III/IV capsular contracture, surgical interventions, and any clinical evidence of rupture), were invited by confidential explanatory letter to participate in the study. Women who agreed to participate provided informed consent, completed a questionnaire, and were given a physical examination to exclude contraindications to MRI and document any problems with their breast implants (*e.g.*, rupture, Baker Grade III/IV capsular contracture). A Philips Gyroscan Intera 1.5T scanner with a dedicated breast coil was used in all cases to obtain axial T2 TSE, axial STIR/FLAIR, and coronal T2 TSE views. Two Consultant Radiologists (Dr. Janet Litherland and Dr. David Ennion) evaluated the scans. Both had an interest in breast MRI, were geographically separate, and not professionally known to each other. Neither radiologist was given any implant or patient details, other than names, addresses, and dates of birth. Patients who had one or both implants reported as ruptured by one or both radiologists were counseled and offered bilateral explantation and implant replacement.

Statistical Analysis Plan

Data for the time from augmentation to MRI and whether or not the implant was determined by the MRI to be ruptured were analyzed in order to estimate the cumulative rupture rate function at both the patient and the implant level using the method of maximum likelihood (see technical appendix). Overt ruptures would have been included in these analyses as well had there been any such ruptures. Because it was known in advance of the analysis that there were no overt ruptures, no provision was made for their inclusion.) Patients were excluded from the analysis if the patient had a missing value for the MRI date. At the patient level, patients who had an explantation of an implant prior to the MRI date were excluded from the analysis. At the implant level, implants were excluded from the analysis if an explantation of the implant was performed prior to the MRI date. Using the estimated cumulative rupture rate function, estimates were obtained of the cumulative rupture rate at annual timepoints after the augmentation date (to obtain an estimate of change in rupture rate over time). The

20/ A small number of women, approximately a dozen, who sought revisional surgery, primarily for capsular contracture, or capsulectomy with explantation and reimplantation, were excluded.

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jackknife procedure²¹ was used to estimate the standard errors of these estimates, which were then used to calculate 95% confidence intervals for the estimates. Rates of change over time in the rupture rate were estimated using conditional probability. A second set of analyses (patient level and implant level) were performed in which an MRI determination of rupture was overridden if, based upon physical examination of the explanted device, the device was determined to be intact (*i.e.*, confirmed ruptures). These analyses were performed in the same manner as the first set of analyses.

Potential Health Consequences of Rupture

The subset of women in the MRI study who had at least one ruptured implant determined by MRI and who subsequently underwent surgical explantation and confirmation of implant rupture were invited to participate in an observational study to assess potential health consequences of rupture of Mentor's silicone gel-filled breast implants. Women who agreed to participate underwent a blinded and standardized rheumatological assessment. The primary objective of the study was to examine the incidence of rheumatologist-diagnosed/confirmed rheumatologic disease among patients with ruptured silicone gel-filled breast implants. Secondary objectives included examination of the number of findings in a rheumatologic physical examination and the number of reported rheumatologic symptoms among patients with ruptured silicone gel-filled breast implants.

21/ Efron and Gong, "A leisurely look at the bootstrap, the jackknife, and cross-validation," The American Statistician, 1983.

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Results and Discussion

Information concerning the cohort evaluated in this study is provided below:

Number of NHS women with cosmetic subglandular Mentor Siltex silicone gel-filled breast implants	204
Number of NHS women with cosmetic subglandular Mentor Siltex silicone gel-filled breast implants who underwent MRI examination included in the patient level analysis	101
Number of women who underwent MRI examination, but were excluded from patient level analysis because one of their implants was removed prior to the MRI examination, but their remaining implant was included in the implant level analysis	2
Number of implants evaluated by MRI and included in implant-level analysis	204
Mean age at implantation	30.6±5.6 years
Mean age at MRI examination	40.0±6.1 years
Mean implant duration	8.8±2.5 years
Mean implant size	
Right	225±35 cc
Left	221±35 cc

The results of the MRI evaluation are presented below:

	Patient	Implant
Number of MRI-identified silent ruptures	12 (11.9%)	19 (9.3%)
Number of ruptures confirmed at surgery	9 (8.9%)	11 (5.4%)
Mean age of implants at MRI-identified rupture (excluding implants confirmed as intact)		9.2±1.5 years
Mean age of implants at confirmed rupture		9.1±1.6 years
Number of extracapsular ruptures	0	0

Results of the analyses to estimate the cumulative rupture rate over time by patient and implant for MRI-identified and confirmed ruptures are provided in Tables 1-4 below.

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Of the patients with at least one ruptured implant who underwent rheumatological examination, only one woman reported possible rheumatological effects (one possible episode of “myalgic encephalitis”), which was not considered by the evaluating rheumatologist to be implant related. Blood analyses revealed no abnormal findings.

In this study, the confirmed (by explantation) overall rupture rate was 8.9% (by patient) and 5.4% (by implant). No ruptures were observed until approximately 7 years after implantation, and, based on the modeling conducted, the rupture rate slowly increased thereafter until, at 12 years, the rate was approximately 12%. The average age of the implant at confirmed rupture was 9.1 ± 1.6 years, which demonstrates the durability of Mentor’s silicone gel-filled implants. Importantly, of the confirmed ruptures, none were extracapsular, and with the possible exception of one woman, none of the women with ruptured implants experienced adverse health consequences.

As shown in the table below, the third generation silicone gel-filled breast implant rupture rate and trends found in the present study conducted by Drs. Sharpe and Collis compare favorably to those reported in the literature.

Reference	Implant Generation	Implant Duration (years)	Rupture Rate (%)		Type of Rupture
			(Women)	(Devices)	
Sharpe & Collis	Third	Mean = 8.8 (4-12) years	8.9 (9/101)	5.4 (11/204)	Silent
Gabriel et al. 1997 (Prevalence study)	Women implanted 1964-1991	Mean = 7.8 (0-25.8)	5.7 (43/749)	3.3 56/1,703	Overt
Hölmich et al. 2003 (Incidence study)	Third generation: 62% of total studied	2-11	6 (12/197)	NA	Silent and Overt
Brown et al. 2000 (Prevalence study)	Third generation: 2% of total studied	Mean = 7.4	16.7 (1/6)	8.3 (1/12)	Silent

The complete Sharpe and Collis report can be found in Attachment 2.

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- a. Please provide the frequency of observed intracapsular gel, extracapsular gel, and migrated gel, as well as the destination of the migrated gel.

2a Response:

Release of silicone from gel-filled breast prostheses can occur as a result of either rupture of the envelope or diffusion of minute quantities of silicone through the intact elastomer envelope. The released silicone remains almost entirely within the confines of the fibrous capsule surrounding the implant (see Responses 1b and 24a). As described by the IOM expert Panel report in its conclusions regarding the animal toxicology studies of silicone and silicone breast implants,

“depots of gel, whether free or in implants, remain almost entirely where injected or implanted. Even low molecular weight cyclic and linear silicone fluids appear to have low mobility” (Chapter 4).^{22/}

Thus, only in rare instances that are described primarily in anecdotal case reports, generally in women who had undergone closed capsulotomy or experienced acute trauma to the chest area,^{23/} has silicone gel been reported to relocate via bulk movement along subcutaneous tissue planes to distant sites. With the virtual elimination of closed capsulotomy as an accepted practice for treating capsular contracture, such reports should continue to become even more rare.

A number of studies, either by evaluating explanted devices or conducting MRI examinations, have reported on the incidence/prevalence of intra- and extracapsular rupture in women with silicone gel-filled breast implants. These studies are summarized in the table below. A number of conclusions can be drawn from the information presented in this table:

- The recent study by Hölmich et al. (2004)^{24/} provides convincing evidence that 90% of the intracapsular and 84% of the extracapsular ruptures remain relatively

22/ Bondurant, S., Enrster, V., and Herdman, R., Eds. 2000. *Safety of Silicone Breast Implants*. Committee on the Safety of Silicone Breast Implants, Division of Health Promotion and Disease Prevention, Institute of Medicine (Washington, D.C.: National Academy Press).

23/ See, e.g., Huang, T.T., et al. 1978. Migration of silicone gel after the “squeeze technique” to rupture a contracted breast capsule. *Plast. Reconstr. Surg.* 60:277-80; Capozzi, A., et al. 1980. Distant migration of silicone gel from a ruptured breast implant. *Plast. Reconstr. Surg.* 62:302-3; Leibman, A.J., et al. 1992. Intra-ductal extension of silicone from a ruptured breast implant. *Plast. Reconstr. Surg.* 89:546-7; Ahn, C.Y., and Shaw, W.W. 1994. Regional silicone-gel migration in patients with ruptured implants. *Ann. Plast. Surg.* 33:201-8; Teuber, S.S., et al. 1999. Severe migratory granulomatous reactions to silicone gel in 3 patients. *J. Rheumatol.* 26A:699-704; Malyon, A.D., et al. 2001. Expanding silicone granuloma. *Br. J. Plast. Surg.* 54:257-9; Baack B.R. and Wagner, J.D. 2003. Silicone gel breast implant rupture presenting as a fluctuant back mass after latissimus dorsi breast reconstruction. *Ann. Plast. Surg.* 51(4):415-8

24/ Hölmich, L.R., et al. 2004. Untreated silicone breast implant rupture. *Plast Reconstr Surg.* 114:204-14.

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stable, *i.e.*, the overwhelming majority of intracapsular ruptures do not progress to extracapsular ruptures, and effusion of gel into surrounding breast tissue in extracapsular ruptures is generally minimal over time.

- Other literature reports that most ruptures are intracapsular, with extracapsular ruptures accounting for 3 to 27% of observed ruptures.
- The lower end of the frequency range for extracapsular ruptures (*i.e.*, 3-12%) was observed in explant studies, whereas the higher, and more common ranges (*i.e.*, approximately 12% to 27%) were observed in the imaging studies.
- In those studies where implant generation was known, most, if not all, extracapsular ruptures occurred in second generation implants, with third generation implants exhibiting minimal or no such ruptures.
- Extracapsular ruptures appear largely to be the result of closed capsulotomy and/or trauma to the chest area. For example, Hölmich et al. (2001) found that there was a significantly higher ($p < 0.001$) prevalence of extracapsular ruptures (14.7%) in patients who had undergone closed capsulotomy as compared to those who had not.^{25/} Collis and Sharpe (2000)^{26/} reported that one patient observed to have severe bilateral silicone granulomas and bilateral extracapsular ruptures, suffered a fractured sternum in a traffic accident. Similarly, in the study by Hölmich et al. (2004)^{27/} investigating the progression of ruptures in Danish women with cosmetic silicone gel-filled implants, three of seven women whose ruptures had progressed from intra- to extracapsular over a period of two years, reported that they experienced trauma to the affected breast during this time period, and a fourth woman had undergone mammography. Importantly, one intracapsular ruptured implant was assessed by MRI as having extracapsular distal spread of silicone, but at explantation, all silicone gel was found to be contained within the capsule.

25/ Hölmich, L.R., et al. 2001. Prevalence of silicone breast implant rupture among Danish women. *Plast. Reconstr. Surg.* 108:848-58.

26/ Collis, N. and D.T. Sharpe. 2000. Silicone gel-filled breast implant integrity: A retrospective review of 478 consecutively explanted implants. *Plast Reconstr. Surg.* 105:1979-1985.

27/ Hölmich, L.R., et al. 2004. Untreated silicone breast implant rupture. *Plast. Reconstr. Surg.* 114:204-14.

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There were no reports of intracapsular or extracapsular silicone or migrated silicone in the Sharpe and Collis study of 190 women with Mentor implants, as described above.

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SUMMARY OF LITERATURE ON INTRACAPSULAR AND EXTRACAPSULAR GEL, GEL MIGRATION, AND DESTINATION

CITATION	DESIGN	FREQUENCY OF INTRACAPSULAR AND EXTRACAPSULAR GEL	GEL MIGRATION/ GEL DESTINATION/ OTHER INFORMATION
Peters et al. 1996; Peters 2000	Analysis of 352 explants from 231 women	Extracapsular gel was observed in 4.2% of second generation implants at time of explantation; no extracapsular gel was observed in first or third generation implants	No information on gel migration or destination beyond breast tissue
Middleton 1998	MRI study 1,626 single-lumen implants	27.2% of implants imaged showed evidence of definite rupture; of those that were ruptured 26.2% were extracapsular	No information on gel migration or destination beyond breast tissue
Cook et al. 1998	Commentary citing other literature and opinion	Extracapsular rupture "reportedly occurs in about 3% of cases"	"Although there are a few case reports of extravasated gel associated with serious local complications at remote sites, serious sequelae are rare, probably because in most extracapsular ruptures the gel is re-encapsulated close to the breast."
Brown et al. 2000; Berg et al. 2002	MRI study of a cohort of 344 women with 687 implants from the NCI study in Alabama	Evidence of extracapsular gel seen in 85 of 687 implants (12.4%) in 73 of 344 women (21.2%); rupture was evident in all but one of these implants; while not specified, it is assumed that these implants were primarily, if not entirely, first and/or second generation as only one rupture was observed in third generation implants	70 of 85 (82%) of breasts with extracapsular silicone exhibited gel "spreading into the breast adjacent to the implant" Agreement concerning extracapsular gel was considered only moderate to substantial (kappa statistic = 0.50 to 0.65)
Collis and Sharpe, 2000	Analysis of 478 explants from 256 women	15 breasts (3%) (11 patients, 4.7%) had pericapsular silicone granulomas at explantation; 13 of these were associated with ruptured implants (all second generation); one patient with severe bilateral silicone granulomas and bilateral extracapsular ruptures suffered a fractured	No information on gel migration or destination beyond breast tissue

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CITATION	DESIGN	FREQUENCY OF INTRACAPSULAR AND EXTRACAPSULAR GEL	GEL MIGRATION/ GEL DESTINATION/ OTHER INFORMATION
		sternum in a traffic accident	
Hölmich et al. 2001	MRI study of 271 Danish women with 533 cosmetic breast implants	110 of 141 implants (78%) determined to be ruptured were intracapsular and 31 of 141 ruptures (22%) in 23 of 271 women (9%) were extracapsular; generation not specified, but given that there were only 36 third generation implants ruptured, it can be assumed that most, if not all, of the extracapsular ruptures were first and/or second generation implants	No information on gel migration or destination beyond breast tissue Significantly higher (p<0.001) prevalence of extracapsular ruptures (14.7%) in patients who had undergone closed capsulotomy as compared to those who had not
Hölmich et al. 2003	Continuation of MRI study cited in Hölmich et al. 2001; repeat (second) MRIs conducted in 186 women with 317 implants from 2001 study	Six of 26 new ruptures (23%) were extracapsular.	No information on gel migration or destination beyond breast tissue
Fryzek 2004 (unpublished)	Subset analysis of overt ruptures in third generation implants from Danish registry cohort epidemiological study	Two of 509 implants ruptured; of those two, one was reported to be intracapsular and the other was unknown.	No information on gel migration or destination beyond breast tissue
Hölmich et al. 2004	Continuation of MRI study cited in Hölmich et al. 2001 and 2003; comparison of MRI images from 64 women who had at least one ruptured implant at the first MRI examination and 98 women who had intact implants at both examinations for comparison	<ul style="list-style-type: none"> • Of the 96 implants ruptured at the first MRI, 77 (80%) were intracapsular and 19 (20%) were extracapsular • Of the 77 intracapsular ruptures, 69 (90%) showed no change at the second MRI examination • One intracapsular ruptured implant (1%) exhibited increasing distal spread of silicone thought to be extracapsular, but at explantation, all silicone gel was found by examination to be contained within the capsule • Silicone was seen outside the capsule in 	No information on gel migration or destination beyond breast tissue

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CITATION	DESIGN	FREQUENCY OF INTRACAPSULAR AND EXTRACAPSULAR GEL	GEL MIGRATION/ GEL DESTINATION/ OTHER INFORMATION
		<p>the 7 (9%) remaining implants originally determined to be intracapsular ruptures , 5 of which were considered to be "minor"</p> <ul style="list-style-type: none"> • Three of the 7 women whose ruptures progressed to extracapsular reported trauma to the affected breast between the first and second MRI examinations, and one had undergone mammography • 16 of the 19 (84%) extracapsular ruptures identified at the first MRI examination had silicone gel that remained stationary; effusion of extracapsular silicone increased marginally in one implant in one woman and significantly in two implants in another woman; neither woman reported trauma 	

References cited:

Baack, B.R., and Wagner, J.D. 2003. Silicone gel breast implant rupture presenting as a fluctuant back mass after latissimus dorsi breast reconstruction. *Ann Plast Surg.* 51(4):415-8.

Berg, W.A., et al. 2002. MR imaging of extracapsular silicone from breast implants: diagnostic pitfalls. *AJR.* 178:465-72.

Brown, S.L., et al. 2000. Prevalence of rupture of silicone gel breast implants revealed on MR imaging in a population of women in Birmingham, Alabama. *AJR.* 175:1057-64.

Collis, N. and Sharpe, D.T.. 2000. Silicone gel-filled breast implant integrity: A retrospective review of 478 consecutively explanted implants. *Plast. Reconstr. Surg.* 105:1979-85.

Cook, R.R., et al. 1998. Rupture of silicone-gel implants. *The Lancet* 351:520-1.

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- Fryzek, J. 2004. Third generation-specific reanalysis of Kjoller et al 2002 (Kjoller, K., L.R. Hölmich, P.H. Jacobsen, S. Friis, J. Fryzek, J.K. McLaughlin, L. Lipworth, T.F. Henriksen, S. Jorgensen, S. Bittmann and J.H. Olsen. 2002. Epidemiological investigation of local complications after cosmetic breast implant surgery in Denmark. *Ann. Plast. Surg.* 48(3):229-237). Unpublished analysis.
- Hölmich, L.R., et al. 2001. Prevalence of silicone breast implant rupture among Danish women. *Plast Reconstr Surg* 108:848-58.
- Hölmich, L.R., et al. 2003. Incidence of silicone breast implant rupture. *Arch. Surg.* 138:801-6.
- Hölmich, L.R., et al. 2004. Untreated silicone breast implant rupture. *Plast. Reconstr. Surg.* 114:204-14.
- Middleton, M.S. 1998. Magnetic resonance evaluation of breast implants and soft-tissue silicone. *Top. Magn Reson. Imaging* 9(2):92-137.
- 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.
- Peters, W.J., et al. 1996. Failure properties of 352 explanted silicone-gel breast implants. *Canadian J. Plastic Surg*

- b. Please provide a detailed description of the local health consequences for all patients with ruptured devices (both symptomatic and silent rupture patients), including the severity of the local health consequences and the clinical course of these patients. In the literature information that you provided on patients with ruptured implants, only reoperations and removals were described. This information does not address our issues regarding potential local health consequences of ruptured implants.

2b Response:

Although there is very little information in the published literature concerning the local health consequences of ruptured breast implants (either symptomatic or silent ruptures), the only associated finding has been capsular contracture (*i.e.*, change in breast shape or size, and breast pain reported as not serious). When women are found to have ruptured silicone gel-filled breast implants, particularly in the U.S., the current standard of care is to explant the ruptured devices. Hence, the major local consequences of rupture are reoperation and removal.

Investigators affiliated with the Institute of Cancer Epidemiology in Denmark, however, have identified and followed a cohort of women whose implant status was determined by MRI, and have reported both local and systemic health findings in women with intact and ruptured breast implants^{28/} (the systemic health findings reported in this cohort of women are discussed in Response 32). In their 2003 study, Hölmich et al. evaluated a cohort of women derived from a larger clinical follow-up study of all women (n=1,308) implanted at three private plastic surgery clinics and one public hospital in Denmark from 1973 through 1998, primarily for cosmetic indications. Women from this cohort for whom medical record abstraction and clinical examination (including blood collection and completion of a self-administered questionnaire concerning medical history, demographics, and lifestyle characteristics) had been completed were considered eligible for MRI evaluation, and of these women (n=630), 436 were selected for participation in the imaging screening study (all women who received their implants prior to 1978 were invited (n=64), and the remaining women were randomly selected). Of the 436 women invited to participate, 298 women agreed. After exclusion of 27 women (for having saline implants or who were implanted for reconstructive indications), 271 women with 533 cosmetic silicone breast implants were included in the MRI study.^{29/}

28/ Hölmich, L.R., et al. 2003. Self-reported diseases and symptoms by rupture status among unselected Danish women with cosmetic silicone breast implants. *Plast Reconstr. Surg.* 111:723-32; Hölmich, L.R., et al. 2004. Untreated silicone breast implant rupture. *Plast. Reconstr. Surg.* 114:204-14.

29/ Hölmich, L.R., et al. 2001. Prevalence of silicone breast implant rupture among Danish women. *Plast. Reconstr. Surg.* 108:848-58 for additional details concerning the study cohort

From this cohort, MRI examination revealed that in 146 women, the implants were intact, 92 women had ruptured implants, and of these 92 women with ruptured implants, 23 exhibited evidence of extracapsular rupture (19 women with evidence of "possible rupture" and 14 women who did not complete the questionnaire were excluded from the analysis). It is important to note that, of the women with ruptured implants, only 1 woman (1% of women with ruptures) had implants in place less than 5 years, with the majority of women with ruptures (55%) having implant durations that exceeded 16 years ($p < 0.0001$ for implant age > 21 years, as compared to women with intact implants). Thus, only one of the women with ruptured implants in this cohort had third generation breast implants.

With regard to local health consequences of rupture, Hölmich et al. (2003)³⁰ found that women with evidence of extracapsular rupture were 6.3 times more likely to report breast hardening (which is indicative of capsular contracture) than women with intact implants (95% CI, 1.7 to 23.5). However, the incidence of capsular contracture in the total rupture group (*i.e.*, intracapsular and extracapsular) was not statistically significant (odds ratio, 1.8; 95% CI, 0.9-3.5) when compared to women with intact implants. Moreover, there was no statistical difference between the number of women with ruptured implants (total or extracapsular) who reported breast pain as compared to women with intact implants (odds ratio, 1.6; 95% CI, 0.8-3.1 for total ruptures, odds ratio, 1.6, 95% CI, 0.5-5.9 for extracapsular ruptures). No other local health effects were reported. The authors speculate that the increased incidence of capsular contracture in women with extracapsular rupture might be the result of a foreign body reaction, triggered by free silicone, resulting in fibrosis. They caution, however, that "the temporal relationship of extracapsular implant rupture and capsular contracture could not be established in this cross-sectional study."

The clinical course of the women reporting local health consequences was not clearly defined. The investigators counseled all women involved in the study, and those women with local symptoms or extracapsular rupture were advised to have their implants removed. Some women declined, electing to leave their ruptured implants in place. All women were invited to participate in a second MRI study, the results of which were reported in Hölmich et al. (2004).

In their 2004 follow-up of the cohort of women who participated in the first MRI examination (Hölmich et al. 2001 and 2003), Hölmich and colleagues compared second MRI images from 64 women who had at least one ruptured implant (96 implants ruptured implants) at the first MRI examination with images from 98 women (193 implants) who had intact implants at both examinations. Women who did not participate in the second MRI examination included those who had their implants removed or exchanged after the first MRI examination or who had declined to participate, and 44 women who had second MRIs were excluded from

30/ Hölmich, L.R., et al. 2003. Self-reported diseases and symptoms by rupture status among unselected Danish women with cosmetic silicone breast implants. *Plast Reconstr. Surg.* 111:723-32.

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analysis because their implants were either not definitely ruptured at the first MRI examination, or were not intact at both MRI examinations. For the second MRI examination, only two of the original three MRI centers were used. (The MRI machine at the third center was unable to generate silicone-excited sequences, and women who were originally examined at this center went to Center 1 for the second examination.) Just prior to undergoing the second MRI examination, the participating women completed a second self-administered questionnaire, which was primarily focused on breast symptoms that occurred between the first and second MRI examinations.

While reporting of non-specific implant/breast symptoms, including change in breast shape and size and breast pain, occurred in both groups, there were twice as many reports from ruptured implants as compared to intact implants (odds ratio, 2.1; 95% CI, 1.2-3.8, and at least one breast symptom was reported for 53% of the ruptured implants, as compared to 37% of the intact implants (odds ratio, 1.9; 95% CI, 1.2-3.1). Other breast symptoms reported at a statistically higher incidence in women with ruptured implants are summarized in the table below.

Self-Reported Breast Symptoms at Breast Level Between First and Second MRI Examinations

Symptom	Ruptured Implants (n=96)		Intact Implants (n=193)		Odds Ratio (95% CI)
	No.	%	No.	%	
Change in breast shape	24	24	22	12	2.5 (1.3-4.8)
Change in breast size	20	21	23	12	1.9 (1.0-3.7)
Pain in breast (reported as not serious)	22	23	23	12	2.2 (1.2-4.2)

The changes were predominantly described as a feeling of a softer breast with a different shape and size (most commonly flatter and smaller). Additional questions concerning breast pain revealed that in no instance was the pain reported as serious or severe enough to require explanation. Interestingly, there was no excess reporting of breast hardness in women with ruptured implants (odds ratio, 0.9; 95% CI, 0.3-2.1), as had been seen in the previous study in women with extracapsular rupture, and no statistically significant difference in the relative few numbers of women who reported pain in the relevant shoulder/arm (odds ratio, 1.2; CI, 0.5-2.9).

These two clinical studies provide the only published populations of information on the local health consequences and clinical course of rupture in women with silicone gel-filled breast implants, particularly in women with ruptured silicone gel-filled breast implants left *in situ* for a period of time. Given the strengths of these studies, they provide reliable information. Both studies were prospectively designed, and the women who participated were randomly selected from a larger cohort of women, with excellent follow-up. In the first study, the women were unaware of their implant status when they completed the health questionnaire, thus diminishing the chance that symptoms were overreported because of anxiety

associated with rupture. The MRIs were conducted using validated criteria and a standardized protocol, and with the exception of women evaluated at the third center, both MRIs were conducted using the same machines. The potential for misclassification of rupture was minimized by reexamination of the first MRI at the time of the second evaluation. A limitation of the second study is that women who experienced more severe complications related to breast implant rupture likely were explanted before undergoing a second MRI examination. However, the authors report that the “majority” of the 44 women who elected to be explanted after the first MRI examination did so because of the rupture diagnosis rather than symptoms. A second limitation is that women knew their implant status (from the first MRI) before completing the local breast symptom questionnaire, which may have influenced the women with ruptures to report symptoms. This potential bias should, however, result in over- rather than under-reporting of symptoms.

In summary, the results of these studies indicate that women who have ruptured implants experience few local health consequences (primarily capsular contracture in women with extracapsular rupture), and women whose ruptured implants are left in place for two years remain relatively asymptomatic, with only small increases in perception of breast size and shape, and reports of non-serious breast pain as compared to women with intact implants. These results led the authors to conclude that “implant rupture is a relatively harmless condition, which only rarely progresses and gives rise to notable symptoms.”^{31/}

c. Please provide the incidence, prevalence, and timing of silent ruptures that progressed to symptomatic ruptures.

2c Response:

As noted above in the Response 2b, when women are found to have ruptured silicone gel-filled breast implants (either overt or silent), particularly in the U.S., the current standard of care is to explant the ruptured devices. Moreover, imaging examinations (*i.e.*, MRI) typically are not conducted to monitor rupture status on a routine basis in asymptomatic women, so it is not possible to assess the incidence and prevalence of purely silent ruptures. Therefore, no published data were identified that describe the incidence, prevalence, or timing of silent ruptures that progressed to symptomatic ruptures.

As described above in the summary of the Sharpe and Collis study, none of the women in the cohort studied experienced a progression of silent rupture to symptomatic rupture.

31/ Hölmich, L.R., et al. 2004. Untreated silicone breast implant rupture. *Plast. Reconstr. Surg.* 114:204-14.

d. Please provide the incidence, prevalence, and timing of intracapsular ruptures that progressed to extracapsular ruptures.

2d Response:

In the one study Mentor identified that evaluated the progression of intracapsular ruptures to extracapsular ruptures, it was found that very few (10%) intracapsular ruptures progressed to extracapsular ruptures (Hölmich et al. (2004).^{32/} In this study, the status of both intracapsular ruptures and extracapsular ruptures was monitored by MRI after a period of two years. Details regarding the design of this study are provided above in the response to Deficiency No. 2.b.

Of the 96 implants determined to be ruptured at the first MRI, 77 were intracapsular and 19 were extracapsular. Of the 77 intracapsular ruptures, 69 (90%) showed no change at the second MRI examination. One intracapsular ruptured implant (1%) exhibited increasing distal spread of silicone thought to be extracapsular on MRI, but at explantation, all silicone gel was found to be contained within the capsule. Silicone was seen outside the capsule in the seven remaining implants originally determined to be intracapsular ruptures (9%), and in five of the new extracapsular ruptures, the amount of gel outside the capsule was considered to be "minor." Three of the seven women whose ruptures progressed to extracapsular reported trauma to the affected breast between the first and second MRI examinations, and one had undergone mammography.

Sixteen of the 19 (84%) extracapsular ruptures identified at the first MRI examination remained stationary; effusion of extracapsular silicone increased marginally in one implant in one woman and significantly in two implants in another woman; with neither woman reporting trauma.

The results of this study indicate that, for at least a period of two years, the vast majority (greater than 90%) of intracapsular ruptures do not progress to extracapsular ruptures. For those ruptures (intracapsular and extracapsular) that do progress, the extent of gel migration is minor, and the migration could be attributed to trauma or mammography in almost half of the cases. While this study does provide information on the incidence, prevalence, and progression of silicone gel-filled breast implant ruptures left *in situ* in this particular cohort, it cannot be used to determine the timing of the progression, because the MRI examinations were snapshots in time taken two years apart. Therefore, it is not known, except in the cases of trauma or mammography, more precisely when the progression occurred.

32/ Hölmich, L.R., et al. 2004. Untreated silicone breast implant rupture. *Plast. Reconstr Surg* 114:204-14.