

Core Study

Although some of the issues below are written specifically for the data set provided in the PMA for the Core Study, we expect that you address these issues in any future updated data set, as per your response to item 1 above. For all of your analyses, it is imperative to provide detailed narratives for each of the different sets of raw data tables to explain how to interpret the data and to explain any apparent discrepancies with other tables. In addition, when updating the tables, please add footnotes to help clarify the data. Lastly, be sure to rectify all discrepancies discussed during informal interactions with you during the review of this PMA, such as use of terminology and denominators consistent with the breast implant guidance document.

4. FDA is unable to interpret the evolution of the diagnosis of potential ruptures in your Core Study. Therefore, please provide the information below regarding all potential ruptures.
 - a. Please provide a chronological history of each suspected implant rupture and for ruptures that were not necessarily suspected but detected via examination at explant/replacement. As part of this history, please include the information below.
 - (1) Please indicate why/how rupture was suspected or detected (e.g., automobile accident, flattening of implant on examination, indeterminate for rupture on MRI screening examination, indeterminate for extracapsular silicone on MRI reading, abnormal mammogram, intracapsular silicone noted at replacement for severe capsular contracture, etc.). In addition, please provide the results of follow-up test(s) performed to determine rupture status.
 - (2) Please provide both a summary and the actual reports (including dates) for all test(s) performed regarding suspected ruptures and detected ruptures. Actual reports include:
 - all radiology reports and readings by both the Local and Central MRI Readers;
 - copies of the “MRI Silicone Breast Implant Evaluation Data Sheet” case report form;
 - all surgical operative notes for patients undergoing explantation (regardless of replacement) due to suspected rupture or with rupture noted at explant; and
 - all ultrasound/mammographic reports if related to a suspected rupture.

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- (3) **Please include indication, implant type, placement (i.e., submuscular or subglandular), as well as any local complications reported for each implant/patient.**

4a Response:

Breast histories have been provided for each patient for whom rupture was suspected and reported in the PMA. Additionally, the history of any new patient for whom rupture was suspected subsequent to the original PMA submission is included.

Rupture was defined as follows:

The following hierarchy (in descending order) was used to determine whether or not a rupture (including “silent” ruptures) occurred. Specifically, the first available of these listed determinations was used. Determination based on visual examination of the device by Mentor was used whenever available.

1. Determination based on visual examination by Mentor following explantation of the implant.
2. Determination based on physical examination by surgeon following explantation of the implant, as indicated on Adverse Event Case Report Form. Implementation of this aspect of the hierarchy was predicated on the assumption that, upon examination of an explanted device, the surgeon would, if needed, update the AE CRF. Specifically, (1) if a rupture was newly identified upon examination, the rupture would be recorded and (2) if an implant which had been previously recorded as ruptured was determined, upon examination, to be intact, the previously recorded rupture would be deleted.
3. Determination based on MRI findings without explantation of the implant, as indicated on Adverse Event Case Report Form. The MRI finding was given precedence over the surgeon’s finding (4 below) without explantation, unless the surgeon had a finding of rupture in a year subsequent to the (last) MRI. A device was considered to be ruptured if either the local radiologist or the Central MRI reviewer indicated any of the following:
 - evidence of rupture;
 - evidence of extracapsular silicone;
 - indeterminate for rupture; or
 - indeterminate for extracapsular silicone.

Subsequently, a suspected rupture was considered to not be ruptured, if a follow up MRI was read by both the local radiologist and the Central Reviewer as not being ruptured, or if upon explant, the device was found not to be ruptured.

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4. Determination based on the surgeon's findings without explanation of the implant, as indicated on Adverse Event Case Report Form. The MRI finding (3 above) was given precedence over the surgeon's finding without explanation unless the surgeon has a finding of rupture in a year subsequent to the (last) MRI.

Complete histories can be found in Attachment 18 and contain the following: chronological histories of the patient's breast implant surgeries, type of implant and placement, why rupture was suspected, method of determination of rupture status, and local and central radiologist evaluations. Hardcopies of all MRI evaluation forms and any available operative or imaging reports have been included. Copies of adverse event forms which document any local health complication have been included as well.

The table below provides a summary of these findings. As shown in this table, there were two implants that were confirmed as ruptured upon explant, and six suspected ruptures. Hence, there are a total of eight devices (six patients) with ruptured implants as defined above.

As discussed in Section 5.4.7 in the attached 3-Year Core Gel Clinical Update, Cox Regression analyses show no correlation between rupture and any operative variable (*i.e.*, surgical approach or placement) or implant surface. Moreover, there was no correlation between rupture and local or systemic health consequences.

History for each Patient for who Rupture was Suspected and/or Confirmed

Pt. ID	Patient Information	History (Hx)	Local Reader	Central Reviewer	Final Determination of Rupture Status	Method of Determination	Adverse Events
	Cohort: Revision DOS: Implant Type: textured round gel Placement: subglandular MRI Substudy: YES MRI Scan Dates: Investigator:	Prev ruptured right implant. MRI reported Ruptures	Bilateral ruptures	Bilateral Ruptures	No rupture		
	Cohort: Augmentation DOS: Implant Type: textured round gel Placement: subglandular MRI Substudy: YES MRI Scan Dates: Investigator:	Possible rupture on right per local MRI reader	possible rupture on right	No rupture	No rupture		
	Cohort: Revision DOS: Implant Type: textured round gel Placement: subpectoral MRI Substudy: YES MRI Scan Dates: Investigator:	Previously ruptured implants & silicone granulomas possible extracapsular silicone on right per MRI	indeterminate for extracapsular rupture on right, correlate with hx of previous implants, current implants intact	Indeterminate for extracapsular rupture on right, correlate with hx of previous implants. current implants intact	No rupture		
	Cohort: Revision DOS: Implant Type: textured round gel Placement: subglandular MRI Substudy: YES MRI Scan Dates: Investigator:	Post closed capsulotomy, possible rupture on the left per local MRI reader	rupture on left side	No rupture	No rupture		

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Pt. ID	Patient Information	History (Hx)	Local Reader	Central Reviewer	Final Determination of Rupture Status	Method of Determination	Adverse Events
	<p>Cohort: Reconstruction</p> <p>extured round gel</p> <p>Placement: submuscular</p> <p>MRI Substudy: YES</p> <p>MRI Scan Date</p> <p>Investigator:</p>	<p>possible extracapsular silicone per local MRI reader</p>	<p>Hyperintense spot, possibly extracapsular rupture Motion artifact on scan</p>	<p>No rupture or extracapsular silicone</p>	<p>No rupture or extracapsular silicone</p>		<p>No Adverse Events submitted</p>
	<p>Cohort: Revision</p> <p>DC</p> <p>Imp smooth round gel</p> <p>Placement: subpectoral</p> <p>MRI Substudy: YES</p> <p>MRI Scan Date</p>	<p>Previously ruptured bilateral implants</p>	<p>Small amount of intracapsular silicone, but no evidence of collapse or rupture</p>	<p>"Extra-capsular silicone, most likely residual from previous implants, no evidence of rupture of current implant"</p>	<p>No rupture</p>		<p>Bilateral. Low nipple sensitivity resolved</p>

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- b. **For the MRI readings in which there was a discrepancy between the Local and Central MRI readings, please provide the actual radiology report/MRI readings from both the Local and Central radiologist, as well as a copy of the “MRI Silicone Breast Implant Evaluation Data Sheet” case report form. Please indicate how a final determination was made regarding assigning of rupture status.**

4b Response:

If either the Local or the Central reviewer determined that there was evidence of rupture, evidence of extracapsular silicone, indeterminate for rupture, or indeterminate for extracapsular silicone, then the device was considered to be ruptured. If a follow up MRI was read by both the local radiologist and the Central Reviewer as not being ruptured, or if upon explant, the device was found not to be ruptured, then the device was not counted as ruptured. Please note that this definition differs from the one employed in the original PMA submission.

The local radiologist’s interpretation was reported on a dictated MRI report; however the local radiologists were not required to complete MRI Evaluation forms. Subsequent to the receipt of this deficiency letter, Mentor completed MRI Evaluation Forms using information from these dictated reports for patients for whom the local and central reviewers did not agree on the rupture status. The Local readers’ evaluations are included in the revised MRI Table 13.2 in the attached 3-Year Core Gel Clinical Study Update provided in this response in Attachment 1.

Copies of all MRI evaluation forms and imaging reports have been included in Attachment 18 separated by patient.

- c. **Please provide Kaplan-Meier silent rupture rates over time for each indication separately and for the combined patients overall on both a by-implant and a by-patient basis. In these tables, please define a silent rupture as occurring if either the Local radiologist or the Central MRI reader indicated any of the following:**
- (1) **evidence of rupture;**
 - (2) **evidence of extracapsular silicone;**
 - (3) **indeterminate for rupture; or**
 - (4) **indeterminate for extracapsular silicone.**

4c Response:

Kaplan-Meier silent rupture rates over time for each indication separately and for the combined patients overall on both a by-implant and a by-patient basis are provided in Tables 13.2.1, and 13.2.2 in Attachment 19. The tables include a silent rupture using the criteria delineated in 1-4 above, whether noted by the local radiologist, the Central MRI reviewer or both. Using this definition of silent rupture, there were eight patients and ten implants with suspected ruptures.

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- d. **Please provide Kaplan-Meier silent rupture rates over time for each indication separately and for the combined patients overall on both a by-implant and a by-patient basis as in item 4c above. However, please modify the definition of silent rupture from 4c above to exclude implants in which explantation was performed and the implant was determined to be intact.**

4d Response:

Kaplan-Meier silent rupture rates over time for each indication separately and for the combined patients overall on both a by-implant and a by-patient basis are provided in Tables 13.2.3, and 13.2.4 in Attachment 19. These rates exclude those patients and devices that were subsequently explanted and determined to be intact as well as implants determined to be intact based on exploratory surgery. As detailed below, excluding devices that were determined to be intact upon exploration or explantation, there are six patients and eight devices with confirmed or suspected ruptures, as defined above.

Indication	Patient (n)	Implant (n)
Augmentation	1	1
Reconstruction	1	1
Revision	4	6
Overall	6	8

- e. **Please provide Kaplan-Meier rupture or silent rupture rates over time for each indication separately and for the combined patients overall on both a by-implant and a by-patient basis. Rupture or silent rupture includes all ruptures noted at explant/removal and silent ruptures defined in item 4c above.**

4e Response:

Kaplan-Meier rupture or silent rupture rates for each indication separately and combined overall on both a by-implant and a by-patient basis are provided in Tables 13.2.5, and 13.2.6 in Attachment 19. Please note that, as all patients with suspected or confirmed ruptures are in the MRI substudy, the overall Kaplan-Meier rupture rate and Kaplan-Meier silent rupture rate are the same: 0.7% by-patient and 0.5% by-implant.

- f. **Please indicate whether the data in Table 13.1 regarding Implant Evaluation and Type of Rupture pertain to the Central reader or to the Local reader.**

4f Response:

Table 13.1 in the attached 3-Year Core Gel Clinical Study Update includes data from both the Central and Local readers.

- g. **There are discrepancies in the numbers reported in Section 3.2, “Core Study Clinical Data Report” (Volume 1) and Table 13.1 (Volume 3) regarding implant**

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rupture that need to be rectified. For example, there were no reports of evidence of definitive rupture based on the Central Reviewer, 7 scans with possible rupture according to the Local radiologist, with 2 of these read as indeterminate for rupture by the Central reader stated in Section 3.2. Table 13.1, however, under “Implant Evaluation” indicates 3 indeterminate MRIs (1 in an augmentation implants and 2 in revision implants), as well as 9 missing readings (3 in augmentation, 4 in reconstruction, and 2 in revision implants). Table 13.1 under “Type of Rupture” indicates 2 revision implants with intracapsular rupture, no implants with extracapsular rupture, and 751 overall implants with missing data. Please rectify these discrepancies.

4g Response:

In the narrative portion of the PMA submission (section 3.2), MRIs scans were classified as “indeterminate” if the Central Reviewer interpreted the scan to be “indeterminate.” In Table 13.1, only MRI reports prepared by the Central Reviewer were presented. This variability in reporting resulted in an apparent discrepancy in data reported in the narrative compared with the tables. In the updated 3-year Core Gel clinical report submitted as Attachment 1, we have used FDA’s defining criteria for rupture; and consequently the data in the narrative and the tables are the same.

Table 13.1 is correct in stating that there are 3 indeterminate MRIs (1 augmentation and 2 revision). There are 3 implants and 2 patients; therefore, the number of patients (2) is the same in Section 3.2 and Table 13.1. The information presented in section 3.2 is by patient and not by breast. The information presented in Table 13.1 is both by patient and by breast.

Table 13.1 is correct in stating that there are 9 missing readings (3 Augmentation, 4 Reconstruction and 2 Revision). There are 5 patients and 9 implants. In Section 3.2 we presented a summary of the MRI data and did not include all the detail, i.e., missing data and intracapsular rupture, presented in Table 13.1. The “type of rupture” data labeled as “missing” in Table 13.1 is a result of a programming error and has been corrected.

It has been confirmed that the reported extracapsular silicone was from previously ruptured implants and the current implants in these patients are intact, with the exception of two patients. See table above in Response 4a for details on these patients.

In section 3.2, Mentor reported those patients on whom the Local and Central reviewers were not in agreement as “Indeterminate for rupture”. At this time, most of the patients in this category have been confirmed as having intact implants as determined by either explant or repeat MRI scans.

- h. There are discrepancies in the numbers reported in Section 3.2, “Core Study Clinical Data Report” (Volume 1) and Table 13.1 (Volume 3) regarding extracapsular silicone which need to be rectified. For example, in Section 3.2, “Core Study Clinical Data**

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Report” (Volume 1), you indicated that there were 3 implants that were indeterminate for extracapsular gel (the source for these readings was not provided), with only 1 of these—in a reconstruction patient—was felt to be indeterminate for free silicone by the Central reviewer. However, Table 13.1 under “Soft Tissue Evaluation” indicates 1 reconstruction and 3 revision implants that are indeterminate for extracapsular silicone, 1 revision implant which is definite for extracapsular silicone, and 9 overall implants with missing data. Please rectify these discrepancies. In addition, please provide the source for the indeterminate readings.

4h Response:

The information in Table 13.1 was prepared from the forms completed by the Central reviewer only. At this time, most of the patients in this category have been confirmed as having intact implants as determined by either explant or repeat MRI scans. The discrepancies noted above have been corrected in the updated 3-year Core Gel Clinical Report in Attachment 1.

As reported in Table 13.1, any indeterminate reading could be based on either the Central or Local Reviewer’s assessment of the MRI scan.