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August 6, 2003

Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center, HFZ-410
9200 Corporate Blvd.
Rockville, MD 20850

RE: Amendment to PMA M020018/M1 Mentor Gel-Filled Mammary Prosthesis
Biocompatibility Module: Response to FDA Deficiency Letter dated March 11,
2003

Mentor Corporation is submitting an amendment to the above-referenced PMA module in order to respond to FDA's letter dated March 11, 2003. Our response is attached.

We consider the existence of this submission and its contents to be confidential and exempt from public disclosure.

If additional information is needed, please contact Donna Crawford at (805) 879-6304.

Sincerely,

A handwritten signature in cursive script that reads "Donna Free".

Donna Free
Vice President, Regulatory Submissions

2005-4101B1-01-D2-RESPONSE+MENTOR

**GEL-FILLED MAMMARY PROSTHESIS PMA
2/13/03 DEFICIENCY LETTER RESPONSE**

- 1. We have not reviewed any information directly from a master access file (MAF). For any of the outstanding toxicology tests referred to in the deficiencies below, please identify the MAF number, a letter of access to the MAF, and the exact location (e.g., volume, section, page) of the testing that you want us to review to address the outstanding issue and support your PMA.**

When possible, Mentor has provided references in Master Access Files (MAFs) by MAF number, Section number and page number (as listed in the MAF Table of Contents) in order to locate referenced testing. Mentor does not have access to the actual MAF documents; therefore, we cannot provide all page numbers for referenced information in the MAF. However, we have enlisted the assistance of SiTech in responding to this request and have provided the references in the appropriate sections.

- 2. The test article used in the immunotoxicity testing on p.1535 and p.1660 was identified only as silicone. The Dow material tested is not the finished sterilized device, nor even the material currently used in the device. The device tested is an early progenitor of the current gel and vendors have been changed more than once (refer to pp.138-139). Therefore, please provide the immunotoxicity testing on the current gel. More recent testing by -----, the source of the current gel, would be acceptable if you provide a letter of access to the appropriate ----- MAF and the exact location of the testing in the MAF. In addition, please provide an explanation the relationship of the test material in the MAF to the current device.**

*The imm-----Silicone Gel that was obtained from
----- @----- Mentor has
----- ed----- (see page 171 of the
Mentor PMA Module 1) which specifies that their gel from implants is " ...designated
----- combined in a ---
ratio..".*

*The gel components -----
testing are the same components that Mentor used when utilizing -----
Mentor later changed from ----- componen-----
----- sim-----nd the same----- ratio
as ----- .*

*As ----- gels are not substantially different, immunotoxicity
test----- of necessary. The rationale for this equivalency in gels
is based upon----- lowing:*

1. Clo----- as evidenced by the direct comparison of ----- (per FDA's 1993 Guidance for Ma----- Silastic Materials) in ----- Sections 1 through 26--
2. Both gels have been used in Mentor's gel-filled mammary assembly process without significant changes to the process. They "behaved" as the same material.
3. Devices made with both silicone gels retain the same physical testing properties. This comparison will be found in the Mechanical Testing Module of Mentor's Gel-filled Mammary Prosthesis PMA submission (to be submitted this fall).
4. Devices made with ----- silicone gels contain chemical extractables that are not substantially different, including the extractables from just the gel of sterile finished devices. Mentor has performed -----d device extractables testing on ----- using the current ----- gel, and compared them to the ----- gel. All the data are provided in Mentor's Chemical Te-----PMA (see Section 5.10, pages 64 to 99). A copy of this section is included in Attachment 1.
5. The chemical tests and toxicity risk analysis show that the types of extractable compounds are equivalent between ----- and that even though the amounts of individual compounds may vary, the extractables in any of the gels do not affect the safety or efficacy of the device. The safety determination is based upon the toxicological risk analysis of ----- gel presented in Mentor's Chemical Testing Module of this PMA (see Section 6.0, pages 101 to 111), and the successful long term biological testing of the ----- Corning gel (see pages 169 to 179 of the Biological Module of this PMA). Copies of the toxicological risk analysis (Section 6) as well as the Summary and Conclusion Section (Section 7.0) are included in Attachment 1.

The efficacy determination is based u-----ng which demonstrated that the devices made from ----- materials continued to exceed the finished product -- ----- ation will be provided in the Mechanical Testing Module of Mentor's Gel-filled Mammary Prosthesis PMA submission.

Additionally, Mentor utilized----- in 1996 through 1998 prior to utilizing ----- Long-term biological testing was successfully completed on ----- The----- exhibited the highest levels of low ----- pecially D₄, D₅, and D₆) of any gel Mentor has used. This further substantiates the safety of the ----- gel. Please see Appendix 2 for ----- access letter, and which can also be found in

Mentor's Low Bleed gel-filled Mammary Prosthesis PMA Amendment P910037/A035, Volume I, page 5, submitted September 20, 1996.

*The above information shows the relationship of the current -----
----- tested for immunotoxicity. Mentor believes that the currently used-----
gel is not substantially different from the -----, therefore no additional
immunotoxicity testing is warranted.*

In addition, please provide an explanation the relationship of the test material in the MAF to the current device.

Please see our response to item 5 for further explanation of the relationship of the test material in the----- to the current device.

- 3. The carcinogenicity testing beginning on p.2006 used ----- with identification numbers different from those in the immunotoxicity testing ----
----- Please explain the relationship between the materials tested-----
----- and relate all of these materials to the current gel and low-bleed shell. Please provide a summary of the methodology and summary tables of the results. The testing beginning on p.2354 uses increasing doses of both the control and test article -----; however, the critical summary tables seem to be missing.**

*We assume that the ----- reference in the question above was meant to read ---
-----*

The carcinogenicity testing beginning on page 2006 (Vol. 8) indicates that one of the study materials was----- . In Mentor's PMA on page 173, there is a summary of this study from the----- of 1991 in which there are several references to ----- in the two tables. ----- is the same ----- gel that was tested in the immunotoxicity testing referenced in item 2 above.

Since the time that Mentor used ----- silicone gel, Mentor has performed finished device extractables testing. The data show that the current gel is not substantially different from the----- gel used originally (see Response 2 above for a more detailed explanation of Mentor's gel equivalency conclusion). This information shows the relationship of the current gel to the gel tested for carcinogenicity.

*The methodology summary and summary tables for the results of study Report Reference 152-----
-----beginning on Vol. 8, page 2006) is provided in the Appendices of the Biological Module of this PMA - see Vol. 8, pages 2006 - 2104. The Materials and Methods section can be found in Vol. 8, pages 2010 - 2016 and the summary tables of the results can be found in Vol. 8, pages 2027 - 2104.*

See Appendix 3 of this deficiency response for the requested testing "...critical summary tables..." related to the----- carcinogenicity testing.

- 4. We are concerned that some MAF materials have been revised and are too remote from your current final, sterilized device to be representative of your device. Therefore, additional data are necessary to more completely address carcinogenicity. You have already provided the results of your bacterial mutagenesis and chromosome aberration assays. Please provide the results of a mouse lymphoma test and in vivo micronucleus assay. If the results of these two additional tests are negative and your response to the carcinogenicity deficiency above is satisfactory, we will not require a repeat of the 2-year carcinogenicity testing.

Mentor completed the mouse lymphoma test and the in vivo micronucleus assay. The results of these tests are acceptable. Please refer to Appendix 4 for the test reports.

Mentor believes that the current device materials and the device materials tested for carcinogenicity are not substantially different; and as a result, all previous carcinogenicity testing performed is applicable.

- 5. The letter from ----- on p.187 (Vol. 2) listed device component numbers as "product" and "biological testing formulation." The purpose appears to be to establish equivalence between the materials tested in the----- and the corresponding materia -----our device. The testing formulation is said to be "representative of the----- product referenced in the compendium." Please clarify whether the d-----nd biological testing formulations are identical, including the relationship between----- If they are not identical, please explain the differences and provide data demonstrating the chemical similarities and differences. In addition, please provide a letter of access to the appropriat----- and the exact location of the testing in the MAF(s) that you want us to review as part of your response.

*----- desi-----its----- material, while-----
----- the ----- m-----al on which biological testing was
performed. In addition, pleas----- ndix 5 for a letter from----- explaining the
-----ical testing formulations for -----
-----*

*----- has informed us of the following: MAF number, Volume and page references
-----the biological testing can be found as well as the MAF number, Volume and
page references (which is the same as the device) where the formulations for each
material can be found.*

<i>Material</i>	<i>Biological Testing Formulation</i>	<i>MAF Formulation</i>
-----	----- ----- last page of "Summary"	Manufacturing Portion, ----- "Original," pg. 22
-----	----- -----, last page of "Summary"	Manufacturing Portion ----- Vol.2, pg. 22
-----	----- last page of "Summary"	Manufacturing Portion, ----- "Original," pg. 23
-----	----- last page of "Summary"	Manufacturing Portion, ----- "Original," pg. 23

A letter of access to ----- (elstomer) was provided in the original Biological Module of the PMA submission. The letter can be found in Vol. 2, p. 186 of the of the PMA Module submission. We have also included a copy of this letter in Appendix 6 for ease of review. As indicated in the table above, Mentor has provided references in Master Access Files (MAFs) by MAF number, Volume, and page number in order to locate the referenced testing. Our response to Question 6 specifies the location of other ----- access letters in a prior gel-filled mammary prosthesis PMA submission.

6. The chart on p.9 referred to the ----- for the testing of -----
----- For the ----- and the corresponding dispersions and crosslinkers, you then referred to -----
----- You provided a letter of access from ----- Please provide a letter of access from ----- for the other two MAFs and the exact location of the material information in the MAFs that you want us to review as part of your response.

Mentor has provided the letters of access for ----- Both letters were submitted in Mentor's Gel-filled Mammary PMA P910037/A49 dated April 9, 1999; Vol. 7; p. 1312 for ----- 1 and p. 1313 for ----- Copies of the letters can be found in Appendix 7 of this submission.

<i>MAF #</i>	<i>Material</i>	<i>Material Equivalence Testing Reference</i>
-----	-----	<i>Testing Compendium,</i> -----
-----	-----	<i>Testing Compendium,</i> -----
-----	-----	<i>Testing Compendium,</i> -----

*There are no page numbers in the Testing Compendium of these MAFs.

7. The reproductive and developmental toxicology presented on p.1999 was conducted on an old----- product and is too far removed from the current device to be considered representative of your device. In addition, it is a 1-generation study, and FDA believes that a 2-generation study is more appropriate. Therefore, please provide a 2-generation reproductive and developmental study using your current gel.

Mentor has proposed an alternate extended one-generation reproductive and teratogenicity study in rats to meet this requirement. The agency has accepted the proposal. A copy of the protocol is attached in Appendix 8. The study results will be submitted upon completion.

8. In cases where the whole textured implant was tested (e.g., tests beginning on p.609 and p.647), FDA is not certain whether the elastomer was ----- or ----- Please identify which materials were used for each test where the whole textured implant was tested.

For the whole textured implant biological testing summarized in Mentor's PMA starting on pages 609 and 647, the ----- was used. A test-by-test identification of the elastomer used is presented below:

WHOLE TEXTURED IMPLANT STUDIES	PMA PAGE #	ELASTOMER
Acute Intracutaneous Reactivity (Siltex Prosthesis)	609	-----
Cytotoxicity (Agarose Overlay) (Siltex Prosthesis)	647	-----
Cytotoxicity (ISO Elution) (Siltex Prosthesis)	677	-----
Acute Systemic Toxicity (Siltex Prosthesis)	711	-----
Material Mediated Pyrogenicity (Siltex Prosthesis)	745	-----
Hemolysis - Direct Contact (Siltex Prosthesis)	777	-----
Hemolysis - Extract Method (Siltex Prosthesis)	819	-----

9. The patches tested for cytotoxicity (p.972 and p.1008) and sensitization (p.1069 and p.1094) were not identified. In your email dated December 17, 2002, you stated that this information was provided on pp.967-970 or on pp.1044-1048. However, those pages did not clarify the issue. Therefore, please identify the patches as smooth or textured and describe any other unique characteristic features. In addition, in your December email, you stated that the smooth and textured patches are both made from ----- silicone; however, p.9 indicates that the textured layer patch is different from the smooth patch. Please rectify this discrepancy.

There were 7 ----- patches utilized for the biological testing; 6 smooth patches (2 of -----104346-001 and 4 of part number 10436-009) and 1 textured patch (part number 104417- 001). Please see Appendix 9 of this submission for the patch drawings. The patches tested for sensitization (p.1069 and p.1094) were both smooth patches (part #s 104346-001 and 104346-009). The location of this information can be found on the 4th page of report HS33.020227.02, next to "Identification No." in the Materials section. As you indicated, the patches tested for cytotoxicity (p.972 and p.1008) were not identified on the test summary. The report (HS33.020227.02) noted that the textured patch (part number 104417-001) was utilized for cytotoxicity testing. The other tests utilized smooth patches (part number 104346-001 and 104346-009).

The on-----ed patches is that the textured patch ----- of silico----- as these ----- mate-----rchang----- hat testin----- f the ----- patches provides adequate biologic----- because the materia----- e patches are equivalent and the ----- process is the same for both patches.

10. For the cytotoxicity (p.647, p.662, p.677, and p.694), cutaneous reactivity (p.609 and p.628), a----- temic toxicity (p.77 and p.728), and hemocompatibility testing of the -----smooth and textured implants, the testing indicates the number of squ-----timeters tested. We assume this represents testing of the shell only, but some of the protocols state it represents the complete device. If this testing represents more than just the shell, please provide statements from the contract testing laboratory describing how the samples were prepared, exactly how the gel, patches, and other components of the device were represented in the samples tested, and describe the meaning of the area tested, as provided in the report.

For each test under evaluation, the entire intact sterile finished device, as would contact the patient, was tested. As testing was performed on 100cc devices (nominal gel fill), the "portion" of device tested represents the approximate surface area of the entire device. The contract laboratory's use of the term "portion" relating to area for

testing purposes, is a misnomer in that the entire intact device was tested, not just a portion of the device. As a result, all of the above mentioned tests involved the extraction of a complete device with a complete shell, patch, and other components. Verification of Mentor's instructions to extract the entire device for the above mentioned tests can be found on pages 619, 638, 655, 670, 686, 703, and 737 of the Biological Module of this PMA.

- 11. The patch, dispersion coating, and patch fill reinforcement, each, represent a very small fraction of the weight of the gel prosthesis but are in direct contact with the patient. When testing the complete device, the gel is so heavy that it overwhelms the weights of these minor components. The minor components should be tested separately (i.e., without the gel) to provide a better test of their safety because these items make direct contact with the body. Testing alone or with the shell is also acceptable. Therefore, please provide cytotoxicity, irritation, and sensitization testing to address this issue.**

In the original Biological Module of this PMA submission, Mentor provided biological testing data on these components (patch, dispersion coating, and patch fill reinforcement) and materials in a form that is essentially the same as these components:

- 1. Patches were tested as device components in Section VI, Biological Testing of Finished Devices or Components From Finished Devices of the PMA (pp. 125 - 127 and 967 - 1118)*
- 2. The patch fill reinforcement is a round approximately 3/8 inch diameter piece of ----- silicone material. That same silicone sheeting material makes up the ----- and -----; therefore, cytotoxicity, irritation, and sensitization testing of the patch and textured shell adequately ensure that the patch fill reinforcement will also pass these tests.*
- 3. ----- was tested in the Low Bleed Gel-filled Mammary Prosthesis Raw Materials Testing section (pp. 92 - 95 and 242 - 278)*

Testing of the components mentioned above can be found in the following locations of Mentor's October 2002 Gel-filled PMA Biological Module:

TESTING	FORM TESTED	PAGE LOCATION IN PMA
Patches (without gel):	----- silicone elastomer sheeting	
Cytotoxicity		125 & 972
Irritation (intracutaneous reactivity)		125, 988, 1025, & 1049
Sensitization		127 & 1069
Patch fill reinforcement (without gel):	----- -----	
Cytotoxicity		(tested above as "Patches")
Irritation (intracutaneous reactivity)		(tested above as "Patches")
-----		(tested above as "Patches")
----- -without gel):	Cured slab of coating**	
Cytotoxicity		93 & 242
Irritation (intracutaneous reactivity)		94 & 278
Sensitization		93 & 259

* - same silicone elastomer sheeting as used for -----
(see patch biological testing)

** the amount tested in this form far exceeds the few cured drops used for the device

- 12. For several of the intracutaneous tests, only male rabbits were used (e.g., p.609, p.628, p.711, p.728). Please provide a rationale for using only male rabbits to test the safety of a device to be used exclusively in females.**

These tests are designed to evaluate local responses to test extracts injected intracutaneously into rabbits. In accordance with ISO 10993-10 Tests for Irritation and Sensitization, §5.2.3, "Healthy young adult albino rabbits of either sex from a single strain...shall be used." The protocol used by NAMSA for this testing is a standard GLP protocol for the assessment of intracutaneous irritation, and is not specific to Mammary Implants. For the purposes of this test, male rabbits generally have better skin than female rabbits. Male rabbits tend to have less dermal blemishing, and have less sensitivity to the clipping of the fur, which could result in a false positive reading if female rabbits were used. For this reason males are preferred, whereas for other in vivo testing no particular gender is prescribed for the test. The same results would be obtained regardless of the sex of rabbit used for the studies. This practice does not deviate from the recommendations of ISO 10993-10 nor FDA's "Guidance for Saline, Silicone Gel, and Alternative Breast Implants" document.

- 13. Please provide a revised Summary of Safety and Effectiveness Data (SSED) that updates the toxicology section to reflect the applicable responses to the deficiencies above.**

A revised Summary of Safety and Effectiveness Data (SSED) is provided in Appendix 10.

APPENDIX 1 (response #2)

(Summary of Mentor's Chemical Testing)

APPENDIX 2 (response #2)

(Copy of ----- access letter)

APPENDIX 3 (response #3)

(----- critical
tables.)

APPENDIX 4 (response #4)

(Mouse lymphoma and in-vivo micronucleus assay data)

APPENDIX 5 (response #5)

----- letter explaining the elastomer samples tested.)

APPENDIX 6 (response #5)

A letter of access to----- elastomer)

APPENDIX 7 (response #6)

(Copies of ----- access letters.)

APPENDIX 8 (response #7)

----- F-1 extension reproductive and teratogenicity protocol)

APPENDIX 9 (response #9)

(Drawings for smooth and textured patch, 104346 and 104417)

APPENDIX 10 (response #13)

(Revised Summary of Safety and Effectiveness Data)