5.10 Chemical Characterization Comparison Between Devices Covered by This Submission and Devices Previously Manufactured by Mentor Corporation

Mentor has been manufacturing Low-Bleed Gel-filled Mammary Prostheses since 1985, using silicone raw materials from several vendors. During this time period, one of the largest silicone material vendors (the Dow Corning Corporation) ceased to make their materials available to manufacturers of long-term implantable medical devices, including mammary prostheses.

Consistent with guidance issued by the U.S. FDA regarding replacement of silicone raw material vendors, whenever Mentor incorporated silicone raw materials from a new vendor, extensive comparative raw material testing was performed by those vendors to demonstrate equivalency with the withdrawn products. This testing was carried out in accordance with FDA's "Guidance for Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials" (July 6, 1993). Such testing included chemical analyses, mechanical testing and short-term biological testing. The results of such testing are included in the vendor's Master Access Files for their materials.

In addition, Mentor itself performed sterile finished product testing using the new vendor materials and compared that chemical data (as well as mechanical data, device manufacturing process information, and short-term biological test results) to previous data from Mentor Gel-filled devices (made with the prior vendor's silicone materials). In particular, Mentor qualified the use of SiTech gel and SiTech shell elastomers in a series of tests performed in 1999 and, previous to that, the use of Applied Silicone Corporation (ASC) gel as a replacement for Dow Corning gel in 1996. All of these qualification tests included a comparison to Dow Corning gel data.

The results of such testing on the raw materials and the finished device mammary prosthesis have demonstrated substantial equivalence per FDA's "Guidance for Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials,"

In addition to ensuring comparable performance characteristics of the finished sterilized devices, one of the primary purposes of such testing was to also ensure the direct applicability of long-term testing, *i.e.*, chronic toxicity/carcinogenicity, immunotoxicity and reproductive/developmental toxicity, conducted on devices that included previous vendor materials.

The substantial equivalence demonstrated by such testing allows direct application to Mentor's current devices of biological compatibility and toxicological data from Dow Corning and ASC silicone gels and on shells produced from Polymer

Technology Corporation (PTC) that had previously been used in the manufacture of Mentor silicone gel-filled mammary prostheses.

In Section 5.0 (Chemical Analysis) extensive chemical characterization of the current Mentor Low-Bleed Gel-filled Mammary Prostheses based upon SiTech LLC raw materials was presented. This section provides comparable data for Mentor devices that included silicone materials from previous vendors. Test methods validation and testing procedures are described in the original reports and, with one exception, have not substantially changed over the years. The one exception that will be described is the change in the method for determining semivolatiles in extracts, because it was upgraded with new, more sensitive GC/MS equipment and included the addition of standards that allowed for a more accurate silicone compound quantification.

It is important to note that the technology for making the two parts (Parts A and B) which comprise each of the shell silicone dispersions (dimethyl dispersion and dimethyl/---------- dispersion) was transferred from Polymer Technology Corporation to SiTech to ensure the equivalence of the dispersions and final shell characteristics. This means that the processes for producing the intermediates and the specifications for and characteristics of those intermediates (molecular weight, viscosity, etc.) are very similar and that the precise combination of those intermediates into the final formulation is similar.

Comparisons of SiTech, Dow Corning, and ASC gels followed by comparison of SiTech and PTC shells are presented in the following section using the results of the same standard comprehensive chemical testing protocols as were used to characterize the current product. These tests include:

- Volatile content
- Extractable content
- Semivolatile content
- Nonvolatile content
- Extent of crosslinking
- Heavy metal content
- Infrared Spectral Analysis

5.10.1 Volatiles Analysis

5.10.1.1 SiTech, Dow Corning and ASC Gels

The objective of this section is to compare the volatile analysis results of Dow Corning, SiTech gels, and ASC gels. The analysis was performed as described in Section 5.1 above. The results[1] are presented in Table 5-17.

The results demonstrate that the concentration of volatile components of the SiTech gel are lower than the Dow Corning gel. Most of the material that makes up the volatile content of the gels consists of the cyclic siloxanes D_3 – D_5. The ASC gel contained a higher total volatiles amount compared to the other two gels, however, the volatile compounds extracted were similar to the other devices.

Table 5–17. Volatile Analysis of Dow Corning, SiTech, and ASC Gel

Material	**Dow Corning**	**SiTech**	**ASC**
Report No./Sample ID	CP 276/57535	CP 358/251121	CP 293/169392
Compound	ug/g		
Cyclic Dimethyl Siloxanes			
D_3	0.7	0.18	72.3
D_4	0.81	0.49	302.0
D_5	47.7	1.60	266.5
Miscellaneous Silicon-Containing Compounds			
Methoxytrimethylsilane	0.02	ND	0.11
Dimethoxydimethylsilane	0.02	NA	0.04
MM	ND	ND	ND
MDM	ND	ND	1.35
MD2M	ND	ND	1.62
Vinylheptamethylcyclotetra-siloxane	ND	ND	3.76
Branched Alkane+Siloxane	ND	ND	0.07
Miscellaneous Solvent Residues and Others			
Methyl Butanoate	ND	0.09	ND
Methylene Chloride	0.1	ND	0.36
Xylenes	NA	<0.09	0.52
Nonane	ND	ND	0.13
Decane	ND	ND	0.31
Undecane	1.17	<0.34	0.85
Dodecane	1.85	NA	0.76
Total Volatiles	52.4	2.8	651.3

[1] Grace H. Chiang, Report Number CP 293, ***Volatile Extractables Analysis of Gel Mammary Prosthesis: SiTech Raw Material Vendor Qualification***, November 23, 1999.

5.10.1.2 Comparison of Shells from PTC and SiTech Dispersion

The purpose of this section is to compare the volatile content of shells made from raw materials from PTC to that of shells made from SiTech raw materials.[2] The results of analysis of textured, non-gelled shell assemblies from PTC and SiTech are presented in the following table.

Table 5-18. Extractable Volatile Compounds from PTC Shells versus SiTech Shells

Material	NuSil/PTC	SiTech/SiTech
Report No./Sample ID	CP 276/175261	CP 358/251121
Compound	µg/g	
Cyclic Dimethyl Siloxanes		
D3	NA	NA
D4	9.3	<0.06
D5	ND	0.28
Miscellaneous Silicon-Containing Compounds		
Methoxytrimethylsilane[2]	2.0	3.13
Methyltriethoxysilane	ND	0.04
Miscellaneous Solvent Residues and Others		
Acetone	ND	1.02
Isopropanol*[1]	ND	<1.06
2-Pentanone	ND	0.05
Methyl Butanoate	ND	0.04
4-Methyl-3-penten-2-one	ND	0.07
Xylenes**[1]	ND	0.06
Decane[1]	ND	0.09
Benzaldeyde[3]	ND	0.04
Undecane[1]	0.67	1.39
Acetophenone[3]	ND	0.03
Dodecane[1]	1.1	3.00
Total Volatiles	13.07	10.36

The results show that the total volatiles, 13.1 µg/g for PTC and 10.4 µg/g for SiTech non-gelled shells, are substantially equivalent.

[2] Grace H. Chiang, Report Number CP 293, ***Volatile Extractables Analysis of Gel Mammary Implant: SiTech Raw Material Vendor Qualification***, November 23, 1999.

5.10.2 Extractable Content

5.10.2.1 Total Extractables Comparison of Dow Corning, SiTech, and ASC Gel

The objective of this section is to present and compare the results of extractable content testing on Dow Corning, SiTech, and ASC Gel filler material. Extractable testing of SiTech gel was reported in Section 5.2 of this module, but is also presented here for comparison in Table 5-19. The testing of Dow Corning gel was carried out and reported in 1999.[3]

Table 5–19. Total Extractables from SiTech, Dow Corning, and ASC Gel (Gel From Siltex Gel-filled Device)

Gel Vendor	Dow Corning	SiTech	ASC
Report No./Sample ID	CP275I/ 275004-6	CP 358/251121	CP275I/275007-9
%Total Extractable (Wt Loss)	85	83	81

*Wt loss at Exhaustiveness - When the level of the analyte for the nth successive extraction is less than one-tenth (< 0.1) of the first extraction.
NA - not available

Exhaustive extraction of Dow Corning, SiTech, and ASC gel samples produce substantially equivalent results, from approximately 81% to 85% weight loss. Variability in the range reported is typical for handling and testing samples with the characteristics of silicone gel.

5.10.2.2 Total Extractable Content Comparison of Shells from PTC and SiTech Dispersion

The objective of this section is to present and compare the results of extractable content testing on samples of shells from finished product made from PTC and from SiTech dispersion. The patches and the texture layer on Siltex products are made either from NuSil (MED 4750) or from SiTech (HCE 4750). Extractable testing of SiTech shell material is presented here[4] with that for PTC shell material in Table 5-20. The testing of PTC materials was carried out and reported in 1999.[5]

[3] C. S. Puckett, Report Number CP 290, ***Total Extractables Analysis of Gel-Filled Mammary Prostheses: SiTech Raw Material Vendor Qualification***, December 2, 1999.
[4] Grace H. Chiang, Report Number CP 357, ***Total and Semivolatile Extractables Analyses of Gel Mammary Implants: Qualification of Manufacturing Process Modifications***, January 16, 2003.
[5] C. S. Puckett, Report Number CP 290, ***Total Extractables Analysis of Gel-Filled Mammary Prostheses: SiTech Raw Material Vendor Qualification***, December 2, 1999.

Table 5–20. Comparison of Total Extractable Results from Shell Assemblies Made with Materials from Different Vendors

	Device Siltex Shell			**Non-gelled Siltex Shell**		
Material Vendor (Report #)	NuSil/ PTC* (CP275)	NuSil/ SiTech** (CP290)	SiTech/ SiTech*** (CP357)	NuSil/ PTC* (CP275)	NuSil/ SiTech** (CP290)	SiTech/ SiTech*** (CP357)
% Total Extractables	14.34	12.52	10.43	1.42	1.66	1.86

* - NuSil/PTC = NuSil 4750 sheeting with PTC shell
** - NuSil SiTech = NuSil 4750 sheeting with SiTech shell
*** - SiTech/SiTech = SiTech 4750 sheeting with SiTech shell

The data in the chart demonstrates that the total extractable content is not substantially different for non-gelled shells made from PTC and SiTech raw materials. The total ranges from 1.42% to 1.86%. It is also evident that the results are not influenced by use of NuSil or SiTech 4750 material for the textured sheeting.

For shells from finished product, the extractable content ranged from 10.43% to 14.34%. The source of the larger extractable amount and greater variability compared to non-gelled shells are the result of exposure to gel and diffusion of some of the gel into the shell, as well as the variability in sample preparation in removal of gel from the surface of the shell.

The results demonstrate that shells made from PTC elastomer and those made from SiTech elastomer are not substantially different. The results also demonstrate that there is no substantial difference between shells with a textured layer made from NuSil material and shells with a textured layer from SiTech material.

5.10.3 Semivolatile Content of Extractables

Semivolatile analysis involves the determination of the concentration of compounds with molecular weights of up to 1500 Daltons in the solvent extractables from a sample (gel filler or shell). Due to the potential concern of the FDA related to lower molecular weight siloxanes, and in particular octamethylcyclotetrasiloxane (D_4), Mentor has worked with its vendor, SiTech LLC, over the past two years to reduce this and other homologous compounds in the intermediates for the production of gel-filled implants, with particular emphasis on gel precursors since the gel component comprises the bulk of the implant structure. This reduction is accomplished through stripping under high vacuums of gel polymer raw materials. This process reduces the concentrations of compounds in relation to their vapor pressure. For a homologous series, such as cyclic siloxanes, vapor pressure is inversely proportional to their molecular weight, i.e., the lower the molecular weight, the higher the vapor pressure. This means that the lower the molecular weight the greater will be the reduction in final concentration. Thus, in a thoroughly stripped intermediate, D_4 will have the lowest concentration, D_5 the next highest, D_6 higher than D_5 and so forth as the molecular weight within the cyclic series increases. The same relationship will apply to the homologous linear series: MM, MDM, MD2M, etc.

Siloxane polymers that are the raw materials in the fabrication of gel-filled mammary implants are formed through equilibration reactions from mixtures of endblocker (MM) or modified endblocker ($M^{Vi}M^{Vi}$), cyclic dimethyl siloxanes (D_4, D_5, D_6, etc.) and modified cyclic siloxanes, such as D^{Vi}_4 or [illegible]. These reactions are catalyzed by strong acids or bases. At the completion of the equilibration reaction, the acid is eliminated, thus stabilizing the polymer. This equilibrium mixture contains from 12 to 15 weight percent low molecular compounds, most of which are cyclic compounds. The preponderance of the light materials is D_4. It accounts for about 50 weight percent of the light species formed during equilibration. After the equilibration catalyst is eliminated, these species can be stripped from the mixture under high vacuum and elevated temperature. If the catalyst is not effectively eliminated, low molecular weight compounds will continue to be created with the result that it would be very difficult to maintain a high vacuum and, as these compounds are removed, the molecular weight of the polymer will decrease. The fact that SiTech is able to strip the polymers provided to Mentor to very low levels is proof that the catalyst has been removed and that the polymer is stable and that no light materials, low molecular weight cyclic siloxanes, will be regenerated in the polymer during further processing into an implant.

5.10.3.1 Change in Semivolatiles Method of Analysis

Over the past two years Mentor has significantly enhanced its capabilities for semivolatile extractables analysis by the addition of new gas chromatography/mass specrotrometer (GC/MS) equipment and the use of additional cyclic dimethylsiloxane standards in the analysis method.[6]

The replacement of a Hewlett Packard Model 5890/5971 with an Agilent 6890 plus 5973N resulted in an increase in the capability to detect low level compounds by factors of from 1.5 to 37, depending

[6] Grace H. Chiang, Report Number CP 351, ***Semivolatile Extractables Analysis of Gel Mammary Implant: Comparison of Instruments and Quantitation Methods***, January 14, 2003.

upon the specific compound. The effects of the increased sensitivity are more pronounced for late-eluting (higher molecular weight) compounds. Simply stated, this means that the analysis using this new equipment would include compounds that could not formerly be detected, especially as the molecular weight approaches 1500 Daltons.

The introduction of additional standards of higher cyclic dimethylsiloxanes (D_{15}, D_{18}, and D_{21}) resulted in more accurate quantification for compounds in the range of D_{14}-D_{21}.

The change in standards and GC equipment resulted in a more precise and accurate capability to detect and quantify silicone extractables, especially those with molecular weights closer to 1500 Daltons. The improvements, however, have made the direct comparison of earlier semivolatiles data to current data problematic at times.

A project was undertaken and completed to identify and, where possible, to quantify the differences that resulted from the previous and newer analytical techniques. Report CP 351 documents a comparative study of the two analytical techniques that included changing the GC/MS instrument and adding the additional standards for the quantification of cyclic siloxanes.

The study samples included Mentor Siltex Round Moderate Gel Implants that have been analyzed previously by the original GC/MS instrument and quantified with the use of then-available standard cyclic dimethylsiloxanes (D_3, D_4, D_5, D_6, D_9, and D_{12}). For the comparative study, the same methylene chloride Soxhlet extraction procedure as was used in prior studies was employed.

The extractions were conducted on device components (gel filler and shell assembly) rather than whole devices. Total extractables were determined gravimetrically following the evaporation of methylene chloride. Total extractables of gel samples were the same (78 weight % from Report Number CP 290, July, 1999 vs. 81 weight % from Report Number CP 351, July, 2002) for the old and new analytical methods.

The semivolatiles present in the extracts were analyzed by both the older and newer analytical techniques through direct liquid injection. The component peaks were identified based on their retention indices, and spectra matched against library reference compounds. Quantitative results were obtained using the same internal and external calibration methods with and without the inclusion of the additional standards D_{15}, D_{18}, and D_{21}.

The change of quantitation method affected the results of D_{14}-D_{21}. Previously, the quantitation of these dimethylcyclosiloxanes was based upon the calibration factor of D_{12} as the standard. This resulted in an underestimation of the values for the higher dimethylcyclosiloxanes since the response factor based upon D_{12} provided inaccurately low results for compounds where the number of dimethyl siloxane units significantly exceeded that of D_{12}. As expected, when additional calibrations standards (D_{15}, D_{18}, and D_{21}) were used to quantify D_{14}-D_{16}, D_{17}-D_{19}, and D_{20}-D_{21}, respectively, significant increases in values were observed. Table 5-21 is abstracted from the data presented in Tables II and III of Report CP 351.[7] The old GC equipment utilizing both the old and new calibration standards was used to demonstrate the improved quantification of siloxane compounds. The analyses were conducted at the same time. Figure 5-7 is a plot of the data on gel filler. When using the same GC with the old and new sets of standards the results up through D_{13} match exactly. For D_{14}-D_{17} the values from the two calibration schemes digress. Values from D_{17}-D_{19} decrease but are still above the values for the old calibration scheme. D_{20} and D_{21} for the new calibration standards are at non-detectable levels.

Recall from the analysis of stripping, presented above, that the values for a homologous series should increase in a stripped polymer. We can conclude from this that the new calibration standards more accurately define the cyclic dimethylsiloxane content of the material. However, it appears that the older instrument is not as capable of accurately detecting (sensitivity) species above D_{19} and the sensitivity is decreasing from D_{17} upward. Since the same sample was analyzed utilizing both the original and newer set of standards, the same concentration of the cyclic materials must be present. Since the analysis with the new standards most closely matches the concentration of homologous compounds that must be present, one can conclude that the new standards provide a more accurate accounting of the composition of the stripped polymer. The critical conclusion, in terms of comparing previous and newer analyses on different materials utilizing the previous and newer standards is that, if there is a good match of concentrations of dimethyl compounds up through D_{12} to D_{13}, then the two materials will be similar if not identical in cyclic dimethyl content, both for individual species and for the cumulative total.

[7] Grace H. Chiang, Report Number CP 351, ***Semivolatile Extractables Analysis of Gel Mammary Implant: Comparison of Instruments and Quantitation Methods***, January 14, 2003.

The linear dimethyl siloxanes in extracts from the same gel analyzed with the same GC and the two standards produced very similar results with a difference of <0.6 µg/g for any specific compound ($MD_{12}M$-$MD_{15}M$). See Table 5-21. Note that the total semivolatiles from the application of the new standards to extracts from gel samples increased from 0.16 to 0.42 weight %. This increase was due solely to the more accurate determination of cyclic dimethyl siloxanes. Note also that, other than cyclic and linear dimethyl siloxanes, no other compounds were detected in the extractables from the gel sample.

The increased sensitivity in the cyclic dimethylsiloxane analytical results when the new GC instrument and additional standards are used to analyze gel filler solvent extractables can be seen in Figure 5-7. The only difference when this comparison is made is that of the sensitivity of the two instruments. Results on cyclic dimethylsiloxanes up through D_{10} are nearly identical. From D_{12} through D_{18}, the new instrument is capable of detecting lower levels than the original GC instrument. From D_{18} through D_{21} the results from the original instrument decrease rapidly to nondetectable values at D_{20} and D_{21} while the values provided by the new instrument and standards remain in the 500 to 800 µg/g range. In a stripped polymer, the concentration of the higher molecular weight cyclic siloxanes would be expected to remain at these levels; therefore, it can be concluded that the new instrument provides a more accurate profile of the cyclic dimethylsiloxanes.

The improved sensitivity of the new GC instrument for linear dimethylsiloxanes is clearly evident in Figure 5-8. Analyses from the old instrument do not show any linear dimethyl siloxanes up through $MD_{11}M$, while results from the new instrument show an increasing concentration from MD_5M through $MD_{13}M$. This would be the expected result in a stripped polymer. The new chromatograph also detects linear materials in the $MD_{16}M$-$MD_{17}M$ range while the older instrument is not sensitive enough to detect any material in this range.

Further proof of the superior sensitivity of the new instrument comes from the fact that it detects and quantifies cyclic vinyl-modified siloxanes in the range of $D^{Vi}D_9$-$D^{Vi}D_{21}$ while the old instrument does not. With the excess of vinyl-modified polymer in the gel precursor formulation, these materials must be present in the final gel. Thus, it is concluded that the new gas chromatograph coupled with the new calibration standards provide more accurate results than the old method and that those results will accurately reflect the expected profiles of the various species in the implant.

For emphasis, the point must be reiterated that, if the results on cyclic dimethylsiloxanes are essentially identical for D_4 through D_{11}, then it can be concluded that the stripped polymers upon which the analyses were conducted will be essentially identical with regard to trace siloxanes.

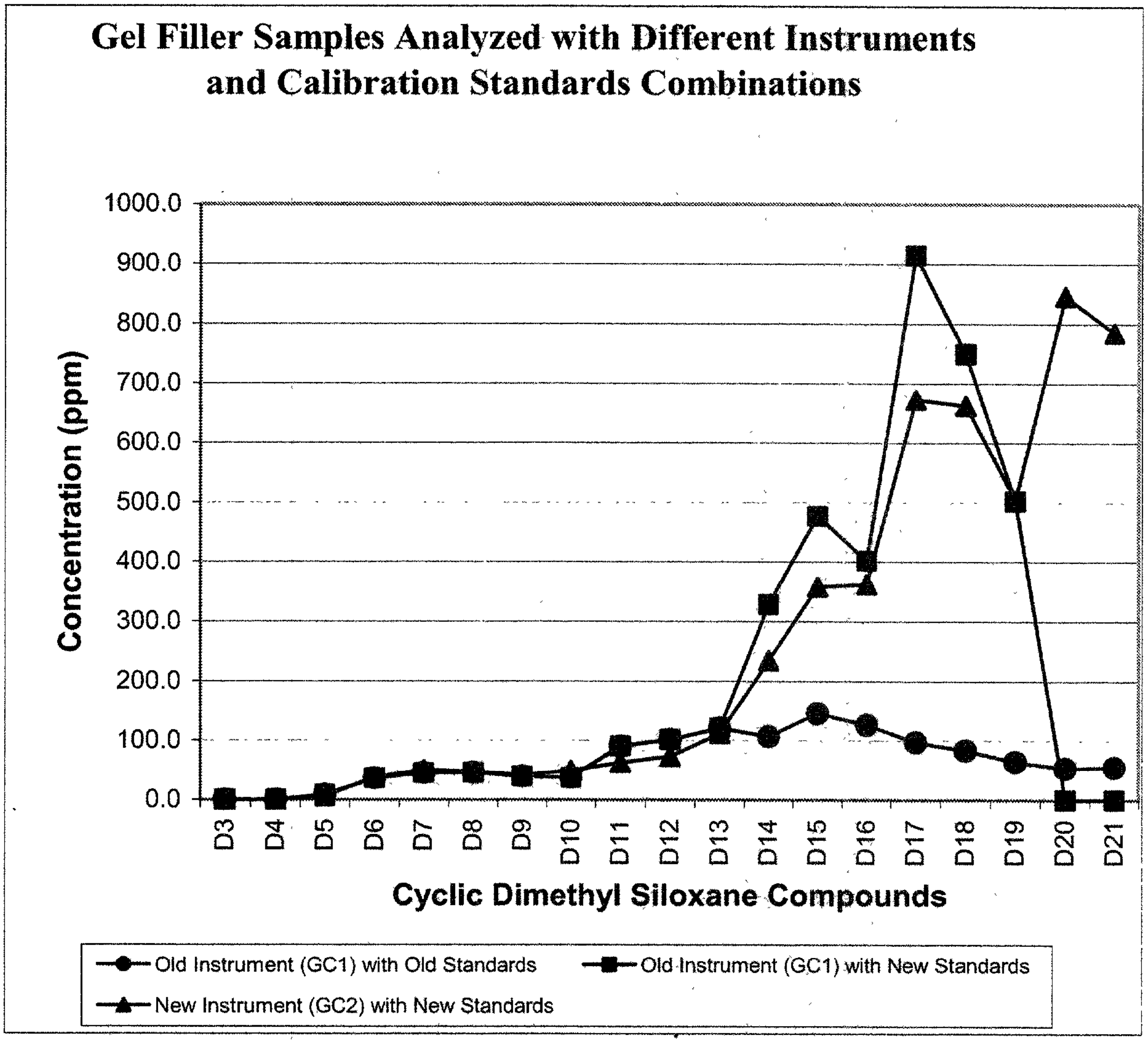


Figure 5-7. Comparison of Analytical Results on Cyclic Dimethyl Siloxane in Gel Filler Samples as determined by Old GC Instrument Employing Original and Additional Calibration Standards and New GC Instrument Employing Additional Calibration Standards

Table 5-21. Semivolatile Extractables from Siltex Round Moderate Profile Gel-Filled Mammary Implants (Lot #188747) - Different Gas Chromatographs and Calibration Standards (CP351)

Method of Calibration	Old Instrument (GC1) plus Original Calibration Standards 1		Old Instrument (GC1) plus New Calibration Standards 2		New Instrument (GC2) plus New Calibration Standards 2	
Compound	Gel Filler	Shell	Gel Filler	Shell	Gel Filler	Shell
	ug/g					
CYCLIC DIMETHYL SILOXANES						
D_3[1]	ND	ND	ND	ND	ND	ND
D_4[1]	ND	ND	ND	ND	NA	ND
D_5[1]	8.0	ND	8.0	ND	6.0	3.3
D_6[1]	36.8	34.4	36.8	34.4	38.2	32.5
D_7[2]	45.2	<31.8	45.2	<31.8	50.5	32.5
D_8[2]	45.9	<72.2	45.9	<72.2	47.7	27.4
D_9[1]	39.8	<72.2	39.8	<72.2	41.5	24.7
D_{10}[2]	37.7	<72.2	37.7	<72.2	49.7	25.7
D_{11}[2]	90.5	<98.5	90.5	<98.5	63.1	47.8
D_{12}[1]	101.4	<98.5	101.4	<98.5	73.3	63.9
D_{13}[2]	120.6	<98.5	120.6	<98.5	111.8	90.3
D_{14}[2]	107.0	<98.5	328.7	<436.6	234.8	194.5
D_{15}[1]	145.5	<98.5	476.9	<436.6	357.7	217.7
D_{16}[2]	126.1	<100.8	401.7	<436.6	361.8	215.7
D_{17}[2]	97.5	<98.5	914.2	<818.1	672.4	379.2
D_{18}[1]	83.6	<98.5	748.7	<818.1	662.1	297.2
D_{19}[2]	64.4	<98.5	502.2	<818.1	503.7	369.3
D_{20}[2]	53.6	<98.5	NA	ND	845.7	456.9
D_{21}[1]	55.4	ND	NA	ND	784.3	505.5
LINEAR DIMETHYL SILOXANES						
MDM[1]	ND	ND	ND	ND	ND	ND
MD_2M[1]	ND	ND	ND	ND	ND	ND
MD_3M[1]	ND	ND	ND	ND	ND	ND
MD_4M[1]	NA	ND	NA	ND	<0.77	NA
MD_5M[1]	NA	ND	NA	ND	NA	ND
MD_6M[1]	<5.56	ND	<5.56	ND	2.5	<4.7
MD_7M[1]	NA	ND	NA	ND	4.9	<5.00
MD_8M[1]	<14.03	ND	<14.03	ND	8.6	<5.3
MD_9M[1]	<20.7	ND	<20.69	ND	16.2	9.2
$MD_{10}M$[1]	<19.0	ND	<18.99	ND	25.7	16.1
$MD_{11}M$[2]	NA	ND	NA	ND	40.6	21.6
$MD_{12}M$[1]	88.4	ND	89.0	ND	73.3	53.3
$MD_{13}M$[2]	86.5	ND	86.8	ND	89.7	57.1
$MD_{14}M$[2]	78.1	ND	78.3	ND	87.6	63.0
$MD_{15}M$[2]	63.0	ND	63.2	ND	95.0	57.6

Method of Calibration	**Old Instrument (GC1) plus Original Calibration Standards 1**		**Old Instrument (GC1) plus New Calibration Standards 2**		**New Instrument (GC2) plus New Calibration Standards 2**	
Compound	Gel Filler	Shell	Gel Filler	Shell	Gel Filler	Shell
	ug/g					
$MD_{16}M$[3]	ND	ND	ND	ND	75.5	48.3
$MD_{17}M$[2]	ND	ND	ND	ND	33.6	39.8
CYCLIC VINYL MODIFIED SILOXANES						
$D^{Vi}D_9$[2,4]	ND	ND	ND	ND	1.2	ND
$D^{Vi}D_{10}$[2,4]	ND	ND	ND	ND	1.5	ND
$D^{Vi}D_{11}$[2,4]	ND	ND	ND	ND	NA	ND
$D^{Vi}D_{12}$[2,4]	ND	ND	ND	ND	3.7	NA
$D^{Vi}D_{13}$[2,4]	ND	ND	ND	ND	6.8	<8.52
$D^{Vi}D_{14}$[2,4]	ND	ND	ND	ND	11.5	13.7
$D^{Vi}D_{15}$[2,4]	ND	ND	ND	ND	15.2	17.9
$D^{Vi}D_{16}$[2,4]	ND	ND	ND	ND	18.3	20.2
$D^{Vi}D_{17}$[2,4]	ND	ND	ND	ND	45.0	<31.1
$D^{Vi}D_{18}$[2,4]	ND	ND	ND	ND	42.1	<36.5
$D^{Vi}D_{19}$[2,4]	ND	ND	ND	ND	33.9	37.9
$D^{Vi}D_{20}$[2,4]	ND	ND	ND	ND	69.9	<144.4
$D^{Vi}D_{21}$[2,4]	ND	ND	ND	ND	67.5	<144.4
MISCELLANEOUS SILOXANES*						
Siloxane[3]	NA	ND	NA	ND	NA	NA
Siloxane[3]	ND	ND	ND	ND	1.0	NA
Siloxane[3]	ND	ND	ND	ND	ND	NA
Siloxane[3]	ND	ND	ND	ND	4.2	1.2
Siloxane[3]	ND	ND	ND	ND	1.9	1.1
Siloxane[3]	ND	ND	ND	ND	6.9	2.2
Siloxane[3]	ND	ND	ND	ND	ND	1.3
Siloxane[3]	ND	ND	ND	ND	3.5	1.8
Siloxane[3]	ND	ND	ND	ND	ND	NA
Siloxane[3]	ND	ND	ND	ND	4.1	1.7
Siloxane[3]	ND	ND	ND	ND	6.2	NA
MISCELLANEOUS COMPOUNDS						
Dodecane[3]	ND	ND	ND	ND	ND	1.7
Ester[3]	ND	ND	ND	ND	ND	1.3
Ester[3]	ND	ND	ND	ND	ND	2.4
Tetradecane[3]	ND	ND	ND	ND	ND	0.9
Phenol derivative[3]	ND	ND	ND	ND	ND	NA
Pentadecane[3]	ND	ND	ND	ND	ND	NA
Ester[3]	ND	ND	ND	ND	ND	1.3
Dibutyl Phthalate[1]	ND	ND	ND	ND	ND	NA

Method of Calibration	**Old Instrument (GC1) plus Original Calibration Standards 1**		**Old Instrument (GC1) plus New Calibration Standards 2**		**New Instrument (GC2) plus New Calibration Standards 2**	
Compound	Gel Filler	Shell	Gel Filler	Shell	Gel Filler	Shell
	ug/g					
Amide[3]	ND	ND	ND	ND	ND	2.5
Di (Ethylhexyl) Phthalate[1]	ND	ND	ND	ND	ND	<4.7
Total Unidentified	ND	ND	ND	ND	1.0	3.8
Total Semivolatiles	1634.3	1269.9	4215.6	4342.3	5803.6	3847.1

ND = Not Detected, S/N <3.0
NA = Not Applicable, at least one of the replicates had a ND value.
Data preceded with a "<" symbol meaning a less than method detection limit value.
*Miscellaneous siloxanes differ based upon retention time (i.e., molecular weights)
[1] Measurement based on external and internal standard calibrations.
[2] Due to unavailability of external standards, measurement is estimated, based on calibrated response factors of closest homologue.
[3] Measurement based on the response factor of closest internal standard.
[4]Tentative identification based on MS pattern.

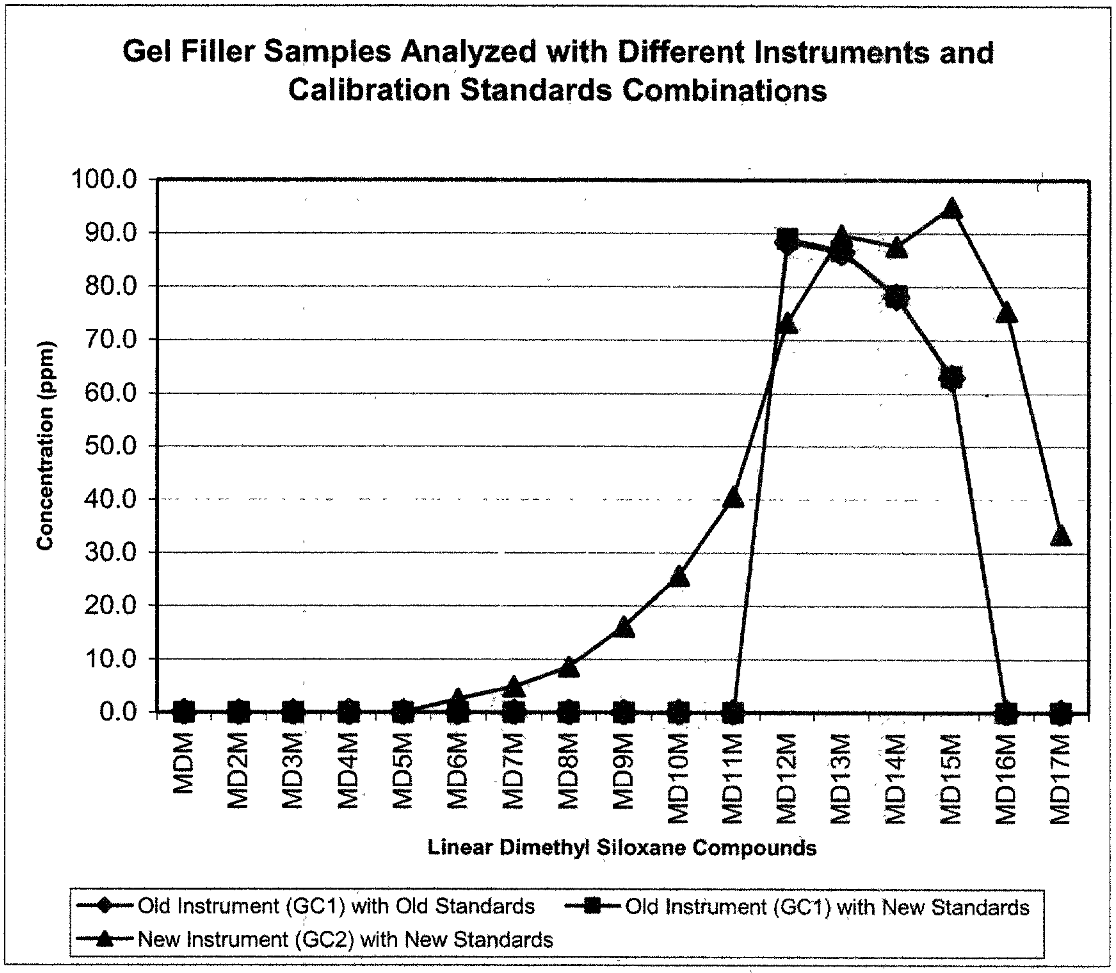


Figure 5-8. Comparison of Analytical Results on Linear Dimethyl Siloxane Compounds in Gel Filler Samples as determined by Old GC Instrument with Original and New Calibration Standards and New Instrument with Additional Calibration Standards

5.10.3.2 Semivolatiles Comparison of Dow Corning, SiTech, and ASC Gel

The objective of this section is to compare the analysis of low molecular weight methylene chloride Soxhlet extractables from Dow Corning, SiTech, and ASC gel filler material using Mentor's GC/MS techniques. Testing of SiTech gel is reported above in Section 5.2.2.[8] and is presented again here for comparison in Table 5-22. Earlier testing of SiTech gel, along with testing of Dow Corning and ASC gel, was reported in 1999.[9]

The change in methodology relating to the use of higher molecular weight standards was explained above. The effect can be noted here in the results from Report Number CP 357 compared to the earlier results. The use of improved standards and more sensitive instrumentation give more accurate quantification of the higher molecular weight species.

The concentration of cyclic dimethylsiloxanes with molecular weight up to approximately 1500 (D_3-D_{21}) for SiTech gel is 3804 μg/g for the recent results compared to 1630 μg/g for the method using the previous standards. The corresponding Dow Corning and ASC gel results from the earlier analysis are 1071 and 3020 μg/g, respectively. As explained above, the concentration of higher molecular weight species in the results of the more recent analysis is a more accurate representation of the cyclic content from $D_{14} - D_{21}$ in the material. The corresponding values for $D_{14} - D_{21}$ in SiTech gel for more recent versus earlier results are 3649 μg/g and 1089 μg/g respectively. The results for Dow Corning and ASC gels from the earlier analysis are 448 and 728 μg/g, respectively.

The results of the lower cyclic compounds $D_3 - D_5$ are 40, 35, and 191 μg/g for SiTech, Dow Corning, and ASC gels, respectively, from the earlier analysis, and 3 μg/g for SiTech gel from the more recent, improved analysis. For D_4, the result for the two analyses of SiTech gel was 0.5 μg/g or less. The D_4 results for Dow Corning and ASC are 11.7 and 81.4 μg/g, respectively.

[8] Grace Chiang, Report CP 357, ***Total and Semivolatile Extractables Analyses of Gel Mammary Implants: Qualification of Manufacturing Process Modifications***, , dated January 16, 2003.
[9] Grace H. Chiang, Report Number CP 292, ***Semivolatile Extractable Analysis of Gel-Filled Mammary Prostheses: SiTech Raw Material Vendor Qualification***, November 22, 1999.

For $D_3 - D_{11}$ the results are 69 µg/g for SiTech (newer assay method) and 295, 449, and 2011 µg/g for SiTech, Dow Corning, and ASC respectively (older assay method).

The corresponding amounts of linear dimethylsiloxanes (MDM-$MD_{17}M$) in SiTech gel are 376 µg/g and 328 µg/g. The values for linears from Dow Corning and ASC gel are 307 and 767 µg/g respectively.

The comparison of low molecular weight ("semivolatile") extractable compounds from Dow Corning and SiTech gels shows that the total amounts by the earlier method are similar at 1378 µg/g compared to 2525 µg/g respectively. (Note that about 500 µg/g of SiTech's 2525 µg/g semivolatile extractables were barely detectable and therefore only quantifiable by assigning a concentration of less than their detection limits). The amount of linear siloxanes in each data set is equivalent. The amount of D_4 and the total amount of low molecular weight cyclics $D_3 - D_{11}$ in SiTech gel are equivalent (about the same or less) than the corresponding amounts in Dow Corning gel. By the recent analytical procedure, the low molecular weight extractable content of SiTech gel is 4350 µg/g. From the result of the analysis of the SiTech gel by the recent improved analytical procedure compared to the results of the earlier procedure, and based on the equivalence of the results for lower molecular weight cyclics from both procedures, the profile and amounts of extractables from this analysis demonstrates that the SiTech and Dow Corning materials are not substantially different.

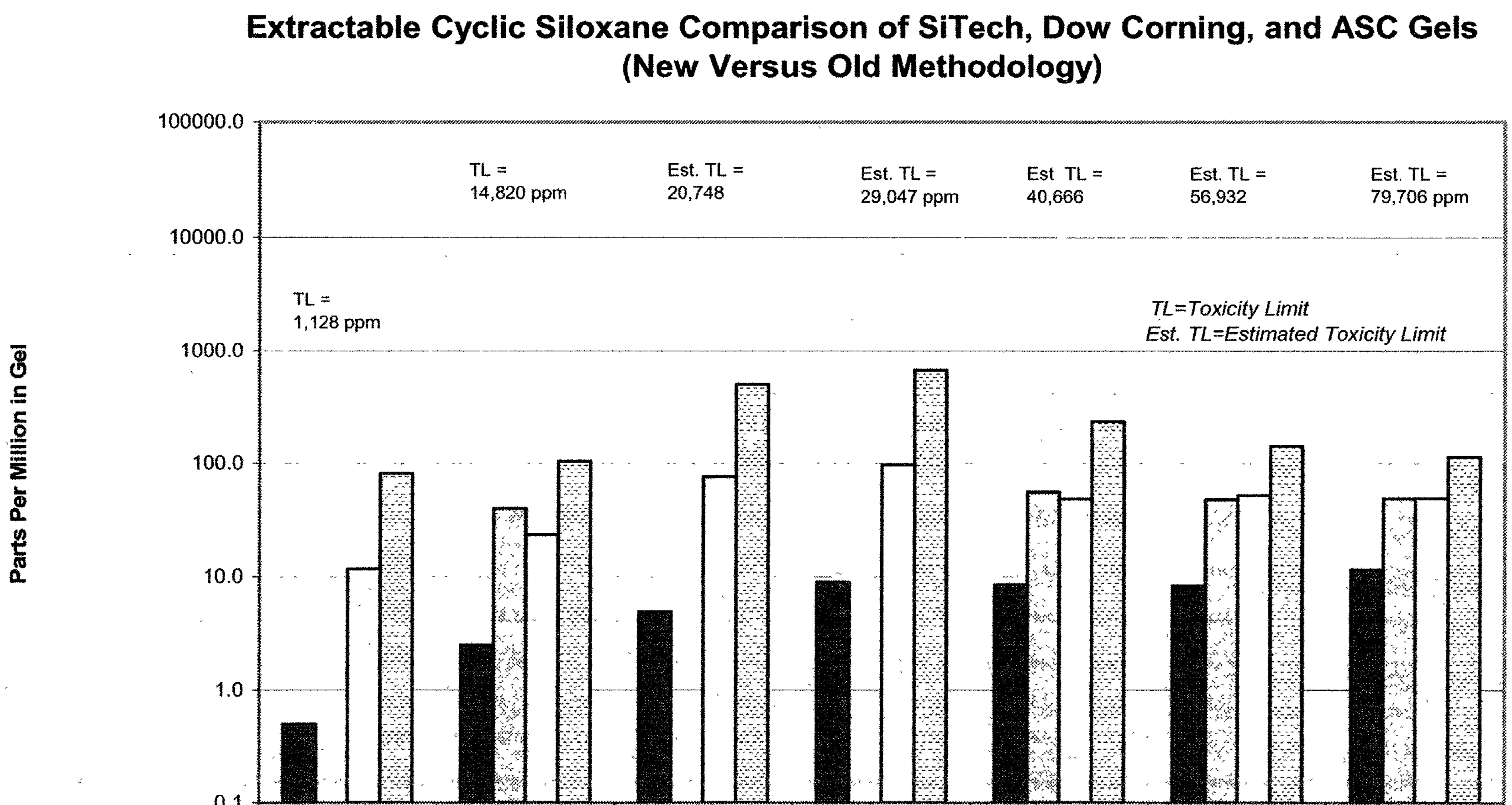
In looking at the semivolatile data for ASC gel, it contains the most semivolatile extractables of all the gels tested by the older method, and more lower molecular weight cyclic extractables ($D_3 - D_{11}$) than any of the other gels. But, as graphically shown in Figure 5-9, the levels of lower molecular weight cyclic siloxanes from all three gels are more than an order of magnitude below their toxic limit. (Note - the D_4 and D_5 toxicity limits were calculated using the data in the toxicity risk analysis section of this module, Section 6-2; more precisely, by multiplying the cyclic siloxane extractable amount per gram of device by the calculated safety factor for that cyclic siloxane compound. The D_6 through D_{10} toxicity limits were estimated by multiplying the D_5 toxicity limit by 1.4 to obtain the D_6 limit, the D_6 limit by 1.4 to obtain the D_7 limit, etc. The rationale for using the 1.4 factor to increase the toxicity limit is explained in Section 6.2.2.)

Table 5–22. Semivolatile Extractable Content Comparison of SiTech, Dow Corning, and ASC Gel (using old and current methodologies)

Material (semivol. analysis method)	SiTech Gel (current method)	SiTech Gel (old method)	Dow Gel (old method)	ASC Gel (old method)
Report No./Sample ID	CP 357/251121	CP 292/ 188747	CP 277I/ 57535	CP 277I/ 169392
Compound	ug/g			
Cyclic Dimethyl Siloxanes				
D_3	ND	ND	ND	5.5
D_4	0.5	NA	11.7	81.4
D_5	2.5	40.2	23.6	103.8
D_6	4.9	ND	76.3	504.5
D_7	9.0	ND	96.0	677.1
D_8	8.5	55.8	48.9	236.1
D_9	8.4	48.1	52.8	142.3
D_{10}	11.5	49.0	49.5	114.2
D_{11}	23.3	101.9	89.9	145.9
D_{12}	35.3	111.8	87.1	138.4
D_{13}	51.0	134.6	87.6	143.5
D_{14}	118.7	156.4	76.9	140.5
D_{15}	181.5	184.3	76.6	135.6
D_{16}	217.8	163.9	68.4	110.9
D_{17}	616.4	141.3	62.4	89.8
D_{18}	560.7	126.4	60.2	76.0
D_{19}	450.9	108.3	57.0	61.2
D_{20}	657.8	114.4	46.6	52.4
D_{21}	845.6	93.9	ND	61.3
Linear Dimethyl Siloxanes				
MDM	ND	ND	ND	ND
MD_2M	ND	ND	ND	4.1
MD_3M	ND	ND	ND	ND
MD_4M	ND	ND	6.5	9.4
MD_5M	ND	ND	12.7	18.3
MD_6M	ND	ND	25.7	33.6
MD_7M	<1.5	ND	27.5	36.4
MD_8M	1.7	ND	33.9	41.3
MD_9M	3.2	ND	42.2	53.2
$MD_{10}M$	7.2	ND	48.4	60.8
$MD_{11}M$	13.5	ND	44.7	55.9
$MD_{12}M$	37.2	<192.2	65.3	124.8
$MD_{13}M$	54.6	162.3	ND	105.5

Material (semivol. analysis method)	SiTech Gel (current method)	SiTech Gel (old method)	Dow Gel (old method)	ASC Gel (old method)
Report No./Sample ID	CP 357/251121	CP 292/ 188747	CP 277I/ 57535	CP 277I/ 169392
Compound	ug/g			
$MD_{14}M$	66.1	<165.9	ND	84.4
$MD_{15}M$	70	<165.4	ND	82.0
$MD_{16}M$	57.2	165.3	ND	57.6
$MD_{17}M$	64.9	ND	ND	ND
Vinyl-Modified Cyclic Dimethyl Siloxanes				
$D^{Vi}D_{14}$	6.8	ND	ND	ND
$D^{Vi}D_{15}$	10.1	ND	ND	ND
$D^{Vi}D_{16}$	14	ND	ND	ND
$D^{Vi}D_{17}$	26.1	ND	ND	ND
$D^{Vi}D_{18}$	40.6	ND	ND	ND
$D^{Vi}D_{19}$	25	ND	ND	ND
-------- -Modified Cyclic Dimethyl Siloxanes				
--_-- --- _	ND	ND	ND	ND
--_ -- --- _ -----	21.9	ND	ND	ND
--_ -- --- _ -----	19.8	ND	ND	ND
--_ -- --- _	ND	ND	ND	ND
Miscellaneous Siloxanes				
Siloxane	4.2	9.4	ND	ND
Residues of Solvents and Plasticizers				
o-Xylene	<0.4	ND	ND	ND
t-amyl alcohol	ND	34.0	ND	ND
Total Semivolatiles (ug/g)	4350.1	<2525.0	1378.4	3787.7

ND = Not Detected, S/N <3.0
Data preceded with a "<" symbol meaning a less than method detection limit value.
* - isomers



	D4	D5	D6	D7	D8	D9	D10
SiTech New Method	0.5	2.5	4.9	9	8.5	8.4	11.5
SiTech Old Method	ND	40.2	ND	ND	55.8	48.1	49
Dow Old Method	11.7	23.6	76.3	96	48.9	52.8	49.5
ASC Old Method	81.4	103.8	504.5	677.1	236.1	142.3	114.2

Figure 5-9 Extractable Cyclic Siloxane Comparison of SiTech, Dow Corning, and ASC Gels (New Versus Old Methodology)

5.10.3.3 Semivolatile Extractable Compounds of PTC Elastomer Shells and SiTech Elastomer Shells

The objective of this section is to present and compare the results of analysis of low molecular weight content of methylene chloride extractables performed on non-gelled shells made with PTC elastomer raw materials to those made with SiTech elastomer raw material analyzed by GC/MS technique. The complete reports[10,11] are appended, and summary data is presented here for comparison in Table 5-23.

The change in methodology relating in the use of higher molecular weight standards was explained above. The effect can be noted here between the results with NuSil textured shells and with SiTech textured shells. The use of improved standards and more sensitive instrumentation give more accurate quantification of the higher molecular weight species.

The comparison of low molecular weight ("semivolatile") extractable compounds, using the older semivolatile method, from NuSil textured PTC shells and SiTech shells shows that the total amount is less than about 2000 µg/g. By the new method, the result for SiTech textured SiTech shells is about 3200 µg/g. These values are not unusual for extractable low molecular weight compounds corresponding to the two different methods of analysis. The amounts are small. The contribution to the low molecular weight extractable compounds of the finished device is very small, given that the weight of the shell is small relative to the total weight of the device.

Cyclics from D_3 through D_{10} either were not detected or were below the limit of quantification of the method for all the samples. The profile and amounts of extractables from these analyses demonstrate that, for low molecular weight extractable compounds analyzed by GC/MS, the NuSil and SiTech textured layers with PTC and SiTech shells are not substantially different.

---

[10] Grace H. Chiang, Report Number CP 292, ***Semivolatile Extractable Analysis of Gel-Filled Mammary Prostheses: SiTech Raw Material Vendor Qualification***, November 22, 1999. Table IIb. The Comparison of Shell Assemblies from Nongelled Siltex Round Low Bleed Gel-Filled Mammary Prostheses.
[11] Report CP 357, ***Total and Semivolatile Extractables Analyses of Gel Mammary Implants: Qualification of Manufacturing Process Modifications***, by Grace Chiang, January 16, 2003. Table II. GC/MS Semivolatiles Analysis of Siltex Round Moderate Profile Gel-Filled Mammary Implants.

Table 5–23. Semivolatile Extractable Content Comparison of PTC and SiTech Nongelled Shells (using old and current methodologies)

Material (Analysis Method)	PTC Shell/NuSil Texture (Old Method)	SiTech Shell/ NuSil Texture (Old Method)	SiTech Shell / SiTech Texture (Current Method)
(Report No./Lot No.)	CP277 II/175261	CP292/194800	CP357/251121
Compound	ug/g		
Cyclic Dimethyl Siloxanes			
D_3	ND	ND	ND
D_4	ND	ND	ND
D_5	ND	ND	ND
D_6	ND	ND	ND
D_7	ND	ND	ND
D_8	ND	ND	<7.8
D_9	ND	<49	<7.8
D_{10}	ND	60	<7.8
D_{11}	ND	118	<12.2
D_{12}	ND	163	22
D_{13}	ND	212	49
D_{14}	73	256	148
D_{15}	76	267	201
D_{16}	77	225	207
D_{17}	ND	159	530
D_{18}	74	116	388
D_{19}	72	<86	273
D_{20}	72	<77	522
D_{21}	ND	ND	326
Linear Dimethyl Siloxanes			
MDM	ND	ND	ND
MD_2M	ND	ND	ND
MD_3M	ND	ND	ND
MD_4M	ND	ND	ND
MD_5M	ND	ND	ND
Vinyl-Modified Cyclic Dimethyl Siloxanes			
$D^{vi}D_{14}$	ND	ND	ND
$D^{vi}D_{15}$	ND	ND	ND
$D^{vi}D_{16}$	ND	ND	ND

Material (Analysis Method)	**PTC Shell/NuSil Texture (Old Method)**	**SiTech Shell/ NuSil Texture (Old Method)**	**SiTech Shell / SiTech Texture (Current Method)**
(Report No./Lot No.)	CP277 II/175261	CP292/194800	CP357/251121
$D^{vi}D_{17}$	ND	ND	ND
--------- -Modified Cyclic Dimethyl Siloxanes			
--_---	ND	ND	<8.9
--_ ---	ND	ND	<8.9
--_ ---	ND	ND	<8.9
--_ ---	ND	ND	85
--_ ---	ND	ND	138
--_ ---	ND	ND	55
--_ ---	ND	ND	<27
Residues of Solvents and Plasticizers			
o-Xylene	ND	ND	ND
Di (Ethylhexyl) Phthalate	ND	ND	<11.2
Chloroform	14.3	ND	ND
Amylene Hydrate	ND	5.6	ND
Total Semivolatiles (ug/g)	458	1794	3167

ND = Not Detected, S/N <3.0
Data preceded with a "<" symbol meaning a less than method detection limit value.

5.10.4 Nonvolatiles Content of Extractables

5.10.4.1 Nonvolatile Content Comparison of Dow Corning Gel, SiTech, and ASC Gel

The objective of this section is to compare the results of molecular weight analysis on methylene chloride Soxhlet extractable content from Dow Corning, SiTech, and ASC gel filler material analyzed by a liquid chromatography (LC) technique [i.e., gel permeation chromatography (GPC)]. Nonvolatile testing of SiTech gel is reported in Section 5.2.3.1 and presented again here for comparison in Table 5-24. The testing of Dow Corning and ASC gel was reported in 1999.[12]

[12] G. Mark Allen, Report Number CP 278I, ***GPC Analysis of Nonvolatile Extractables from Gel-Filled Mammary Prosthesis Gel***, May 20, 1999.

Table 5–24. Polysiloxane Molecular Weight Comparison of Dow Corning, SiTech, and ASC Gel Samples by GPC/RI Detector

Report No. (Sample ID)	Device	Mw	Mn	Mw/Mn
Dow Corning Gel (CP 278I/57353)	Siltex Gel-Filled Device	48808	26682	1.8
SiTech Gel (CP 359/251121)	Siltex Gel-Filled Device	53900	22300	2.4
ASC Gel (CP 278I/169392)	Siltex Gel-Filled Device	48926	28310	1.7

Polydimethylsiloxane standards were used for calibration. The molecular weight range from the lowest to the highest is less than 30%. No compounds were detected by LC using UV-Vis detection, which indicates that no -------- containing compounds were present at or above the detection limit of the method.

Based on the analysis of nonvolatile content from the Soxhlet extraction procedure, the Dow Corning, SiTech and ASC gels are not substantially different.

5.10.4.2 Comparison of Nonvolatile Extractable Content Between PTC Raw Material Shells and SiTech Raw Material Shells

The objective of this section is to compare the nonvolatile extractable content of shells made from PTC and SiTech raw materials. The results of analysis are presented in Tables 5-25 for shell samples from finished devices and Tables 5-26 for shell samples from non-gelled shells.

Table 5-25. Nonvolatile Compounds in Finished Gel-filled Mammary Prosthesis Shells[1]

Tentative Compound Identity	Property	Siltex Round Gel-Filled Shell (100cc, SiTech/SiTech,[2] Lot# 251121)	Siltex Round Gel-Filled Shell (100cc, NuSil/SiTech,[3] Lot# 188747)	Siltex Round Gel-Filled Shell (200cc, NuSil/PTC/ASC,[4] Lot# 169392
------- HTV Prepolymer	Mw	ND	71,658	ND
	Mn	ND	56,653	ND
	Mw/Mn	----	1.3	----
------- Polysiloxane	Mw	770	804	ND
	Mn	770	801	ND
	Mw/Mn	1.0	1.0	----
------- Polysiloxane	Mw	550	561	446
	Mn	540	560	444
	Mw/Mn	1.0	1.0	1.0
------- Polysiloxane	Mw	260	293	288
	Mn	250	292	286
	Mw/Mn	1.0	1.0	1.0
------- Polysiloxane	Mw	170	182	141
	Mn	170	181	139
	Mw/Mn	1.0	1.0	1.0
------- Polysiloxane	Mw	ND	ND	82
	Mn	ND	ND	82
	Mw/Mn	----	----	1.0
Polydimethylsiloxane	Mw	17,400	17,596	16,459
	Mn	9,900	14,182	9,359
	Mw/Mn	1.8	1.2	1.8

[1]Reports CP 291 and CP 359 ND = not detectable
[2] SiTech/SiTech = SiTech 4750/SiTech shell and gel
[3] NuSil/SiTech = NuSil 4750/SiTech shell and gel
[4] NuSil/PTC/ASC = NuSil 4750/PTC shell/ASC gel

Table 5-26. Nonvolatile Compounds in Nongelled Low-Bleed Shells

Tentative Compound Identity	Property	Siltex Round Shell (100cc, SiTech/SiTech,[2] Lot# 251121)	Siltex Round Shell (325cc, NuSil/PTC,[3] Lot# 175261
------- HTV Prepolymer	Mw	61,600	91,222
	Mn	49,100	64,232
	Mw/Mn	1.3	1.4
------- Oligomer	Mw	3,900	4,746
	Mn	2,320	2,322
	Mw/Mn	1.7	2.0
------- Polysiloxane	Mw	790	ND
	Mn	780	ND
	Mw/Mn	1.0	----
------- Polysiloxane	Mw	560	448
	Mn	550	445
	Mw/Mn	1.0	1.0
------- Polysiloxane	Mw	290	298
	Mn	280	292
	Mw/Mn	1.0	1.0
------- Polysiloxane	Mw	170	129
	Mn	170	125
	Mw/Mn	1.0	1.0
------- Polysiloxane	Mw	ND	80
	Mn	ND	80
	Mw/Mn	----	1.0
Polydimethylsiloxane	Mw	341,100	ND
	Mn	270,100	ND
	Mw/Mn	1.3	----
Polydimethylsiloxane	Mw	4,820	4,697
	Mn	3,860	3,766
	Mw/Mn	1.2	1.3

[1] Reports CP 278II and CP 359
[2] SiTech/SiTech = SiTech 4750/SiTech shell
[3] NuSil/PTC = NuSil 4750/PTC shell

The results show that the extractables from PTC raw material shells and SiTech raw material shells have extractable compounds of higher molecular weight, between about 50000 and 350000, and polydispersity values not exceeding 2. In addition, similar lower molecular weight compounds are found in both shells and are typical and characteristic of the silicone polymers used as materials of construction. Those compounds of molecular weight less than about 1500 are characterized very thoroughly and in greater detail in Section 5.2.2 (semivolatile extractables analysis). They comprise only a small fraction of the total extractables.

The higher molecular weight compounds comprise the largest fraction of the non-volatile extractables. These are typical and characteristic of the materials of construction. These results demonstrate that the shells made from PTC and SiTech raw materials are not substantially different in their nonvolatiles content.

5.10.5 Extent of Crosslinking, Swell Ratios, and Percent Extractables

5.10.5.1 Extent of Crosslinking Comparison of Dow Corning, SiTech, and ASC Gel

The objective of this section is to summarize and compare the results of analysis of the extent of crosslinking for comparison of gels made with precursor materials from different vendors. The analysis was performed as described in Section 5.3 Sol Fraction Equilibrium Swell Ratio, and Crosslink Density. The values are from samples of gels taken from finished product made with Dow Corning,[13] SiTech,[14] and ASC gel raw materials. Results are shown in Table 5-27.

Molar crosslink density and crosslink chain density for ASC and SiTech gel are a little higher than for Dow Corning gel. As a result, SiTech and ASC gel have a somewhat lower average network chain molecular weight between crosslinks, a lower swell ratio, and a lower amount of extractables. (It should be noted that long-term biological testing of the Dow Corning gel is therefore a worst case situation

[13] G. M. Allen, Report Number CP 273 I, ***Crosslink Density, Sol Fraction and Equilibrium Swell Ratio of Gel-Filled Mammary Prosthesis Gel***, January 21, 2003.
[14] C. S. Puckett, Report Number CP 361, ***Sol Fraction, Equilibrium Swell Ratio, and Crosslink Density of Gel Mammary Implants: Qualification of Manufacturing Process Modifications***, February 6, 2003.

compared to testing SiTech gel because Dow Corning gel has fewer crosslinks and more extractables.)

TABLE 5–27. Comparisons of Dow Corning, SiTech, and ASC Gel Crosslinking, Swell Ratios and Percent Extractables (from Siltex Low-Bleed Devices, M:V ~ 1:100)

Gel (Report #)	M_c (g/mol)	ρ_c (mol/cm^3)	$\rho_c N_{AV}$ (chain/cm^3)	Swell Ratio	Extractables %
Dow Corning Gel (CP 273I)	18.3E+05 (4.1E+05)*	0.60E-06 (0.14E-06)	3.61E+17 (0.86E+17)	60.6 (7.8)	82.1 (1.9)
SiTech Gel (CP 361)	6.89E+05 (1.38E+05)	1.46E-06 (0.30E-06)	8.81E+17 (1.83E+17)	36.9 (4.0)	73.8 (3.5)
ASC Gel (CP 273I)	6.92E+05 (1.58E+05)	1.60E-06 (0.41E-06)	9.61E+17 (2.49E+17)	35.5 (4.5)	75.0 (3.1)

Mc = Network Chain Molecular Weight
ρ_c = Molar Crosslink Density
$\rho_c N_{AV}$ = Crosslink Chain Density
* - mean (standard deviation)

5.10.5.2 Extent of Crosslinking Comparison of PTC and SiTech Shells

The objective of this section is to describe and compare the extent of crosslinking measured on shells from PTC raw materials with the corresponding values for shells from SiTech raw materials.[15] Results are shown in Table 5-28.

[15] G. M. Allen, Report Number CP 273 II, ***Crosslink Density, Sol Fraction and Equilibrium Swell Ratio of Gel-Filled Mammary Prosthesis Shell***, January 21, 2003.

Table 5–28. Comparisons of PTC Shell/NuSil Texture, SiTech Shell/NuSil Texture, and SiTech Shell/SiTech Texture Crosslinking, Swell Ratio and Percent Extractables (Shells from Finished Devices)

Shell/Texture (Report #)	M_c (g/mol)	ρ_c (mol/cm^3)	$\rho_c N_{AV}$ (chain/cm^3)	Swell Ratio	Extractables %
PTC/NuSil (CP 273II)	6303 (406)*	1.66E-04 (0.10E-04)	9.98E+19 (0.62E+19)	3.7 (0.02)	11.7 (0.5)
SiTech/NuSil (CP 273II)	6032 (176)	1.73E-04 (0.05E-04)	10.4E+19 (0.31E+19)	3.3 (0.03)	10.6 (0.4)
SiTech/SiTech (CP 361)	8400 (336)	1.31E-04 (0.05E-04)	7.90E+19 (0.32E+19)	3.7 (0.1)	8.3 (0.2)

Mc = Network Chain Molecular Weight
ρ_c = Molar Crosslink Density
$\rho_c N_{AV}$ = Crosslink Chain Density
* - mean (standard deviation)

The data indicate that the crosslinking, swell ratio, and extractable % results for textured PTC shells and textured SiTech shells are not substantially different.

5.10.6 Heavy Metals

5.10.6.1 Heavy Metals Content of Dow Corning, SiTech and ASC Gel

The objective of this section is to compare the heavy metals content of Dow Corning, SiTech, and ASC gels. The analysis was performed as described in Section 5.4 of this module. Report CP 279[16] contains data on Dow Corning and ASC gel and report CP 360[17] contains current device SiTech gel data. The results for the gels are presented in Table 5-29.

[16] Boggess, K. Report CP 279, ***Heavy Metals Analysis of Gel Mammary Implants***, December 2, 1999.
[17] Julian, N. Report CP 360, ***Extractable Metals Analysis of Gel Mammary Implants: Qualification of Manufacturing Process Modifications***, February 17, 2003.

Table 5–29. Heavy Metal Analysis of Dow Corning, SiTech, and ASC Gels

	Aqueous Extract , µg/g			Organic Extract, µg/g		
	Dow Corning	SiTech	ASC	Dow Corning	SiTech	ASC
Mg	ND	0.37	0.019	ND	ND	0.0074
Co	0.0016	0.06	0.0029	0.0014	ND	0.0013
Ni	0.12	0.048	0.048	0.015	0.0049	0.0061
Cu	0.043	0.0067	0.040	ND	0.018	0.0041
Zn	0.12	ND	0.094	ND	ND	ND
Mo	ND	ND	ND	ND	ND	ND
Ag	ND	ND	0.0035	ND	ND	ND
Cd	0.0019	0.0019	ND	ND	ND	ND
Sn	0.018	ND	0.015	0.084	ND	ND
Sb	0.0015	0.0025	0.0012	0.00095	0.010	0.0015
Ba	0.014	ND	0.015	0.0024	ND	ND
Pt	ND	0.018	ND	0.082	0.31	0.061
Pb	0.033	0.0085	0.040	ND	0.0019	ND
Be	ND	ND	ND	ND	ND	ND
Ti	ND	ND	0.0036	0.011	0.029	0.017
V	ND	ND	ND	ND	ND	ND
Cr	ND	ND	ND	ND	ND	ND
As	ND	ND	ND	ND	ND	ND
Be	ND	ND	ND	ND	ND	ND
Hg	ND	ND	ND	ND	ND	ND

With the exceptions of Co, Mg, Sn, Ti and Zn, the levels of the elements detected in most cases were similar in magnitude to those of the extraction fluids (solvent controls). From each type of gel, Dow Corning, SiTech, and ASC, the total metals from aqueous extracts (0.36 µg/g, 0.52 µg/g, and 0.28 µg/g respectively) and organic extracts (0.20 µg/g, 0.37 µg/g, and 0.10 µg/g respectively) were about equal.

Comparing the results, the Dow Corning gel, SiTech gel, and ASC gel are not substantially different in heavy metals content.

5.10.6.2 Heavy Metals Content of PTC Shells and SiTech Shells

The objective of this section is to compare the heavy metals content of shells from PTC raw materials with those of shells made from SiTech raw materials (see Table 5-30). Data on textured PTC material shells came from CP 279 while the textured SiTech material shell data came from testing of the current PMA device (see Section 5.4 in this module).

TABLE 5–30. Heavy Metals Analysis of SiTech and PTC Shells (µg/g)

	SiTech Shell		PTC Shell	
Element*	**Aqueous**	**Organic**	**Aqueous**	**Organic**
Be	ND	ND	0.0041	ND
Mg	0.454	0.016	0.16	ND
Ti	ND	0.004	0.0028	0.012
V	ND	ND	ND	ND
Cr	ND	ND	ND	ND
Co	ND	ND	0.038	ND
Ni	0.017	0.010	ND	ND
Cu	0.024	ND	0.075	ND
Zn	0.126	0.011	0.13	ND
As	ND	ND	ND	ND
Se	ND	ND	ND	ND
Mo	ND	ND	ND	ND
Ag	ND	ND	0.047	ND
Cd	0.0024	0.0010	0.0032	ND
Sn	ND	ND	0.0041	ND
Sb	0.020	0.0016	0.0017	0.0037
Ba	0.0020	ND	0.0012	0.00089
Pt	0.055	0.078	0.0080	0.029
Hg	0.003	ND	ND	ND
Pb	0.015	0.0031	0.011	ND

With the exceptions of Co, Mg, Zn, Ti and, Sn the levels of the elements detected were similar in magnitude to those of the extraction fluids (solvent blanks). As will be discussed in detail in the toxicity risk analysis section of this module (Section 6.1), for those heavy metals which did not closely match levels in SiTech and PTC shells (e.g., Co, Mg, Zn, etc.), there are no toxicity issues associated with the observed values.

Based upon the heavy metals data and the toxicity risk analysis information, the PTC and SiTech shells are not substantially different in their heavy metals content.

5.10.7 Infrared Spectral Analysis

5.10.7.1 IR of Dow Corning, SiTech, and ASC Gels

The objective of this section is to compare the IR spectra of gel samples from finished sterile devices made by Dow Corning, SiTech, and ASC.[18,19] The infrared spectra were obtained using a Fourier transformed infrared spectrophotometer (FT-IR) with an attenuated total reflectance accessory (ATR).

The spectra of the samples show identical absorbance maxima of gel samples from finished devices made with raw materials from the two sources. This technique is qualitative, and shows absorbance bands that are representative of the composition of silicone materials used in the finished devices. Specifically, the spectra are typical of polydimethylsiloxane, which is the prevalent moiety. There was no evidence of ---------character, which would show in the range of 3020 to 3080 cm^{-1} if present in sufficient amount to be detected. That would typically require the presence of a few percent of the -------- moiety in the composition.

The spectra demonstrate that the gel samples from finished devices made with Dow Corning, SiTech, and ASC raw materials are substantially equivalent.

[18] Grace Chiang, Report CP 280, ***Surface Chemical Composition of Dow, ASC, and SiTech Gel-Filled Mammary Prostheses***, November 21, 1999, Appendix D, IR Spectra of Samples.
[19] Wenkai Ma, Report 362, ***Infrared Spectral Analysis of Gel Mammary Implants: Qualification of Manufacturing Process Modifications***, February 10, 2003, Appendix C, IR Spectra of Samples.

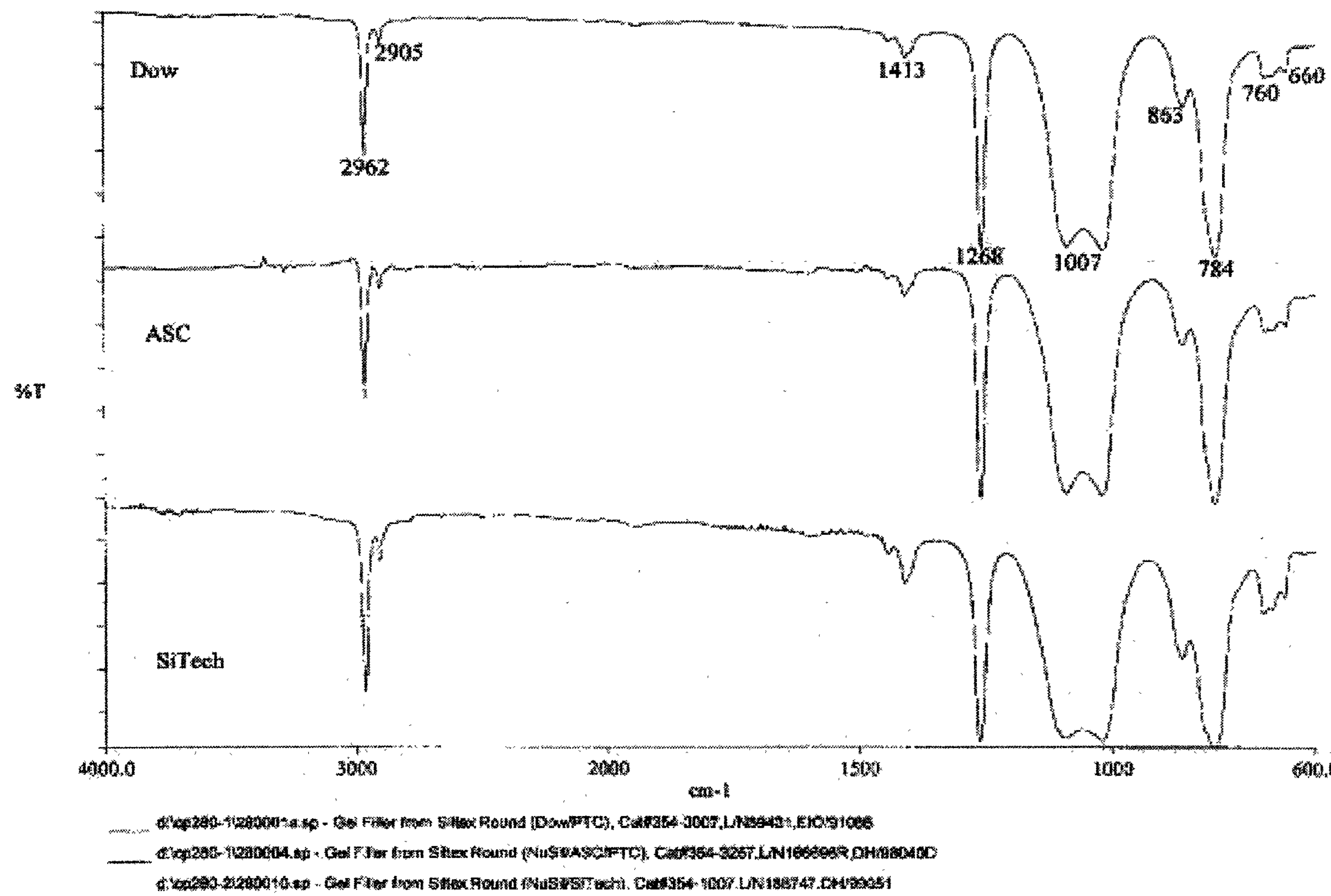


Figure 5-10 IR Spectral Comparison of Gel Fillers from Siltex Round Low-Bleed Devices (Dow, ASC and SiTech)

5.10.7.2 Infrared Spectral Analysis of PTC and SiTech Shells with NuSil and SiTech Texture Layers and Shell Patches

The objective of this section is to compare infrared spectra of shell samples from PTC and SiTech materials.[20,21] The infrared spectra were obtained using a Fourier transformed infrared spectrophotometer (FT-IR) with an attenuated total reflectance accessory (ATR).

The spectra show identical absorbance maxima of shell samples from finished devices made with raw materials from the two vendors. This technique is qualitative, and shows absorbance bands that are representative of the composition of silicone materials used in the finished devices. Specifically, the spectra are typical of polydimethylsiloxane, which is the prevalent moiety in the composition of each material. There was no evidence of -------- character, which would show in the range of 3020 to 3080 cm^{-1} if present in sufficient amount to be detected. That would typically require the presence of a few percent of the -------- moiety at the surface of the material being analyzed. ----------------------------------- --- ------------------------- It is surrounded by layers of dimethylsiloxane from dimethyl silicone elastomer dispersion used in the shell dipping process; therefore, the absence of -------- character by FT-IR ATR surface analysis is expected. No -------- character was observed in the other materials of the patch or texture layer, also as expected.

The results demonstrate that the elastomer samples from finished devices made with PTC and with SiTech shell dispersion materials are substantially equivalent when analyzed by FT-IR spectroscopy using ATR surface analysis.

---

[20] Grace Chiang, Report CP 280, ***Surface Chemical Composition of Dow, ASC, and SiTech Gel-Filled Mammary Prostheses***, November 21, 1999, Appendix D, IR Spectra of Samples.
[21] Wenkai Ma, Report 362, ***Infrared Spectral Analysis of Gel Mammary Implants: Qualification of Manufacturing Process Modifications***, February 10, 2003, Appendix C, IR Spectra of Samples.

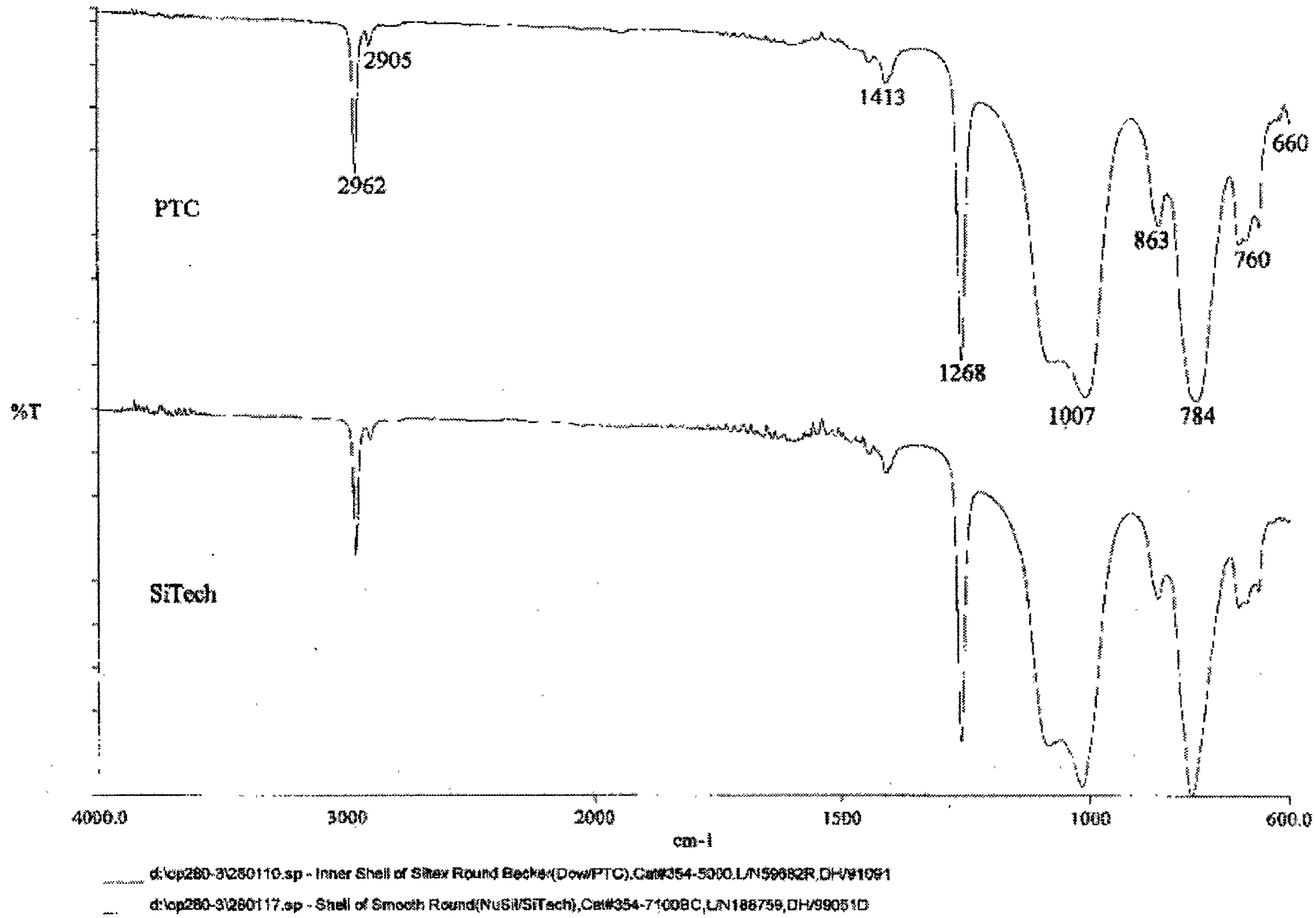


Figure 5-11 IR Spectra Comparison of HTC Smooth Shell (PTC vs SiTech)

7.0 SUMMARY AND CONCLUSION

This chemical testing PMA module has presented data to characterize Mentor's Gel-filled Mammary Prosthesis and its major components (shell and gel). Testing was performed in accordance with FDA's Guidance for Saline, Silicone Gel, and Alternative Breast Implants; Guidance for Industry and FDA (February 11, 2003) whenever possible. The data were used for a toxicity risk analysis of the chemical compounds extracted from the device, verification that certain manufacturing changes did not cause significant changes in the chemical extractables profile of the device, and to support Mentor's conclusion that long term biological safety testing performed on gel-filled mammary devices and components made with prior vendor silicone materials is still directly applicable to the devices in this PMA submission.

The chemical testing consisted of a total extractables quantitation coupled with detailed qualitative and quantitative analyses of the volatile and semivolatile compounds, and a mostly qualitative nonvolatile extractables analysis. The analytical techniques utilized included gravimetry for overall extractables, dynamic headspace purge/trap with gas chromatography/mass spectroscopy (P/T-GC/MS) for volatiles, direct liquid injection gas chromatography/mass spectroscopy (GC/MS) for semivolatiles, and liquid injection gel permeation chromatography (GPC) for nonvolatiles. Compounds up to 1500 molecular weight were targeted for identification and quantitation.

In addition to the above extract testing, determination of extractable heavy metals, component crosslink densities, and surface composition analysis were conducted. Where necessary, a solvent extraction comparison and verification of exhaustive solvent extraction were performed. All sample preparation and analysis methods were validated by including spiked recovery of selected analytes and assessment of quantitation methods for linearity, precision, and detection limits. Reference libraries of standard compounds were developed from consideration of raw materials, additives, synthesis byproducts and manufacturing process aids and were used for positive identification of extractable compounds.

The data showed that the gel-filled mammary devices being submitted in this PMA are chemically not substantially different from earlier gel-filled mammary prostheses Mentor has manufactured and performed safety testing on in the past or for which testing has been published in the literature. In particular, Mentor's current gel (manufactured by SiTech, LLC) has been compared to the Dow Corning gel, on which most of the original safety testing was performed, in order to show that the existing biological safety testing is directly applicable to the SiTech gel. SiTech has provided a side-by side evaluation of the two gels in its Master Access File for their Gel-2167/Gel-2168 (MAF #1039) using the tests required by FDA's "Guidance for the Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials" (July 1993). These tests demonstrated that the SiTech gel is not substantially different from the Dow Corning Gel Q7-2167/Q7-2168. Additionally, the processes used to fabricate Mentor's gel-filled mammary devices did not need to be changed in order to convert from using the Dow Corning gel to the SiTech gel.

In addition to gel testing, Mentor has performed sterile finished product extractables testing on devices made with both SiTech and Dow Corning gels and has determined that the finished products are not substantially different. This means that the profile of the device extractables is similar for the two devices. The SiTech gel taken from a device has less overall extractables, less volatile compounds, slightly more cross-linked (based on gel volume), similar quantities of most semivolatile compounds, similar extractable nonvolatile materials based upon their molecular weights, no significant differences in their heavy metals content, and similar FTIR profiles when compared to the Dow Corning gel taken from devices. Because of these comparative results, Mentor believes that the safety testing data on Dow Corning's Q7-2167/Q7-2168 gel is directly applicable to SiTech, LLC's Gel-2167/Gel-1268 when used in Mentor's Gel-filled Mammary Prostheses. The gel materials are not substantially different by all criteria established in FDA's "Guidance for the Manufacturers of Silicone Devices Affected by Withdrawal of Dow Corning Silastic Materials" (July 1993).

[Besides the above comparative testing, it needs to be noted that Mentor has provided similar comparative extractables data of SiTech gel to Applied Silicone Corporation (ASC) gel from sterile devices. Even though ASC gel has higher extractables, in the potentially more significant lower molecular weight range when compared to Dow Corning and SiTech gel, the ASC gel has been tested for long-term toxicity with no unaccounted for adverse effects (see Master Access File #645). This set of findings combined with the Dow Corning gel safety testing provides strong evidence of the lack of any potential long term adverse effects with the SiTech gel.]

The chemical data provided also demonstrates that gel-filled mammary shells made with SiTech dispersion materials are not substantially different from shells which were made from PTC dispersion materials and which were used in chronic toxicity/carginogenicity, reproductive and teratology, immunotoxicity, and adjuvancy testing. The results show that for volatiles, total extractables, semivolatile extractables, nonvolatile extractables, crosslink density (including swell), heavy metals and IR spectra data, the SiTech shell is substantially equivalent to the PTC shell in type and quantity of extractables and chemical characteristics. This would be expected since SiTech's formulation for the methyl and ---------- dispersions were based directly upon PTC's specific formulations.

In addition to the safety testing of the gels and shells, the toxicity risk analysis on the extractable compounds from Mentor devices made with SiTech gel, shell, and 4750 elastomer has shown that there are no compounds extracted from a gel-filled mammary device in a quantity which might pose any toxicological concern when compared to the published toxicity information for those materials.

Information was provided on the issue of platinum extractables and the valence state of the platinum. Review of the published literature indicates that both theoretically and based upon available experimental data, the valence state of the platinum in platinum catalyzed silicone materials is zero, the least toxic of the different platinum valence states.

Data were provided showing that the change in dipping mandrel material from Ertalyte to Teflon coated stainless steel and the use of laser marking on the device patch to provide identification information did not cause any appreciable changes in the device extractables profile.

The chemical testing data in this module of Mentor's Gel-filled Mammary Prosthesis PMA strongly support the safety of this device for its intended use and strongly support the relevance of all the biological testing data in this PMA to Mentor's current PMA devices.