

Chemistry

20. In response to item 10 of our January 6, 2004 email, you stated the metal analysis you conducted on the extracted residue will represent "bioavailable" compounds. This does not represent the worst case scenario. Please provide either (a) metal analysis on the un-extracted gel filler and shell materials or (b) the metal concentration in the finished final device taking the total metal amounts of catalyst used and the catalyst's metal analyses.

20 Response:

Analytical results for un-extracted gel - ---- and shell materials show that 6 ppm residual -----m catalyst is prese----- ppm is present in the two ----- shell -----mers ----- . The analytical testing d----- these ----- silic----- ture of Mentor's silicone gel-filled ma----- prostheses are included in their Master Access Files #1049 ----- 40 (dimethyl dispersion), Section 6; and MAF #1041 ----- , Section 6.

21. Please provide an updated risk analysis based on the total platinum present in the whole device as per your response to the item above.

21 Response:

As noted above, the total concentration of platinum present in the whole device is 6 ppm (6 mg/kg). Mentor has recently completed a gel bleed study (Report CP246, see Response 26) in which the diffusion of platinum from Mentor silicone gel-filled breast implants was measured in a physiologically relevant media, porcine serum, that has a very similar composition to that of human extracellular fluid that would be in contact with the implant surface contained within the collagenous fibrous capsule. The estimated diffusion rate, based on seven measurements made between days 0 to 45 of the 120-day study,^{1/} and adjusted to the ~460 cm² surface area of 800 cc implants,^{2/} was 270 ng/d for a single implant. For two maximum-sized 800 cc silicone gel-filled implants, this diffusion rate would be equivalent to potential release of 0.54 µg Pt/day (540 ng/d). As discussed previously in the Biological Module of this PMA submission, the Institute of Medicine (Bondurant et al. 1999) noted that Stein et al. (1999) reported that "the platinum in breast implants is in zero valence form in the final cured state in excess vinyl." Platinum in the zero valence state exhibits relatively low toxicity and is recognized to be several orders of magnitude less toxic than soluble platinum salts (e.g., ACGIH 2001). Mentor recently sponsored state-of-the-art x-ray absorbance spectroscopy testing by Dr. Robert A. Scott, as

1/ The 0 to 45 day period represents the rate prior to any plateauing of the release based on Fig. 1 of Report CP246.

2/ Surface area of 800 cc implant was calculated based on area of an oblate ellipsoid of a given volume.

described in Report CP 368 in Attachment 24, performed at the Stanford Synchrotron Radiation Laboratory, to determine the platinum valence in the catalyst used in Mentor's silicone gel-filled breast implants. Dr. Scott did not detect any platinum with a valence other than zero, and based on the detection limits achieved, demonstrated that $\geq 95\%$ of the platinum catalyst was in the zero valence state. IOM (1999) also pointed out that "many silicone-containing implants other than breast implants (listed in Chapter 2) are found at high frequency in the general population and presumably contain platinum also; the committee is not aware of any evidence that platinum toxicity is present in these persons." The IOM report went on to conclude that "[s]ome have speculated that platinum found in silicone gel and elastomer may be responsible for allergic disease in women with silicone breast implants. Very little platinum (microgram quantities) is present in implants, and most investigators believe it to be in the zero valence state. Platinum likely diffuses through the shell over a considerable period of time. Evidence for resulting systemic disease at such exposures is lacking." The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value - Time Weighted Average (TLV-TWA) for platinum metal (zero valence state) is 1 mg/m^3 , which translates to a daily exposure of $10,000 \text{ } \mu\text{g}$, as compared with the estimated daily exposure from Mentor silicone gel-filled implants of $0.54 \text{ } \mu\text{g}$ total platinum, representing a more than 18,000-fold margin.

As a worst case, one could assume that that the remaining 5% of platinum not definitively ascertained as zero valence state by Dr. Scott was entirely platinum soluble salts. The ACGIH TLV-TWA for platinum soluble salts is 0.002 mg/m^3 , which translates to a daily exposure of $20 \text{ } \mu\text{g}$, as compared with an estimated reasonable worst-case daily exposure from Mentor silicone gel-filled implants of $0.027 \text{ } \mu\text{g}$ platinum soluble salts (5% of the 0.54 ug/d total platinum release rate), representing a minimum 740-fold margin.

- 22. In response to item 14 of our January 6, 2004 email, you stated that free silica will be washed away by isopropyl alcohol. Please provide information to support your statement that isopropyl alcohol washings remove free silica.**

22 Response:

Effectiveness of Isopropanol Wash in Manufacturing Process to Remove Potential Silica Particle Contamination from Surface of Implant Shells (Report M 043 in Attachment 25)

While it was inadvertently inferred from the initial PMA narrative that free silica could be present on the device surface, this is not the case. Amorphous fumed silica is formulated into the dip molding dispersion that comprises the device assembly. The dip molding dispersion is prepared at the raw material vendor, not at Mentor Texas Operations. Loose silica powder is not used in the implant manufacturing environment at all, and it is not likely to be found on the surfaces of in-process shells or finished product. Isopropanol ("IPA") washing is used in the

implant shell manufacturing process for the purpose of general cleaning. IPA washing was not implemented for the purpose of silica removal. The implant surfaces do have adhering particles (non-silica) and fibers due to electrostatic forces. The Mentor manufacturing rooms are environmentally controlled to function as class 10000 clean rooms to minimize airborne particulate contamination during manufacture and assembly of devices.

In direct response to this inquiry posed by the FDA, Mentor Gel-Filled Mammary Implants were analyzed to determine if IPA would remove free silica on the implant surface if it was inspected by microscopy before and after surface washing was performed by (see Report M 043). Analysis was performed on smooth gelatin caps that represented sterilized, packaged finished product manufactured in Texas.

The test results indicated that fibers and particles were observed on all devices. None of the devices were observed to have the translucent particles characteristic of silica aggregates. Device surfaces that were intentionally dusted with silica demonstrated that silica aggregates could be observed by microscopy on the device surface and on the filter membrane after filtration of the solvent wash. The use of IPA in the washing procedure was effective in removal of loose silica as well as some of the fibers and other particles. The washing procedure was not intended to precisely duplicate a manufacturing process nor was it intended to accomplish removal of all surface particles. It was intended to demonstrate the efficacy of any isopropanol wash to remove silica particles. The effectiveness of the manufacturing process to remove surface particles would be demonstrated through validation of this process. The details of this testing is documented in test report M043.