

## Silicone Gel Bleed Testing

26. Silicone gel bleed, which is the diffusion of gel constituents (e.g., low molecular weight silicones) through an intact shell, appears to occur continuously for silicone gel-filled breast implants. To address silicone gel bleed, you provided extended ASTM F703 testing and a gel loss analysis.

The ASTM F703 test methodology quantifies the extent of gel bleed. However, as you stated, the results from this testing has limited clinical correlation because the ASTM F703 test method was established for the purpose of allowing comparison between device models rather than quantifying in-vivo gel bleed. In addition, the ASTM F703 test method was not established to identify and quantify the gel bleed constituents. Thus, FDA does not believe that this test methodology provides adequate data to address gel bleed for the purposes of a PMA.

The gel loss analysis in Section 8.5 of the PMA was intended to determine the rate of gel loss over time in-vivo from intact explanted devices. The gel loss was determined based on a comparison of the explant weight to the design weight specifications. One major weakness of your gel loss analysis is that you based your rationale of why the minimal weight change was not due to diffusion of materials entering the device and mixing with the gel filler on the visual appearance of the gel. Another major weakness is that you had no unimplanted control devices for comparison purposes. FDA does not believe that an accurate assessment of overall gel bleed over time can be made on these data as a result of these study weaknesses. More importantly, FDA believes that the use of explanted devices to assess gel bleed is problematic because the in-vivo and in-vitro environmental conditions for explanted devices are variable and unknown.

As stated in our January 2004 breast implant guidance document, we believe that information regarding the amount and identity of gel bleed constituents should be provided. Neither your ASTM F703 testing or gel loss analysis provide this information. Therefore, please provide the identity of the gel bleed constituents (including the platinum species or other catalysts) and the rate that these gel constituents bleed out over time. To address this item, you should consider a new gel bleed bench test based on a protocol that mimics in-vivo conditions (e.g., incubate the breast implants in a lipid-rich medium prior to testing and conduct testing in a physiologic environment). This information is needed to provide adequate labeling for women who may be considering breast implants.

26 Response:

Gel Bleed Test Results (CP 246, CP 246 Addendum I in Attachment 28, CP 411, and CP 411 Addendum I in Attachment 29)

2005-4101B1-01-04-RESPONSE-MENTOR

Mentor has performed new *in vitro* bleed experiments to determine the identity and diffusion rate of potential bleed materials (see Report CP 246 in Attachment 28). This testing utilized an intact device in physiological media (*i.e.*, porcine serum), which was selected to simulate the composition, including lipid content, of the extracellular fluid within the fibrous capsule that is in direct contact with the implant in the patient.<sup>1/2/</sup> Data for low molecular weight dimethylcyclosiloxane, linear siloxane, and vinylterminated linear siloxane diffusion (by gas chromatography/mass spectroscopy), and platinum diffusion (by inductively coupled plasma/mass spectroscopy) from a device into serum were collected. Based upon the results, only D4, D5, D6, and platinum exhibited measurable diffusion into the serum over a 120-day period at 37°C; however, a time-dependent trend was evident for platinum, but not the siloxane compounds. All diffusion of these compounds into serum ceased by 120 days. The largest total amount of low molecular weight siloxane compound (D<sub>5</sub>) diffusing into the serum from a 125cc Smooth Round Moderate Profile Gel-filled device was only 2.8 µg. Only a total of 4.1 µg of platinum was detected in the serum. These data suggest that the amount of silicone and platinum diffusing from intact gel-filled devices into physiological surroundings *in vivo* is very low, *i.e.*, in the microgram range.

These *in vitro* bleed data strongly support Mentor's previous finding that intact explanted gel-filled devices have virtually no detectable weight loss due to gel bleed, even after as long as fifteen years of implantation. Bleed from these devices into physiological surroundings is very low compared to the weight of these devices.

Extensive testing, including the new gel bleed studies, demonstrated that there is little gel bleed from the device. Thus, the conclusions reached in the weight loss report included in our original PMA submission are supported by the following additional information provided in this PMA amendment: an amended copy of that explant weight loss report (Report M 054 in Attachment 30), new gel bleed studies, and a report providing data to demonstrate that gel-filled devices implanted in patients for as long as about nine years did not take up appreciable amounts of water, protein, or lipids (the most common biological materials surrounding the implant) into the device shell or gel filler (see attached report CP 411 in Attachment 29, Explant Testing: determination of Moisture, Protein, and Fat). Three explanted devices (implanted for 3.5, 6.4, and 8.9 years) were analyzed for water, protein, and lipid content. At most, biological materials with a total weight of only approximately one-third of a gram for an 800cc device were taken up over about nine years. Therefore, one can only conclude that the lack of noticeable device weight change over the nine to fifteen years of implantation presented in the original device weight loss report was due to the relative lack of gel bleed from the device.

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1/ Ostrowska, E., Gabler, N.K., Sterling, S.J., Tatham, B.G., Jones, R.B., Eagling, D.R., and Dunshea, F.R. "Consumption of Brown Onions (*Allium Cepa* Var. Cavalier and Var. Destiny) Modulates Blood Lipids, Haematological and Haemostatic Variables in Healthy Pigs," *Br. J. Nutr.*, 91(2), 211, 2004.

2/ Tietz, Textbook of Clinical Chemistry, Edited by Burtis, C.A. and Ashwood, E. R. 3rd Edition, p. 826-827 (1999).

Originally, Mentor did not test unimplanted control devices as part of the device weight loss study because such controls would not have provided any useful information to help understand whether the explant bleed rate determination was meaningful or an artifact. Any weight loss from an unimplanted device packaged for at least nine years would have represented gel bleed onto or into the packaging material for that period of time. How these control bleed rates would be expected to compare with the *in vivo* bleed rates is not known, so that one cannot meaningfully interpret any differences observed between unimplanted control and *in vivo* bleed rates. (Recall that Mentor has already presented data in the Chemistry Module indicating that device bleed into one polymeric material, *i.e.*, a silicone disc, is much different from *in vivo* bleed rates.) If the packaged unimplanted control devices (stored for at least nine years on a shelf) had shown an appreciable increase in weight that increase could only have been due to water uptake from humidity. Since water content was measured in some of the explanted devices and was found to be almost nonexistent, unimplanted controls are not necessary to account for this possibility.

However, subsequent to the original device gel bleed report, as part of a project investigating semivolatiles compounds in gel, the weight of an unimplanted Mentor smooth and three unimplanted textured control d-----r-----  
-----r at least nine years was measured at -----  
----- Based upon their measured weight-----k-----  
-----ed device weight specification, these devices were 102 – 103% of their nominal specification weights. These weight percentages are within the range of those seen with the explanted devices in the original device weight loss report. Based upon these unimplanted control data and the knowledge that virtually no water, protein, or lipids have entered the device, the original device weight loss data strongly suggest that in the worst case only very small amounts of gel bleed may leave the device *in vivo* (*e.g.*, a fraction of a gram from an 800cc device) even over an implantation period as long as nine years.