

REPORT REVISIONS FEBRUARY 18, 2004 AND APRIL 9, 2004

The original report has been revised with two sets of changes, first to encompass changes encountered as a result of questions and requests from FDA (received February 11, 2004) (Amendment I) and later to document re-weighed device weights performed because of potential inaccuracies discovered in the original weighing of devices used in this analysis (Amendment II).

In the course of responding to FDA's February 11, 2004 questions, it was discovered that a counting error and duplicate device entries existed in the data table. As a result, the total number of devices tested was reduced from ninety-nine (99) to ninety-three (93) and necessary changes to the text and figures were made to reflect this. In addition, FDA requested information on the percent of explant fill weight compared to the minimum and maximum fill specifications, and not just the nominal fill weight specification. This was added to the data table along with the minimum and maximum specifications for each device. These changes constitute Amendment I.

At a later date, it was noted that some of the out of specification devices may have been inaccurately weighed when they were originally entered into the data base, especially in the case of devices which weighed significantly more than the maximum specification. As a result, all available devices used in the original analysis were taken from storage and re-weighed. Seventy-four (74) of the original ninety-three (93) were available for re-weighing. Those data were added to the revised data table under the columns "Reweighed Explants (3/04)" and "New % Implant Weight (nominal fill spec.)" and new Figures 1 and 2 generated based upon the most recent device weights.

Because the conclusions in the original report were not changed due to any subsequent findings or analysis during the re-weighing, this latter data was only added to the report as an amendment section at the end of the report. No report text was changed to include this information. These changes constitute Report Amendment II (see section after Appendix 3).

REPORT AMENDMENT I
(Changes Associated With FDA's Requested Information, Feb. 18, 2004)

After reviewing the original explanted gel-filled device weight loss report, FDA requested additional information and analyses pertaining to the lower and upper fill weight specifications, and not just the nominal fill weight specification as originally provided in the report. In addition, FDA wanted more information on how devices were selected for analysis from the original data base (to assure randomness of the selection) and to know the number of explanted devices which were outside of their fill weight specification.

In the course of replying to FDA's requests, it was determined that duplicated device data table entries existed; therefore, the data base actually contained ninety-three (93) devices instead of the ninety-nine (99) as originally stated in the report. Changes in the report text were made to reflect this corrected number of devices. The data table attached to this amendment was also revised (and denoted as Revision I) to reflect this change and to provide additional information as requested by FDA. The following columns were added to the data table: "% Implant Weight (min. fill spec.)," "% Implant Weight (max. fill spec.)," "Fill Spec. Min.," and "Fill Spec. Max." Finally, some reference numbers under the "Drw. Spec." column were determined to be in error and were corrected.

MENTOR LOW BLEED GEL-FILLED MAMMARY PROSTHESIS GEL LOSS ANALYSIS ON INTACT EXPLANTS

I. PURPOSE

The purpose of this study was to determine the rate of gel loss over time in vivo from intact explanted Mentor Smooth and Siltex Low Bleed Gel-filled Mammary Prostheses. This data analysis is relevant to public questions concerning the long term safety of gel-filled mammary implants.

II. INTRODUCTION

There is public concern for the long term safety of gel-filled mammary prostheses, including the loss of gel into an implant patient's body over time (referred to as "gel bleed"). The question concerns whether compounds from the device's silicone gel filler will leak into a patient's body while the device is implanted due to the diffusion of gel filler components through the device shell. That bleed process has been measured in vitro for intact Mentor Smooth Low Bleed Gel-filled prostheses using the test suggested in ASTM F 703-96, Standard Specification for Implantable Breast Prostheses (Appendix X2, Feasibility Protocol for Gel Bleed In-vitro Testing by Means of a Silicone Disk, in that document).¹ (The ASTM document does not recommend that test for textured surface mammary prostheses because the total contact area between the device surface and the silicone pad used in the test to collect the bleed cannot be determined.) Unfortunately, that test method does not replicate the in vivo environment of the implanted mammary prosthesis, and therefore still leaves the question of how much gel bleed from an intact device actually occurs in a patient.

The measured in vitro silicone gel bleed rate is assumed to be an exaggerated rate since gel bleed diffuses into a silicone pad much easier than into a hydrophilic material such as human tissue. The tissues surrounding the implanted device are mostly made up of water. Since the solubility in water of the vast majority of silicone gel's extractable compounds is very low, if not unmeasurable, one could easily postulate that the rate of gel bleed in vivo would be less than the in vitro measured rate. In an attempt to accurately determine the in vivo rate of bleed, Mentor decided to analyze the weights of a sample group of intact explanted gel-filled devices. These devices had been examined by Mentor Texas' Product Evaluation (PE) Department and were determined to be intact devices.

Both smooth and textured Low Bleed Gel-filled devices were chosen for examination. Even though the in vitro bleed rate of Siltex textured devices was not determined, the analysis of explanted Siltex devices could still provide some information on their change in weight over years of implant. Device weight at the time of gel fill is known within a specified range for each device size. As a result, by comparing a returned intact device's weight to its original specification nominal weight, an approximate

percentage of original device weight at explant can be determined. This percent for each device can then be plotted versus the time that device had been implanted. Some amount of error would be inevitable due to the tolerance on the device fill weight. For a population of explanted Smooth Gel-filled Prostheses, this data can be compared to a calculated theoretical loss of gel over time due to the in vitro bleed rate to understand how close or different the in vivo compared to in vitro bleed rate is.

III. SAMPLES FOR ANALYSIS

A sample of intact devices was chosen from a PE Department database consisting of devices which were returned to Mentor for the complaint of rupture. Those devices had been gently wiped to remove obvious loose surface attachments. The devices had undergone an examination, and as a result were deemed to be intact (i.e., were not ruptured), contrary to the complaint. As with all returned devices when possible, the weights of those devices were recorded. From that population of intact devices, a sample of forty-three (43) Siltex Low Bleed Gel-filled Mammary Prostheses and fifty (50) Smooth Low Bleed Gel-filled Mammary Prostheses were chosen to provide a wide range of years of implantation for each type of device (0.1 to 9.4 years for Siltex devices and 0.2 to 15.2 years for Smooth devices). The samples also represented a wide range of device sizes. (See Appendix 1 for device details)

The Low Bleed devi-----

For all Low Bleed Siltex-----

-----.)

IV. METHODS OF ANALYSIS

The sampling of devices for the analysis consisted of various sizes of smooth and textured devices. Because varying device sizes have varying weights, the analysis was performed by comparing the device weight at explant to its original nominal weight after filling, i.e., expressed as a percentage of its original fill weight. The whole population of smooth or textured devices could then be plotted as percent of original

weight versus time implanted to see whether devices lost weight over the time they were implanted.

For comparison purposes, a theoretical calculation of gel loss from a smooth gel-filled device over several years was performed using an average ASTM in vitro gel bleed rate, as measured in Texas report HS72.030826.01 (Revision AdB). This gel loss calculation was performed for the smallest device (100cc) and the largest device (800cc). (See Appendix 3 for the actual theoretical calculations.)

V. RESULTS

The plotted Smooth Low Bleed and textured Siltex Low Bleed Gel-filled explanted device data can be seen in Figures 1 and 2, respectively. The trend-line for the smooth device data is horizontal at about 100% of implant weight at explant suggesting that the devices have lost little, if any, weight during the implant time ranging from 0.2 to 15.2 years. Based upon a flat trend-line, the data indicate that the bleed rate for smooth devices over the fifteen years would be extremely low assuming that no materials have diffused into the device during that time.

The trend-line for the textured Siltex device data is close to horizontal at about 100% of implant weight at explant for the 0.1 to 9.4 year implant time range, in actuality showing a slight rise over the implant period. All weights are within the fill weight tolerance, so this slight variation is likely the result of varying initial fill levels. Unlike the smooth device data plot, no comparative theoretical gel loss data has been plotted because the ASTM F 703-96 gel bleed test is not recommended for textured devices and there is no other widely accepted method to use for measuring gel bleed. Based upon the trend-line, the data indicate that the bleed rate over about nine and one half years of implant would be approximately zero assuming that no materials have diffused into the device during that time.

VI. DISCUSSION

The gel loss data for Mentor's intact Smooth and Siltex Low Bleed Gel-filled Mammary Prostheses suggest that very little gel is lost from the devices if no other materials diffuse into the device over time. Based upon the explant data, almost no change in weight occurs in the device over time, while based upon the in vitro calculated bleed rate a 100cc device would theoretically be expected to lose all of its gel in seven years and an 800cc device in about fifteen years. The data indicate that the in vivo bleed rate of intact devices is not similar to the measured in vitro data using the ASTM method and that the in vitro method creates an exaggerated scenario for gel bleed. This finding is plausible considering that fact that almost all gel extractable compounds have very low solubility in water; therefore, they are likely to collect on the surface of the device in vivo. This would theoretically slow and eventually stop the gel bleed if the compounds are not removed from the device surface in vivo.

Mentor's smooth and textured devices, in general, appear to have similar in vivo bleed rates. The slight upward slope of the explanted textured device percent of implant weight trend-line could perhaps be explained by the device absorbing material from its in vivo surroundings. Additional chemical analysis of explanted devices will be performed to understand whether this phenomenon is occurring. The likelihood of no apparent weight change in the devices over an extended number of years in the body due to total replacement of the gel filler by materials from the body is virtually nil. If appreciable amounts of gel were being replaced by materials entering the device and mixing with the gel filler, then one would expect to see noticeable changes in the consistency and appearance of the explanted gel in devices. These types of noticeable changes are not seen with intact explants. Only a slight yellowing of the gel with age is seen.

A more plausible reason for the slight -----

VI. CONCLUSIONS

For Mentor's Smooth and Siltex Low Bleed Gel-filled Mammary Protheses which are intact at explant, the analysis of percent of implanted weight at explant versus time implanted shows that these devices change their weights very little, if at all, over a period of fifteen years in the body for smooth devices and almost nine and one half years for textured devices. There is no sign of substantial weight loss from Smooth devices during these periods. When compared to a theoretical smooth device gel loss calculation (based upon an ASTM measured in vitro gel bleed rate), it is clear that the in vitro measured bleed rate is an exaggeration of the actual in vivo bleed rate.

The Siltex Gel-filled Mammary device exhibited a sm-----

With regard to long term safety of these devices when used clinically, the data suggest that very little gel appears to be diffusing through an intact shell and into a patient's body over at least fifteen years for smooth devices and almost nine and one half years for textured devices.

VII. REFERENCES

1. ASTM F 703-96, Standard Specification for Implantable Breast Prostheses (Approved June 10, 1996).
2. HS72.030826.01 AdB - Addendum to the Engineering Study Report for Evaluation of Gel Bleed for Mentor Gel Filled Implants.

Fig. 1: Gel Loss Analysis of Intact Explants (Smooth Gel-filled, n = 50)

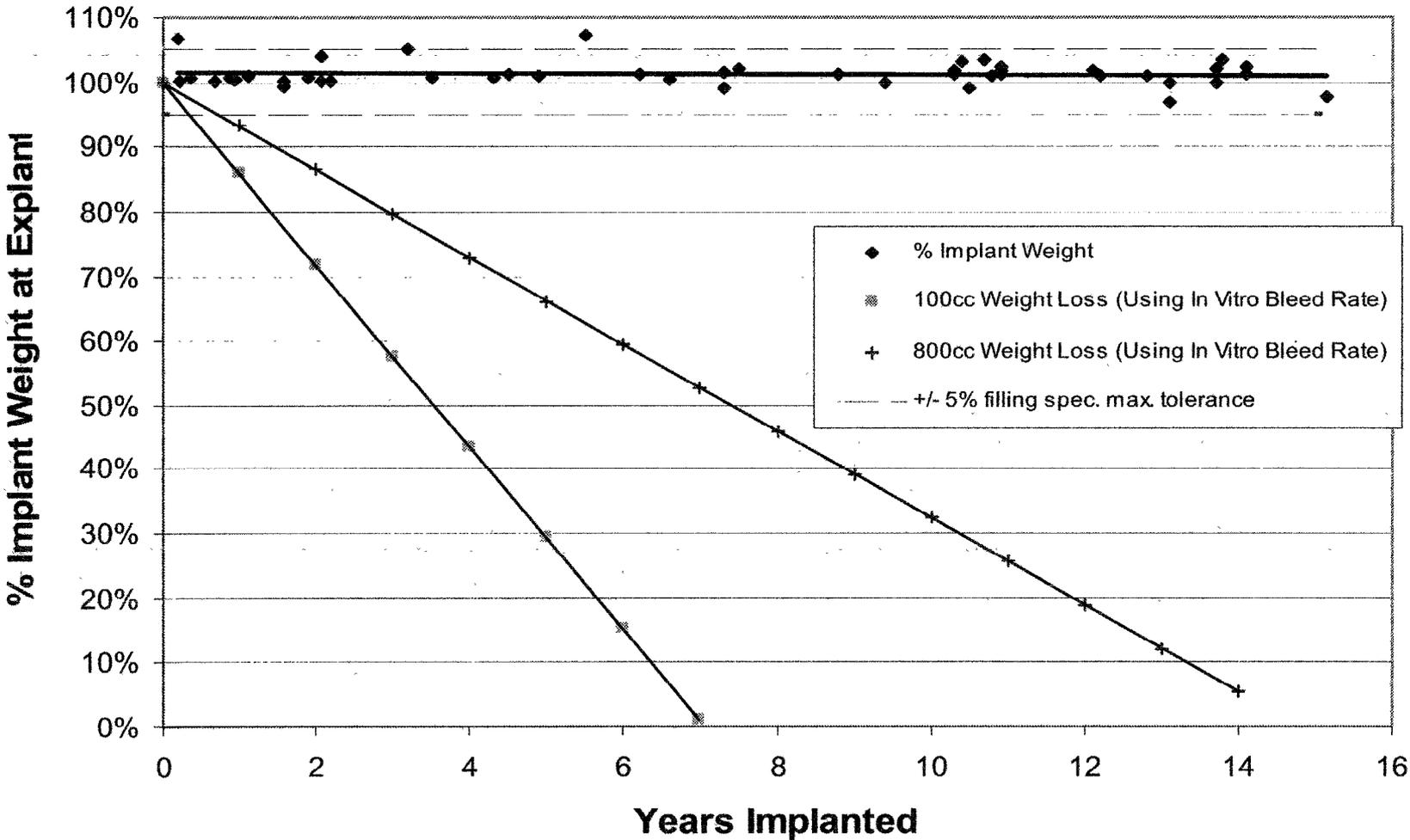
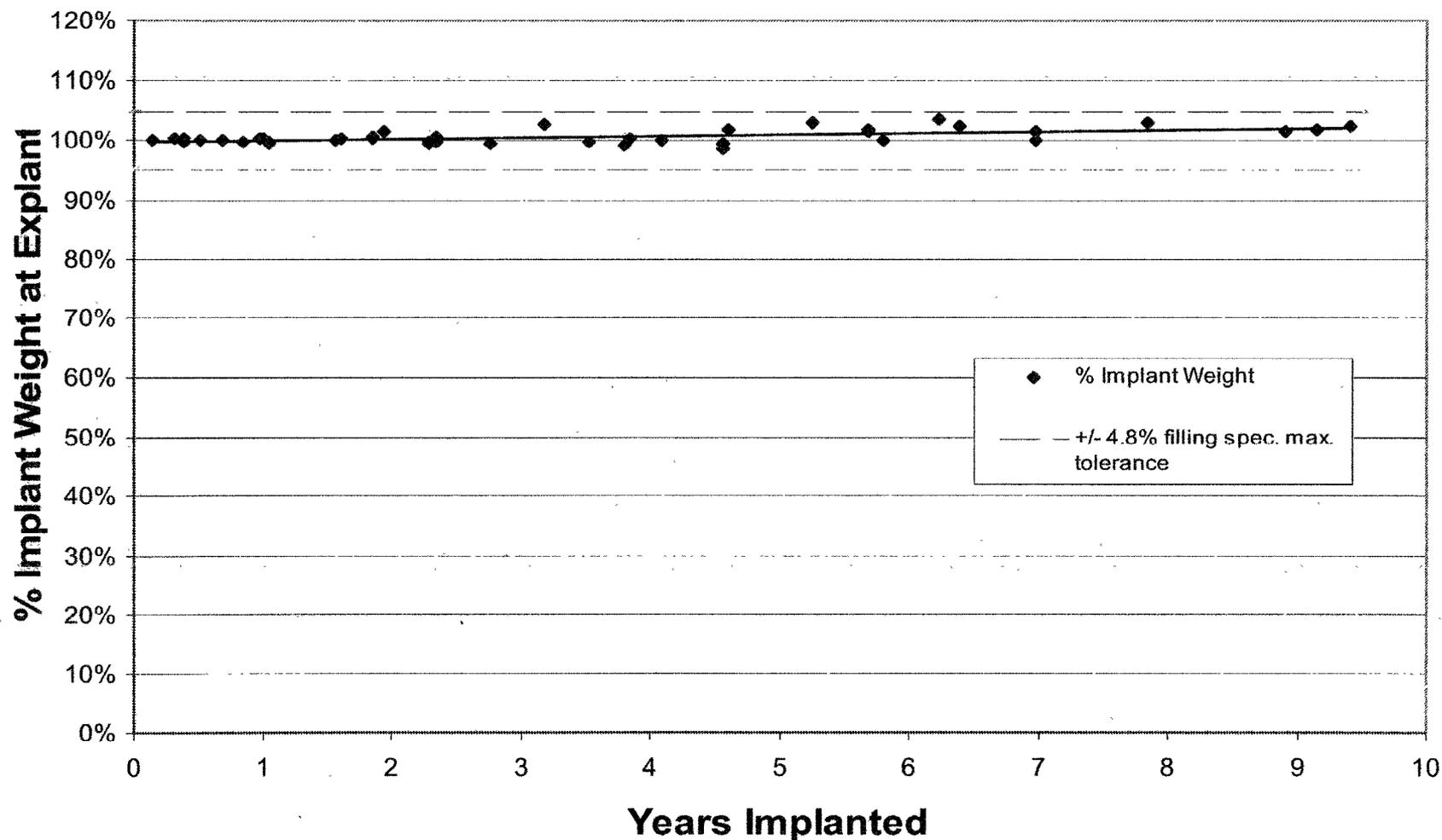


Fig. 2: Gel Loss Analysis of Intact Explants
(Siltex Gel-filled, n=43)



APPENDIX 1

EXPLANTED DEVICE DATA

APPENDIX 2

GEL-FILLED PROSTHESIS SPECIFICATION DRAWINGS

(SEE ORIGINAL HARD COPY OF THE REPORT FOR DRAWINGS)

APPENDIX 3

THEORETICAL GEL LOSS CALCULATIONS

THEORETICAL GEL LOSS CALCULATIONS

- Assumptions:
1. The surface area of the device can be approximately modeled as two flat discs representing the anterior and posterior surfaces of the shell. The diameter of the discs is equal to the diameter of the device. The surface area of the radius edge of the device is not included in this calculation, but is small compared to the anterior and posterior surface area combined.
 2. An in vitro bleed rate of 0.0020 g/cm²/wk was used. This value is approximately half way between the fastest (0.0035 g/cm²/wk) and the slowest (0.0011 g/cm²/wk) bleed rates measured (see attached table at the end of this Appendix for calculated weekly bleed rates from report HS72.030826.01 AdB - Addendum to the Engineering Study Report for Evaluation of Gel Bleed for Mentor Gel Filled Implants).
 3. Diameter of the 100cc Smooth Low Bleed Gel-filled Mammary Prosthesis is 9.3 cm. Device contains 100 gm gel.
 4. Diameter of the 800cc Smooth Low Bleed Gel-filled Mammary Prosthesis is 18.2 cm. Device contains 800 gm gel.

Calculations:

100cc Smooth In Vitro Bleed Rate (100 gms gel)		
Yrs Imp.	Gel Weight	% orig. weight
0	100	100%
1	85.9	86%
2	71.7	72%
3	57.6	58%
4	43.5	43%
5	29.4	29%
6	15.2	15%
7	1.1	1%
8	0	0%

800cc Smooth In Vitro Bleed Rate (800 gms gel)		
Yrs Imp.	Gel Weight	% orig. weight
0	800	100.0%
1	745.9	93.2%
2	691.8	86.5%
3	637.7	79.7%
4	583.6	73.0%
5	529.5	66.2%
6	475.4	59.4%
7	421.3	52.7%
8	367.2	45.9%
9	313.1	39.1%
10	259	32.4%
11	204.9	25.6%
12	150.8	18.9%
13	96.7	12.1%
14	42.6	5.3%

Dia. = 9.3cm
 Tot. Area = 135.8 cm²
 Bld. rate = 0.27166509 gm/week
 Bld. rate = 14.1265847 gm/yr

Dia. = 18.2 cm
 Tot. Area = 520.21242 cm²
 Bld. Rate = 1.04042484 gm/week
 Bld. Rate = 54.1020917 gm/yr

CALCULATED BLEED RATES FROM REPORT HS72.030826.01 AdB

	TESTING INTERVAL								
	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8
W_g^* (g/cm ²)	0	0.0035	0.0055	0.0072	0.0085	0.0096	0.0104	0.0114	0.0123
R_g^{**} (g/cm ² /wk)	0	0.0035	0.0028	0.0024	0.0021	0.0019	0.0017	0.0016	0.0015

	TESTING INTERVAL						
	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15
W_g^* (g/cm ²)	0.013	0.0136	0.0142	0.0147	0.0153	0.0158	0.0162
R_g^{**} (g/cm ² /wk)	0.0014	0.0014	0.0013	0.0012	0.0012	0.0011	0.0011

* W_g = cumulative average weight of gel diffusion per surface area

** R_g = average weight of gel diffusion per surface area per week ($R_g = W_g / \text{Time in weeks}$)

REPORT AMENDMENT II

REPORT AMENDMENT II (Re-weighed Device Data, April 9, 2004)

The potential for inaccurate explant device weights was discovered while re-checking the weights of intact explanted devices which were originally determined to be outside of their fill weight specifications. As a result, all available devices analyzed in the original explanted gel-filled device weight loss report were re-weighed in March, 2004 by the Texas Product Evaluation (PE) Department to ensure the accuracy of the device weight loss data when comparing unimplanted device fill weight specifications to explanted device weights. Not every device could be re-weighed, only seventy-four (74) of the original ninety-three (93). Twelve (12) devices had been destroyed during other explant testing, two (2) devices were found to be ruptured upon re-examination, and five (5) devices could not be located. (Note that all explanted devices which could not be re-weighed were determined to be within their fill specifications when originally weighed.)

After re-weighing, it was determined that instead of the original seven Smooth devices reported to be out of their fill weight specification range, only four (4) Smooth devices were out of their specification range (two above and two below). As was reported in the original report, no Siltex gel-filled devices were outside of their fill weight specification. All conclusions stated in the original report remain true based upon the data from the re-weighed devices.

The data table listing all devices and their pertinent information has been revised due to the re-weighing (and has been denoted as Revision II) to include the columns "Reweighed Explants (3/24/04)" and "New % Implant Weight (nominal fill spec.)." Those device weights in bold type under the column "Reweighed Explants (3/24/04)" are the devices with out of specification weights. In addition, Figure 1 Gel Loss Analysis of Intact Explants (Siltex Gel-filled) (Rev. 1) and Figure 2 Gel Loss Analysis of Intact Ex-----

Fig. 1: Gel Loss Analysis of Intact Explants
(Smooth Gel-filled, n=40, Weighed 3/24/04)

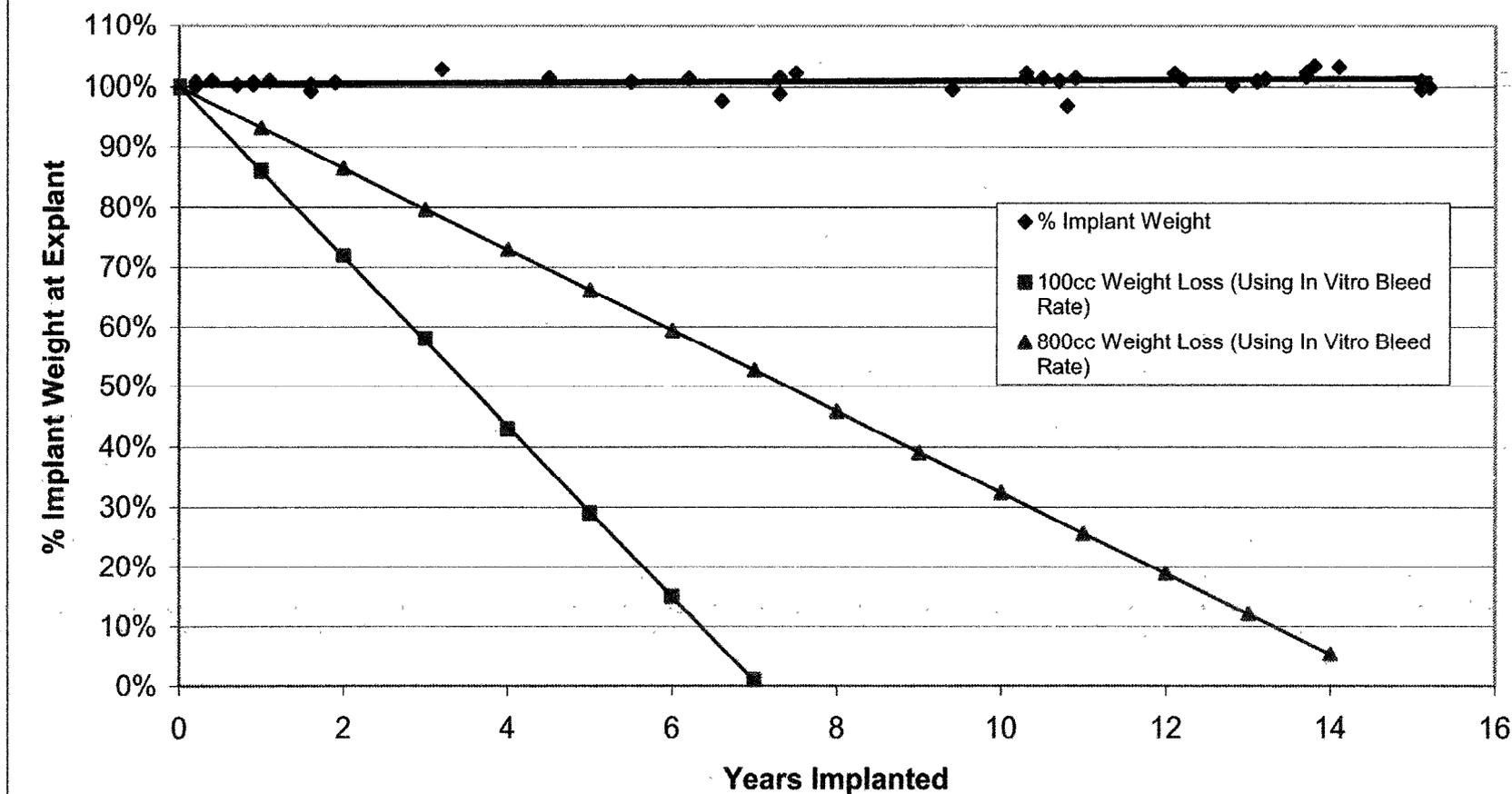


Fig. 2: Gel Loss Analysis of Intact Explants
(Siltex Gel-filled, n=34, Weighed 3/24/04)

