
PANEL MEMORANDUM

TO: Panel Members

FROM: Samie Allen, ODE/DGRND/PRSB

DATE: June 11, 2002

SUBJ: P990075
Mentor Corporation
Saline-Filled and Spectrum Mammary Prostheses
Status of PMA Conditions of Approval

Background:

On May 10, 2000, the Mentor Saline-Filled and Spectrum Mammary Prostheses were approved for females for the following indications:

- ?? Breast Augmentation. A woman must be at least 18 years old for breast augmentation.
- ?? Breast Reconstruction.

There were 5 conditions of approval for this PMA:

1. Post-approval study
2. Focus group study
3. Retrieval study
4. Fatigue testing
5. Shelf life testing

The status of each condition of approval is presented below.

1. Post-Approval Study

The purpose of the post-approval study is to collect additional safety data out to 10 years on patients already enrolled in the Saline Prospective Study (SPS). Mentor referred to their post-approval study as the Post-Approval Study (PAS). Mentor provided all available 5-year data, collected as per the original protocol of the SPS. The date of database closure is 3/13/02.

The augmentation data and reconstruction data are presented together.

Tables 1 and 2 summarize the patient disposition information to establish the number of patient eligible for participation into the PAS.

Table 1: Patient disposition information for the SPS¹ (by patient)

	Augmentation	Reconstruction
Number of patients implanted in SPS who were not protocol violations	1264	416
Number of deaths by end of SPS	2	13
Number with removal of all study implants by end of SPS	10	28
Number living with implants remaining by end of SPS (Expected follow-up)	1252	375
Number living and with implants with 3-year follow-up by end of SPS (Actual follow-up)	955	283
Percent follow-up of PAS at 3 years ²	76.3%	75.5%

Notes: ¹Saline Prospective Study, a 3-year prospective study, which was the basis for PMA approval.

²Actual follow-up divided by expected follow-up (theoretical/implanted minus deaths and removals without replacements).

Table 2: Patient disposition information for the PAS¹ (by patient)

	Augmentation	Reconstruction
Number living with implants remaining at end of SPS	1252	375
Number of additional deaths by start of PAS ²	1	7
Number of additional removals of all study implants by start of PAS ²	1	17
Number living and with implants remaining at the start of the PAS (Expected follow-up at PAS start)	1250	351

Notes: ¹Post-approval study: investigators in the SPS were sent letters in July of 2000 (following PMA approval in May of 2000) notifying them of the PAS; mailings to patients began in October of 2000.

²These occurred after the 3-year follow-up of the SPS was complete but prior to initiation of the PAS.

Tables 3 and 4 below summarize the **patient accounting** over the 10-year time period of the PAS, as summarized by Tables 1.1A by Mentor. In these tables “actual” follow-up reflects the follow-up year for returned questionnaires. Mentor has only recently improved their efforts to contact patients and many patients had exceeded their 5 year follow-up visit at the time of the start of the PAS, which is why the follow-up rate of 6 and 7 years is superior to that of 5 years.

Table 3: Patient accounting for PAS **augmentation** patients over time

Augmentation Patient Accounting	5 years	6 years	7 years	8 years	9 years	10 years
Theoretically due ¹	1264	1221	1212	1132	769	27
Deaths	3	0	1	0	0	0
Removals ²	40	9	25	16	4	0
Not yet due for follow-up	0	0	54	347	738	27
Expected ³	1221	1212	1132	769	27	0
Actual	60	289	505	371	14	0
Follow-up rate ⁴	5%	24%	45%	48%	52%	0%
Number (%) of patients with any data ⁵	661 (54%)	655 (54%)	591 (52%)	372 (48%)	14 (52%)	0 (0%)

Notes: ¹Excludes patients who are not yet due for follow-up, as well as deaths and removals from prior timepoint.

²Number of patients with removal of all study implants without replacement.

³Theoretically due minus deaths and removals.

⁴Actual divided by expected.

⁵Cumulative values with denominator based on expected. Returned questionnaires are assumed to be applicable to all previous time(s), which significantly improves the follow-up rate. While this approach may be reasonable for definitive events, such as implant removal, or over short periods of time (i.e., 1-2 years), it is probably not appropriate for events other than implant removal or for periods of time greater than 1 or 2 years.

Table 4: Patient accounting for PAS **reconstruction** patients over time

Reconstruction Patient Accounting	5 years	6 years	7 years	8 years	9 years	10 years
Theoretically due ¹	416	335	319	87	49	3
Deaths	24	3	3	0	0	0
Removals ²	57	13	3	2	0	0
Not yet due for follow-up	0	0	226	36	46	3
Expected ³	335	319	87	49	3	0
Actual	175	187	47	27	1	0
Follow-up rate ⁴	52%	59%	54%	55%	33%	0%
Number (%) of patients with any data ⁵	245 (73%)	220 (69%)	58 (67%)	28 (57%)	1 (33%)	0 (0%)

Notes: ¹Excludes patients who are not yet due for follow-up, as well as deaths and removals from prior timepoint.

²Number of patients with removal of all study implants without replacement.

³Theoretically due minus deaths and removals.

⁴Actual divided by expected.

⁵Cumulative values with denominator based on expected. Returned questionnaires are assumed to be applicable to all previous time(s), which significantly improves the follow-up rate. While this approach may be reasonable for definitive events, such as implant removal, or over short periods of time (i.e., 1-2 years), it is probably not appropriate for events other than implant removal or for periods of time greater than 1 or 2 years.

Tables 5a and 5b below summarize Mentor’s **patient contact information** as of May 2002. Table 5a covers all patients while Table 5b focuses on rows 6 and 7 of that table. More specifically, since March 2002, Mentor has provided FDA with weekly updates of their contact efforts. These contact efforts were made because there were a large number of patients who were eligible for the PAS whom Mentor had not contacted. Mentor categorized these patients into non-responders and packets undeliverable patients. The primary steps that Mentor took to contact these patients included re-approaching investigators whose patients had not responded and increasing the incentives if the investigator was successful in contacting patients; making multiple mailings to the same patient via the United States Postal Service; mailing via Federal Express requiring patient signature in order to track and verify patient receipt; and using the National Change of Address (NCOA), US Search, ChoicePoint, and 411 databases to obtain updated addresses and phone numbers for patients.

Table 5a: Patient contact responses as of May 21, 2002.

Overall Contact Information	Augmentation	Reconstruction
1. Patients expected for PAS follow-up ¹	1250	351
2. Patients excluded from participation in PAS (discontinued due to “other,” illness, or physician request) ²	94	25
3. Patients to whom packets were mailed	1156	326
4. No questionnaire received but patient discontinued due to explant or death	2	1
5. No questionnaire received but patient discontinued by choice	75	27
6. No response to packet (non-responder patient) ³	45	10
7. Packet returned undelivered (packet undeliverable patient) ³	110	14
8. Lost to follow-up ⁴	140	7
9. Questionnaires received but patient had outstanding issue before data could be entered	11	4
10. Questionnaires received but patient ineligible due to death or explantation ⁵	101	47
11. Questionnaires received but patient declined to participate in PAS (but available data included)	32	8
12. Questionnaires received and patients agreed to participate in PAS	642	209
13. Number of patients contacted ⁶	863	296
14. Percentage of patients contacted ⁷	75%	91%
15. Patients with any data reported at any time ⁸	777	265

Notes: ¹Derived from number of patients theoretically due minus deaths and explants prior to start of PAS.

²Mentor confirmed that these patients were not sent questionnaires. Of these 119 discontinuations, 96 were due to physician request: either (1) the physician did not want patients contacted via mail due to confidentiality or (2) the physician did not want to participate in the PAS. There were 3 physicians who comprised the 96 discontinuations due to physician request. Mentor provided documentation of their efforts with those physicians to have the physician or Mentor themselves contact the patients for enrollment into the PAS.

³Mentor is continuing their efforts to contact these patients.

⁴Includes patients whom Mentor was unable to locate and patients who did not respond to contact attempts.

⁵For patient deaths in this category, Mentor confirmed that either a physician or family member returned the questionnaire.

⁶Sum of rows 4, 5, 9, 10, 11, and 12.

⁷Row 3 as denominator.

⁸Sum of rows 4, 10, 11, and 12. Represents the number of patients with questionnaire returned at least once for that patient.

Table 5b: Patient contact results specific to non-responder and packet undeliverable patients as of May 28, 2002.

Contact Efforts for Non-Responder and Packet Undeliverable Patients	Non-Responder (N=150)		Packet Undeliverable (N=367)	
	As of 3/25/02	As of 5/28/02	As of 3/25/02	As of 5/28/02
Packets undeliverable	1	NA	1	NA
Not all addresses verified	1	17	34	84
Outstanding issue	4	4	2	4
No	8	15	10	25
Yes	8	29	47	91
Explanted	9	14	5	13
Expired	0	0	1	2
Lost to follow-up	20	36	53	110
Still waiting for patient response	99	35	214	38

As shown in the table above, as of 5/28/02, Mentor has come to resolution on 943 (63%) of the non-responders and 241 (66%) of the packets undeliverable patients. Mentor is continuing their efforts with these patients.

Based on the large number of patients lost-to-follow-up, FDA requested Mentor to assess for non-response bias and adjust the data for non-response bias. Mentor defined responders as those patients returning a questionnaire, or who were ineligible due to death or implant removal, which is a generous definition of responder. Of the 1601 patients expected at the start of the PAS, there were 909 responders, as defined above, and 692 non-responders. Chi-square and two sample t-test analyses of these groups with respect to baseline demographic and surgical characteristics showed no statistically significant differences with respect to race/ethnicity, education level, and overweight (BMI ≥ 24). Statistically significant differences between responders and non-responders were noted for the following:

- ?? age at time of implant - responders older than non-responders (mean of 36 versus 33 years; $p < 0.001$)
- ?? marital status at time of implantation - responders more likely married than non-responders (56% versus 43%; $p < 0.001$)
- ?? household income at time of implantation - responders more likely to have annual household income in excess of \$60,000 than non-responders (25% versus 17%; $p < 0.001$)
- ?? indication for implantation - responders more likely to be reconstruction patients than non-responders (27% versus 15%; $p < 0.001$)
- ?? unilateral implantation - responders were more likely to have unilateral implantation than non-responders, most likely reflecting the reconstruction indication (16% versus 10%; $p = 0.002$)
- ?? surgical approach - responders more likely than non-responders to have a surgical approach other than periareolar, again reflecting the reconstruction indication (65% versus 51%; $p < 0.001$)
- ?? implant placement - responders more likely undergoing submuscular placement than non-responders, again reflecting the reconstruction indication (78% versus 73%; $p = 0.05$)
- ?? incision size - responders having larger (> 3 cm) incision size than non-responders (66% versus 57%; $p < 0.001$)
- ?? surface texturing - more responders implanted with a non-smooth surfaced implant than non-responders (75% versus 65%; $p < 0.001$)

In summary, even with Mentor's generous definition of a responder, which is still only approximately half of the entire cohort--909 of the 1601 patients (57%)--given the numerous significant differences between responders and non-responders, it is problematic to generalize the results from the responders to the entire cohort of patients. Because of the numerous differences between the responders and non-responders, interpretation of the Kaplan-Meier complication risk rates as being applicable to the entire

population is not possible. The low response rate and the differences between the responders and the non-responders is a major limitation of this study.

Mentor conducted a re-analysis of the estimation of the cumulative incidence of complications and re-operations that involves imputation of missing data that adjusts for statistically significant differences in baseline demographics and in surgical characteristics between responders and non-responders. Mentor submitted this the first week in June; however, it is still under FDA review. Mentor will also be asked to ascertain whether the presence of a complication at an earlier time is associated with being a non-responder at a later time and, if so, with which complication(s).

Tables 6 and 7 below summarize the 3 and 5-year, by-patient, cumulative **Kaplan-Meier risk rates** for augmentation and reconstruction patients, respectively, for the endpoints which were assessed in the PAS.

Table 6: By patient cumulative Kaplan-Meier risk rate of first occurrence (95% confidence interval) of complications at 3 and 5 years of follow-up in **augmentation** patients.

Kaplan-Meier Risk Rates	3-Year Risk Rate ¹		5-Year Risk Rate	
	N = 1264		N = 1264	
Complication	Rate	95% CI	Rate	95% CI
Reoperation	13.2%	(11.2, 15.2)	20.2%	(17.5, 22.8)
Implant Removal	8.1%	(6.5, 9.7)	14.2%	(11.9, 16.5)
Capsular Contracture III, IV, or unknown	9.0%	(7.3, 10.7)	10.1%	(8.3, 11.9)
Implant deflation	3.3%	(2.2, 4.5)	9.7%	(7.6, 11.8)
Breast Pain	5.1%	(3.8, 6.5)	7.2%	(5.6, 8.9)

Notes: ¹As reported in the original PMA.

Table 7: By patient cumulative Kaplan-Meier risk rate of first occurrence (95% confidence interval) of complications at 3 and 5 years of follow-up in **reconstruction** patients.

Kaplan-Meier Risk Rates	3-Year Risk Rate ¹		5-Year Risk Rate	
	N = 416		N = 416	
Complication	Rate	95% CI	Rate	95% CI
Reoperation ²	40.1%	(35.0, 45.3)	43.0%	(37.9, 48.1)
Implant Removal	26.8%	(22.2, 31.5)	30.3%	(25.5, 35.1)
Capsular Contracture III, IV, or unknown	30.0%	(24.5, 34.8)	29.4%	(24.6, 34.2)
Breast Pain	17.2%	(12.5, 21.9)	18.0%	(13.7, 22.2)
Implant deflation	9.2%	(5.7, 12.7)	16.1%	(11.8, 20.4)

Notes: ¹As reported in the original PMA.

²Excludes reoperation for which the only reason was staged reconstruction.

Mentor provided Kaplan-Meier cumulative risk rates for 10 years post-op. The number remaining for each of these years is sufficient (i.e. >150) up to approximately 7 years; these data are not summarized for the purpose of this review.

Mentor performed an unplanned analysis of conditional probability - the probability of an event occurring assuming that it had not occurred before. For augmentation patients, there was an increased risk over time for implant deflation and there was a decreased risk over time for capsular contracture grade III/IV/unknown. For reconstruction patients, there was a decreased risk over time for capsular contracture grade III/IV, implant removal, and reoperation.

The reasons for **reoperation** through 5 years are summarized in Tables 8 and 9, respectively for augmentation and reconstruction patients. Note that Mentor collected reasons for reoperation and types of additional surgical procedure data at 3 years; however, only reasons for reoperation were collected at 5 years as per the PAS protocol. The 3-year labeling for this product only includes types of additional surgical procedures; therefore, the tables below do not include these data for comparison purposes.

In augmentation patients through 5 years, there were 343 reoperations (additional operations) reported in 198 patients and involving 312 implants. On a per reoperation basis, the most common reasons for reoperation were patient request for size/shape change (28.6%), leakage/rupture/deflation (18.7%), capsular contracture (16.9%), and wrinkling (11.1%). On a by patient basis, the most common reasons for reoperation were leakage/deflation/rupture (29.3%), patient request for size/shape change (26.3%), capsular contracture (19.7%), and wrinkling (11.1%).

Table 8: Reasons for reoperation¹ through 5 years for **augmentation** patients.

Reason for Reoperation	5 Years N = 343 Reoperations	5 Years N = 198 Patients with = 1 Reoperation
Patient request for size/shape change	98 (28.6%)	52 (26.3%)
Leakage/deflation/rupture	64 (18.7%)	58 (29.3%)
Capsular contracture	58 (16.9%)	39 (19.7%)
Wrinkling	38 (11.1%)	22 (11.1%)
Ptosis	32 (9.3%)	16 (8.1%)
Asymmetry	27 (7.9%)	21 (10.6%)
Hypertrophic scarring	22 (6.4%)	13 (6.6%)
Breast mass/tumor/cyst excision or biopsy ²	15 (4.4%)	12 (6.1%)
Infection	15 (4.4%)	13 (6.6%)
Hematoma/seroma ³	15 (4.4%)	15 (7.6%)
Aesthetic revision ⁴	15 (4.4%)	9 (4.5%)
Contralateral replacement	11 (3.2%)	11 (5.6%)
Breast pain	3 (0.9%)	3 (1.5%)
Delayed wound healing	2 (0.6%)	1 (0.5%)
Irritation/Inflammation	2 (0.6%)	2 (1.0%)
Extrusion	2 (0.6%)	2 (1.0%)
Not reported	2 (0.6%)	1 (0.5%)
Lymphadenopathy	1 (0.3%)	1 (0.5%)

Notes: ¹If there was more than one reason reported per patient, all reasons are included in this table.

²There were 12 breast mass/cancer, 2 fibroid tumors, and 1 mole/cyst removal reports in 10, 1, and 1 patients, respectively.

³There were 11 hematoma and 4 seroma reports in 11 and 4 patients, respectively.

⁴Includes dimpling on pectoral muscle, revise inframammary, position/shape change, and trauma.

In reconstruction patients through 5 years, there were 232 reoperations reported in 162 patients occurring with 196 implants. On a per reoperation basis through 5 years, the most commonly reported reasons for reoperations were capsular contracture (28.9%), asymmetry (20.3%), and patient request for size/shape change (15.9%). On a per patient basis, through 5 years, the most commonly reported reasons for reoperation were capsular contracture (32.1%), asymmetry (22.8%), and leakage/deflation/rupture (20.4%).

Table 9: Reasons for reoperation¹ through 5 years for **reconstruction** patients.

Reason for reoperation	5 Years N = 232 Reoperations	5 Years N = 162 Patients with = 1 Reoperation
Capsular contracture	67 (28.9%)	52 (32.1%)
Asymmetry	47 (20.3%)	37 (22.8%)
Patient request for size/shape change	37 (15.9%)	29 (17.9%)
Staged reconstruction ³	35 (15.1%)	30 (18.5%)
Leakage/deflation/rupture	35 (15.1%)	33 (20.4%)
Infection	34 (14.7%)	28 (17.3%)
Delayed wound healing	18 (7.8%)	12 (7.4%)
Breast pain	17 (7.3%)	14 (8.6%)
Hematoma/seroma ²	16 (6.9%)	13 (8.0%)
Hypertrophic scarring	13 (5.6%)	12 (7.4%)
Wrinkling	12 (5.2%)	8 (4.9%)
Extrusion	10 (4.3%)	10 (6.2%)
Necrosis	9 (3.9%)	6 (3.7%)
Aesthetic revision ⁴	9 (3.9%)	6 (3.7%)
Irritation/inflammation	8 (3.4%)	7 (4.3%)
Breast mass or cancer	5 (2.2%)	5 (3.1%)
Ptosis	2 (0.9%)	1 (0.6%)
Valve malposition	1 (0.4%)	1 (0.6%)
Lymphadenopathy	1 (0.4%)	1 (0.6%)
Contralateral replacement	1 (0.4%)	1 (0.6%)

Notes: ¹If there was more than one reason reported per patient, all reasons are included in this table. This table excludes patients in which staged reconstruction was the only reason for reoperation.

²There were 4 hematoma and 12 seroma reports in 4 and 9 patients, respectively.

³These patients reported both staged reconstruction and other reason(s). See footnote 1 above.

⁴Includes dimpling on pectoral muscle, revise inframammary, position/shape change, and trauma.

The reasons for **implant removal** (excluding staged reconstruction only) through 3 and 5 years are summarized in Tables 10 and 11 below.

Of the 2526 augmentation implants, there were 211 implant removals (8.4%) through 5 years for any reason. Of the 1264 augmentation patients, 132 patients (10.4%) had an implant removed through 5 years.

Table 10: Primary reason for removal through 3 and 5 years for **augmentation** patients.

Primary Reason for Removal ¹	3 Years ²	5 Years
	N = 136 Implants Removed	N = 211 Implants Removed
Patient request for size/shape change	50 (36.8%)	63 (29.9%)
Leakage/deflation	31 (22.8%)	61 (28.9%)
Capsular contracture	22 (16.2%)	31 (14.7%)
Wrinkling/asymmetry/ptosis/scarring	22 ³ (16.2%)	25 ⁴ (11.8%)
Other	-	14 ⁵ (6.6%)
Infection	7 (5.1%)	8 (3.8%)
Breast mass or cancer	1 (0.7%)	4 (1.9%)
Hematoma/seroma	3 (2.2%)	3 (1.4%)
Not reported	-	2 (0.9%)

Notes: ¹In the case where more than one reason for removal is reported, the following hierarchy is used to determine the primary reason: leakage/deflation, capsular contracture, infection, necrosis/extrusion, hematoma/seroma, asymmetry, breast pain, patient request, other.

²As reported in the original PMA.

³Includes wrinkling/asymmetry (16 cases), ptosis (3 cases), and hypertrophic scarring (3 cases). Mentor has been asked to determine the individual number of wrinkling and asymmetry cases.

⁴Includes asymmetry (7 cases), wrinkling (13 cases), ptosis (3 cases), and hypertrophic scarring (2 cases).

⁵Includes aesthetic revision (4 cases) and contralateral replacement (10 cases).

Of the 572 reconstruction implants, there were 135 implant removals (23.6%) for any reason through 5 years. Of the 416 reconstruction patients, 112 patients (26.9%) had an implant removal through 5 years.

Table 11: Primary reason for implant removal through 3 and 5 years for **reconstruction** patients.

Primary Reason for Removal ¹	3 Years ²	5 Years
	N = 116 Implants Removed	N = 135 Implants Removed
Capsular contracture	30 (25.9%)	39 (28.9%)
Leakage/deflation	25 (21.6%)	34 (25.2%)
Infection	30 (25.9%)	29 (21.5%)
Patient request for size/shape change	7 (6.0%)	11 (8.1%)
Necrosis/extrusion	6 (5.2%)	7 (5.2%)
Asymmetry/wrinkling/ptosis/scarring	13 ³ (11.2%)	5 ⁴ (3.7%)
Other	-	6 ⁵ (4.4%)
Breast pain	4 (3.4%)	4 (3.0%)
Breast mass or cancer	1 (0.9%)	See footnote 5

Notes: ¹In the case where more than one reason for removal is reported, the following hierarchy is used to determine the primary reason: leakage/deflation, capsular contracture, infection, necrosis/extrusion, hematoma/seroma, asymmetry, breast pain, patient request, other.

²As reported in the original PMA.

³Mentor has been asked to determine the individual number of wrinkling, asymmetry, ptosis, and hypertrophic scarring cases.

⁴Includes asymmetry (5 cases). See footnote 5 below.

⁵Includes wrinkling (1 case), breast mass or cancer (2 cases), delayed wound healing (2 cases), staged reconstruction (2 cases), and aesthetic revision (1 case). Mentor provided 8 “other” reasons for 6 implants. Mentor has been asked to determine the primary reason for removal of the 6 implants and then the table will be modified accordingly.

2. Focus Group Study

The ultimate goal of this study was to improve the patient brochure approved in May 2000. An independent study was conducted by Communication Sciences Group in accordance with the FDA-approved protocol. The focus group study involved 2 augmentation and 2 reconstruction groups of 7-10 women each who have considered, are considering, or have had implants.

The objectives of the independent focus group study were:

- ?? To determine whether the brochure achieves its educational and informed decision objectives and, if not, how it should be revised.
- ?? To assess whether the information in the brochure is clearly understood.
- ?? To identify unintended effects associated with the brochure exposure (e.g., inaccurate perceptions).
- ?? To assess its effectiveness in conveying the risks and benefits.
- ?? To get patient suggestions for improvement in the brochure.
- ?? To identify additional information needed by patients after having read the brochure.

Some of the key findings from the focus group study were:

- ?? Women had an overall good understanding of the risks and benefits (i.e., brochure met educational goal).
- ?? Women reported that brochure content, on the whole, was clear and easy to understand with the exception of the clinical studies section. Most women had difficulty in understanding and/or interpreting the safety data. Therefore, many skimmed or skipped the entire section.
- ?? Most of the reconstruction women readily accepted the information; however, the augmentation women expressed a degree of cynicism regarding the extensive list of complications. They believed that it was a disclaimer tactic used by the manufacturer to avoid liability. They concluded that the occurrence of complications was exaggerated and not to be taken at face value.
- ?? The brochure was effective in conveying information on the risks and benefits. Some were surprised that the number of risks with which they were unfamiliar.
- ?? Several suggestions for improvement were provided (e.g., separate augmentation and reconstruction information, add explanation to safety tables, table of contents, glossary of terms, more white space).
- ?? All women agreed that it was the most comprehensive brochure seen on breast implant. Small points of clarification were requested.

However, FDA considered the findings from both Inamed's and Mentor's focus group studies and requested changes to the patient brochure. The changes were categorized into the primary areas of:

- ?? Add clarification and/or make corrections (lead-ins and contents of safety tables)
- ?? Improve organization/layout (stratify augmentation and reconstruction, position of safety information)
- ?? Make easier to follow (table of contents, glossary, pagination)
- ?? Make easier to read (graphics, fonts, headers)

Mentor incorporated all changes requested by FDA. FDA considers this condition of approval fulfilled by Mentor.

As a note, Mentor is currently updating their patient brochure, as well as the package insert, to reflect 5-year post-approval study results. Once FDA has finished the review of these two pieces of labeling, Mentor will finalize them for public distribution.

3. Retrieval Study

This study involves a good-faith effort to retrieve explanted breast implants and perform appropriate analyses to determine the mode of failure.

The stepwise approach to the retrieval study analyses is as follows:

- ?? All implants undergo a visual or “gross” evaluation. In addition, most devices undergo a microscopic visual inspection. However, microscopic examinations are only performed if patient authorization is received.
- ?? Physical/mechanical testing will be performed.
- ?? If necessary, chemical testing may be performed.

Mentor provided a summary of the findings for all explanted devices received between 4/3/01 and 8/9/01. Clinical information and laboratory device observations were recorded. Mentor stratified the results by style, but based on the few implants involved, FDA pooled the data across the 7 styles identified.

Retrieval Study Summary			All Styles	
Total retrieved between 4/3/01 and 8/9/01			38	
Clinical (Physician) Observations	Deflation		38 ¹	
	Non-deflation		0	
	Intra-operative (e.g., shell puncture during surgery)		1	
Laboratory Observations of Device Failure Characteristics [Deflation vs. Non-deflation]	Smooth crease-edge openings	Deflation	5	
		Non-Deflation	0	
	Sharp-edge openings (not at crease)	Deflation	11	
		Non-Deflation	0	
	Material Separation Unknown Cause ²	Deflation	19	
		Non-Deflation	0	
	Leaky valves	Deflation	2	
		Non-Deflation	0	
	Functional devices (e.g., torn plug strap, partial patch delamination)	Deflation	0	
		Non-Deflation	0	
	Location of Shell Defect	Anterior Shell		12
		Posterior Shell		24
Radius		1		

¹Includes one device that the fill tube was not removed resulting in failure to activate kink plug valve.

²“Material Separation Unknown Cause” is used to designate a material separation in the shell component only. Microscopic examination of the edges of the material separation showed an irregular surface without definitive pattern. Definitive patterns are observed in material separation caused by instrument damage (e.g., parallel striations) and crease/fold flaws (e.g., a shell taper wear pattern).

The 2001 annual report included limited information for this study.

In the 2002 annual report, Mentor submitted a final report of this retrieval study. As part of that final retrieval study report, Mentor stated that material separation occurs more often in Siltex (textured surface) devices than smooth devices. Mentor conducted a separate study to investigate the probable causes of material separation in Siltex devices. Results from the study suggest that material separation is ultimately a result of high stress caused by an acute or tight fold in the shell. In addition, to understand whether differences in device mechanical properties could in any way have contributed to the material separation, selected groups of explanted devices exhibiting material separation were tested for their physical properties and compared to each other. It was determined that differences in physical properties do not appear to be a contributing factor in the occurrence of material separation. Additionally, Mentor conducted tensile strength, ultimate break force, ultimate elongation, shell thickness and joint strength measurements, and compared them to the specifications to determine if the physical properties had significantly deteriorated.

The 2002 annual report is still under FDA review; therefore, the adequacy of Mentor’s retrieval study efforts has not been determined.

4. Fatigue Testing

The purpose of this testing is to determine the fatigue strength of the product line. Mentor provided only an interim report of fatigue testing because they have not completed testing on Style 5000PT.

Styles 1600 (gamma), 1400 (dry heat), 2600 (dry heat), and 5000PT (dry heat) were chosen for fatigue testing as representative of Mentor’s product line. To date, testing has been completed on 3 of the 4 styles – Style 5000PT testing is scheduled. All implants tested were final, sterilized versions with a minimum shell thickness of 0.014” for the smooth styles and 0.022” for the textured styles. Testing was performed at 1 Hz at the higher loads and at 5 Hz at the lower loads after Mentor demonstrated comparable results at both frequencies at 70 lbs for Styles 1400 and 2600. A minimum of 3 implants for each style was tested for each load value.

Runout (RO) was defined as 10M cycles, which was based on a person walking 1 step per second for 8 hours per day for 1 year. Although it is not clear why 1 year of life should be considered acceptable, it is also unrealistic that the average person walks for 8 hours a day.

The acceptance criterion for each style takes into account the full force on the device without accounting for surrounding tissue support, considered by Mentor to be a worst case situation. The force on the device during walking/running is 2x the mass. With a safety factor (SF) of 2, the acceptance criterion is 1.2 lbs for Styles 1400, 1600, and 2600 and 1.4 lbs for Style 5000PT. As a note, Inamed used a fatigue acceptance criterion of 10 lbs based on the use of their largest implants in their calculations. Mentor’s calculations, based on their smallest size implants for each style, showed that the expected in-vivo loading is 75x greater for the largest size than for the smallest size. If Inamed had used their smallest size implant in their calculations, the expected in-vivo loading would have been 70.7 lbs. Add a SF of 2 and you would get 141.4 lbs for the fatigue acceptance criteria of Inamed’s smallest size implant. In addition, Mentor is testing out to 10M cycles RO while Inamed only tested out to 6.5M cycles RO. This makes Mentor’s and Inamed’s fatigue testing acceptance criteria comparable.

The results were:

	STYLE 1600 Smooth Round Saline, 125cc, gamma sterilized	STYLE 2600 Siltex Round Saline, 125cc, dry heat sterilized	STYLE 1400 Smooth Round Spectrum, 125cc, dry heat sterilized
Static ultimate load*	636 ? 85 lbs (n=10)	1001 lbs (n=10)	606 ? 86 lbs (n=10)
Endurance Load Limit at 10M Cycles RO	10 lbs	10 lbs	10 lbs

*Testing equipment limit was 1000 lbs. Loads are greater than those expected during mammography (55 lbs).

The acceptance criterion of 1.2 lbs for the 3 styles tested were met. FDA expects Mentor to provide the final report of fatigue testing with the Style 5000PT results as part of the 2003 annual report.

5. Shelf Life Testing

The purpose of this testing is to support a 5-year expiration date on the package label. Mentor is allowed to use their existing 4-year expiration date while this testing is being completed. Testing is performed at baseline (year 0) and then at 4 and 5 years to support a 5-year expiration date. Mentor was advised of the risk at not performing the tests at each year; however, they are confident that they will be able to provide adequate data to FDA.

The shelf life testing involves the following representative styles from those approved (not all styles were part of each test based on rationales provided in the protocol):

- ?? Style 1600 - Smooth Round Saline-Filled
- ?? Style 2600 - Siltex Round Saline-Filled
- ?? Style 2700 - Siltex Contour Saline-Filled
- ?? Style 1400 - Smooth Round Spectrum
- ?? Style 2400 - Siltex Round Spectrum

A year-zero report was provided. The results were as follows:

Test	Results
Sterility Confirmation	Pass
LAL Endotoxin Test	Pass
Inner Lid Packaging Seal Peel	Pass
Outer Lid Packaging Seal Peel	Pass
Valve Function	Pass
Tension Set	Pass
Shell/Patch Joint Strength	Pass
Burst Pressure	Pass
Ultimate Elongation	Pass
Shell Break Force	Pass

FDA expects Mentor to submit baseline shelf life testing for Style 5000PT by June 2002 and to submit the next report of shelf life testing for all styles at year 4.