

1 DR. WHALEN: We have a brief amount of
2 remaining time so if there is anyone, who has not
3 yet addressed the panel, who wishes to address us
4 in this public session, would you please so
5 indicate by raising your hand right now? I see
6 none.

7 This is a convenient time for us to take a
8 break. I have 10:07. We will reconvene here at
9 10:25 and resume our activities.

10 [Brief recess]

11 DR. WHALEN: I would like to remind the
12 public observers at this meeting that while this
13 portion of the meeting is, of course, open to
14 public observation, public attendees may not
15 participate unless specifically requested by a
16 member of the panel.

17 Before we begin the first presentation
18 from industry, I would like to ask Dr. Celia Witten
19 to make some brief remarks about what the conduct
20 of our day's activities is going to be.

21 DR. WITTEN: Thank you. I just want to
22 describe what we are going to be doing for the rest
23 of the day. I will start with just mentioning
24 something that I think everybody here probably
25 already knows, which is that at the time that we

1 approved the two saline breast implant PMAs several
2 years ago, we asked the sponsors to continue to
3 study their product in the form of several
4 conditions of approval, which have been outlined in
5 the panel packet.

6 The purpose of the meeting today is to
7 give the sponsors an opportunity to describe their
8 progress in those studies to date, and there will
9 also be an FDA presentation on each of those
10 studies. Following that, there is an opportunity
11 for the panel to comment on the data and the
12 studies as presented.

13 We think it is very important that the
14 panel get an opportunity to see what the data is
15 that the sponsors have generated to date, and also
16 for the public to get an opportunity to see this
17 data. This is important information and will be
18 incorporated into the sponsors' labeling as part of
19 an ongoing effort to make sure all the information
20 is available to physicians and patients.

21 I would like to thank everybody here on
22 the panel in advance for your discussion of the
23 data, and I would like to thank the members of the
24 public, who gave presentations this morning
25 already, for their input as well.

1 DR. WHALEN: Thank you, Dr. Witten. So,
2 as we proceed, as long as the day flows as we
3 anticipate, we will have one of the sponsors give
4 their presentation before lunch. There will be
5 three speakers, and I would ask the panel members
6 to make note of any questions they have for any of
7 those speakers. Then, following all three speakers
8 we will ask them to entertain our questions.
9 Following that question and answer period and
10 comments, we will have FDA's presentation for that
11 particular sponsor's presentation, followed, in a
12 similar fashion, by questions, answers and
13 comments. We will then have a general discussion
14 on that particular status. Then, we hope to break
15 for lunch and then duplicate that for the other
16 sponsor following lunch.

17 I would ask that we begin with Mentor
18 Corporation's presentation, with the three speakers
19 who are going to address us.

20 **Panel Update Regarding Post-Approval Conditions of**
21 **Approval for Saline-Filled Breast Prosthesis**
22 **Mentor Corporation**

23 DR. MICHAEL: Ladies and gentlemen, good
24 morning. My name is Maher Michael. I am the
25 medical director and vice president of clinical and

1 regulatory affairs for Mentor Corporation.

2 We are here today to update the panel
3 members and FDA staff on the status of the
4 conditions of the post-PMA approval for Mentor
5 saline-filled and Spectrum mammary prostheses.

6 First, I would like to give you an
7 overview of Mentor's saline prospective study which
8 constitutes the basis of our approved PMA. There
9 were 1680 patients enrolled in this study. That
10 study was designed for a three-year patient
11 follow-up. The devices that were used were 30
12 percent smooth and 70 percent textured. The last
13 patient was enrolled in September of 1995. The PMA
14 was approved by FDA on May 10 of 2000, with some
15 conditions.

16 The first condition was the post-approval
17 study, and the purpose for that study was to extend
18 the patient follow-up from three years to ten years
19 to collect longer-term safety data. That study was
20 not designed really to collect any patient
21 satisfaction data. Today, five-year data will be
22 presented by Mr. Cliff Kline, director of clinical
23 programs.

24 The second condition was the focus group
25 study, and the purpose for that study was to

1 evaluate the effectiveness of the patient brochure
2 in communicating information to prospective
3 patients about risks and benefits of breast
4 implants. The status of that study will be
5 presented by Ms. Donna Crawford, director of
6 corporate regulatory affairs.

7 The third condition was the retrieval
8 study, and the objective of that study was to
9 better understand causes of deflation and further
10 analyze the failure modes.

11 The fourth condition was the fatigue
12 testing study, and the purpose of that study was to
13 characterize fatigue resistance of the devices
14 using methods, as requested, in the breast implant
15 guidance document.

16 The fifth, and last, condition was the
17 real-time shelf-life testing, and the purpose of
18 that study was to support our four-year shelf-life
19 data submitted in our PMA, and to extend the
20 real-time shelf-life testing to five years.

21 The status of the last three conditions
22 will be presented this morning by Mr. Ron Crouther,
23 vice president of advanced development.

24 Now I would like to present Mr. Cliff
25 Kline who will present and discuss the

1 post-approval study. Thank you.

2 MR. KLINE: Thank you, Dr. Michael. Good
3 morning. As Dr. Michael said, I will be presenting
4 the five-year clinical results for Mentor's
5 post-approval study, or PAS, on our saline-filled
6 and Spectrum mammary prostheses.

7 I will first briefly discuss study design
8 and the chronology of our efforts to contact and
9 follow-up on the majority of patients. Then, I
10 will provide five-year complication data.

11 The objective of the post-approval study
12 was to assess the long-term ten-year safety for
13 Mentor saline-filled and Spectrum breast implants
14 by assessing the cumulative incidences of capsular
15 contraction, deflation, breast pain, reoperations
16 and explantations.

17 Patients were included in this study if
18 they had participated in the saline prospective
19 study and they consented to participate in this
20 post-approval study. They were excluded if they
21 had died, had all their implants removed or
22 discontinued by choice.

23 Patients could either complete a mail-in
24 questionnaire or they could elect to be seen by
25 their physician. The questionnaires are sent to

1 each patient once every year around the anniversary
2 date of her surgery.

3 Mentor has conducted extensive and varied
4 efforts to contact and follow-up with all potential
5 patients, and I would like to share these efforts
6 with you now.

7 We received PAS protocol approval in May
8 of 2000. During July we contacted all saline
9 prospective study investigators and confirmed with
10 them that Mentor would contact their patients
11 directly. Three physicians did deny us direct
12 access to their patients so those patients were not
13 contacted about participating in the study.

14 Prior to the first mailing, we worked with
15 the participating sites to confirm the patients'
16 addresses. We also used the National Change of
17 Address database, NCOA, to update this information.
18 We then initiated a patient mailing of informed
19 consents and questionnaires, and at the end of 2000
20 we did a second certified mailing to those patients
21 who had not responded, the non-responders.

22 You will hear me using those two phrases
23 throughout the presentation, responders and
24 non-responders. Responders are those patients on
25 whom we have data, whereas non-responders are

1 those patients who we have not yet had success in
2 contacting.

3 In 2001, we continued to collect an
4 analyze the data as well as send out annual
5 questionnaires. We increased our efforts to
6 contact non-responders by using the nationwide 411
7 telephone directory.

8 This year, we continued to collect and
9 analyze the data as well as mail out annual
10 questionnaires. We have increased our contact and
11 follow-up rate by approaching investigators who
12 have non-responders and, if they were successful in
13 contacting these patients, we provided financial
14 incentive. We also began to correspond with
15 non-responders via FedEx, which allows tracking and
16 verification of patient signatures. We did this by
17 using the ChoicePoint nationwide database to
18 identify all possible addresses for the
19 non-responders, and then we followed up by sending,
20 via FedEx, packets to all these addresses.

21 These extra efforts have resulted in
22 increased contact and follow-up in 2002. As noted
23 in FDA's memo to panel, Table 5(a), currently the
24 augmentation patient contact rate is 75 percent and
25 the reconstruction contact rate is 91 percent.

1 This graph shows the improvement in
2 patient follow-up from March to May of this year.
3 Augmentation improved from 54 percent to 64 percent
4 and reconstruction from 73 percent to 79 percent.
5 The rates are different for contact and follow-up
6 because these two are defined differently. Contact
7 rate is made up of all patients whom we have been
8 able to get a hold of, whereas follow-up rate only
9 includes those patients on whom we have data. So a
10 patient is counted as contacted whether she says
11 yes or no to participating in this post-approval
12 study, but she is only counted in the follow-up if
13 we have data. Please note that the complication
14 data in this presentation are from the March, 2002
15 data set.

16 Before I address complication rates, I
17 would like to address the issue noted in FDA's memo
18 to the panel regarding responders and
19 non-responders. When we analyzed the study data we
20 did find that non-responders were significantly
21 different in some demographic and operative
22 characteristics. Adjustment for these differences
23 showed essentially no change in the cumulative rate
24 of complications at five years. Therefore, Mentor
25 concludes that responders adequately represent the

1 entire study population at five years. This
2 analysis is currently being reviewed by FDA.

3 The complication rates were calculated via
4 Kaplan-Meier analysis. This is a statistical
5 method used when 100 percent patient follow-up is
6 not available, and it provides an estimated
7 probability of a complication at a given time
8 period.

9 The remainder of this presentation is
10 divided into the augmentation and reconstruction
11 cohorts. I first want to talk about the
12 augmentation patients. They are defined as a
13 patient who is normally healthy and at least 18
14 years of age or older, and desires breast
15 enlargement. The average age of augmentation
16 patients in the saline prospective study at the
17 time of surgery was 32 years of age. Almost half
18 were married. The remainder, 30 percent, were
19 single, and 22 percent were widowed, divorced or
20 separated, and 80 percent has at least some college
21 education.

22 This table details both the three- and the
23 five-year cumulative Kaplan-Meier rates, as well as
24 95 percent confidence intervals for the
25 complications of reoperation, explantation,

1 capsular contracture, implant deflation and breast
2 pain. For each of the complications at five years
3 the cumulative rate increased. For example,
4 reoperation went from 13.2 at three years to 20.2
5 at five years. Capsular contracture, 9.0 to 10.1.
6 This is expected as this is a cumulative rate.
7 That is, occurrences of complications that occurred
8 in years four and five were added to the three-year
9 cumulative rate.

10 But it is important to note that for
11 reoperation, explantation and breast pain there was
12 no significant change in the complication risk rate
13 per year during this five-year time period. The
14 risk rate to the patient for capsular contracture,
15 Baker grades 3, 4 and unknown, decreased. Only for
16 deflation was there an increased risk rate per
17 year.

18 If we compare this five-year deflation
19 rate to the published literature, we can see that
20 the post-approval study rate is within the range of
21 published literature which is 0-27 percent. As you
22 can see, the rate for explantation also falls
23 within the published rate. Reoperation and
24 capsular contracture actually fall slightly under
25 the published rate. Literature rates for breast

1 pain were not captured.

2 This table details the top ten reasons for
3 reoperation. The first column is categorized by
4 number of reoperations by breasts; the second
5 column, reoperation by patient. So, 52 patients of
6 198 patients and 98 breasts of the 343 breasts had
7 capsular contracture as a reason for reoperation.
8 The top three reasons in both columns are patient
9 requested size exchange, leakage/deflation and
10 capsular contracture.

11 Explants, which are a subset of
12 reoperations, are discussed in this table. This
13 details the primary reason for explantation at both
14 three and five years if the rate occurred at a rate
15 greater than five percent. The primary reason at
16 both three and five years was patient request for
17 size exchange.

18 Now, before I discuss the reconstruction
19 data, I would like to more specifically define a
20 reconstruction patient. This is a patient
21 undergoing breast reconstruction as a result of
22 breast cancer or congenital deformity. She could
23 be expected to face a more extensive initial
24 surgery and require additional treatment such as
25 radiation therapy, or chemotherapy. Skin coverage

1 over the implant, as well as achieving symmetry is
2 more difficult than in augmentation patients.

3 Saline prospective study demographic data
4 shows that at the time of surgery a woman had an
5 average age of 46 years. Approximately two-thirds
6 of the women were married, and almost
7 three-quarters of the women had some college
8 education.

9 This table details the three- and
10 five-year Kaplan-Meier rates, as well as the 95
11 percent confidence intervals for reoperation,
12 explantation, capsular contracture, breast pain and
13 implant deflation. Again, this represents a
14 cumulative rate so the five-year rates are higher
15 than those at three years. Please note that the
16 five-year numbers are updated, whereas the
17 three-year numbers are those as presented at the
18 2000 panel.

19 At five years there was no increased risk
20 rate per year for any complication, while there was
21 a decreased risk rate per year for implant removal,
22 explantation, and reoperation, as well as capsular
23 contracture Baker grades 3, 4 and unknown.

24 If we compare these rates to those in
25 published literature, we can see that three of the

1 five rates were within the range from the
2 literature. While reoperation did have rates above
3 those in published papers, it is important to note
4 that the patient risk rate per year actually
5 decreased at five years.

6 We would also like to note that the
7 cumulative three-year rate, as presented in our
8 saline PMA, was 40.2 percent. So, in the
9 intervening two years the rate has increased less
10 than three percent. Literature rates for breast
11 pain were not captured.

12 This table details the top ten reasons for
13 reoperation. Again, the first column represents
14 the percentages as categorized by number of reops
15 by breasts, and the most commonly reported reasons
16 were capsular contracture, asymmetry and patient
17 request. The second column, by patient, the top
18 three reasons were capsular contracture, asymmetry
19 and leakage/deflation.

20 This table details the primary reasons for
21 explantation surgery at three and five years. As
22 you can see, the primary reason was capsular
23 contracture.

24 In overview, patient contact and follow-up
25 rates have increased. The responders adequately

1 represent the entire study population through five
2 years. The risk rate per year for the
3 complications discussed decreased or stayed the
4 same for four of five complications in the
5 augmentation cohort and all five of the
6 complications in the reconstruction cohort. For
7 deflation, in the augmentation cohort the rate was
8 within published literature.

9 In summary, Mentor's saline-filled and
10 Spectrum implants continue to perform in a safe and
11 effective manner. As presented today, the
12 complication rates are comparable with published
13 rates. We will continue to follow patients through
14 ten years and seek to continue to increase the
15 total number of responders.

16 Thank you. I would now like to present
17 Ms. Donna Crawford.

18 MS. CRAWFORD: Thank you, Cliff. Good
19 morning. My name is Donna Crawford. I am director
20 of corporate regulatory affairs for Mentor
21 Corporation.

22 I will be discussing the focus group study
23 or the patient informed decision brochure. Mentor
24 conducted this study as one of the post-approval
25 conditions of saline breast implant PMA.

1 There were four major purposes of the
2 focus group study. The first was to determine
3 whether the patient brochure effectively
4 communicates information about the risks and
5 benefits associated with breast implants.

6 Secondly, it was important to assess
7 whether the information in the brochure is
8 presented in an understandable way and is clearly
9 understood by prospective patients.

10 Thirdly, we wanted to identify any
11 unintended effects of the brochure and also any
12 unanticipated effects of the brochure.

13 Finally, we wanted to obtain patient
14 suggestions for improvement and identify any
15 additional information needed by the patients.

16 The focus group study was conducted under
17 an FDA-approved protocol by an independent research
18 group by the name of Communications Sciences Group.
19 Four focus group discussions were held, two in
20 Dallas and two in San Francisco. The focus groups
21 consisted of reconstruction patients or patients
22 considering augmentation. There were eight to ten
23 individuals in each focus group, and each group was
24 balanced across age, employment status, income
25 level and educational level.

1 Data were collected in two ways. First,
2 the participants were asked to read the brochure
3 and complete a self-administered survey prior to
4 participating in the focus group interviews.
5 Secondly, the focus group interviews were led by a
6 moderator who followed a discussion guide which was
7 part of the focus group study protocol.

8 Some of the key findings of the study are
9 as follows. In general, the educational and
10 informed decision objectives of the brochure were
11 met. The majority of women had a good
12 understanding of the risks and benefits associated
13 with breast implants after reading the brochure.
14 Eighty-eight percent of the respondents reported
15 that they had learned new information about breast
16 implants after reading the brochures, and 85
17 percent felt better able to ask their doctors
18 questions about breast implants after reading the
19 brochure.

20 Most respondents felt that the brochure,
21 on the whole, was clear and understandable, with
22 the possible exception of the clinical data tables.
23 Most respondents rated the brochure highly on
24 comprehension and relevance, and 88 percent felt
25 that the information in the brochure was useful to

1 them.

2 The study identified only one possible
3 unintended effect of the brochure, and that was
4 that some of the respondents felt that complication
5 rates were not to be taken at face value because
6 they were overstated in order to protect the
7 manufacturer.

8 Both the focus group discussion and the
9 survey results found that the brochure was
10 effective in conveying information, and 73 percent
11 said that the information in the brochure was not
12 confusing, and only six percent of the respondents
13 felt that the brochure was confusing. There was
14 some difficulty in understanding the meaning of
15 cumulative risk rates and interpreting the data
16 tables.

17 The major suggestions for improvement had
18 to do with improving the layout and format of the
19 brochure; adding explanatory information to the
20 data tables; choosing the content order to group
21 augmentation data together and reconstruction data
22 together; and adding a glossary and table of
23 contents. The additional information amounted to
24 small points of clarification only.

25 In response to the focus group findings

1 and suggestions from FDA, the following changes
2 were made: A table of contents and glossary were
3 added. The clinical study section was revised to
4 separate augmentation and reconstruction data; and
5 to simplify and explain the data tables. Some
6 minor wording changes were made to improve the
7 clarity. For example, an introductory paragraph
8 was added to the clinical study section to explain
9 how Mentor's clinical study data may relate to each
10 patient's own experience. Sentences were added
11 prior to each clinical data table to explain what
12 the numbers in the table mean and how they were
13 calculated.

14 The brochure is in the process of being
15 revised to add the five-year follow-up data from
16 the post-approval study. The revised brochure will
17 be available on the Mentor's web site and a printed
18 version will be available in approximately six
19 weeks following FDA approval. Therefore, this
20 condition of approval has been fulfilled.

21 I would now like to introduce Mr. Ron
22 Crouther.

23 MR. CROUTHER: Good morning. My name is
24 Ron Crouther. I am vice president of advanced
25 development for Mentor, and I would like to present

1 interim results on three studies, our explant
2 retrieval study, our post-approval fatigue testing,
3 and also our real-time shelf-time testing.

4 First on the explant retrieval study, the
5 objective of this study was to retrieve 300 devices
6 that were explanted because of deflation and
7 perform appropriate analyses to determine the mode
8 of failure. The 300 devices were selected to cover
9 a range of saline device types, that is, smooth and
10 textured devices, various shapes, and devices
11 containing our two valve types, diaphragm valves
12 and Spectrum kink plug valves.

13 Upon receipt of the explanted devices, we
14 first captured the device descriptive information
15 and clinical information. This included device
16 type, date of manufacture, time in vivo and time of
17 surgery. All devices were then visually examined
18 and additional microscopic examination of the
19 surface of the defect area was conducted to better
20 characterize the type of failure mode. Leak
21 testing was performed, as was necessary, to confirm
22 that all leak sites had been located. The last
23 phase of our testing was physical and mechanical
24 property testing.

25 We provided an interim report on 38

1 devices to the FDA in August of 2001. We completed
2 our study of 310 devices and submitted the final
3 report in our May, 2002 annual report. Because we
4 have just submitted the final report and the FDA
5 has not had adequate time to complete its review,
6 the presentation today is based only on the interim
7 report on 38 devices.

8 This table summarizes the failure modes we
9 saw on the 38 devices for both smooth and textured
10 devices. The first failure mode is material
11 separation, a term which Mentor has used for many
12 years to describe a tear or split in the device
13 without very significant abrasion or thinning at
14 the site of the defect. Material separation is the
15 primary failure mode of our Siltex devices. As
16 supported by a wider study of Siltex devices, most
17 material separation failures do exhibit evidence of
18 folding at the site of the defect, often compound
19 folding in which the outer surface of the implant
20 is in tension causing the split to propagate from
21 the outside in.

22 The second failure mode is smooth
23 crease-edge opening or crease-fold failures on
24 smooth devices. These are similarly related to
25 folding and, in contrast to material separation

1 defects, do exhibit very obvious abrasion and
2 thinning at the failure site.

3 Sharp-edge openings can be duplicated by
4 puncture with a surgical instrument and are very
5 likely indicative of iatrogenic damage. We also
6 had two reported cases of leaking valves, however,
7 one could not be confirmed and, if you will notice,
8 the numbers in the left-hand column do not add to
9 19 as we had one Spectrum kink plug valve device in
10 which the tubing was not fully withdrawn per our
11 instructions for use, and when the tubing was
12 withdrawn the device did not leak.

13 To summarize, the failure modes that we
14 saw in this interim report reflect what we have
15 seen in our clinical study information, as well as
16 our product evaluation or complaint database.
17 There is evidence of folding present in a majority
18 of the failures that did not exhibit evidence of
19 instrument damage. Again, Mentor's final report
20 covering the 310 devices is under review by the
21 FDA. The general findings in that study are
22 similar to what we saw in the preliminary report.

23 The next topic I will briefly discuss is
24 Mentor's fatigue testing of our saline-filled
25 breast implants. Fatigue testing involves cyclic

1 compression testing for our implants up to 10
2 million cycles and utilizes an apparatus that is
3 schematically represented here. The sample is
4 located here, between two flat platens, one of them
5 fixed and one of them movable. The movable platen
6 oscillates up and down to apply the compressive
7 force to the implant. The implant is immersed in a
8 saline bath that is kept at 37 degrees Celsius.

9 We had two phases and two objectives to
10 our fatigue testing. The first objective was to
11 create AF/N curves, that is, applied force versus
12 number of cycles to failure for the various device
13 types. There were four device types chosen for the
14 study. Along the Y axis we have the applied force;
15 along the X axis are cycles to failure. As you can
16 see, as you decrease the applied force the device
17 will withstand more cycles until failure.

18 The second phase of our testing was to
19 conduct long-term fatigue testing and calculate
20 fatigue safety factors for each of the four device
21 types. The fatigue safety factors are calculated
22 according to the formula you see here. I am not
23 going to try to point to it, but it is the force to
24 achieve 10 million cycles without failure, what we
25 call our run-out load, divided by the estimated

1 device load during walking, which we conservatively
2 estimate to be two times the device weight. The
3 safety factor chosen for this, in consultation with
4 the FDA, was greater than or equal to 2.

5 The protocol was approved by the FDA.
6 Four device types were chosen for the study. Those
7 four were the smooth and Siltex round diaphragm
8 valve devices, smooth round kink valve devices and
9 contour tall profile devices. The tested devices
10 include all sterilization methods that we currently
11 use and that are approved by the PMA.

12 We chose for the testing the smallest
13 devices of each device type as those typically have
14 our thinnest wall thickness. We also made special
15 runs of those devices in which we ran at the
16 absolute minimum of our tolerance extreme for shell
17 wall thickness as well as texture layer thickness.
18 As such, this device configuration represents
19 worst-case physical testing as defined in the FDA's
20 breast implant PMA guidance document.

21 These are the results to date for three of
22 the four devices completed. This is the phase one
23 testing, which was the generation of the AF/N
24 curves. Again, along the Y axis we have load
25 amplitude; along the X axis we have cycles to

1 failure. It is a logarithmic scale so, again,
2 10,000, 100,000, a million and so forth. The three
3 devices are the smooth Spectrum device, the Siltex
4 diaphragm valve device and the smooth diaphragm
5 valve device. So, for example, for the Siltex
6 diaphragm valve device a load amplitude or force
7 applied of 50 lbs requires approximately one
8 million cycles to generate failure.

9 Based on this phase one testing, as well
10 as other experimental data, a run-out value of 10
11 lbs was chosen for our second phase of testing,
12 which was the long-term fatigue testing. Again,
13 the goal of that was to withstand the 10 million
14 cycles without failure at the 10 laboratory load
15 level. We have successfully completed testing on
16 three of the devices. Again, if we calculate a
17 safety factor based on the formula here, the
18 run-out load of 10 lbs is divided by the estimated
19 device load during walking, or two times the device
20 weight. Since we chose the same size device for
21 each of the three device types, 125 cc device in
22 each case, the device weights were very close to
23 the same thing, so ten divided by two times the
24 device weight for all three devices turns out to be
25 16.7. Again, if you recall, our acceptance

1 criterion was a safety factor greater than 2.

2 To summarize, three of the four device
3 types have been completed. The fourth is scheduled
4 to begin shortly, probably within about the next
5 month to month and a half. AF/N curves have been
6 generated, and fatigue safety factors have been
7 calculated for three of the four devices, which far
8 exceeds the protocol requirements, again using
9 worst-case test samples.

10 The last topic I would like to discuss
11 this morning is our real-time shelf-life testing.
12 As Dr. Michael mentioned, this was twofold in terms
13 of objectives. First, to support our current shelf
14 life of four years and then, secondly, to extend
15 that shelf life out to five years.

16 The testing is being performed under an
17 FDA-approved protocol. Seven device types are
18 included in the testing in order to cover small and
19 large devices; all packaging types and sizes; all
20 sterilization methods; and all different device and
21 component configurations.

22 The testing includes mechanical and shell
23 tensile property tests, which include tensile and
24 elongation, tension set, joint strength and valve
25 competency tests. The packaging seal peel

1 strength, microbial challenge and dye penetration
2 tests are performed to ensure maintenance of
3 sterility.

4 Our status is that all devices have been
5 tested at the time zero time point, with all
6 devices meeting all specifications, and the
7 four-year testing will be completed in the year
8 2005. The five-year testing will be completed in
9 the year 2006.

10 This concludes my presentation, and I
11 would now like to reintroduce Dr. Michael.

12 DR. MICHAEL: The overall summary of our
13 presentation this morning is that we presented
14 five-year data for the post-approval study, and we
15 will continue to follow all our patients through
16 ten years, and we will continue to update the
17 agency in our annual reports.

18 For the focus group study, the study has
19 been completed. For the retrieval study, we have
20 completed the study. It is under FDA review.
21 Fatigue testing, we tested three out of four
22 styles. The last style is scheduled to start six
23 weeks from now. Lastly, the shelf-life testing is
24 ongoing through five years.

25 Mr. Chairman, panel members, FDA staff, I

1 would like to thank you for your attention and,
2 after FDA's presentation, we would be glad to
3 answer any questions you may have. Thank you.

4 DR. WHALEN: Actually, if you wouldn't
5 mind, we will ask you to answer some questions
6 before FDA's presentation and then perhaps again.

7 DR. MICHAEL: That is fine.

8 DR. WHALEN: If I could start off, Ms.
9 Crawford, the focus groups had relatively small
10 numbers as most focus groups do, but it was unclear
11 to me what the composition of that group was
12 vis-a-vis thinking about having the implant, having
13 had the implant, having had it and having had it
14 removed.

15 MS. CRAWFORD: Yes, the augmentation focus
16 groups consisted of patients who were considering
17 augmentation. The reconstruction focus groups were
18 primarily patients that had already had
19 reconstruction with breast implants.

20 DR. WHALEN: And all of them were still in
21 place?

22 MS. CRAWFORD: Yes.

23 DR. WHALEN: Dr. Dubler, do you have any
24 questions about the focus group results?

25 DR. DUBLER: Yes, I have one question

1 about the focus groups, that is that it seemed to
2 me that one of the findings was that they really
3 didn't understand the data sets and what they said.
4 Would you agree?

5 MS. CRAWFORD: There was some confusion
6 about exactly what the meaning of what a cumulative
7 risk rate was, and there was some confusion in
8 terms of the data tables, which often switched from
9 identifying data by patient, some by implant, some
10 by total patient population. We have addressed
11 that and made clarifications to the data tables to
12 address that confusion.

13 DR. DUBLER: Have you left them in table
14 form?

15 MS. CRAWFORD: Yes, the data tables still
16 are included in the brochure, yes.

17 DR. DUBLER: Have you translated them into
18 reasonable lay language, or simply left them in the
19 table form?

20 MS. CRAWFORD: It is in table form by
21 patient and each table has at least a couple of
22 sentences of introduction to explain what the
23 numbers are.

24 DR, DUBLER: I have another question about
25 the presentation. Would it be appropriate to ask

1 it now?

2 DR. WHALEN: Yes.

3 DR. DUBLER: I believe it was Dr. Michael
4 who stated that there were three exclusions from
5 your follow-up cohort.

6 DR. MICHAEL: It was Cliff Kline in his
7 post-approval study presentation.

8 DR. DUBLER: The three exclusions were
9 patients who had died? What were the three
10 exclusions, please?

11 MR. KLINE: The three exclusions were
12 patients who had died, had their implants removed
13 or had withdrawn by choice, discontinued by choice.

14 DR. DUBLER: Discontinued what?

15 MR. KLINE: They elected not to
16 participate in the post-approval study when we
17 asked for their participation and consent.

18 DR. DUBLER: I see, and what percentage of
19 your cohort was represented by those three
20 categories, total cohort?

21 MR. KLINE: I would have to look and
22 determine those numbers by those three groups. I
23 don't have that information available at the
24 moment.

25 DR. DUBLER: Why did you decide to exclude

1 patients who had removed the implants? One would
2 think that they would be an important source of
3 information.

4 MR. KLINE: You are exactly right, in that
5 we captured all complications, including removal,
6 and reported those complications today. After a
7 patient has her breast implants removed, she no
8 longer has a study device in her body and,
9 therefore, she is no longer studied. But, of
10 course, until the device is removed we do study her
11 and collect and report on all complications.

12 DR. WHALEN: Dr. McCauley?

13 DR. MCCAULEY: I just have a question
14 related to the focus group study. Did these groups
15 have group leaders, and if they did, how were they
16 chosen?

17 MS. CRAWFORD: There was a moderator that
18 was an employee of Communications Sciences Group
19 that followed the discussion guide that was part of
20 the protocol. There wasn't a leader of the focus
21 group participants per se, but there was a
22 moderator who conducted the discussion among the
23 focus group participants.

24 DR. MCCAULEY: After your separation out
25 of the data, was there significant improvement in

1 the confusion level or decrease in confusion that
2 some of the participants expressed?

3 MS. CRAWFORD: Well, since we did the
4 focus group study on the original version of the
5 brochure before the data were separated out, we
6 haven't gotten feedback on the brochure with the
7 data separated. So, I can't answer that question.
8 It was primarily so that somebody undergoing
9 reconstruction would not have to sort through the
10 augmentation data that wasn't applicable to them.

11 DR. WHALEN: Dr. DeMets, would you have
12 any questions or comments about the statistics that
13 were presented to us, or any particular vantage
14 point on the percent follow-up that they have
15 vis-a-vis other clinical studies in a population
16 similar to this?

17 DR. DEMETS: Yes, I actually have two sets
18 of questions, one for Mr. Crouther and one for Mr.
19 Kline. You said that you recovered 310 implants
20 and those reports have been done and submitted.
21 Why is that we aren't privileged to see that today?

22 MR. CROUTHER: We just submitted those to
23 the FDA with our annual report and it is still
24 under review by the FDA.

25 DR. DEMETS: Is there some regulatory

1 reason why we can't see that data? I mean, you are
2 giving us 38 and there are 310, or something, that
3 are available.

4 DR. WITTEN: We usually review data and
5 send it to the panel before it is presented in a
6 panel session.

7 DR. DEMETS: All right. On the time to
8 failure, how many actual samples are tested in
9 that? Is it one sample from each of the devices?

10 MR. CROUTHER: No, for the long-term
11 fatigue testing a minimum of three, and for the
12 AF/N curves three also.

13 DR. DEMETS: Did you calculate or compute
14 any time to failure? You only have three but you
15 presented your data on how many cycles it took, but
16 is there some way you can translate that into
17 failure time?

18 MR. CROUTHER: Not directly into failure
19 time. The 10,000 cycles, again, was agreed to with
20 the FDA and 10,000 cycles represents walking for
21 eight hours a day at a rate of one Hertz or one
22 cycle per second.

23 DR. DEMETS: The remainder of my questions
24 are for Mr. Kline. Can you explain to me in a
25 little more detail the process that you went

1 through to capture information from the patients
2 just to get responses?

3 MR. KLINE: Certainly. In terms of how we
4 got the patients to agree to participate or not?

5 DR. DEMETS: Just the process. I am not
6 understanding the process that you went through
7 because the response rate is low relative to
8 standards that I am used to. So, I am trying to
9 understand what you did do.

10 MR. KLINE: Well, once we did get protocol
11 approval through working with FDA, we then
12 contacted first the investigators to see what
13 information they had on the patients because, as
14 you know, a patient population can move. So, once
15 we determined first from the investigators that
16 they wanted us to contact the patients directly, we
17 then worked with them to get the addresses. Once
18 we had the updated addresses from them, we then
19 also checked with NCOA to make sure that the
20 doctor's address was verified by NCOA. Then we
21 began to correspond via mail with the patients.
22 The SPS study only had patients consented for the
23 three-year study. That is why in the first mailing
24 we included a questionnaire as well as a consent to
25 ask them to participate in the study through ten

1 years. So, the first step, once we had the address
2 was to see if the patient would consent to
3 participate in this additional follow-up.

4 DR. DEMETS: Was there a reason that you
5 didn't ask the investigators themselves--not the
6 investigators, the surgeons to collect this
7 information from their patients as opposed to doing
8 it directly from a mailer?

9 MR. KLINE: It was an option, and we asked
10 each doctor if they wanted to contact the patients
11 themselves or they wanted Mentor to, and they all
12 elected--except for the three that declined any
13 contact with their patients--us to be their
14 representative and to contact the patient directly.

15 DR. DEMETS: And, was the questionnaire
16 such that the patient would be able to fill out all
17 of the items accurately?

18 MR. KLINE: Yes, once they got the
19 questionnaire, the form was fairly basic but also
20 had an explanation as to what we were asking them
21 to do. There was a letter accompanying that as
22 well as, of course, the informed consent in the
23 first mailing. If they had any questions, they
24 could call us. There was a phone number for them
25 to call. Additionally, if there was something that

1 was incorrectly filled out on the form, the
2 clinical research associate working on that study
3 would contact the patient directly and get
4 clarification.

5 DR. DEMETS: Do you have any insight as to
6 why the response rate is what it is?

7 MR. KLINE: Well, the response rate, as we
8 have heard today, has improved. We will continue
9 to work to improve the number of responders. I
10 would say that many of the patients are
11 transient--not transient but have moved from their
12 location where they were being seen by their
13 doctors as part of the SPS study. The doctors
14 sometimes did not know where they were at, or
15 thought they knew and it turned out that they
16 didn't. So, some of it was just finding the
17 patients, which is one of the ways that we improved
18 follow-up by using the ChoicePoint database, which
19 is a database which gives more current addresses
20 than even NCOA. Then, using that as well as FedEx,
21 we were able to track the patients down and
22 determine, if there were three addresses for one
23 patient, which address was the correct one, if any,
24 and then work with the patient.

25 DR. DEMETS: Do you have any sense of what

1 you think you can get this response rate to be, and
2 what a target should be?

3 MR. KLINE: Well, I don't. I don't want
4 to give a hypothetical because we don't know, but
5 we are continuing to work even as we speak to
6 improve the contact and follow-up rate.

7 DR. DEMETS: Do you have a sense of what a
8 target rate should be?

9 MR. KLINE: Well, as in an FDA guidance
10 document, for a two- or three-year study we would
11 hope 80 percent. Obviously, at ten years I would
12 estimate we would like to have 60 percent. We are
13 obviously somewhere in between there and are
14 working to improve both contact and follow-up.

15 DR. DEMETS: So, you think an 80 percent
16 response rate at five years and a 60 percent at ten
17 years would be adequate for your purposes?

18 MR. KLINE: Yes, 80 percent at two to
19 three years and 60 percent at ten years.

20 DR. DEMETS: Do you have any sense of what
21 a typical clinical trial expects in follow-up
22 response rates?

23 MR. KLINE: Just talking about the breast
24 implant studies today, the breast implant study
25 guidance document indicates 80 percent follow-up at

1 least at two to three years and, of course, we are
2 enrolling adequate patients in other breast studies
3 for adequate follow-up for ten years.

4 DR. DEMETS: Well, I will comment later
5 but I worry a lot about the adequacy of even those
6 response rates given the potential biases that
7 exist, and those biases can be very powerful.

8 I would like to follow-up on a comment or
9 a claim that you made that the responders are the
10 same as the non-responders. Could you detail that?
11 That is a strong statement you make and I am trying
12 to understand that.

13 MR. KLINE: That is a very good question,
14 and I would like to have Dr. Eugene Poggio,
15 managing vice president and executive director of
16 biostatistics and epidemiology at ACT, address that
17 since he is a biostatistician and can more
18 correctly address your question. Is that okay?

19 DR. WHALEN: Sure.

20 DR. POGGIO: My name is Gene Poggio and,
21 as Cliff indicated, I am managing vice president of
22 biostatistics and epidemiology at APT Associates
23 Clinical Trials. We are under contract to Mentor
24 to do data management and statistical analysis for
25 both the original SPS study and the follow-on

1 post-approval study.

2 I have no personal financial connection
3 with Mentor, aside from the fact that the firm I am
4 employed by has contractual arrangements. My
5 travel was paid through that contract by Mentor. I
6 am not involved in any lawsuits whatsoever, and I
7 certainly derive no income from implant surgery.

8 With regard to the issue of
9 response/non-response, the way we dealt with that
10 is we took all the information we had on baseline
11 characteristics and operative characteristics and
12 conducted logistic regression. This was done
13 separately for the augmentation cohort and the
14 reconstruction cohort. We used logistic regression
15 to identify variables that were significantly
16 related to response/non-response. I should say
17 that for purposes of that analysis,
18 response/non-response was defined as participating
19 in the PAS versus not participating in the PAS, and
20 didn't deal with loss to follow-up before that.

21 Through that, we identified some variables
22 that were related. For example, for augmentation
23 it was age and annual income, and for
24 reconstruction it was several variables, some
25 operative characteristics and some demographics.

1 Having identified those variables, we then
2 stratified the population by that set of variables,
3 conducted a Kaplan-Meier analysis within each
4 stratum and then computed a weighted average of the
5 Kaplan-Meier estimates with the weights being the
6 initial number of patients in each stratum. The
7 result was numbers that were remarkably close to
8 the original estimate. The largest deviation of
9 the adjusted number to the original number was half
10 a percentage point.

11 DR. DEMETS: So, what percent of those
12 risk factors that you identified explained the
13 response/non-response rate?

14 DR. POGGIO: What was the total percent
15 explained?

16 DR. DEMETS: I know it is not easy to
17 answer in a logistic regression but in analysis of
18 variance you could do that. There are such
19 measures, by the way.

20 DR. POGGIO: I don't know the answer to
21 that question.

22 DR. DEMETS: So, suppose it didn't explain
23 much, would your analysis or your adjustments be
24 useful? You are making a claim that these two
25 groups are the same so I am challenging that.

1 DR. POGGIO: I guess my statement would be
2 that we did everything we could to adjust for it.
3 We looked at the information we had about baseline
4 variables, both demographic characteristics and
5 operative characteristics. We looked at which ones
6 related to response/non-response and then adjusted
7 for those. It is obviously conceivable there is
8 some other variable that we don't have access to
9 that could explain part of it.

10 DR. DEMETS: I am not sure who wants to
11 answer this, but there was a comment that there was
12 no follow-up of those patients in whom the implant
13 was removed. Somewhere else it was said that you
14 used a Kaplan-Meier methodology to censor that
15 observation. There are some assumptions that are
16 required to employ the Kaplan-Meier method about
17 censoring. Can you comment on how that was
18 investigated in the study?

19 MR. KLINE: This is Cliff Kline. Dr.
20 Poggio can explain how the Kaplan-Meier was used in
21 this setting.

22 DR. POGGIO: I think you are referring to
23 some of the earlier comments that we excluded
24 patients with explants.

25 DR. DEMETS: Let me be specific. The

1 assumption is that the censoring mechanism is
2 independent of the process that is going on. So, I
3 am trying to understand how you came to that
4 conclusion.

5 DR. POGGIO: Let me make clear at the
6 outset that patients that were explanted were
7 certainly kept in the analysis up until, if you
8 will, the day after they were explanted. If we had
9 data after that, all that data was reported to the
10 FDA. In order to be conservative, we didn't feel
11 patients were at risk for the complications once
12 the implant was removed. You are not really at
13 risk for capsular contracture after removal. So,
14 if we were to include them after that point the
15 estimates would actually go down, and we didn't
16 think it would be appropriate to do that.

17 In terms of the issue of the censoring,
18 yes, obviously the underlying assumption in
19 Kaplan-Meier is that the people who aren't censored
20 look like the people who are censored--rather, the
21 other way around. Obviously, the adjustment we
22 made was a refinement on that in that we don't
23 assume that the censored people look like all of
24 the uncensored people. We assume they look like
25 the uncensored people in the stratum that we

1 defined by the variables that we stratified.

2 DR. DEMETS: I am still not sure I fully
3 understand the statement you are making. The other
4 issues I want to ask about have to do with if you
5 censor the patients at the time of the implant
6 being removed, do I understand that complications
7 that may take place after that point are not
8 captured? I mean, we have heard this morning's
9 testimony that some of these complications can
10 occur--

11 DR. POGGIO: They are captured in the data
12 provided to the FDA, in data listings. They are
13 not included in the analysis because we don't
14 feel--I mean, it was really my decision. We didn't
15 keep them in the Kaplan-Meier because we don't feel
16 they are appropriately included predominantly
17 because those patients are not at risk for most of
18 the complications with the device no longer in
19 place.

20 DR. DEMETS: That is an assumption, it
21 seems to me.

22 DR. POGGIO: I guess if you asked a
23 surgeon if they could have capsular contracture, a
24 new case of capsular contracture after the device
25 was removed, I would assume they would support

1 that.

2 DR. DEMETS: But my question was not about
3 that; it was about other complications.

4 DR. POGGIO: As I said, we didn't feel
5 they should be included in the analysis because
6 they are certainly not at risk for many of the
7 complications.

8 DR. DEMETS: Which is what the data are
9 trying to understand, if they are there. Aren't
10 you precluding that if you take them out?

11 DR. POGGIO: If I include them in I assume
12 that they are at risk and, in fact, I think that
13 would lower the estimated complication rates. You
14 could do a special analysis to look at that
15 question. I would be very reluctant to include
16 them in a principal analysis when I no longer think
17 they are at risk.

18 DR. DEMETS: It seems to me that you get
19 rid of some of the complications if you don't
20 follow them beyond that censoring point.

21 DR. WHALEN: If I could interject, would
22 it be a more graphic example to state that
23 deflation would be rather ridiculous to continue to
24 measure in someone who has had an explant because
25 it is hard to deflate something that isn't there?

1 Indeed, if they kept those patients in the
2 denominator it would dramatically lower the
3 deflation rate falsely.

4 DR. DEMETS: I am thinking about other
5 kinds of complications.

6 DR. WHALEN: I am only trying to interject
7 to say that it seems to me that there have to be
8 different sets of data of complications, ones that
9 could continue with the implant in place and ones
10 that would not.

11 DR. POGGIO: And, remember that the ones
12 we are looking at are deflation, capsular
13 contracture, explantation which, obviously could
14 only happen if they had a reimplantation.
15 Obviously, breast pain could. But my view is it
16 would be reasonable to look at that as a separate
17 issue but I still would be very reluctant to
18 include it in a principal analysis because they are
19 not at risk for some of the complications, and
20 certainly much lower risk for some others.

21 DR. DEMETS: My last question is about the
22 table at five years that you compare to three
23 years, the denominators are different. In fact,
24 they are larger at five years than at three years.
25 Can you explain that?

1 DR. WHALEN: Could you give a number that
2 you are looking at so we can make sure we are
3 looking at the same thing?

4 DR. POGGIO: It is certainly true that we
5 did get additional three-year data in the PAS study
6 also.

7 DR. DEMETS: It is your slide 19 in your
8 presentation. At five years you report 211
9 patients, at three years you report 138. There are
10 several like that but that is one.

11 DR. POGGIO: Sure. In that table the N
12 under five years, which is 211, indicates the
13 number of implants that had reoperations, whereas
14 at three years the number of implants involved in
15 reoperations was 136. Therefore, the denominator
16 increases because we had more implants involved in
17 reoperations.

18 DR. DEMETS: So, are we looking at
19 comparable groups?

20 DR. POGGIO: You are looking at 211
21 explants at five years and 136 explants at three
22 years. So, there are obviously more explants as
23 time goes on.

24 DR. DEMETS: Thank you.

25 DR. WHALEN: Dr. Dubler?

1 DR. DUBLER: Could I ask one more
2 question, please, about the focus groups? I am
3 very concerned about how the resurgery rate is
4 presented and defined. So, can you tell us, and
5 this may be unreasonable, how that was explained in
6 your first "informed consent" or what I prefer to
7 call disclosure document, and after your focus
8 groups how you might have restated that? So, if
9 there is a table about the chance of resurgical
10 interventions?

11 MS. CRAWFORD: Yes, I am looking at the
12 version of the brochure that we did the focus group
13 study on right now. There is a section on
14 reoperations. It does give the three-year risk
15 rate of reoperation by patient and by implant.

16 DR. DUBLER: So, there is a table?

17 MS. CRAWFORD: There are tables.

18 DR. DUBLER: And what do you say about the
19 tables? Are there declarative sentences?

20 MS. CRAWFORD: Prior to the tables, for
21 example, it just indicates that the following are
22 the cumulative risk rates, first occurrence for the
23 following complications.

24 DR. DUBLER: So that is the text? Could
25 you read us the particular language?

1 MS. CRAWFORD: Certainly. I just want to
2 make sure I am looking at the right place here.
3 The question at the heading of the section is what
4 were the three-year cumulative complication risk
5 rates of first occurrence? Then the sentence
6 following that says the cumulative risk rate of
7 first occurrence which occurred in at least one
8 percent of the patients are shown in the following
9 tables, including all levels of severity, mild to
10 severe. Then it lists the complications. This
11 particular section is talking about augmentation
12 and it lists the complications that were found in
13 augmentation patients.

14 DR. DUBLER: Are there any other
15 declarative sentences that surround the table?

16 MS. CRAWFORD: Not in the original
17 version.

18 DR. DUBLER: And in the version that was
19 modified by the focus groups, is it very different?

20 MS. CRAWFORD: Yes, the column by implants
21 was eliminated, and there were some explanatory
22 sentences. I don't have that right in front of me
23 at this moment, but that was added. In the
24 introduction of the whole section on cumulative
25 risk there were a couple of sentences explaining

1 how the risk rate can be interpreted and what it
2 means to the patient.

3 DR. DUBLER: Let me ask anyone to answer
4 the following question, what is your chance of
5 going back in for surgery, what is your five-year
6 chance of going back in for surgery after receiving
7 a breast implant? That is my question. What would
8 you say to me? What is your percentage chance?

9 DR. MICHAEL: Are you talking about
10 augmentation?

11 DR. DUBLER: I want to know how you would
12 translate that table.

13 DR. MICHAEL: Are you talking about the
14 augmentation group or the reconstruction?

15 DR. DUBLER: Either one, take your choice;
16 augmentation. What is the chance that you are
17 going to have another surgery in the next five
18 years?

19 DR. MICHAEL: Well--

20 DR. DUBLER: What percentage chance?

21 DR. MICHAEL: Let me mention something
22 here for the augmentation group, in one of the
23 tables that was presented this morning 30 percent
24 of reoperations in the augmentation group was the
25 patient's choice for change of size. In the

1 reconstruction group 16 percent was the patient's
2 choice for a larger size or a different size, and
3 15 percent in that cohort was expected because that
4 was stage reconstruction. So, one-third out of
5 that.

6 DR. DUBLER: I want to say to you I know I
7 may want to decide to change my size but, given all
8 of the factors that lead to surgery, what is the
9 chance, including my changing my mind--what is the
10 chance that I am going to have another surgery in
11 the next five years?

12 DR. MICHAEL: Based on what we presented
13 in our data this morning, the chance, if using the
14 same mix of the product that was used in the SPS
15 study, at five years the probability of having a
16 deflation is 9.7 percent.

17 DR. DUBLER: That is not what I asked you.
18 What is the chance in the next five years, for any
19 reason, that I am going to have to have surgery
20 again? What do your data show?

21 MS. CRAWFORD: It shows that there is a 20
22 percent risk rate at five years, and the way that
23 is explained in the patient brochure is that 20 out
24 of 100 patients will experience at least one
25 reoperation during five years. That is how it

1 would be explained. There is an example given, and
2 to translate that to a reoperation number, that is
3 how it would read.

4 DR. DUBLER: So, your statement is that
5 there is a 20 percent chance in the next five years
6 that you will have to have another surgery.

7 MS. CRAWFORD: That is how it would be
8 interpreted. For example, the brochure right now
9 gives an example for a cumulative risk rate of two
10 percent for infection. That means that
11 approximately two patients out of 100 will
12 experience at least one infection sometime during
13 the first year. So, since our five-year risk rate
14 was 20.2 percent for reoperation, that is how it
15 would be interpreted.

16 DR. DUBLER: Thank you.

17 DR. WHALEN: Can I just interject, more in
18 comment, if a third of your reoperations are
19 patient choice for a different size, would it not
20 perhaps be more appropriate to say there is a 20
21 percent chance I am going to have another
22 operation; there is a 14 percent chance I am going
23 to have to have another operation? Since the
24 wording you use was I am going to have to have
25 another operation?

1 DR. MICHAEL: I would like to take a
2 couple of minutes to introduce Dr. Roger Freedman.
3 He is a clinical instructor--

4 DR. WHALEN: For what purpose?

5 DR. MICHAEL: To elaborate on that issue
6 of the percentage of reoperations based on his
7 experience in practice.

8 DR. WHALEN: I don't think that is
9 necessary. Thank you. Dr. Newburger?

10 DR. NEWBURGER: I have a question for Mr.
11 Kline regarding the attempts to contact patients to
12 participate in the post-marketing study. How long
13 is the questionnaire that they are sent?

14 MR. KLINE: One page.

15 DR. NEWBURGER: How many questions on that
16 one page?

17 MR. KLINE: Of course, we ask them to
18 verify that their name is spelled correctly, but
19 there is a question on capsular contracture,
20 explantation, reoperation. So, there is just a
21 very small list of questions to specifically ask
22 them about the complications we are collecting.

23 DR. NEWBURGER: Is there any incentive to
24 the patient to return the questionnaire?

25 MR. KLINE: Yes, there is.

1 DR. NEWBURGER: And what would that be?

2 MR. KLINE: I don't recall the exact
3 amount. It is minimal. It would be somewhere
4 under \$30.

5 DR. NEWBURGER: And, how do you explain
6 your protection of patient confidentiality?

7 MR. KLINE: Well, that is explained both
8 in the original letter they get as well as the
9 informed consent that they sign which, of course,
10 indicates that we will try to protect their
11 confidentiality; it may not be able to be done if,
12 for example, a government agency such as FDA needs
13 to review these data.

14 DR. WHALEN: Dr. Doyle?

15 DR. DOYLE: I have a question regarding
16 the reoperations. How are these women included in
17 the further data? Is that reoperation considered a
18 new start, or is it a continuation of the patient?
19 Also, I am confused about your three-year and your
20 five-year cohorts of women. They are not
21 necessarily the same patients, is that correct?

22 MR. KLINE: To answer your second question
23 first, all post-approval study patients were
24 originally SPS, saline prospective study patients.

25 DR. DOYLE: But the people who answer at

1 five years and the people who answer at three years
2 are not necessarily the same group of patients. As
3 you might ordinarily expect where you have
4 attrition, that those who were left at five years
5 would have answered at three. In this you have two
6 separate groups actually who all started together
7 but the five years may not be in the three-year
8 data and the three years may not be in the
9 five-year??

10 MR. KLINE: I would agree with that, but
11 most of the patients--as the panel members
12 saw--that were present two years ago, our follow-up
13 rates were a little bit higher so most of the
14 patients that were reported on at the three-year
15 PMA were also included in this study.

16 DR. DOYLE: But some of your five years
17 were not included in your three years.

18 MR. KLINE: Pardon?

19 DR. DOYLE: Some of your five years were
20 not included in your three years.

21 MR. KLINE: There were a couple of
22 patients that we were able to collect additional
23 information on that we didn't have three-year
24 information on at the time of the PMA.

25 DR. DOYLE: Okay, and what about how you

1 handled the patients with the reimplantations? Do
2 they start at year one or do they continue?

3 MR. KLINE: They continue unless the
4 reoperation--as I said, explants are a subset of
5 reoperations, obviously if they are explanted they
6 are no longer--

7 DR. DOYLE: No, these are the ones who
8 were reimplanted. They start out as year one or
9 continue?

10 MR. KLINE: They continue.

11 DR. WHALEN: Are there any questions by
12 any of the panel members about the biomaterials
13 presentation? Dr. Miller?

14 DR. MILLER: I just have a couple of
15 questions on that. Ten million cycles in that
16 machine, how many years of walking does that
17 represent?

18 MR. CROUTHER: That is one year of walking
19 eight hours a day, one second per cycle.

20 DR. MILLER: How do you feel that system,
21 that test that was devised--I know it was all
22 agreed upon by FDA, but how do you feel that
23 actually simulates what that implant is
24 experiencing, especially considering the fact that
25 so many failures occurred at the site of a fold?

1 Do you think that testing in this way is a good
2 simulation of what the implant experiences?

3 MR. CROUTHER: It is a good simulation of
4 some of what an implant experience is; it is not a
5 good simulation to duplicate a fold failure like a
6 material separation defect.

7 DR. MILLER: Which is how most fail.

8 MR. CROUTHER: Correct, most of the
9 textured devices that are non-instrument damaged
10 devices fail that way.

11 DR. MILLER: The other question I had is
12 that several of the presenters this morning
13 suggested that there are materials released from
14 the device that may be toxic, and platinum was
15 mentioned several times today. Is it fair for me
16 to ask about your response to the manufacturing
17 methods that employ platinum, and is this a concern
18 that you have about the presence of such trace
19 materials?

20 MR. CROUTHER: I am going to ask Phil
21 Yang, who is our corporate vice president of
22 technology submissions, to answer that question.

23 MR. YANG: Phil Yang. We have done a risk
24 analysis based upon what we know. We do a specific
25 analysis for I believe 20 heavy metals, of which

1 platinum is one. We do do that. That is compared
2 against what is in the literature for toxicity
3 data. So, we do compare that. That is all part of
4 the PMA.

5 DR. MILLER: When you determined those
6 materials are released, do you look at an implant
7 subjected perhaps to a type of environment as
8 described in your mechanical study?

9 MR. YANG: We can't do that because
10 probably we would find metals from the platens
11 themselves. So, we do it on sterilized, finished
12 devices from the package because that is what would
13 go into a patient.

14 DR. MILLER: Is it possible that a device
15 subjected to the environment in vivo would have a
16 different profile of release of trace elements?

17 MR. YANG: It is possible. The problem
18 becomes when you try and analyze for them, you then
19 have to somehow correct for what the patient
20 contributed to that device. That becomes very
21 complicated. We tried to do that in some cases but
22 the techniques that we use are not designed--things
23 like proteins get in the way. So, it is hard to
24 do. It is not impossible to do that; some people
25 have tried to do that but the question is how good

1 is the analysis, and that has always been a
2 question.

3 DR. MILLER: Thank you.

4 DR. WHALEN: Dr. Choti?

5 DR. CHOTI: Just a couple of questions,
6 Mr. Kline. One, just to clarify again the
7 follow-up of the two different cohorts that you
8 looked at, you showed a five-year follow-up rate in
9 the new analysis of 60 percent, 50-60 percent on
10 average I think, depending on whether it was
11 reconstruction or augmentation. What was the
12 three-year follow-up given the new follow-up that
13 you have, a better follow-up, and how does that
14 compare to the original PMA data? In follow-up to
15 that, when you compared the three-year to the
16 five-year, why did you use the new follow-up data
17 rather than the original PMA data?

18 MR. KLINE: The follow-up in the PMA was
19 approximately 70 percent for both cohorts.

20 DR. CHOTI: Three years?

21 MR. KLINE: Yes, at three years, the PMA
22 submission at three years. The analysis that we
23 did does include all data, whether it is five-year
24 or updated three-year. So, the analysis is on all
25 the data that we have. The numbers for the PMA and

1 the numbers that I showed for the three-year
2 columns were just for consistency's sake. The
3 three-year numbers submitted in the PMA just varied
4 slightly because of some new patient data that we
5 got.

6 DR. CHOTI: The other question is
7 regarding the textured versus the smooth. In the
8 clinical data, did you look at differences in
9 deflation, capsule and reoperation between the two
10 groups? Also, what were the relative percentages
11 of the two types?

12 MR. KLINE: We did look at the difference
13 in deflation rates between smooth and what we call
14 Siltex or textured product. The rate for smooth
15 products, for all products was approximately 5-6
16 percent and the rate for Siltex was approximately
17 11-12 percent.

18 DR. CHOTI: As the population as a whole
19 of the two types, what did you have in the group?

20 MR. KLINE: We presented that in Dr.
21 Michael's first slide, 30 percent smooth and
22 approximately 70 percent textured.

23 DR. CHOTI: And how was that changed near
24 the end of the trial or more currently?

25 MR. KLINE: You are exactly right, with

1 the current mix of product, with the product mix
2 that we had in the study those were the rates. You
3 know, doctor preferences have changed. At this
4 point it would be appropriate to bring up Dr.
5 Freedman to discuss the current preference mix that
6 he uses in his own practice. As Dr. Michael was
7 explaining before, Dr. Freedman is a clinical
8 instructor for plastic and reconstructive surgery
9 at George Washington University. He is a clinical
10 assistant professor for plastic and reconstructive
11 surgery at Georgetown University, and a consultant
12 to the Department of Plastic and Reconstructive
13 Surgery for the NIH.

14 DR. FREEDMAN: My name is Roger Freedman.
15 Approximately 35 percent of my practice is breast
16 surgery

17 DR. WHALEN: I am sorry to interrupt, but
18 could you identify with the questions?

19 DR. FREEDMAN: Oh, I am sorry. I am not
20 involved in any suits. I have provided my own
21 travel today. I do put in breast implants and I am
22 also involved in the core gel breast implant study
23 provided by Mentor. So, I do get some compensation
24 for that study.

25 My practice consists of approximately 35

1 percent breast surgery, which encompasses all
2 aspects of both cosmetic and reconstructive breast
3 surgery. My implant usage is pretty consistent
4 with that of the norm for the nation, which is
5 probably 98 percent to 99 percent smooth round,
6 with a rare case of using textured today.

7 I think people have appreciated that there
8 is more of an incidence of rippling in the textured
9 implant which, therefore, then gives a potential
10 for fold failures which you were addressing earlier
11 and, therefore, by switching over to the smooth
12 round and placing these implants under muscle, that
13 muscle is then providing pressure on the implant
14 which has a tendency to help smooth out that
15 implant even more. That is consistently the norm
16 today.

17 The issue then is the issue of filling an
18 implant. There are recommendations, nominal
19 recommendations by the manufacturer. It has been
20 appreciated that if you under-fill an implant to
21 maintain a softer implant there is a higher
22 incidence of rippling and, again, a higher
23 incidence of fold failure. So, that is not the
24 current norm so people typically, including myself,
25 fill them to their nominal value or slightly

1 overfill those implants, but not beyond the
2 recommendations of the manufacturer. The numbers
3 that I personally experience in my practice are
4 less than those which are quoted in this report.

5 DR. CHOTI: So, can you tell us again the
6 difference of smooth versus the textured in the
7 study as far as the complication rates?

8 MR. KLINE: We stratified for deflation,
9 and for deflation smooth is approximately 5-6
10 percent deflation rate, whereas our textured
11 product, Siltex, is 11-12 percent through the five
12 years.

13 DR. CHOTI: Other parameters?
14 Reoperation, capsular formation?

15 MR. KLINE: I don't have that information
16 available right at the moment, but we could
17 certainly look at it and provide it to FDA.

18 DR. WHALEN: Dr. Chang?

19 DR. CHANG: Even though the data was not
20 presented, can anyone give me an answer with regard
21 to the explanted implants that were examined? Was
22 there any relationship between thickness of the
23 shell in those that were explanted and that did not
24 have surgical sharp instrumentation?

25 MR. CROUTHER: Not within a population of

1 a given type. You know, our textured devices are
2 thicker, for example, than our smooth devices, but
3 I am assuming you are talking just about the
4 textured, did those where we had fractures exhibit
5 lesser wall thickness? And, there was no evidence
6 of that, nor was there any correlation with
7 physical properties.

8 DR. CHANG: My second question is that
9 previous testimony from public comment just
10 mentioned some questions about investigators about
11 good manufacturing practices so I would ask the
12 sponsor if there are any outstanding questions or
13 communication with the FDA regarding improvement in
14 good manufacturing practices that are outstanding
15 at this time.

16 MR. CROUTHER: I will ask Clark Sheriff,
17 from Mentor, to discuss that.

18 MR. SHERIFF: Good morning. I am Clark
19 Sheriff, vice president of regulatory compliance
20 for Mentor Corporation. At this point there are no
21 outstanding issues with the FDA. The last
22 inspection was this last February. There was a
23 comprehensive GMP inspection by the agency, in
24 Dallas, and the few issues that they brought up
25 have been all addressed satisfactorily.

1 DR. CHANG: Thank you.

2 DR. WHALEN: Dr. Dubler?

3 DR. DUBLER: If I heard the previous
4 discussion correctly, the textured implants have
5 twice the deflation rate, approximately twice the
6 deflation rate as the smooth. Is that correct?
7 Is there any point in the brochure that makes a
8 statement that says our textured implants have two
9 times the deflation rate as the smooth?

10 MS. CRAWFORD: No, that is not currently
11 in the brochure. Most of this information was
12 developed after the brochure was printed. We can
13 certainly work with FDA in determining what is
14 appropriate to add to the brochure at this point.

15 DR. DUBLER: So, there is no statement
16 that reflects those data?

17 MS. CRAWFORD: That is correct.

18 DR. WHALEN: Thank you. We will now
19 proceed to the FDA's presentation with Ms. Allen
20 and Dr. Dawisha.

21 **FDA Presentation**

22 MS. ALLEN: Good afternoon. FDA will now
23 summarize the status of the conditions of approval
24 for Mentor' saline-filled breast implant PMA. For
25 your convenience, we have provided you with a hard

1 copy of FDA's slides.

2 There are five conditions of approval:
3 post-approval study; a focus group study; a
4 retrieval study; fatigue testing; and shelf-life
5 testing. Dr. Sahar Dawisha will present the status
6 of the post-approval study and I will present the
7 status of the remaining four conditions of
8 approval. I will now hand it over-expression to
9 Dr. Dawisha.

10 DR. DAWISHA: It is still morning so I can
11 say good morning. I am a medical officer and I had
12 reviewed and presented the breast implant
13 information back in March of 2000. As you recall,
14 at that time one of the conditions of approval was
15 that the sponsors provide long-term safety
16 information on their products.

17 To meet this condition, Mentor Corporation
18 has been conducting a post-approval study which is
19 an extended follow-up of the patients in the saline
20 prospective study, which was originally designed as
21 a three-year study, out to ten years postop in an
22 abbreviated protocol.

23 As you just heard this morning, this
24 protocol consists of annual mailing or a physician
25 visit, and the endpoints of interest in the study

1 include implant deflation, implant removal and
2 reason for removal, additional surgery and reasons
3 for surgery, presence and grade of capsular
4 contracture, and breast pain related to implants.

5 As just discussed by Mentor, the protocol
6 was approved in May of 2000, which is when the PMAs
7 were approved. Mentor began contacting their
8 investigators in July of 2000, asking them to
9 contact their patients or allow the sponsor to
10 contact them. The initial patient mailing began in
11 October of 2000. The database that we are going to
12 be discussing today was closed in March of 2002.

13 It is FDA's goal to update the patient
14 labeling, the physician package insert and the
15 summary of safety and effectiveness, which I will
16 refer to as the labeling, every few years to
17 reflect the current complication information. We
18 plan on updating the labeling to reflect the
19 five-year data that I am going to be discussing in
20 the next few slides.

21 Before discussing the post-approval study
22 or PAS study results, I would like to briefly
23 review the saline prospective study patient
24 accounting. Recall that the saline prospective
25 study served as the basis for the PMA.

1 The number of patients living and with
2 implants by the end of the saline prospective
3 study, as shown on this table, was 1252 for
4 augmentation and 375 for reconstruction. By the
5 end of the saline prospective study and before the
6 start of the post-approval study in October--so,
7 there is about a five-month period there--there
8 were a few additional patient deaths and implant
9 removals, making 1250 augmentation and 351
10 reconstruction the number of patients available for
11 participation in the post-approval study. You will
12 see these numbers in a subsequent table.

13 With that background, we can now discuss
14 the patient accounting for the post-approval study
15 patients over time, which is shown in this table
16 for augmentation. Based on the actual follow-up,
17 divided by the expected follow-up where we define
18 expected follow-up as the theoretically due minus
19 deaths and removal of all implants during the
20 interval, the follow-up rate is shown here for five
21 years through ten years postop. For example, the
22 follow-up rate at five years is 5 percent, 24
23 percent at 6 years, 45 percent at 7 years, etc.

24 Because some patients had exceeded their
25 five-year follow-up visit at the time of the start

1 of the PAS and because the sponsor has recently
2 improved their efforts to contact patients, the
3 follow-up rates beyond six years are superior to
4 that at five years.

5 The bottom row of this table shows the
6 number and percent of patients with any data at any
7 time, where a returned questionnaires are counted
8 for all previous time points. For example, using
9 this method the follow-up rate at five years is 54
10 percent at five and six years.

11 The patient accounting information for the
12 reconstruction patients in the PAS study are shown
13 on this table. As you can see, the follow-up rate
14 for reconstruction patients is superior to that for
15 augmentation patients in the previous slide. For
16 example, the rate at five years is 52 percent, at
17 six years 59 percent, and at seven years 54
18 percent.

19 Because of the low follow-up rate, FDA has
20 been working with the sponsor to improve patient
21 contact efforts, which are summarized in this
22 table. Of the patients expected for participation
23 in the PAS, which is shown in row 1, some patients
24 were excluded, in row 2, primarily because a few
25 physicians didn't want to participate in the PASS,

1 which reduced the number of patients to whom
2 packets were mailed, which is shown in row 3.

3 Taking augmentation as an example, of the
4 original cohort of 1250 patients, approximately
5 half, which is shown in row 12, have agreed to
6 participate in the PAS, and 777 patients have some
7 data reported at least once in the PAS, which is
8 shown in row 15.

9 Of the 351 reconstruction patients,
10 approximately two-thirds of the original cohort,
11 which is shown in row 12, have agreed to
12 participate in the PAS, and 265 have some data
13 reported at any time, which is shown in row 15.

14 Rows 6 and 7 are of interest because they
15 reflect the patients whom the sponsor is pursuing
16 to continue to contact.

17 Because of concerns with missing
18 information and how this would impact the results,
19 the sponsor was asked to determine whether and to
20 what extent there was bias in the results due to
21 missing information from patients who were
22 considered non-responders, and whether and how the
23 complication information should be adjusted to
24 reflect missing information from these patients.

25 The results of this analysis are currently

1 under review by us, and additional information has
2 been requested and is ongoing to further clarify
3 this issue.

4 What I can discuss are the results of
5 preliminary analysis to answer these questions in
6 which the baseline demographic and surgical
7 characteristics were compared between patients who
8 were and were not responders.

9 There were no significant differences with
10 respect to race, ethnicity, marital status,
11 incision size and obesity, defined as a body mass
12 index of greater than or equal to 24.

13 For augmentation, there was a significant
14 difference with respect to age at the time of
15 implantation, with responders older than
16 non-responders.

17 For reconstruction, there were significant
18 differences with respect to surgical approach,
19 implant placement and surface texturing. Again,
20 these analyses are still being developed.

21 I will now discuss the safety results from
22 the data that we have available from the
23 responders, first for augmentation and then for
24 reconstruction.

25 Table 5 summarizes the cumulative

1 Kaplan-Meier risk rate of first occurrence and the
2 corresponding 95 percent confidence interval of
3 complications at three and five years for the
4 augmentation patients. These values represent the
5 cumulative risk of having the first occurrence and
6 do not capture repeat occurrences.

7 The three-year rates shown in this table
8 reflect the data from the saline prospective study
9 that appear in the current labeling, and the
10 five-year rates are an update based on the
11 post-approval study.

12 While the cumulative risk rates at five
13 years are higher than at three years for all the
14 complications shown here, it is only for
15 reoperation, implant removal and implant deflation
16 where the confidence intervals are not overlapping,
17 suggesting that the rates at these time points are
18 significantly different.

19 I would like to point out that we had not
20 asked Mentor to do any statistical analyses
21 comparing whether the rates were different at one
22 time point to another. However, they have a
23 slightly different interpretation where they found
24 an increased risk only for implant deflation and a
25 decreased risk for capsular contracture. They

1 reached these conclusions based on a separate
2 analysis where the risk of each complication was
3 estimated over time for patients who had not had
4 the complication, and then linear regression was
5 used to determine whether there was a statistically
6 increased or decreased risk at five years.

7 Again, we did not ask Mentor to do these
8 analyses and the Kaplan-Meier shown here are what
9 are in the current labeling and will be included in
10 the updated labeling.

11 The reasons for reoperation in the
12 augmentation patients are shown in this slide based
13 on the number of reoperations. If more than one
14 reason was reported, then all the reasons are
15 included in this table. Note that the current
16 labeling reports the types of reoperation
17 procedures, again, because these were physician
18 elicited responses rather than the reasons for
19 reoperation, which is what was elicited on the
20 questionnaire.

21 The three-year information shown here was
22 provided by the sponsor at our request to show the
23 progression from three to five years. I have
24 combined the rows for the purposes of projecting
25 the slide, as described in the footnotes below the

1 table.

2 Through five years there were 343
3 reoperations or additional procedures reported in
4 198 patients, involving 312 implants. On a per
5 reoperation basis, the three most common reasons
6 for reoperation at five years are cosmesis, and
7 this includes wrinkling, ptosis, asymmetry and
8 aesthetic revision, approximately 36 percent;
9 followed by patient request for a size or shape
10 change, 28.6 percent; and followed by
11 leakage/deflation, 19.2 percent.

12 The primary reason for implant removal at
13 three and five years is shown for augmentation in
14 Table 7. If more than one reason was reported, the
15 same hierarchy was used as that reported in the
16 current labeling.

17 Through five years, implant removal was
18 reported for 211 implants in 132 of the
19 augmentation patients. The four most common
20 primary reasons for implant removal at both three
21 and five years was patient request for a size or
22 shape change, approximately 30 percent, which was
23 equal to the number of leakage/deflation, also
24 approximately 30 percent; followed by asymmetry,
25 wrinkling, ptosis or scarring, 18.5 percent; and

1 then followed by capsular contracture, 14.7
2 percent.

3 Moving on to the reconstruction
4 information, the by-patient Kaplan-Meier values are
5 shown in this table, with the three-year rates
6 based on the current labeling and the five-year
7 rates representing the updated information.

8 While the risk rates are slightly higher
9 at five years compared to three, the confidence
10 intervals are overlapping for these time points,
11 suggesting no differences. Note that the
12 overlapping confidence interval is least
13 superimposable for the complication of implant
14 deflation compared to the other complications.

15 The reoperation information, which
16 excludes planned procedures, is summarized for
17 reconstruction patients in Table 9. As with
18 augmentation, the three-year information was
19 recently provided by the sponsor and is not in the
20 current labeling. Through five years there were
21 232 reoperations reported in 162 patients, and
22 occurring with 196 implants.

23 On a per reoperation basis through five
24 years, the three most commonly reported reasons are
25 cosmesis, which includes wrinkling, asymmetry,

1 aesthetic revision and ptosis which is 31 percent;
2 followed by capsular contracture, approximately 29
3 percent; and followed by a scar or wound revision,
4 25.4 percent.

5 The implant removal information is shown
6 in this slide for the reconstruction patients.
7 Through five years, implant removal was reported
8 for 135 implants in 112 of the reconstruction
9 patients. The three most common primary reasons at
10 both three and five years is capsular contracture,
11 leakage/deflation and infection.

12 This concludes the post-approval study
13 presentation for Mentor and Ms. Allen will now
14 continue with the focus study results.

15 MS. ALLEN1: The ultimate goal of the
16 focus group study was to improve the existing
17 patient brochure. Mentor already described how an
18 independent study was conducted to obtain feedback
19 regarding their patient brochure. They also
20 described some of the key findings from that
21 independent study.

22 FDA considered the independent study
23 reports submitted by both Mentor and Inamed and
24 required the same types of changes for both
25 companies, if applicable. The primary changes to

1 Mentor's patient brochure were as follows:

2 They made significant modifications to the
3 lead-in as well as to the content of the safety
4 tables because most women had difficulty in
5 understanding the safety data. They stratified
6 augmentation and reconstruction information, and
7 they added a table of contents and a glossary.

8 Mentor incorporated all requested changes
9 into the patient brochure and received FDA
10 approval. Therefore, FDA considers this condition
11 of approval fulfilled. Mentor has just submitted a
12 revised patient brochure and package insert that
13 reflect five-year post-approval data. After FDA
14 review and approval of this supplement, Mentor will
15 finalize them for public and product use.

16 The purpose of the retrieval study is to
17 determine modes of failure. This information may
18 lead to changes in manufacturing design
19 specifications, mechanical testing requirements,
20 and/or labeling.

21 In their 2001 report, Mentor submitted
22 limited data on 38 explants collected over a
23 four-month period. Mentor provided clinical or
24 physician observations collected at the time of
25 explantation. They provided laboratory

1 observations, or device failure characteristics,
2 such as smooth and sharp crease-edge opening.
3 These were noted with respect to whether the device
4 was deflated or non-deflated.

5 Based on the limited number of retrieved
6 implants, Mentor made no conclusions regarding
7 whether the device failure characteristics were
8 representative of a true failure or the result of
9 an artifact, such as shipment, excessive handling
10 or the method of explantation. Accordingly, no
11 hypotheses regarding modes of failure were provided
12 in that report.

13 Mentor submitted a final report of the
14 retrieval study which is under FDA review.
15 Therefore, FDA considers this condition of approval
16 still open.

17 The purpose of the fatigue testing is to
18 determine the fatigue strength of Mentor's product
19 line. These data provide additional information on
20 the expected long-term performance of the device.
21 There are 12 styles across the saline-filled and
22 Spectrum families. Mentor chose styles 1400, 1600,
23 2600 and 5000PT as representative of their entire
24 product line.

25 Mentor completed fatigue testing on three

1 of the four styles. The resulting endurance load
2 limit was 10 lbs at 10 million cycles run-out for
3 those three styles tested, which did meet the
4 acceptance criteria.

5 As part of the test report, Mentor also
6 supplied the ultimate static rupture results for
7 those three styles. The results were over 600 lbs
8 for all three styles, which shows that the implants
9 failed at static loads much greater than that
10 expected during mammography, which is about 55 lbs.

11 FDA expects Mentor to submit fatigue test
12 results for style 5000PT as part of their 2003
13 annual report. Accordingly, FDA considers this
14 condition of approval still open.

15 The purpose of the shelf-life testing is
16 to support a five-year expiration date on the
17 package label. Mentor's shelf-life protocol
18 involves real-time package integrity and mechanical
19 testing performed at year zero or baseline at years
20 four and five.

21 In their 2001 annual report, Mentor
22 provided an interim report with year zero data.
23 The results were adequate. However, this report
24 did not include style 5000PT data. An updated
25 report of year zero testing with style 5000PT data

1 has been submitted and is under FDA review.

2 FDA expects Mentor to submit an updated
3 report of shelf-life testing year-four data in 2005
4 and year-five data in 2005. Accordingly, FDA
5 considers this condition of approval still open.

6 This is an overall summary of Mentor's
7 five conditions of approval. The post-approval
8 study will remain open until ten-year data are
9 provided.

10 The focus group study is complete. Mentor
11 has already revised their patient labeling to
12 reflect the focus group study findings.

13 The retrieval study is currently open,
14 however, Mentor has submitted the final report and
15 it is under FDA review.

16 The fatigue testing is complete on three
17 of the four styles. Testing on the fourth style is
18 expected to be submitted in the 2003 annual report.

19 The shelf-life testing will remain open
20 until five-year data are provided.

21 I will now turn it over to the panel for
22 discussion.

23 **Panel Discussion**

24 DR. WHALEN: Thank you. Questions of Ms.
25 Allen or Dr. Dawisha from the panel?

1 DR. DEMETS: I have a question.

2 DR. MCCAULEY: I do too.

3 DR. WHALEN: Dr. McCauley, I heard you
4 first.

5 DR. MCCAULEY: Based on the focus group
6 study, initially the brochure revealed that one out
7 of four of the focus group participants did not
8 understand the data, or it was confusing, and the
9 brochure was revised. But this was not taken back
10 to the focus groups to see if they understand that
11 data before it is approved? Is that not true?

12 MS. ALLEN: That is correct. The protocol
13 was for that first feedback on the existing
14 brochure, approved back in May, 2000. There are no
15 plans right now to go back and conduct a second
16 focus group study.

17 DR. MCCAULEY: Then how do you know if the
18 consumer understands the data?

19 MS. ALLEN: Good question. We worked with
20 ODE and OHIP, Office of Health and Industry, in
21 order to provide input on making it more in
22 layman's terms. I don't know, maybe Mentor can
23 provide more input on that.

24 DR. WITTEN: I would say we think we
25 addressed the issues that were raised by the focus

1 groups. As Ms. Allen mentioned, we have someone in
2 another office who looks at patient labeling
3 specifically for us to address issues related to it
4 being understandable to the patient or to the
5 consumer.

6 DR. WHALEN: Dr. Doyle?

7 DR. DOYLE: I am concerned about the
8 follow-up rate, whether the data is even viable
9 given the low follow-up rate. In addition to that,
10 20 percent of the patients have reimplantation and
11 they are considered in the group that goes out to
12 five years rather than starting over as a new
13 implant. Wouldn't that give falsely low
14 complication rates at five years because these
15 women may have only had the implant at one, two or
16 three years and their second implant, yet, I think
17 I understood that they are within the group that
18 has been carried out to five years.

19 DR. DAWISHA: If a patient undergoes a
20 revision, gets their implants removed and gets a
21 second set of implants, as far as I know, they are
22 not included in the Kaplan-Meier values because
23 they are considered revision patients and we have
24 reported them separately in the labeling, as a
25 separate group that gets complications following

1 revision.

2 DR. DOYLE: Perhaps I misunderstood but I
3 thought when I asked Mentor this question they said
4 they were left back in the data. Maybe I
5 misunderstood.

6 DR. DAWISHA: Well, they continue to
7 follow the patients and they report the study
8 results to us, but they are in a separate table in
9 the labeling. They are reported as patients who
10 have complications following revision.

11 DR. WHALEN: Dr. DeMets?

12 DR. DEMETS: Yes, I am bothered by the
13 response rate. I appreciate the challenges and
14 difficulties of follow-up in any study, any
15 clinical study that is done. Having said that, I
16 am still troubled I guess as much as my predecessor
17 Dr. Blumenstein was by the response rate, and what
18 you can make of any kind of strong conclusion based
19 on that kind of response rate.

20 There has been some comment by both the
21 FDA and the sponsor about comparing responder and
22 non-responder at baseline. That is nice. Maybe it
23 is necessary, but it is hardly sufficient because
24 the real assumptions have nothing to do with that.
25 The real assumption has to do with the outcomes.

1 Are the outcomes in responders the same as in the
2 non-responders? Suppose it turned out that the
3 patients who didn't respond all had bad experiences
4 and were so angry that they threw the questionnaire
5 in the trash, that is the kind of bias that you
6 worry about and until you can begin to address that
7 you never know with the non-responder is
8 introducing a bias or not. So, that is why it is
9 such a problem.

10 That is why in good clinical trials the
11 response rate that you go after is in the higher
12 90's because nobody believes that non-response is
13 independent of what is going on. If we did that,
14 we wouldn't pursue mortality trials to have almost
15 no loss to follow-up. So, I am really troubled by
16 this, much, as I said, as Dr. Blumenstein was. I
17 think this issue of comparing responders and
18 non-responders at baseline is nice.

19 The second point about that is when you do
20 any kind of an adjustment procedures, logistic
21 regression or anything else, they add a little bit
22 but, you know, they don't explain much. If those
23 regression models explained a lot of the outcome,
24 then those adjustments would be meaningful but they
25 don't explain much, I am guessing. We don't know;

1 we didn't hear that data, but they don't explain
2 much. Therefore, the adjustments are sort of a
3 very modest correction and, you know, analysis can
4 never correct for flawed designs. We need good
5 design and a low response rate is one of those kind
6 of design problems we all wrestle with in a trial.

7 So, I am very troubled by this response
8 rate. But I guess my question is, given the
9 passion that the patients undergoing this procedure
10 have, it seems like we ought to be able to get 99
11 percent response rates. So, I am puzzled by why we
12 are where we are.

13 DR. DAWISHA: Well, I would just like to
14 add I think we share your concern. I am glad you
15 brought up the issue of the responders and
16 non-responders and whether or not they have
17 suffered a complication. I had indicated that the
18 analyses are under way and we actually asked the
19 sponsor that specific question, whether having a
20 complication at an earlier time predicted whether
21 someone was or wasn't a responder. I mentioned in
22 my presentation that the analyses are continuing.
23 That is one of the analyses. I guess what we do
24 with that data and how we adjust the data or how
25 much sort of remains to be seen. But we certainly

1 share your concern as well.

2 DR. WHALEN: Dr. Choti?

3 DR. CHOTI: Dr. Dawisha, it still is not
4 clear to me. You mentioned certain things that you
5 asked Mentor to provide you or certain analyses.
6 Did you specify in this what the response rate
7 should be, what your minimal expectation for a
8 follow-up is? I guess the bottom line is are you
9 happy, are you satisfied with the data that you
10 have gotten? You say you are currently working
11 with it, reanalyzing it so we don't have the final
12 but is this kind of sufficient to address the
13 concerns of the panel in 2000, the data you got?

14 DR. DAWISHA: Well, I think our goal is to
15 update the patient labeling and the labeling
16 information, and we would like the labeling to be
17 the most valid information that we have.
18 Certainly, you know, we are not happy with the low
19 follow-up rate. We are sort of stuck between do we
20 put this information in the labeling and update it,
21 or do we not put it in. I think our position is
22 that we would rather at least put the information
23 that we have in the labeling, explaining what the
24 limitations are, just so that at least that
25 information is available to patients.

1 DR. CHOTI: I guess my question though is
2 were there some specific metrics that you requested
3 in this follow-up data set, and were those met,
4 follow-up being one? I mean, it is possible that
5 they could ramp up the effort even more to get
6 better follow-up data if necessary, if it was
7 specified that this is the information we need at
8 this follow-up time. Was there some specific
9 information requested of them?

10 DR. DAWISHA: There were no specific
11 follow-up target rates that we had asked the
12 company to follow. The breast implant guidance
13 document has some general guidelines, one of which
14 is that we expect follow-up to be about 60 percent
15 at ten years. That is based not just on this
16 product but several other types of products. We
17 are lucky to get 50 percent follow-up at ten years
18 for those types of studies. So, no, there was no
19 set follow-up rate. There was no target set for
20 the sponsors. We certainly would like to see high
21 follow-up rates out to ten years but we may not.

22 DR. DAWISHA: Dr. Dubler?

23 DR. DUBLER: Back to my current interest,
24 which is this reoperation rate. On Table 8, which
25 is the Kaplan-Meier risk rate for reconstruction,

1 the five-year risk rate, as I read it, is 43
2 percent.

3 DR. DAWISHA: That is right.

4 DR. DUBLER: In your revision of the
5 informed consent document that you were provided,
6 is that rate stated in that document in any way?

7 DR. DAWISHA: You mean the patient
8 labeling?

9 DR. DUBLER: No, in the brochure, the
10 company brochure. It is my sense that patients
11 read labels, the really savvy ones, but a lot of
12 them will rely on the company brochure, and after
13 the focus groups you have seen a revision.
14 Correct?

15 MS. ALLEN: The company has already
16 submitted the supplement with the labeling with the
17 focus groups findings and we approved that. But
18 they have just recently submitted an updated
19 package insert and the patient brochure with the
20 five-year post-approval data.

21 DR. DUBLER: And does that say 43 percent
22 of patients who have reconstruction will have
23 surgery in the next five years?

24 MS. ALLEN: Yes, it does.

25 DR. DUBLER: It does?

1 MS. ALLEN: Yes.

2 DR. WHALEN: Seeing no other questions at
3 this point, thank you. We will go into the
4 concluding discussion. I would like to do this by
5 asking everyone at the table to make their comments
6 about what we have just heard and, since you were
7 last at the microphone, we will start with Dr.
8 Dubler.

9 DR. DUBLER: This has been a puzzle to all
10 of us for the last decade. Clearly, a woman does
11 have a right to choose. The problem is that she
12 has had the right to choose between procedures that
13 don't appear, by their own data, to be terrific.
14 So, then the right to choose has got to be
15 supplemented by information that makes that choice
16 a truly informed one.

17 I am impressed, someone gave us the
18 statistic that the industry had spent six million
19 dollars supporting one of the industry
20 organizations. We did hear that figure, didn't we?
21 That is a lot of money. And, I would think with
22 one fraction of that money and some creative people
23 we could come up with a process that would bring
24 together various independent groups that analyze
25 the data and the company that analyzes its own

1 data, and agree upon the data that a woman had to
2 confront in a form that wasn't the Kaplan-Meier
3 adjusted risk rates, which no lay person, quite
4 frankly, understands, and come up with a script
5 which could then be put in an interactive video
6 format. We could think of lots of creative ways of
7 making an informed consent process independent of
8 the physician, who is likely to say, "yes, of
9 course, I have to give you this but, hey, I do this
10 all the time; I think it is terrific. I gave my
11 16-year old breast implants for her birthday."

12 There are ways of ensuring that this
13 prospective patient, indeed, focuses in the most
14 constructive circumstance on the data that she has
15 to consider. Once she has considered that, so be
16 it. But there are ways of presenting it, of
17 designing it, of agreeing on what has to be
18 presented that I think we are technically capable
19 of doing. I think that a written brochure, handed
20 out by the surgeon who does this and thinks it is
21 really quite a good process, is a very 18th century
22 way of thinking about what to do. We could do a
23 lot better, and I would hope that the FDA would
24 work with the companies to devise really creative,
25 new, independent solutions to the problem of

1 helping a woman confront and analyze the data in
2 terms of her own values.

3 DR. WHALEN: Dr. McCauley?

4 DR. MCCAULEY: I agree. I think the
5 entire issue we are dealing with here is about
6 choice. In order to really make a proper choice
7 you have to have informed consent, and that
8 informed consent has to be based on reliable data
9 in terms of complications or problems that the
10 patient may experience.

11 I think that when we start looking at
12 data, herein lies the problem and I can appreciate
13 the fact that certainly for implant surgery, not
14 only in plastic surgery but even in orthopedics,
15 the follow-up can be not quite as reliable as some
16 patients with cancer problems, as you have
17 mentioned. However, I think it is imperative that
18 we really try to push the envelope here to try to
19 get as much follow-up as we can in terms of
20 percentage on these patients that have undergone
21 these types of procedures.

22 The other issue relates to integrity and
23 perception. I think this has been a problem of
24 some consumer groups that have spoken to us earlier
25 this morning. I am happy to hear that the issues

1 related to good manufacturing practices have been
2 addressed and this is no longer an issue.

3 However, I think it is imperative that the
4 FDA continues to work closely with Mentor to try to
5 improve the data collection, and also to improve
6 the statistical analysis. Certainly this issue of
7 responders versus non-responders is a crucial issue
8 I think, and I am not sure how that can be resolved
9 but I think it is something that we really need to
10 take into account.

11 The last point I wanted to make really
12 relates to consumer education, and I think that if
13 we take on a project or the FDA takes on a project
14 that states that what you have to do is appropriate
15 for a study, then for closure would be to take that
16 information back to the focus groups to see if they
17 understand truly what the risks are. It is a
18 matter of concern, having a proper consent and
19 information for the patient to make a proper
20 choice.

21 DR. WHALEN: Dr. Doyle?

22 DR. DOYLE: I resonate with the idea that
23 the breast implants really represent a choice for
24 women. I have a sister who went through
25 reconstruction surgery for cancer so I know that

1 this is a very important choice for women to be
2 able to make. I also believe that the informed
3 consent process needs to be based on accurate
4 information and that the important thing is that
5 the informed consent contain all the information to
6 make a choice.

7 I am actually not sure an interactive
8 video is going to alter the fact that once a woman
9 understands what the risks are that they are still
10 not going to make this choice. I don't think we
11 can protect people from wanting to do something
12 once they understand what the risks are. So, I
13 believe the informed consent process is the key
14 here.

15 DR. WHALEN: Dr. Miller?

16 DR. MILLER: If I could just try to
17 provide some perspective on this, when I look at
18 what is going on, we have an unusual problem with
19 the breast implant in that we are trying to balance
20 a benefit/risk ratio where the benefit is extremely
21 subjective to the patient, and even within a
22 particular patient it can change over time. So,
23 getting a handle on that side of the equation is
24 very difficult. The risk is difficult to get a
25 handle on.

1 It is difficult to study this. You can't
2 do it as nice and cleanly as you can a drug where
3 you have a limited number of patients and a limited
4 number of follow-up time. It is difficult to
5 conduct a study for ten years in patients who are
6 basically healthy, patients who don't want to
7 consider themselves patients, who want to disappear
8 into the landscape as soon as they have their
9 implants.

10 I mean, these are all challenges to doing
11 this. I think that we have to be careful in how we
12 look at addressing this in terms of methods that we
13 have become very comfortable with in looking at
14 other problems. That is one thing.

15 On the other hand, we have to do the best
16 possible job we can do. I share everyone's
17 sentiment about the inadequacy of the studies, the
18 follow-up. Those need to be done in an
19 unassailable fashion so that this is laid to rest,
20 so that we are not discussing this five years from
21 now. I think we are all weary of discussing this,
22 and I think a study can be designed where we
23 address this.

24 I don't know what the follow-up rate is
25 for pacemakers but I know it is pretty darned good.

1 I mean, if you have a patient with a pacemaker that
2 was put in 15 years ago, you call up a number and
3 the person on the other end of the line practically
4 knows the entire life history of that person who
5 had that pacemaker. Maybe that is an extreme
6 example because of the nature of that device, but I
7 think that something needs to be done to not permit
8 three physicians to say I won't participate in this
9 study. I mean, if they won't participate maybe
10 they shouldn't have access to the implants. I
11 mean, if you have the implant you have to, as a
12 responsible citizen of the medical community,
13 participate in confirming how these implants are
14 used and whether they are safe or not and
15 effective. If you don't want to participate in
16 that, then perhaps you shouldn't place any
17 implants.

18 I think those sorts of things could
19 possibly be done. But I want to avoid the tendency
20 to treat this like other medical problems because
21 it is very unique. I guess that is my main
22 philosophical point.

23 DR. WHALEN: Dr. Chang?

24 DR. CHANG: I think two years ago the
25 advisory panel and finally the final decision of

1 the FDA was to keep the option of having saline
2 implants available to women for augmentation or
3 reconstruction. It wasn't a decision made without
4 controversy, and it is certainly on the record that
5 there have been many reservations regarding
6 process, statistics and other questions which have
7 led to the conditions for premarket approval.

8 Today is an update of presentation of
9 sponsors trying to meet these conditions of
10 approval and they are in process. I would urge
11 sponsors to continue to examine the physical
12 properties of their product to try to decrease the
13 preliminary studies of safety, to continue to make
14 improvements and weigh what are the benefits of
15 lessening implant failure with perhaps increasing
16 thickness, comparing to the benefits of pliability
17 and cosmetic effect and perception of pliability.
18 So, that is one question and request that I would
19 make of the sponsor.

20 The other question, I would second Dr.
21 McCauley's comments regarding the focus group.
22 Again, follow-up is necessary to be sure that what
23 we presume to be understandable by the lay public
24 is, indeed, understood in terms of reading
25 information provided to them so that they can make

1 that informed decision.

2 I am astounded, but maybe I shouldn't be,
3 that reported comments by members of the focus
4 group felt that these statistics were not true;
5 that these numbers were merely presented as a
6 disclaimer by the manufacturing and that this
7 really couldn't happen and won't happen as an
8 individual makes a decision of choosing the saline
9 implant. So, there is some issue of credibility in
10 terms of presenting this data.

11 However, I feel that statistically
12 speaking in terms of percentage of follow-up being
13 on the far extreme of what normally is acceptable
14 in a scientific clinical study, it is some data to
15 give us an idea of what happens to these implants
16 after three and five years. So, there is some data
17 and, despite good efforts of sponsor to collect
18 this, perhaps higher remuneration, perhaps a larger
19 bonus for returning the survey might increase the
20 numbers. Be that as it may, we would say these are
21 scientifically suspect data just because of the
22 numbers of responders, but there are some numbers
23 and I think that they should continue to be made
24 available to consumers.

25 Finally, my comment is that, yes,

1 continued efforts should be made to carry out to
2 ten years to find out what happens with these
3 implants, but ultimately I don't think we are
4 really going to get an answer until there is a
5 report by an independent registry that has, again,
6 good follow-up on the people who are registered to
7 see what happens to these implants.

8 DR. DAWISHA: Dr. DeMets?

9 DR. DEMETS: Well, I have already said
10 some of the things I have been thinking about. I
11 am obviously not going to quarrel with the issue of
12 the right to choice and assess the risk/benefits,
13 but I worry about information that those decisions
14 and thoughts are based on.

15 I would only urge I guess the FDA and the
16 panel to appreciate how sensitive results can be to
17 issues of non-response, to excluding patients, to
18 censoring patients from follow-up. I am a
19 professional statistician and I am still amazed and
20 astounded at times at the power of these biases
21 that work in data. So, I think that we really need
22 to set a higher standard for something that has
23 been so controversial, so much discussed and is so
24 important.

25 I think that if we don't do something

1 different than we are doing now, at the ten-year
2 mark we will still be arguing just as much as we
3 are arguing now. Sixty percent as a target at ten
4 years, I guaranty you, is going to bring more
5 controversy and discussion because 40 percent
6 non-response is overwhelmingly an opportunity for
7 bias to enter into any kind of results.

8 The trouble with numbers, if you produce
9 tables such as we have today and put 95 confidence
10 intervals on them, is that they take on a
11 credibility that they sometimes don't deserve
12 because of the power of the biases that are at
13 work. So, I am not saying we should not present
14 the data that we have, but there is a danger to it
15 of misleading the perhaps less sophisticated
16 readers of those tables.

17 But I would go back to where I started,
18 that is, the response rates that we are observing
19 here and perhaps other devices are simply not
20 acceptable if the decisions really depend on the
21 data that comes out of those surveys. So, we may
22 have to challenge ourselves across the board and
23 certainly in this arena with all the interest and
24 importance this has to do a lot better than the
25 target we set for ourselves.

1 DR. WHALEN: Dr. Newburger?

2 DR. NEWBURGER: As my colleagues at the
3 panel have expressed their discomfort with what has
4 been presented, and have constructive suggestions
5 on how to ameliorate the situation, I join their
6 concerns. Augmentation mammoplasty is the second
7 most frequently performed plastic surgical
8 procedure in the U.S. Something upward of 300,000
9 were done this last year, 2001. It is
10 mind-boggling to me that we have so little data
11 available on a procedure that was done in 300,000
12 individuals in one year. The rate is going to
13 increase geometrically as it has been. This is
14 from the American Society of Plastic and
15 Reconstructive Surgery web site, by the way.

16 So, I would hope that the efforts to get
17 more accurate follow-up on increasing the numbers
18 of patients in this study would be done to the
19 point of maybe sending investigators to really look
20 for the patients. I am also concerned that the
21 products appear to have a high rate of product
22 failure. I think that the high reoperation rate
23 wouldn't be acceptable in other type of prosthetic
24 devices. I question two standards. Perhaps
25 because this is considered to be cosmetic, it is

1 not held to the same exactitude that other
2 prostheses are.

3 DR. WHALEN: Dr. Choti?

4 DR. CHOTI: I echo the comments of my
5 fellow panel members. It was clear in the review
6 two years ago there were concerns when this was
7 approved, and I commend the FDA and the industry on
8 working on the conditions of approval. I think we
9 have learned a lot based on the data of these
10 conditions. Yet, it is astounding, particularly
11 the post-approval study, how weak the data is
12 still. As we heard, in spite of how common this
13 procedure is, we still are faced with a procedure
14 and device that clearly is important, and it is
15 clear I think that we do not have sufficient data
16 or good enough data.

17 So, I really do echo what has been said,
18 that coming up with better registries, independent
19 data collection so that we really can have the real
20 answers rather than the data we have been working
21 with today, and I am concerned that it is not going
22 to be improving that much with continued follow-up.

23 It is interesting that these products have
24 problems. I mean, we are learning that there is
25 device failure. The performance is not as good as