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by D. Woods

SUMMARY

An FDA Advisory Committee gave the FDA mixed advice on what to do about silicone breast implants. The panel ***recommended against approval of Inamed's*** devices, criticizing the company's data collection, predictions for ruptures, and rupture explanations. However, panel members also ***recommended approval of Mentor's*** silicone breast implants – with conditions – praising Mentor's data collection, even though the data was shorter-term. It's starting to look likely that silicone breast implants will eventually gain approval; the question is simply one of timing. Is the FDA too risk averse to approve them this year? Perhaps, but sources doubt the Agency will approve one device and not the other, predicting either both get approved or both get turned down again.

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MIXED VOTES AT FDA ADVISORY COMMITTEE ON SILICONE BREAST IMPLANTS

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The FDA's General and Plastic Surgery Devices Panel recommended approval, with conditions, of Mentor's silicone breast implant, but turned down Inamed's request for approval of a similar device. The three-day Advisory Committee meeting was an emotional roller-coaster, filled with heated public testimony, both pro and con, on the first day, rejection for Inamed on the second day, and, finally and surprisingly, approval for Mentor on the last day. **The nine voting members rejected Inamed's premarket approval application (PMA) 5 to 4, but approved Mentor's request 7 to 2.**

The advisory panel members voting against Inamed were skeptical about Inamed's methodology and data collection, including its long-term prediction of ruptures as well as how ruptures occurred.

Before it was Mentor's turn before the panel, Mentor was seen as having weaker prospects than Inamed because it had followed its patients for an even shorter period of time than had Inamed. However, the panel effusively praised Mentor's data collection, and most said they were "comfortable" with the long-term safety of its devices. Several members who had criticized Inamed for lack of long-term data voted to approve Mentor's even shorter-term data. The panel also basically dismissed the testimony of the dozens of women who had testified about what they said were the devastating effects of silicone implant ruptures.

The final decision is now up to the FDA, and the conflicting votes make it impossible to predict what the FDA will do. Will only Mentor get approved? Will the FDA approve the devices from both Inamed and Mentor to avoid giving Mentor such a marketing advantage? Will the FDA delay Mentor because of the concerns about the Inamed implants? It isn't safe to assume the FDA will do what the advisory committee recommended. In January 2004, the FDA rejected the panel's recommendation to approve Inamed's device, citing insufficient safety data. Mentor did not seek approval in 2003. The FDA banned silicone implants in 1992 for all except breast cancer patients and patients with deformities after the FDA determined that manufacturers had not proven the devices to be safe. The FDA is being closely watched these days for the way it deals with safety concerns, and that may put pressure on the agency to act cautiously on silicone breast implants.

It should be noted that Dr. Michael Olding, a George Washington University School of Medicine plastic surgeon, who had voted for silicone breast implant approval in 2003, was not at the meeting. A letter he wrote to the panel said that the FDA had determined that he had a conflict of interest because of his stock holdings. He has stock in a company that merged with Inamed. The FDA wanted him to participate as a non-voting member, but Dr. Olding declined to attend the meeting.

THE PUBLIC TESTIMONY

The advisory panel's first day of hearings lasted more than 12 hours, filled with emotional testimony from patients and doctors on both sides of the issue. Although studies have not been able to link silicone implants to cancer, connective tissue disease (CTD), immune disorders, or other illnesses, many women testifying said they had those illnesses and blamed it on their silicone breast implants. Many said their blood and urine contained high levels of platinum, and numerous speakers questioned the lack of long-term data on silicone breast implant (SBI) safety. A former FDA staffer, Dr. Suzanne Parisian, said, "On average, women began to report problems seven to 10 years after implantation. Three- to four-year studies are not adequate and we don't have adequate long-term safety data."

Speakers also mentioned complications from ruptures. A former director of the FDA's Office of Women's Health directed the panel to look at the FDA's own data, including a rupture study that noted "Over time, more than 64% of women in the study were found to have at least one ruptured implant, and more than 21% had silicone gel outside the capsule in one or both breasts."

Several speakers complained that the FDA advisory panel is lopsided, with too many plastic surgeons. A Center for Science in the Public Interest spokesman said that panelist Michael Miller, a plastic surgeon, made a CD-ROM paid for by Inamed, in which he said, "Studies show implants don't cause disorders such as cancer or auto-immune diseases. Based on these studies, it appears these implants are safe."

Another speaker pointed out that very few African-American and Asian women were included in any manufacturer-sponsored studies.

The first morning saw emotional testimony from the public, including angry former silicone breast implant patients, the widower of a patient who had committed suicide, and a sobbing child of a mother she said is in chronic pain because of complications from silicone breast implants. Among the comments were:

- *Kathy Keithley Johnston, CEO of Toxic Discovery (used to have silicone breast implants):* "Silicone breast implants shouldn't be approved until a company can assure safety of devices for long-term use…Our organization has serious concerns about the integrity of studies conducted by Inamed and Mentor…Please protect the women of this nation."
- *Susan Hellman (had breast implants for 15 years):* "My implants ruptured and the last surgeon said there was no way to remove it all. Silicone as well as platinum was found in my lymph nodes, urine, and blood. My body is full of ionized platinum with no known way to remove it …I don't want anybody else to suffer this way."
- *Ed Brown:* "My wife had silicone breast implants for ten years…But then she began to get sick and was diagnosed with fibromyalgia, and she committed suicide in 2000, leaving behind seven children. The two children she breast fed are now sick."
- *Lisa Beth Hickey, former silicone breast implant consumer:* "I had four surgeries in four years due to complications from implants. Two surgeries were back-to-back after the rupture occurred. I experienced systematic illnesses which improved slightly after the implants were removed…Things don't add up to safety when it comes to silicone gel…Is silicone research taking place in the morgue?"
- *Pam Dowd:* "My failed reconstruction surgeries included three ruptured implants that had me literally pulling out my hair."
- *Brenna Dowd:* "I have never known a healthy mother… She has to sit in a hot bath maybe three times a day or more to ease the pain because of silicone breast implants."

Public testimony continued through the morning with more anti-SBIs than pro-implant speakers. Among the speakers:

- Dr. Susan Maharaj, a chemist, introduced raw data that showed high levels of platinum present in silicone breast implant gel, cells, and capsular tissue of implanted women. The data also showed high rates of platinum concentrate and oxidation rates in women with implants and in children conceived after implantation, compared to children conceived before implantation. Her conclusion:
  - Platinum in the gel and shell is actually much higher than reported by manufacturers.
  - Platinum in many different types of samples is consistently higher in women exposed than in those not exposed.
  - Platinum occurs in silicone breast implants in highly reactive forms.
- A woman who received a silicone implant more than 28 years ago testified that about three years ago she started coughing up "hard, greasy, dough-colored plugs" of silicone. She said silicone continues to exude from her nipples and eyes, and a glob of silicone moved from her breast to her armpit, causing excruciating pain. Her left breast collapsed 28 years after implantation and an MRI showed that both implants were extensively ruptured. She said another MRI showed more than 20 lesions on her brain, and her platinum level is more than 20 times normal.
- Plastic surgeon Dr. Edward Melmed said he had a "change around" in the 1990s when he started seeing complications from breast implants. His own experience with more than 500 patients from 1992 to 2004 showed a rupture rate at 10 years of approximately 50% and a rupture rate at 15 years of 70%. He showed video clips of

some of his procedures to remove ruptured implants; one didn't have a wall left and was a lake of gel.

- A teenager speaking against silicone breast implants mentioned the popularity of reality shows such as ***The Swan*** and ***Extreme Makeover*** and the current practice of giving gifts of breast implants to 16-year-olds as birthday presents. She claimed that, this past year, 3,962 women age 18 or younger received breast implants.

Afternoon testimony included satisfied silicone breast implant patients as well as plastic surgeons and representatives from the American Society of Plastic Surgeons (ASPS) and the American Society for Aesthetic Plastic Surgery (ASAPS), who advocated the use of silicone breast implants. They referred to women's stories from the morning session as "anecdotes" with no scientific support. They also said the problems described in the morning testimony were largely caused by older implants, stressing that the current generation is much safer. Emphasis was put on physician and patient education. Plastic surgeons stressed women's right to choose, lamenting that silicone implants are restricted in the U.S. to use in reconstructive surgery.

National Organization for Women (NOW) President Kim Gandy gave an opposing view, saying women need longer-term data in order to make informed opinions. She told the panel that four years of data are not enough to make an informed decision on the safety of silicone breast implants, "What sort of message is the FDA sending to the public and to industry petitioners when it backs down so quickly on its demands for patient safety? FDA reviewers agree that little can be learned from such short duration. Agency reviews estimated that (as many as) 93% can rupture within 10 years. These projections, and the absence of clinical data, are solid reasons for rejecting (silicone breast implants)." She also cited concerns about:

- The effects of silicone breast implants on children conceived after implantation.
- Mammogram readings. She cited a study that showed breast implants obscure and greatly reduce the accuracy of mammogram readings, saying, "These women are asking the FDA to take responsibility for regulating an industry that cannot or will not regulate itself."

In a rather odd exchange, Gandy was questioned by panelist Dr. Michael Miller about NOW funding and special interests:

Dr. Miller: "Your organization is funded by gifts. Do you have any idea what percentage of gifts you receive that are related to this issue?"

Gandy: "A fraction of a percent. We have a women's health project that occasionally gets gifts. The largest grant the women's health project has received is about $300,000 for the work we did on tobacco."

Dr. Miller: "Is there any way to determine the specific concerns of those who decide to support the organization in terms of one issue or another?"

Gandy: "No, not in terms of our individual contributes. Over 99% of our income comes from gifts from individual members, and if you added it all up and divided by the number of individuals, the average gift is about $42."

Other interesting testimony included:

- Dr. James Wells of ASPS said he is concerned at the current climate of questioning of physicians on the panel, referring to Dr. Olding as "being singled out for a perceived conflict." He said, "We are doing a disservice…We cannot let special interests and private agendas interfere…The devices have been reviewed and re-reviewed…Virtually every surgical specialty today uses some sort of silicone devices…Why in the U.S. do we only allow women with cancer and anatomical deformities to have (these implants)? If the device is okay for some, why not all? We believe that implants are an informed choice, offering a choice for women."

- Panelist Dr. Amy Newburger, a dermatologist, asked Dr. Wells about the ASPS website. She said, "It has a section on risks, but the only risks you mention in it are surgical risks. Instead of providing statistics, you tell patients to ask their doctors. My thought is, as a professional society, you should be providing that information and putting it on the website. If you don't, can we count on physicians to do that? My second question is, do you offer help to patients who cannot afford to remove their implants?" Dr. Wells replied that the website is new, and it will be updated periodically. As for helping patients remove their implants, he said, "It is under discussion; it is not a closed option."

- Results of an ASPS survey faxed to 4,610 ASPS members on March 23, 2005, got 906 responses. It showed that most surgeons did not experience local problems from ruptures. Doctors told the Society that silicone breast implants are safe and should be added to their options for patients in order to provide them with the best care, and they said their patients are fully capable of making informed decisions.

- Dr. Deborah Bash, head of cosmetic surgery at the Mayo Clinic in Scottsdale AZ, told the panel that she herself has silicone implants. She said, "Most of the tragic stories we are hearing are older implants." She said that she had her own implants replaced as they aged. She then had this exchange with a panel member:

Panel chair Dr. Michael Choti, a surgical oncologist: "Do you recommend changing implants to your patients?"

Dr. Bash: "I do – every 10 years or so."

Dr. Choti: "Without evidence of a leak?"

Dr. Bash: "I do."

Over the three days of the panel meeting, the question of when and why an implant should be replaced was raised repeatedly. It was generally agreed that implants should be replaced within a ten-year period, but no specific time period was agreed upon.

Satisfied silicone breast implant patients testified as well, and their comments included:

- "I was concerned when silicone breast implants were taken off the market, but my concerns were put to rest… The issue has been greatly overstated."
- "I used to weigh over 400 pounds. Over the past four years, I've had a series of operations. I needed an operation on my breasts, and I chose silicone. They feel much more life-like than saline."
- *Patient and anesthesiologist:* "Saline implants are hard, cold, heavy, and do not feel natural…My breasts (with silicone breast implants) feel the same as they did in 1985."
- "I regret that women today don't have the same empowerment of choice as I did. I believe American women deserve the same choice as those around the world and I had."

Several plastic surgeons also testified, and their comments included:

- *Dr. Laurie Casas, Northwestern University:* "Education, safety, and satisfaction are of the utmost importance, as well as a woman's right to choose."
- *Dr. Richard D'Amico of ASPS:* "We believe in women's right to choose. We also believe there is a need for a post-operative registry."
- *Dr. Lorraine Tafra, a breast surgeon:* "Why is this device available for reconstructive patients but not for augmentation? What message does that send to our breast cancer patients? Conclusive data have not found that these devices pose significant risks to patients; they should be made available to consenting patients."
- *Dr. Malcolm Roth of New York:* "For many women who choose breast implants, silicone gel is more likely to retain a natural feel. If patients are educated about the risks and benefits and receive pre-op materials and consent forms, women should have the right to decide for themselves."
- *Dr. Maurice Nahabedia, a Maryland plastic surgeon:* "Silicone breast implants are the most thoroughly investigated medical device in medical history. Women have the right to choose which implant they will get… Silicone gel implants can improve quality of life for women who have received them. Scientific evidence is clear that silicone gel implants are safe and effective devices that pose no adverse health effects for women who have them."
- *Dr. Scott Glasberg, a cosmetic plastic surgeon:* "There is no demonstrable link between silicone breast implants and the safety and health concerns of women. It's time to pass the rhetoric and focus on reality…I have many patients waiting for approval."

With more than 200 speakers scheduled the first day, public testimony continued into the evening. However, during the session, fill-ins read most of the testimony. Each speech began, "I am reading testimony for XXX who was too sick to be here today." Testimony often began with an explanation of why the woman got an implant, followed by a list of symptoms, a section blaming physicians for not disclosing risks, and then expressions of disappointment that more time couldn't be spent with family, ending with a plea to the panel to keep the ban on silicone breast implants. The language and vocabulary of the speeches were strikingly similar.

Pro-silicone breast implant speakers also seemed to have their talking points. A plastic surgeon and silicone breast implant patient told the panel that she is a "pro-choice plastic surgeon," insisting that women should be able to choose silicone implants. Other pro-silicone breast implant speakers also started to sound extremely similar in terms of vocabulary, tone, and message.

Testimony included these comments:

- *Dr. Roger Friedman, a Washington DC-area plastic surgeon:* "Silicone breast implants are safe. The long term information requested by the FDA is available…no connective tissue disorder is associated with silicone breast implants, so women should have an opportunity to decide which implant is right for them…I'm here representing my patients, some of whom are mothers who are just trying to restore their appearance to improve their body image, self-confidence, and increase their self-satisfaction."
- *Dr. Ben Gitterman of Children's National Medical Center talked about the lack of studies of the long-term effects of silicone breast implants on breast milk, infants, and children:* "Few studies have been done on the effect on breast milk of any kind of breast surgery…in 1990 a silicone gel implant (made with polyurethane) was taken off the market because the foam broke down into carcinogens…We don't know much about the impact of lead in breast milk…or the impact of metals in breast milk. That hasn't been answered because the questions haven't been asked...Studies of sick children whose mothers have implants rather than a random sample don't tell us what we need to know. Silicone breast implants should not be approved by the FDA until adequate tests are done."
- *Virginia Tanner* spoke about her daughter's bad experience in a silicone breast implant trial, sobbing throughout her testimony. She was questioned by panel member Dr. Newburger, a New York dermatologist:

Dr. Newburger: "What were your daughter's consequences with this trial? Has she been removed from the surveillance population?"

Tanner: "I believe she has never been monitored. Of any of the illnesses she told the doctor, the doctor has given her no referral."

Dr. Newburger: "She was enrolled through an RIB?"

Tanner: "Yes."

Dr. Newburger: "Has the RIB responded?"

Tanner: "No. He sent the letter in January, and I had it served…"

Dr. Newburger: "So if she is not reported as part of the database…"

Tanner: "Exactly. That's exactly the…methodology of the record-taking, monitoring the patient? Every time she went to the plastic surgeon, he said, 'Oh, you have the flu.' Her symptoms were totally ignored (sobs), and the medical community is unaware. She was perfectly healthy. She had everything going for her. She just did it because…she wanted to do it for herself, and I told her I'd give her every gift, it's your life."

Several breast cancer survivors spoke in favor of silicone breast implants, saying they were like real breasts and they were very happy with them. Among these were:

- *Judy Pendleton:* "I had silicone breast implants for more than 20 years without any problem…An MRI showed the implants might be leaking…I didn't have to think twice. I'd been happy with the old implants...and I decided to get another pair. I was surprised to find out after 20 years that my implants were in such (good) condition."
- *Mindy Tapscott:* "Silicone gel implants look and feel most like me."
- *Yvonne Thompson:* "I am very pleased with the results and, in fact, have been an inspiration to a friend…I am certainly glad that my representatives in the government are attentive to the needs of their constituents, but I believe that there should be some limitations on their reach. I think that medical decisions are best left to informed patients and excellent doctors."
- *Lydia Charney:* "Without silicone implants I would not feel the complete woman that I do today."

Dr. Kenneth Shestak, a surgeon specializing in breast cancer reconstruction, made an impassioned plea for silicone breast implants, saying that the third generation implants are far superior to their predecessors. He said, "During the 1990s I used saline implants exclusively for reconstruction. Those left a lot to be desired in terms of symmetry, shape, and softness. This changed six years ago in a dramatic way with the use of silicone breast implants. Now, I am able to consistently achieve what I consider very good results for breast reconstruction, and it has given me a whole new enthusiasm; and it's especially timely since we are seeing more patients (of this type). The third generation implants provide patients with a real hope that we can provide them with a good base…and with the lowest ever incidences of complications." Dr. Shestak said he has placed 261 implants in 169 patients over the past six years, "I've carefully examined every patient every six months following surgery…There have been no instances of silicone implant ruptures and no known silicone extrapolations in any of these patients. The rate of capsule contracture has been 5%, and there were 16 re-operations, for a re-operation rate of 9%. There have been no complaints of problems with skin, joints, or constitutional symptoms. In this group, 165 out of 169 are happy or extremely happy following the outcome, a satisfaction rate of 96%."

Panel chair Dr. Choti questioned Dr. Shestak:

Dr. Choti: "Do you recommend routine imaging on your patients?"

Dr. Shestak: "I follow with a combination of physical examination and imaging."

Dr. Choti: "What kind?"

Dr. Shestak: "A mammogram and sonogram done in combination or MRI."

Dr. Choti: "And if you saw a leak in MRI, would you recommend removal?"

Dr. Shestak: "I routinely recommend removal."

Dr. Choti: "You haven't had a single one with silent rupture?"

Dr. Shestak: "Over the past six years we have not."

Outside the hearing room, Dr. Shestak insisted that there are indeed a lot of data, including long-term data, and all data show that silicone breast implants are safe. He complained, "We cannot, as specialists, provide women with state-of-the-art care (unless surgeons can add silicone breast implants to their arsenal)." Asked how the panel will vote, he shrugged his shoulders and said, "It depends on what the agenda is. The fact is that we need to look at the data. We have lots of data, and there is no evidence that silicone implants are unsafe. There is no smoking gun."

The Panel Rejects Inamed's Implants

Inamed got off to a rocky start on the second day of the meeting. After the company's presentation, in which officials stressed that silicone breast implants are completely safe, Inamed officials were questioned sharply by some members of the FDA advisory panel on several points, including gel implant and migration data, rupture rate data, quality of life issues, and Inamed's description of how ruptures occur. Inamed representatives seemed ill-prepared, fumbling through their slides and failing to satisfy several panel members with their responses. This comment by panel member Dr. Steven Li appeared to sum up the panel's attitude about the Inamed presentation: "I hear your words, I just don't see the evidence."

An Inamed official told the panel that the company would present additional safety data that "expands on the vast body of peer review. This research provides reasonable assurance of the safety of silicone fill for these products, both in terms of liability and longer term use." He said the company has fulfilled the commitments it made to the FDA in October 2003, including a promise to do post-marketing clinical studies.

During the FDA presentation, speakers criticized Inamed's MRI data on ruptures in augmentation patients' implants, taken from its CORE study at one and three years. The FDA presenters said that rupture rates were unpredictable by providing several alternate models showing very different results. While Inamed predicted that rupture rates would remain constant over a 10-year period for a 14% rate, FDA presenters argued that the rupture rate could also increase linearly or quadratically over the same period of time. Inamed's CORE study enrolled a total of 940 patients (500 augmentations, 220 reconstructions, and 220 revisions) to be followed over 10 years. About a third of the total was to receive an MRI at one, three, five, seven, and nine years following implantation. Total rupture rates for the MRI cohort at four years was 3.4% for augmentation, 20.5% for reconstruction, and 10.9% for revision. Total rupture rates in the non-MRI cohort for the same time period were 1.1% for augmentation, 4.9% for reconstruction, and 1.7% for revision.

Dr. Patricia Walker, Inamed's Executive Vice President of Research and Development and Chief Scientific Officer, gave the company presentation, telling the panel that silicone breast implants are reliable and safe, are superior to saline implants, and are preferred by women for a variety of reasons, including:

- More natural appearance and feel.
- Provide more choice to match patients' needs.
- Ideal for reconstruction.
- Silicone levels in breasts of millions of women with implants are the same as those in women without implants. In vivo animal studies showed no problems with reproduction or birth defects with implanted silicone.

Showing slides of the CORE and ADJUNCT study results, Dr. Walker said, "As horrible and heartbreaking as (yesterday's) testimonials were, we must rely on science to establish if there is a causal relationship between wellness and silicone breast implants. The effectiveness of silicone gel implants has been demonstrated…The key question is whether the implant has an acceptable safety profile." She said third-generation silicone breast implants incorporate several technological improvements, including improvements to the implant shells – the thickness is increased more than 50% – as well as a more cohesive type of gel, and tighter manufacturing specifications: "They have also undergone rigorous mechanical testing and can withstand extreme stresses. Implants are unlikely to rupture in blunt force trauma or physical activity."

Dr. Walker also discussed gel bleed, exposure to silicone constituents, gel migration, risk of platinum in implants, reasons for rupture, durability, and general safety. Among the points she made were:

➢ **Gel bleed.** There is a very low rate of gel bleed which decreases with time.

➢ **Gel migration.** Inamed did a series of animal tests and found that 99.4% of the gel remained in place.

➢ **Biocompatibility.** Standard toxicological studies demonstrate implant materials are biocompatible.

➢ **Animal studies.** Pre-clinical modeling shows minimal exposure to silicone constituents.

➢ **Platinum.** Platinum is approved for use in *in vivo* devices, and the literature shows no concern at expected exposure levels in breast implants. Platinum used in implant materials is in a zero oxidation state and is biologically inactive. A panel member asked Inamed's chemist about the chemistry and valence state of the platinum, wondering if the platinum is small enough to go through the wall of a blood vessel, but the chemist didn't know.

➢ **Newer technology.** Third generation implants have an acceptably low rate of rupture.

➢ **Surgical damage.** Surgical damage is the leading cause of device failure, such as sharp instruments. Inamed is working with surgeons on techniques to minimize surgical damage. Later in the meeting, Inamed's plastic surgery devices analyst was grilled by two panel members about the claim that most ruptures are caused by surgical instruments.

Inamed: "To determine if failure is caused by a surgical device, it's nice to know what the flaw looks like before you start to look for it. We artificially tried to make cuts in gels. Using that technique, we were able to determine that it was a physical failure."

Panel member: "That's crucial, in my view. I'd think some feature, geometry of the scalpel – if I could only see evidence of one…"

Inamed: "If the flaw is induced with a suture needle, you can see a triangular cut."

Panel member: "I didn't see any of them on the micrographs…I think what's missing is the control samples."

Inamed: "We can get those for you."

Panel member: "I hear your words; I just don't see any evidence."

➢ **Ruptures.** Implant rupture does not prove serious health risk. Dr. Walker said that 86% of ruptures are silent, and she predicted the rupture rate is 2.5% at three years. Extending the CORE study data out 10 years, Inamed predicted a 13.9% rupture rate. Reconstructive patients have a higher failure rate (10.6%) than saline implant patients (6%). She mentioned that more than half of the reconstructive group (64%) had the Style 153 implant, which had a higher incidence of rupture than other models (8.3% at three years).

Inamed compared silicone gel implants to saline implants, finding comparable rupture rates, and the company looked at explanted implants. Dr. Walker said that mechanical properties of explanted devices were analyzed and did not change over time in terms of ultimate break force, elongation, and tensile strength. She also said that the most obvious consequences of rupture included asymmetry and visibility.

Retrieval Study Results: CORE and ADJUNCT Studies

Device failure mode	Implants with openings n=133
Surgical damage	47%
Posterior sharp edge opening (Style 153 implant)	36%
Surgical impact	4%
Manufacturing defect	3%
Fold flaw failure	1%
Unknown	9%

The rupture rate was characterized as:

- For all PMA devices: ~14% at 10 years
  - Constant rate: ~ 1.4%/year
- For all single lumen implants: 3% at 10 years
  - Constant rate: ~ 0.3%/year
- The rate is reasonably constant out to 10 years

Inamed's recommendations to patients and physicians include:

- Patients should contact their surgeon for symptoms such as asymmetry, pain, swelling, redness, or other changes with their implants.
- Annual breast exams with a physician familiar with breast implants.
- Further diagnostic imaging as recommended by a physician.
- In case of suspected rupture, the implant should be removed.

Dr. Walker said that Inamed would:

- Provide current techniques to prevent ruptures.
- Inform patients of risks.
- Continue ongoing studies, including a large-scale, 10-year CORE study.
- Establish a registry linked with a warranty program.
- Actively work with surgeons to develop surgical practices that reduce the risk of rupture.
- Actively educate patients about the risks of breast implants.

ASPS president Dr. Scott Separ closed the presentation by telling the panel that Inamed has kept the promises it made to the panel in 2003. He said, "We have provided long-term rupture rates and improved device retrieval and failure analysis. Can we characterize the rupture rate? My answer is, yes. For all PMA devices, the rupture rate at 10 years is 14%; it is a constant rate at 1.4% a year or less. For all single lumen implants, it is 3% at 10 years, 0.3% a year and, yes, reasonable out to 10 years. Can we characterize the consequences of rupture? The answer again is, yes. What percentage of ruptures are extracapsular? Twenty percent in the worst-case scenario…Is the proposed labeling for patient management adequately supported? We say, 'Yes'…Although there is no one perfect study to show you, we do have the safety evidence. Patients deserve the right to make an informed decision regarding the choice of silicone- or saline-filled implants. Surgeons deserve the right to recommend the most effective implant. The preponderance of evidence supports the safety of silicone implants, and evidence-based medicine should drive our decisions. In 2005, we clearly have far better implants and a lot more independent scientific information to reassure us about the safety."

Panel questions for Inamed

The panel asked Inamed officials and experts and the FDA staff about tissue expanders, breast milk evaluation, Inamed's plans for physician and patient education, quality of life issues, gel bleed, MRIs, and methodology. Asked what the estimate for the yearly implantation rate would be if silicone breast implants were approved, an Inamed official said, "That is more of a marketing estimate, and, to be honest with you, I don't know…Our estimate…suggests somewhere initially between 30%-35%...Roughly, ASPS has suggested approximately 250,000 a year."

➢ **Gel bleed.** An Inamed official explained Inamed's animal study, in which gel was subcutaneously implanted in a rat, "99.94% of material remained in place, 0.02% was excreted, and the remaining amount of material was found in the liver, muscle, and remaining carcass." A panel member asked if the human patients with gel bleed had any symptoms, and an FDA official responded, "Neither local complications nor suspended complications were reported in these two patients."

Another panel member asked about the animal studies of gel bleed and how the model is actually capable of preventing migration. An Inamed official responded, "I have to apologize. I don't know the details of how that implantation was done. I think it was subcutaneous insertion of gel into the animal model." The panel member wondered if that methodology has any validation, whether it would show migration if something else were implanted, but Inamed did not have a clear answer for this. An Inamed official said, "We know from the literature that if you biopsy the area around the implant, you'll have silicone levels. We know that if you biopsy a woman without implants, you'll have silicone levels. If you look at the liver of a cadaver, there is silicone. There is silicone in multiple products we use like toothpaste, deodorant, and plastic products. Patients and surgeons aren't enthusiastic about biopsying an area. Biopsying won't be of

value without having the proper controls…It's no surprise that some microscopic silicone can be in the lymph nodes. What's most important to remember is to put it into context. None of these patients with 30 years experience with silicone implants have systemic illnesses associated with that."

➢ **MRIs.** The panel chair asked how it was determined which patients received MRIs, and an Inamed official said a third of patients received them and these were patients who lived near sites that had radiological facilities nearby. The following exchange then occurred:

Panel chair: "There is a little bit of confusion with silent and symptomatic rupture…You suggested that silent rupture rates make up 80%-86% of total ruptures, so we're a little confused. What is the true silent rupture rate?"

Inamed official: "The true silent rupture rate is 86%. The SURVEILLANCE data (Inamed's voluntary program) is better than symptomatic rupture. If a patient has an explanted device, and the device is ruptured, the patient returns it, so we actually have more data…Does that help?"

Panel chair: "It's still confusing. We're interested in knowing what the rupture rate is. If the 86% are silent, then the total rupture rate…?"

Inamed official: "…would be the 14.9% predicted at 10 years. That includes silent as well as symptomatic."

➢ **Methodology.** The panel found the FDA's projections a variation from the Kaplan-Meier curves they are used to seeing.

➢ **Toxicology.** A toxicologist who is an FDA consultant said he found no developmental toxicity in the silicone implants.

➢ **Quality of life.** A panel member asked some contentious questions about quality of life issues:

Panel member: "I want to see data presented at the last meeting on the changes in signs and symptoms and connective tissue disease over a long time. I wanted to know if you wanted to talk about it (quality of life) this time, or if you don't want to discuss it at all!"

Inamed official: "We have performed…We can provide it, but we didn't do it for this presentation."

Panel member: "You don't have to say anything about it at all – just wondering if you wanted to say anything here."

Inamed official: "The data have been extensively reviewed by our consultant here…."

Panel member: "And what is that supposed to mean?"

Inamed official: "Looking at the data from the CORE study, augmentation, we see on all eight scales, very high in social functioning, vitality, mental health…"

Panel member: "And what happens to them? ***Is this a difficult question?*** There's data in there, but you're choosing not to present it here in this public forum."

Another panel member criticized Inamed:

Panel member: "If this were to be approved for general use, what's your estimate of the yearly implantation rate?"

Inamed official: "That is more of a marketing estimate and to be honest with you I don't know."

Panel member: "Well, what is predicted? Two times? Five times? Twenty times?"

Inamed official: "Our estimate…suggests somewhere initially 30%-35%...Roughly ASPS has suggested approximately 250,000 a year (in 2004)."

Panel member: "And how many clinical associates do you have for your CORE study?"

Inamed official: "We have 21 clinical research associates at Inamed and the numbers will go up . We will hire more, and we also will use outside contractors and monitors to expand."

Panel member: "That's 21 for 1000 patients…If there were to be a post-market study…"

Inamed official: "If there were to be a post-market study we would have to evaluate how to handle that sort of thing and that would be more."

A panel member also grilled Inamed's chemistry expert about platinum levels:

Panel member: "Could you tell me the absorption? What is the valence state of the platinum? What's the chemistry of the platinum after? What's left over?"

Inamed analyst: "It's platinum metal, but small. A couple of nanometers."

Panel member: "Small enough to go through a blood vessel wall?"

Inamed analyst: "I don't know what that is."

Panel member: "It's a couple of nanometers!"

FDA questions about Inamed's implants

Question 1. Considering the rupture information provided in their submission and given that the majority of ruptures for silicone gel-filled breast implants are silent, please discuss whether Inamed has adequately characterized the rupture rate and how this rate changes over the expected lifetime of the device?

Panel members offered mixed views on this. Most felt confident about the short-term data but had questions about longer-term data. Comments included:

- "I think there is a reasonable estimate of what happens over time to 10 years…What happens after that we don't know."
- "The key word is 'adequately'…and the answer is no."
- "I think it's adequate…in the short-term, but not in more than five years."
- "I'm not comfortable at all."

Question 2. Has Inamed adequately characterized the consequences of rupture for devices with regard to:

a. Frequency of observed intracapsular gel, extracapsular gel, and migrated gel, as well as the destination of the migrated gel.

b. The local health consequences of patients with ruptured implants.

c. The incidence, prevalence, and timing of silent ruptures that progress to symptomatic ruptures.

Panel members again had mixed opinions, but the general consensus was that they have "somewhat" of a grasp of the consequences as to frequency of intracapsular and extracapsular gel and migration. The incidence from silent to symptomatic was less clear, though the panel felt there is "some" information. Panel comments included:

- "I think the MRI cohort did a very good job of demonstrating the type of migration that happens…(On local health consequences) It is difficult to categorize signs and symptoms with an aging population…I think that's a very difficult thing to nail down, but, given the previous historical data, it hasn't shown a sign of health consequences. Silent ruptures will be very difficult to identify."
- "I don't think we have complete data on these issues because there wasn't a study designed to collect that data."
- "I think the MRI gives us data about observing intracapsular and extracapsular gel with respect to local health consequences. I think those have been presented …My concern is problems can be caused by the occurrence of breast cancer. That has to be evaluated as well as mammography."
- "Our knowledge is incomplete."
- "I'm extremely uncomfortable using the data, especially in clinically-related issues."
- "I don't think we have enough information (on platinum and silicone) yet...Several heavy metals cause neurologic damage."

Question 3. Inamed's proposed labeling includes recommendations for the method and frequency of screening for silent rupture, silent management, or suspicious and confirmed intracapsular and extracapsular rupture, and the potential health consequences of extracapsular and migrated gel.

The panel continued to have mixed responses, but the chair commented, "I think many felt that the method and frequency is fairly well defined. I, personally, don't think that is the case. I think we don't know how to follow patients, particularly in regard to silent rupture. By definition, it is not picked up by that annual two-year exam. I didn't hear anything about screening or frequency. Some panel members feel patients should have a routine MRI scan, and some felt that is not the case; I didn't hear a clear consensus. On management, the consensus seems to be the implant should be removed. On health consequences, the group felt we should include this with some recommended changes." Other panel comments included:

- "Patients should have at least one evaluation before five years. I'd probably agree with plastic surgeons that it's clear there is a percentage of rupture in the first couple of years."
- "I see a lot of changes that I think should be included under the section of rupture causes and symptoms."
- *What would you recommend to a woman with extracapsular migrated gel?* "My sense is explantation."
- "There is risk, but the risk seems very small."
- "I think the patient should be seen by a physician with respect to management. I agree with removal of the implant."
- "If (a patient) wants assurance, she can have an MRI as often as she wants…On health consequences, I think the company has outlined…that fairly well, but I think they might be encouraged to add some things that are well beyond what has been proven."

Question 4. Considering the rupture information provided in the submission and given that the majority of ruptures for silicone gel-filled breast implants are silent, please discuss whether Inamed has adequately characterized the rupture rate and how this rate changes over the expected lifetime of the device.

There was more agreement among panel members on this issue. The panel chair summarized the discussion: "I think the group had somewhat more of a consensus. Most felt these things were a good thing, particularly the long-term CORE study follow-up. They were mixed on whether collecting data on children is useful…On using other registries and information, the consensus was that the information is important, and all efforts should be made in that direction." Panel comments included:

- "I think they have characterized the rupture rate, and I do think the saline data are material to this…I think that is a reasonable estimate of what happens over time to 10 years, which is what is considered the lifetime of an implant…What happens after that we don't know."
- "I think it's adequate in the short term, but not more than five years…I have concerns about projecting beyond that point."

- "A surgeon must document that they're trained, competent to do it, and have skills that are necessary to minimize the problems."

Question 5. Based on answers to Questions 1-4, as well as other safety data/information, and pre-clinical testing presented at the October 2003 panel meeting, discuss whether you believe there is reasonable assurance that this device is safe over its expected lifetime for the proposed indications of breast augmentation, reconstruction, and revision.

The panel seemed surprisingly reassured about safety of Inamed's silicone breast implants, with the exception of the newer Style 153 model. The panel chair summarized the discussion: "Most panel members feel a reasonable assurance of safety over the lifetime of the implants, although some question what a lifetime is, and there are some questions about Style 153." Panel comments included:

- "There is a reasonable assurance that for most people they are safe. Not all people are the same, and so there are going to be some people (in whom) this happens with devices and medicines. So, there is a reasonable assurance of safety. I have concerns about (Style) 153; that's very different."
- "The whole thing here is based on whether an adequate informed consent can be created and informed consent comes without good data. I think a good part of the data hasn't been analyzed correctly yet. Furthermore, we don't have data beyond three years, and I can't see how we can say anything about safety beyond three years."
- "I'm not sure I have the information to assess whether or not it is reasonable."
- "The device is, for many people, safe over the expected lifespan of the device. Those who calculate the risk should be able to have them."
- "I agree with comments about the 153 concern. I don't think it matters how healthy you are; the more surgeries you have, the more at risk you are. But I would certainly hope that the physician who is doing the implant or explant would be good enough to recognize that a problem may exist if you supplied all the information on what to do. I think the key word is ***reasonable*** assurance, and I had the feeling throughout the day that the company has been very forthcoming with giving information that we've asked for."
- "I feel comfortable with the plan. I think that more precision for the longer-term follow-up is really needed. We have to be really stringent in terms of determining these risks. We are looking at big, big numbers of people who will take advantage of the availability of these devices, so we're going to see the 1:100,000 adverse events. And I don't have a really good feeling people will follow-up in the recommended fashion because 'if it ain't broke, don't fix it.'"

During discussion of this last question – and before the final vote on Inamed's silicone breast implants – panel members appeared ready to vote in favor of approval. However, at least one panel member wanted to open the discussion up again, saying, "I feel intense pressure to approve this, and I don't know why. I don't have confidence thus far…On the basis of that, how can we get informed consent with this vagueness? It makes me very uneasy, and I wonder what the urgency is at this time when there are alternatives?" She asked if, during the voting, it was "all or nothing" with regard to Style 153. An FDA official replied that Inamed had not proposed to remove Model 153 from consideration but, instead, had mentioned it would modify the model, adding that Dr. Newburger was free to make a recommendation to eliminate 153 from the PMA.

Among the interesting exchanges during this discussion were:

- **On the lifetime of the implants:**

Inamed official: "We have four year data, silicone implants have been on the market for 30 years, they are available in Europe, and there is an extensive body of literature supporting the safety of these products. We can't give an actual lifetime, but we feel that serial MRIs and examinations…are still the most appropriate thing, with clear labeling, out to 10 years."

Panel member: "So this is an open-ended financial (cost) for the patient?"

Inamed official: "These are not considered to be lifetime devices. A patient would need to be informed that these are not considered lifetime devices, and part of the ongoing care may require (additional spending)."

- **On Inamed Model 153:**

Panel member: "If you take 153 out (of the equation), is there any other feature of 153 that's different from the rest?"

Inamed official: "We've taken it out and can provide to the FDA those data sets. We've looked at it alone and together, and it doesn't change the statistics in either direction. It doesn't change any parameters."

- Panel members had this exchange among themselves:

Chair: "There was some concern about the meaning of lifetime. Is it like changing your tires? You don't wait for a blowout. Should we be waiting 10 years before changing these out?"

Panel member #1: "The problem is that it has yet to be demonstrated that a ruptured implant causes a health hazard. I don't like the idea, but the fact is they're silent. There are no manifestations. If it ruptured and patients began experiencing health problems, we'd know. I'd like

to know the lifetime, but is it required in order to judge adequately the benefit that women derive from them to exceed the risk?...The reason I want to get this resolved is because of the women I'm going to see next year."

Panel member #2: "But aren't you sacrificing something?"

Panel member #1: "Of course. I'd like to know everything, but I consider the evidence pretty compelling on the lack of systemic disease."

Panel member #3: "We don't have enough follow-up to know about systemic diseases. That's the state I'm in."

The advisory committee rejects Inamed's implants

The choices facing the advisory committee on Inamed were: (1) approvable with no conditions attached; (2) approvable with specific conditions, such as physician or patient education, labeling changes, or analysis; and (3) not approvable, meaning the data didn't provide reasonable assurance the device is effective or safe. **The panel voted 5-4 that Inamed's silicone breast implants are not approvable.**

Panel members voting not approvable: Stephen Li, PhD, president, Medical Device Testing and Innovations; Dr. Joseph LoCicero III, cardiothoracic surgeon; Dr. Amy Newburger, dermatologist; Brent Blumenstein, PhD, TriArc Consulting (clinical trial consulting company); Barbara Manno, PhD, professor of psychology and a toxicology specialist.

Panel members voting against the not-approvable motion: Dr. Cheryl Ewing, breast surgeon; Dr. A. Marilyn Leitch, breast surgeon; Dr. Michael Miller, plastic surgeon; Leigh Callahan, PhD, epidemiologist and specialist in rheumatic diseases.

Among the panel member explanations of their votes were:

- "I believe there are not adequate data to assess efficacy data, which was part of the study which was not realized."
- "I voted against because…there were no long term plans to monitor their patients…but as a physician I'm somewhat disappointed."
- "I voted non-approvable at this time, but it is in no way denigrating. I don't feel right about the safety. I don't think at this time patients are given informed consent, and informed consent is really what this is all about."
- "I voted non-approvable because the data, though magnificently manipulated, are only two data points. We need more data."
- "I'm the weakest *yes*. Although I'm not comfortable with all the data from this particular study about the connective tissue diseases, I am confident with the studies, and I think that a lot of cases that have been made would have won complete approval if a lot of the constraints that have been discussed were in place."
- "I'm in personal agony here. My *no* is the weakest of *no's*, and in 2003 I had the weakest of *yeses*, so I'm on the fence at the end of the day. I hope the FDA allows you (Inamed) to continue to conduct your business in the manner that you have, in reconstruction and revision. I would vote for this unequivocally if you had a third data point…I don't know where the line is going after those two data points. If you have the wherewithal to continue, and I hope you do, you'll come back with five-year data and, if it looks good, then you've got a *yes*."
- "I voted against the motion. I appreciate the efforts of all the panelists to try and sort through this. I think that each one of us on the panel goes through something like a cost-benefit analysis. You look at the data available, and you have to judge whether it is adequate to justify the benefit. The threshold for me is the requirement for full knowledge of the devices may be a little lower. I'd love to know everything about the device – an impossible standard – but at some point we have to cross over and say we know enough to have one available. More data are only going to help. If any evidence unfolds in the future which shows it's harmful to women, I can assure you that I and my colleagues would be the first ones to oppose their use."
- "(Had the vote been on Model 153), 153 would not be approved because the rupture rate is too great for the patients it's used in – patients with reconstruction. Overall, silicone breast implants (should) be available widely…Some of the issues in rupture are related to perhaps technical issues and, as a surgeon, I'd expect the surgical societies to have a commitment…I think we, on a panel like this, are all affected by the stories we hear, the patients who come up and present information both pro and con, and a physician never likes to hear about someone having a bad outcome and being unhappy. I suppose the other admonition I'd have to the sponsor is that when I hear stories of patients who participate in a study or think they did and are not feeling they're being followed up in the study, that is the only way we can accumulate data."
- "In terms of lung cancer, we have literature rife with great studies at three years, and then at five years don't look so hot. Give us a little more data."

The panel chair asked members to make some suggestions to Inamed, and they suggested:

- "When it comes to the point of getting approval, there would be an intent for specific certification of surgeons to put the implants in."
- "You may ask, 'How long before we can come up with data that's deemed safe?' It's a little frustrating still not to know what the gel bleed rate is…If you have an answer, it makes it easier to accept 3-, 4-, 5-year data and project it to 10 years."

- "It's fairly clear the task to do is provide 10-year data."
- "I think women should have a choice, but we weren't charged with that. This short time of gathering data bothered me more than I thought, in that things that we're seeing are at the 5-year mark, and as the thing gets fatigued. I'm afraid that we'll get a different slope of the line (with time), and you'll be legally at risk."
- "You've proven efficacy. It's an issue not so much of the long-term complications but the short-term complications – rupture and re-operation. That might be true in all cases, but exposing a patient to another operation (should be avoided)."

MENTOR SUCCEEDED WHERE INAMED FAILED

After the Inamed vote, some people who attended the panel meeting were convinced that Mentor's device didn't have a chance for approval. Sid Wolfe, of the Center for Science in the Public Interest, said he thought Mentor should withdraw its PMA before the next morning's session.

Mentor began the third day of the panel meeting by predicting that the day would be very different from the previous day – that its data would be more convincing than Inamed's data. The presentations started out well, but the company relied heavily on published literature.

Mentor's President and CEO Josh Levine told the panel that his company's PMA presentation would be "new and distinguished from yesterday's panel discussion," promising a more detailed discussion of gel bleed tests and rupture data, related experiments on silicone and platinum, and a "safety profile from 3-year CORE data that departs from the other sponsor's CORE results." He added that Mentor would present 12-year clinical data that defines silent and symptomatic ruptures.

Another Mentor official told the panel that Mentor's PMA devices are third generation and none has more than one lumen (Inamed's Model 153 has two lumens). He described Mentor's CORE gel study of 1,007 women, saying that 89% of them had three-year follow-up, "Complication rates are essentially the same from those reported in the August 2004 update." He claimed that most ruptures were minor events (97%) which could be resolved without hospitalization, 33% received no treatment, 17% received medication, and 39% had a secondary procedure.

Mentor vice president Jerry Barber talked to the panel about implant biocompatibility, silicone diffusion, modes and causes of failure, and prediction of long-term device life.

- **Diffusion:**
  - Negligible diffusion from intact, implanted devices.
  - D4, D5, and D6 were the only siloxandes detected.
  - Total amount of diffusion was equivalent to 0.001 x the weight of the head of a straight pin.
- **Total rupture rate.** ~ 1% of total implants rupture, based on total U.S. complaints from 1985 through September 2003.
- **Rupture causes.** A Mentor official said that a small number of devices rupture, "Mentor devices have an overt failure rate of 1% of total implants, based on total U.S. complaints from 1985-2003." He described modes and causes of failures up to 10 years as:
  - Shell-thin line failure caused by sharp instrument damage (cut) or local stress induced during implantation.
  - Patch internal – thin line (sharp instrument damage).
  - Shell/patch junction – thin line (fatigue failure).
  - Localized shell failure (fatigue failure resulting from fold in shell).
  - Shell/patch delamination – shell/patch bond failure.

A Mentor official said that 22% of 240 devices returned to Mentor failed inter-operatively and were not implanted. Most inter-operative failures were due to instrument damage and local shell stress. Fatigue failures require time to develop, and initial failures from fatigue were seen for the first time at the one- to two-year level. He told the panel that modes and causes of device failures have been well-defined up to 10 years.

Reasons for Explanted Mentor Implants

Model	Cause	Percent of 240 returned devices
Shell-thin line	Sharp instrument damage (cut) Local stress induced during implantation	40%
Patch internal – thin line	Sharp instrument damage	40%
Shell/patch junction – thin line	Fatigue failure	8%
Localized shell fatigue	Fatigue failure resulting from fold in shell	7%
Shell/patch delamination	Shell/patch bond failure	4%

Another Mentor official presented data from the CORE gel MRI substudy on rupture rates: 420 patients were randomly enrolled and 372 patients had one and 2-year MRI follow-ups. The Mentor official said, "Of the 1,007 patients there was only one patient, in the revision cohort who had a bilateral rupture confirmed at explantation." He said, "Using the most conservative approach of confirming confirmed and suspected ruptures, the rate was 4.8% for revision patients and 8% for reconstruction patients. The overall confirmed and suspected rupture rate by patient was 1%." Mentor estimated a 15.1% rupture rate at 12 years and an expected median lifetime range of 25-47 years for gel implants.

Most of the rest of the company's presentation on rupture rates and epidemiological data relied heavily on published literature. An official said the literature shows no evidence of an association between connective tissue disease (CTD) and the use of silicone implants over time.

Mentor's president closed the company's presentation with a promise to "follow whatever assurances the panel or agency requests." He said that Mentor will continue the CORE study for its 1-year duration, with post-approval reports or reports at any interval requested by the FDA. Among the points he made were:

- **Compliance.** "The question has been raised about… compliance. For our saline breast implants, we're in our ninth year of study and for our saline testicular implants we're now in our fifth year of study. There is strong evidence the company has and will continue to fulfill our post approval compliance."
- **Informed consent.** "We have a continued commitment to provide informed consent process post-market, so that patients have reviewed and understood all the risks and benefits."
- **Rupture data.** "Rather than respond to FDA's concerns through projections and hypothesis…our preclinical science is state-of-the-art, and we have a three-year critical study on 1,000 of our patients. The story is…that ruptures are negligible…We ask you to fully consider what so many women and doctors have told you in the past – improving an individual's self-esteem and self-confidence are as integral to her well-being as any other health issue."

Panel questions for Mentor

The panel's first round of Mentor questioning was not nearly as contentious as at Inamed's session the day before. Mentor officials were asked about the reasons some women's implants were removed, implant fusion rates, platinum levels, infection rate analysis, and device lifetime.

Highlights include these panel questions/comments and Mentor answers:

- **Why did patients request implant removals?** A Mentor official said, "The largest single patient request was size change. We feel that's a parameter that could benefit from physician education…The other major class for implant removal was a capsule problem."
- **There seemed to be a high level of platinum ions** in patients who testified in the public session on the first day of this panel meeting. A Mentor official said, "I think they are being subjected to erroneous analysis."
- **Is the infection rate quite low in augmentation and revision patients, and ~5.3% for reconstruction patients?** A Mentor official said, "If you look over the three years, I think the immediate five or so percent of post-operative infections included women with trans flap reconstructions and some of them had problems with mesh…In the reconstructive group, saline has a higher complication rate generally than gel."
- **What is the lifetime of the device?** A Mentor official answered, "We've given that to you in a variety of ways: 25-47 years…The rupture rate out to 47 years appears to be very, very low. After that the rupture rate seems to come up." A Mentor statistician added, "The estimates of 25-47 years were obtained by extrapolating from the Sharpe and Collis (study) numbers."
- **What is the risk of rupture at 25 years?** A Mentor statistician estimated, "We'd say half of women would have a rupture at that point." Asked if that is within the lifetime of the device, he responded, "When one says what is the lifetime of the device, when characterized by the median – that is a typical measure." This prompted the following exchange:

Panel member: "I thought it was a fatigue life of 60 years? Let's say that the lifetime is 60 years, and if 80% of ruptures are related to surgical manipulation, and if those mostly happen in the first 10 years, let's say, of the device being present, then how would you account for the failures subsequent to that time if the fatigue is 60 years?"

Mentor official: "I think the vast majority (of implants) are damaged when they are taken out…You're trying to remove it, being careful, but using a knife to get in. You may be grabbing with a clamp and pulling it out. When we think about some of the devices that get returned, we can't tell when those devices were damaged…(Surgeons) are very careless with them. We can't tell how many of those events either propagate or cause a rupture."

Panel member: "Once you got rid of the ruptures you thought were related to surgical intervention, if the material is strong and fatigue is so low, could you postulate that the rupture rate would go down at a certain point?"

Mentor official: "We only saw three overt failures after 10 years, and we hypothesized that's what we would see. You have some damage from instruments, from implantation, folding, and I believe once that's done, then you proceed to this longer-term fatigue failure."

- **What about a woman who testified she had an illness she attributed to a Mentor implant?** A Mentor official said, "We did look through all of our studies for a woman by the name she stated in the public record, and we don't have a record of a patient by that name in the ADJUNCT study or the CORE study. We've been unable to find her documentation. We went to the FDA website, and we checked her name but could not find her."
- **Has anything been done to validate the use of a combination of equations for determining fatigue failure?** A panel member commented, "At the end of the day, you're trying to calculate a lifetime based on what

you call the combination of equations. My experience is that both of these equations were designed for metals, and coming from the plastics industry, it's an extremely difficult task. You've taken two equations of limited value in polymers and gotten a 60-year estimate." A Mentor official responded, "Have we validated it? No. The good news is that we have a good model. The bad news is that the increasing failure rate hasn't started. Then, we can ask, have we hypothesized correctly? We continue to test, but it's not like having failures we can point to and touch and examine."

FDA officials argued that Mentor's methodology and data were flawed and inadequate. One FDA official said, "There are no definitive data to support (Mentor's) position that insert failures were due primarily to surgical instrument damage or localized shell stress." As for modes and causes of rupture, she said, "Mentor is relying primarily on physician training to address failures related to surgical procedures. The company didn't identify any in vitro studies they are going to perform regarding stress. With regard to fatigue testing, that can't be validated without studies." Another FDA official argued, "The ability to predict a rate of rupture from these (CORE study) data is limited…Mentor relied on the published literature, recognizing that the literature is not specific to their product…One- and two-year data are limited in trying to project (rupture rates). Because of this, Mentor relied on published literature to address these issues.

Mentor's labeling proposals also were criticized by an FDA official. She said, "Mentor advocates annual or biannual exams (to assess silent rupture). However, the method is not specified. An MRI is said to be considered if there is suspicion of rupture. This addresses asymptomatic rather than silent rupture…Silent rupture issues are not addressed in (Mentor's) labeling."

During questioning, a panel member asked why patients who had implants removed were not followed up, I'd like to know what happened to these patients. They aren't included in the quality of life, signs and symptoms, or local health problems questionnaires…This could be meaningful. Why were these patients not followed?…Do you have a sense of what happened to them? One of the reasons I ask is that, during the break, I was given a note by an individual attending this open-panel meeting – a young woman in the ADJUNCT study who had adverse events that made her…quite sick. She had an explantation, and when she looked at her (paper) it was noted as, 'No complaint.' I'm concerned about the record-keeping and the bookkeeping and wondering if we're getting an accurate picture here."

The panel held an open discussion period in the afternoon. One panel member said, "I'm curious about the sponsor's response to questions raised by the FDA concerning rupture rate projections. When I listen to the sponsors, it appears to make reasonable assumptions and provide a not-inclusive but meaningful prediction, and when I listen to the FDA presentation I hear valid and significant questions raised about how those projections were done."

A statistician on the panel discussed Mentor's long-term study, saying, "It is a well-designed study with excellent follow-up, and the analysis was presented well…There are significant changes in the connective tissue disease signs and symptoms augmentation data. They pooled some of the symptoms together, and I pulled all that were listed. The significant signs and symptoms of skin, appendage, and joints are significant…We have something here we have to look at…In my opinion, I find these results disquieting and my conclusion is the follow-up interval is too short to estimate reliably the relationship between CTD signs and symptom increases and CTD diagnoses. We are in a state of inconclusiveness with respect to what these things are." He also made these points:

- Reference of these findings to the saline study or literature is largely irrelevant.
- What is presented is a well-designed study with subjects serving as their own control.
- The specific findings are inconsistent with *a priori* expectations (after adjusting for age).
- Connective tissue disease signs and symptoms changes are similar to some quality of life changes that have been seen.

Another panel member made the following suggestions:

- Create an individual patient symptom score using statistical methods.
- Find patients with high symptoms scores.
- Study these women, plus sample women with low scores in a supplemental study.
- Find out what's going on because there's something going on.

A third panel member brought up lifetime fatigue testing and Mentor's methodology. He said, "My own experience is it's better than a sharp stick in the eye, but it's not a great predictor of the life of the device…You can come up with 60-something years; but until there is some validation, we don't know how much to believe it. You could be right, or you could be off by a factor of four or five."

Panel discussion of FDA questions

The FDA had six questions for the panel. Following are excerpts from the debate as well as the vote on each.

Question 1. Has Mentor adequately characterized the rupture rate and how that rate will change over the expected lifetime of the device? YES

The consensus of the panel was that the early rupture rate is adequate, but there were mixed opinions regarding long-term data. Among panel comments were:

- "I don't feel that the characterization of the rupture rate is adequate at this time for several reasons…I guess I need a third data point…I don't have a level of comfort."
- *(A panel member who voted against approval of Inamed's implants):* "The sponsors provide good CORE data for the first two or three years. Their long-term information begins to look a lot like curves of other (devices), with rupture rates beginning to rise at seven years. The actual magnitude may be different, but I'm much more comfortable with this (than Inamed's)."
- "I'm comfortable with the characterization in the short-term and somewhat comfortable with the long-term."
- "The early results find minimal (evidence of rupture). The other (results) gives you some data you could feel comfortable with up to the 10-year period. The comfort you have about the fatigue data is that implants aren't going to just fall apart at 10 years. But what happens from 10-25 years? We don't have the data to know that."
- "The short-term data are excellent. I'm a little uncomfortable in projecting out very far in the absence of a failure mechanism. In the absence of actual data, I think it's characterized well in the short-term, and I'd like to see it in the long-term."
- "The data are excellent through follow-up."
- "The data collection and rupture rate…are acceptable data."

Question 2. Has Mentor adequately characterized the consequences of rupture for its device with regard to:

a. Frequency of observed intracapsular gel, extracapsular gel, and migrated gel, as well as the destination of the migrated gel.

b. The local health consequences of patients with ruptured implants.

c. The incidence, prevalence, and timing of silent ruptures that progress to symptomatic ruptures.

YES

The panel was in relative agreement that the data provided by the studies conducted by Mentor were limited in response to these questions, but there was a level of comfort based on the literature. Panel member comments included:

- "There is such a low rupture rate that we don't have much data. For your particular implant, you don't have a lot of data frequency, and you have to rely on other literature. So it's a question: Is the literature relevant to your device? I think it's fairly similar, I'd have to say, for your particular device."
- "The sponsor did a very good job looking at what data are available. They can pick out their devices from other studies, and they did the best job they could based on what information is available."

Question 3. Is Mentor's proposed labeling appropriate? It includes:

a. Method and frequency of screening for silent rupture.

b. Clinical management of suspicious and confirmed intracapsular and extracapsular rupture.

c. Potential health consequences of extracapsular and migrated gel.

The panel chair said, "It's a difficult thing to pin down the labeling, depending on the patient. The rupture rate and consequences of the rupture may dictate the label, and for that reason the view of the panel reflects the responses of the first question." Few panelists had anything to say about this.

Question 4. Are Mentor's post-approval plans adequate? YES

The panel chair concluded: "I think there was a consensus, somewhat, from the panel in general, that they're enthusiastic about some of the post-approval plans. Three members felt strongly about collecting data on children of women with implants…and following up with explant patients as recommended." Panel member comments included:

- "You (Mentor) did a terrific job of designing the study. You are in a lot better shape than when we reviewed the five-year saline data. This is a turnaround…If this device is approved, more than 50% (of patients) will use silicone opposed to saline – more than 200,000 in the next year – which gives a tremendous opportunity to capture that 1 in 100,000 event. I encourage you to take advantage of the opportunity to really define that."
- "I was happy with the commitments made. You (Mentor) can lay to rest a lot of the concerns that you hear from panel members about long-term outcomes."

Question 5. Is there a reasonable assurance that the device is safe over its expected lifetime? MIXED OPINIONS

The panel chair concluded: "Mixed panel view. Many felt there is an assurance of safety over at least some period of time, but there were some panel members who felt they were not assured. There was also some discussion about what a lifetime is. At least many, if not most, felt that 10 years…is safe." Panel member comments included:

- "We now have some information. The curve looks similar to other devices with failure at seven years, so the lifetime might be 10-15 years."

- "Over the expected lifetime of the device, if it's 25 years, I don't have assurance that the device is safe. Eighty percent of breast implants are used for augmentation, and more than half will be in the 19-34 year age group, so I guess we'll find out pretty soon what the life expectancy is."
- "Ten years gives me some reasonable assurance in the absence of data, that it is reasonably safe. The data don't allow me to go beyond 10 years."
- "I don't think there are adequate data for assurance safety …There needs to be a lot more study of these things, and there needs to be a lot more follow-up before we discover the relationship between signs and symptoms."

Question 6. Is there a reasonable assurance that the device is effective for the proposed indications? YES

The panel chair said, "I think there was a majority or somewhat of a consensus, depending on how efficacy is defined, that the device is effective." Panel member comments included:

- "I have a residual doubt but not large."
- "I don't have a good sense, other than increasing chest size, that this really is that effective…I'm concerned people are dropping out when they're explanted, (which may explain) the high percentage of patients saying they are satisfied. There was a further big drop-off in patients being queried between Years 2 and 3."
- "The sponsor made its primary endpoint, and it was that it increased chest size."

Panel voted to recommend approval of Mentor's implants

The Advisory Committee determined that Mentor's silicone breast implants can be approved, with certain requirements. First, the panel voted **7-2 AGAINST** a motion for *Not Approvable*. Then, a panel member made a motion for Approvable with Conditions, and the panel voted **7-2 IN FAVOR** of that. The conditions considered and the votes were:

1. **An education component. Yes, unanimously.**

In the ensuing discussion, a panel member said she wanted to add a condition of some kind of physician training. Another panel member said that, considering the high number of failures due to physician error, board-certified/board-eligible plastic surgeons should have to take and document a course that includes hands-on experience in order to implant the device.

2. **Better data collection for the CORE and ADJUNCT studies, with an FDA panel to meet in five years in order to review the data. Yes, unanimously.**

A panel member said he was concerned about what would happen if the implant's performance worsens over the years. Another panel member proposed a panel to review the data in five years, saying, "To look at the data not only from the CORE group but also to review the data that becomes available through the registry…I'm very concerned that we miss patients whose signs and symptoms are ignored. I'd put it at eight years for the CORE data."

3. **An independent data monitoring panel for the CORE study. Approved: 8 Yes, 2 No.**

4. **A separate and distinct patient education program and consent process for women getting silicone breast implants. Yes, unanimously.**

5. **Amend the CORE study to maintain records of symptoms and quality of life data on patients who have their implants removed (not on re-implanted patients). Yes, unanimously.**

6. **A voluntary registry with additions. Approved: 8 Yes, 1 No.**

A panel member recommended the sponsor modify its registry proposal with the suggestion that it include data on mammography results, CTD data, MRI data, explant data, children of women with implants, and more. The dissenting panel member said he wasn't convinced such a registry is necessary because there isn't evidence of harm to children.

7. **Commitments made by Mentor post-approval be followed through. Yes, unanimously.**

8. **Make tracking implants mandatory. Approved: 8 Yes, 1 No.**

9. **A condition relating to follow-up for MRI and silent rupture. Approved, with 4 abstentions.**

10. A proposal that Mentor begin a study to look at changes in symptoms identified in patients was rejected. **Not approved, 6 No, 2 Yes.**

Panel members voting in favor of approvability: Dr. Cheryl Ewing, breast surgeon; Dr. A. Marilyn Leitch, breast surgeon; Dr. Joseph LoCicero III, cardiothoracic surgeon; Dr. Michael Miller, plastic surgeon; Leigh Callahan, PhD, epidemiologist, specialist in rheumatic diseases; Stephen Li, PhD, president, Medical Device Testing and Innovations; Barbara Manno, PhD, professor of psychology and a toxicology specialist.

Panel members voting against approval: Dr. Amy E. Newburger, dermatologist; Brent A. Blumenstein, PhD, TriArc Consulting (clinical trial consulting company).

Panel member concluding comments included:

- "Choice for patients with breast cancer is critical. I still want them to have a saline implant if they want it. The data support it as a safe choice for them."
- "I felt the sponsor made an effort to follow the new draft document…The conditions that we applied made me feel comfortable that it demonstrates commitment. The fact that we're going to come back in five years made me very comfortable."
- "I want to explain how you can vote yes on one and no on the other. One, they are two different devices; they're not the same device…The (Mentor) implant data were short term like yesterday's (Inamed's). The difference is they (Mentor) had an extremely low rupture rate…It's a little awkward to penalize them for that…So, another question is what about the long-term rupture rate? Well, yesterday we didn't have the fatigue testing. They (Mentor) did it here as well as anyone can…The other thing they (Mentor) had that was not available yesterday (with Inamed) was only 100 patients after 10 years. That's still 100 patients after 10 years, and the statistics and the follow-up were excellent…I think the post-approval commitments are above and beyond what we normally ask for an implant. I believe we are holding it (Mentor) up to higher standards than other implants. This device has a 30-year history at best, and it is checkered, and it behooves us to have a higher standard for this device. I believe they have at least committed to a higher standard."
- "We have sufficient knowledge to justify their use and their availability."
- "Given the testimony here…if the doctors and company provide the information, I think we've got enough to approve this, and that means the recipients of the device will have a choice. It isn't (just) to have a choice, they can make a choice."
- "I felt the data were sufficient."
- "I voted not approvable because I feel that this is a 10-year study. I feel that I don't understand why this was presented now. I think that it's still too soon to accurately define what is happening to that group of patients that has vastly increased signs and symptoms, and since hundreds of thousands of patients will be exposed to this, I felt that the urgency was not warranted at this time."
- *The other panel member who voted against approval said:* "Limited follow-up, particularly in light of the CTD signs and symptoms finding, prevents me from feeling confident. In short, there's too much uncertainty." ♦

Advisory Committee Votes on Silicone Breast Implants

Name	Specialty	2003 Vote on Inamed (9-6 for approval)	2005 Vote on Inamed (5-4 against approval)	2005 Vote on Mentor (7-2 in favor of approval)
Brent Blumenstein, PhD	Clinical trial consultant	No	Against: Voted not-approvable	Against: Voted not-approvable
Leigh Callahan, PhD	Epidemiologist, specialist in rheumatic diseases	Wasn't on panel	For: Voted against not-approvable	For: Voted against not-approvable
Dr. Michael Choti, Panel chairman	Surgical oncologist	No	Didn't vote	Didn't vote
Dr. Cheryl Ewing	Breast surgeon	Wasn't on panel	For: Voted against not-approvable	For: Voted against not-approvable
Dr. Marilyn Leitch	Breast surgeon	Yes	For: Voted against not-approvable	For: Voted against not-approvable
Barbara Manno, PhD	Professor of psychology and a toxicology specialist	No	Against: Voted not-approvable	For: Voted against not-approvable
Dr. Michael Miller	Plastic surgeon	Yes	For: Voted against not-approvable	For: Voted against not-approvable
Stephen Li, PhD	Device testing specialist	Yes	Against: Voted not-approvable	For: Voted against not-approvable
Dr. Joseph LoCicero	Cardiothoracic surgeon	Wasn't on panel	Against: Voted not-approvable	For: Voted against not-approvable
Dr. Amy Newburger	Dermatologist	No	Against: Voted not-approvable	Against: Voted not-approvable