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Quick Pulse

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SILICONE BREAST IMPLANTS

The day after issuing a non-approvable letter to Inamed for its silicone breast implant, the FDA issued a draft of a revised guidance document for manufacturers of breast implants. This updates previous guidance issued in February 2003. The key issue appears to be continuing concern over silicone implants that rupture.

FDA Commission Dr. Mark McClellan issued a statement: "The FDA, sponsors, and the clinical community have learned a great deal about breast implants, especially silicone gel-filled breast implants, over the last 10 years. Based on this knowledge, this revised guidance is our view on the information needed to provide a reasonable assurance of safety, and to allow women and physicians to make informed decisions about silicone implants."

The key changes in the new guidance document involve mechanical testing, modes and causes of rupture, clinical study information, post approval requirements, and labeling.

Highlights from the new recommendations are:

Mechanical Testing

1. **Mechanical testing.** A new test needs to be designed to predict clinical outcomes, such as how long breast implants will last before rupturing in the body.
2. **New Fatigue Rupture Testing.** The FDA feels the methods currently used do not appear to simulate the observed rates of rupture and is recommending that a sponsor ***develop a new test methodology*** that can accurately predict rates of rupture over time. The FDA also appears to want retrieval study data, at least as part of development of the new test.
3. **New Bleed Testing.** The FDA wants a new gel bleed test developed that more closely mimics conditions in the body to identify and quantify the chemicals that bleed (leach) out of the shell over time.

Modes and Causes of Rupture

4. **More Data on Modes and Causes of Rupture.** The FDA clarified its recommendation that a sponsor characterize the modes and causes of rupture. The agency wants data that will help predict how rupture rates change over time and help allow an adequate assessment of the safety of the product.

The FDA is specifically recommending:

- A **retrieval study** involving examination and testing of breast implants that have been removed from patients.An assessment of a sponsor's manufacturing processes for the shell to determine whether any allowances for imperfections, such as bubbles and contaminants, may be related to device rupture.
- An assessment of the surgical techniques that increase the risk of rupture to better guide doctors on the best way to implant these devices.
- A comprehensive literature review of durability based on studies of explanted devices.

Clinical Studies

5. **Longer Data.** Although a sponsor may submit a PMA with a minimum of two years of clinical data, this data may not be sufficient to demonstrate a reasonable assurance of safety and effectiveness. For example, if, after two years, a sponsor does not have a sufficient number of patients, sufficient follow-up, or appropriate analyses to reliably predict the rupture rate and the clinical consequences of rupture over time, additional clinical follow-up may be recommended to allow an adequate assessment of the safety and effectiveness of the device.
6. **More Data on Ruptures.** The focus is on rupture as a whole, not just silent rupture, and the FDA wants more data on ruptures, including:
   - The rate and rate of change of rupture over the expected lifetime of the device.
   - The frequency of ruptures observed (intracapsular, extracapsular, and migrated gel). The FDA also recommends tissue sampling data on ruptured implants that are explanted.
   - Characterization of any local health consequences of ruptured implants.
   - Sufficient follow-up in patients undergoing MRI screening for rupture in a way that defines the silent rupture rate and, accordingly, the overall rupture rate.
7. **More Data on Connective Tissue Diseases** (CTDs). The FDA wants sponsors to collect information on diagnoses of CTD as part of the overall safety assessment on a device.
8. **Additional Supplemental Clinical Information. This is a new requirement** for sponsors to provide additional clinical information on a device (e.g., retrospective or prospective data from adjunct and/or European studies), as well as relevant information from the published literature, to address these rupture-related issues:
   - Frequency of observed intracapsular gel, extracapsular gel, and migrated gel, as well as the destination of the migrated gel.
   - Detailed description of the local health consequences experienced by all patients with ruptured implants, including the severity of these consequences, and their clinical course.
   - The incidence, prevalence, and timing of silent ruptures that progress to symptomatic ruptures.
   - The incidence, prevalence, and timing of intracapsular ruptures that progress to extracapsular ruptures.
9. **Supplemental Literature Information.** FDA continues to recommend that a sponsor provide a supplemental literature review on specific topics such as CTDs (including fibromyalgia), mammography issues, neurological disease, ability to lactate, and offspring issues (safety of milk for breastfeeding and second generation effects). However, the FDA now also wants a current literature review beginning with the 1999 Institute of Medicine (IOM) report in order to provide up-to-date information for women who might be considering breast implants.
10. **Post approval Requirements Strengthened.** The FDA emphasized that, post-approval, it may require a sponsor to:
    - Conduct a Core post approval study. For silicone gel-filled breast implants, an **annual physician follow-up**, rather than a mail-in survey, may be appropriate.
    - Continue to collect bench data regarding modes and causes of rupture.
    - Implement an education and certification program to train doctors with regard to proper surgical technique, patient selection, patient monitoring, and management of complications in order to obtain access to the implant.
    - Continue or initiate a registry.

Labeling

11. The **Physician Labeling** and **Patient Labeling. The FDA now** recommends that a sponsor include information in the labeling for breast implants on the following:
    - Method(s) and frequency of screening for rupture.
    - Clinical management of suspicious intracapsular and extracapsular rupture.
    - Gel bleed results.
    - Other supplemental information based on a current literature review.

FDA COMMENTS

Dr. David Feigal, Director of the FDA's Center for Devices and Radiological Health (CDRH) and Dr. Daniel Schultz, Director of CDRH's Office of Device Evaluation answered reporters questions about the new guidance documents. They would not discuss the Inamed application or non-approval letter directly since they are not allowed to talk about the status of a pending application: "A non-approvable letter is not a final action…This is still an action under review."

Among the points they made were:

➢ **The FDA is not sure what rupture rate is acceptable for silicone breast implants** – 3%, 6%, 10% or something else. "It is important to understand what predicts failure and rupture because that is the most important problem relating to failure and frequently to surgical removal…There have been implants manufactured in the past in other countries that had rates that are probably unacceptably high…and there are important questions about the rate of rupture…Does it level off over time or steadily increase?…Do we know the long-term rupture rate?…We need enough data on the silent ruptures -- which can only been done through MRI -- and how they progress to symptomatic ruptures…If we had a better handle on silent ruptures and some long-term data from other sources to look at some symptomatic ruptures, that information put together can give us a picture of what will happen with a device from the time it is implanted to when it may cause symptomatic problems and may need to be removed… Increasing the MRI cohort is one piece of information we need…We are also asking for new ways of looking at mechanical testing to see if we can relate those to long-term performance."

➢ **The consequences of ruptures need to be better understood.** "One of the difficult things for the (Inamed) advisory committee was what to do if an implant ruptures…Sometimes these are silent ruptures…In the past we wouldn't have had the ability to find them, and now we can with MRI…Do they lead to local complications? The advisory committee had a difficult time making recommendations about silent ruptures – whether watchful waiting was enough or if they should be explanted. Surgeons and patients also need to know how often they occur and what the consequences are."

➢ **Necessary follow-up times are not clear.** "We have a good idea of what happens when several thousand women get (saline) implants and have follow-up for two, three or four years, but we also know that manufacturers have observed symptoms that probably need to be better described and defined so people understand what the product is and what the consequences are."

➢ **The FDA cannot say whether any silicone breast implants are safe and/or effective at this point – or unsafe either.** "These are investigational devices. We are trying to give our best advice to manufacturers…We can tell women more about these products than in the past…There are 40,000-50,000 (American.) women in all different types of studies using silicone implants…This is an investigational product." Another official added, "Safe needs to be defined…There is no such thing as a safe product."

Following are some of the questions and the FDA answers:

Question: Will current sponsors be grandfathered or subject to these rules as well?
Answer: "This is guidance, not a rule…This is our best advice, not a requirement…All silicone breast implants are investigational and subject to establishing safety and efficacy. The guidance is our best advice on the issues…It is not a requirement…We only require a sponsor establish safety and efficacy…If you can do that with a different timeframe than we suggest or with different methods on the rupture issue, then we are open to that."

Question: What do you mean by "more than two-year data may be necessary?" How many more years?
Answer: "The minimum time is the shortest time we think likely to lead to enough information to provide evidence of safety and effectiveness…We do not specify how long a company needs to study something, even understanding that women will have these much longer…Manufacturers need to see what occurs early that is a signal for something later, and that implies having some later data…It could be prospective data, other experiences with the product, uniqueness because of a history in the U.S. or marketing elsewhere."

Question: Please clarify the reference to 10-year follow-up data.
Answer: The saline (breast implant) products which were approved and the studies which were part of the applications at the public hearing were all 10-year studies…The question is how early you can bring in studies for a marketing approval decision and then continue the follow-up in post-marketing and that has not changed…We think a product should be studied 10 years, but sponsors can submit experience with the first early years for approval and complete the study on the market—and that is what is happening with saline implants which are in Year 5 or 6 of the 10 years, even though they are approved…But manufacturers also can look at the issues which really matters – the consequences of failure, predictors of failure, and changes."

Question: What is the most significant aspect of the new guidance?
Answer: "We know any type of implant will have a defined failure rate, not just breast implants but all implants and devices. What is significant here is that there is a material that will be leaking out when they rupture, and we need to know how often, when and why and the ultimate consequences of that. The issue of time is that we really want a picture of the performance of the device over its lifetime…That doesn't mean that in a single prospective study sponsors will be asked to follow each patient to the end of the lifetime of the product, but there needs to be enough information from prospective trials that can be related to the long-term experience to give a picture."

Question: There was guidance (in February 2003), and this is very different guidance…Do you see problems based on the change-- telling a manufacturer what it needs to do, they did it, and now they are told they have to do something different?
Answer: "Guidance is our best advice, and we often have to revise it. We often have ongoing discussions with manufacturers and how well they addressed the issues in the guidance…If you look at this guidance and compare it to the open advisory committee (on Inamed) you will see they have similar themes."

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