DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

NOV 17 2006

William B. Schultz
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Washington, D.C. 20036-2638

Re: Citizen Petition - Docket Number 2005P-0204
Dated: May 23, 2005
Received: May 24, 2005

Citizen Petition Supplements 1 and 2
Dated: September 21, 2005
Received: September 22, 2005

Dear Mr. Schultz:

This letter responds to your citizen petition (Petition) dated May 23, 2005 submitted on behalf of several organizations and individuals. You ask that the Food and Drug Administration (FDA), pursuant to section 515(d) of the Federal Food, Drug, and Cosmetic Act (FDC Act or the Act), deny approval of Mentor Corporation's (Mentor) and Inamed Corporation's (Inamed) premarket approval applications (PMAs) for their silicone gel-filled breast implants. Specifically, you ask that FDA determine that Mentor and Inamed have not met their statutory burden of providing reasonable assurance that their devices are safe and effective.

This letter also responds to your Petition supplements, both dated September 21, 2005 (Petition Supplement 1 and Petition Supplement 2). In Petition Supplement 1, you ask that FDA withdraw its approvable letter to Mentor and you reiterate your request that FDA deny Mentor's PMA. In Petition Supplement 2, you ask FDA: (1) to reopen the record of the Inamed PMA; (2) to make any new data and FDA analysis of the new data publicly available; (3) to permit public comment on Inamed's recent PMA amendments; and (4) to withdraw its approvable letter.

Your requests are denied. FDA has approved the Mentor and Inamed PMAs because the data considered in support of each PMA meet the statutory standard for approval. Under the FDC Act and FDA's regulations, the agency may approve a PMA where the data in support of the approval, taken as a whole, provide reasonable assurance that the device is safe and effective for its conditions of use. We are denying your requests because we find your argument that a reasonable assurance of safety and effectiveness was not established for these devices unpersuasive and contrary to the law.

Section I of this response summarizes the regulatory history of breast implants, discusses certain clinical findings about silicone gel-filled breast implants, and sets forth the regulatory history of the Mentor and Inamed PMAs. Section II discusses the agency's review and analysis of your Petition and its supplements. Section III sets forth the agency's summary conclusion.

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I. HISTORY OF SILICONE GEL-FILLED BREAST IMPLANTS

Breast implants were on the market when Congress enacted the Medical Device Amendments of 1976 (MDA), granting FDA broad authority to regulate medical devices. The MDA directed FDA to classify every marketed device in one of three regulatory classes according to its degree of risk and FDA's level of understanding about the device. Following reports of adverse events in the literature, FDA proposed that all breast implants be classified into class III (premarket approval), a classification that became final in 1988.[1]

In 1991, FDA issued a *Federal Register* notice calling for PMAs for silicone gel-filled breast implants in accordance with FDC Act § 515(b).[2] Although FDA concluded that none of the PMAs submitted at that time contained sufficient data to support approval, the agency found, in accordance with section 515(d)(1)(B)(i) of the Act, that the continued availability of the device for patients undergoing breast reconstruction or replacement of existing silicone gel-filled breast implants (revision) was necessary for the public health. The agency determined that, to address this public health need, access to silicone gel-filled breast implants for reconstruction and revision patients should continue to be available through Adjunct Studies. The agency denied approval of the devices for augmentation.

Both the Mentor and the Inamed Adjunct Studies began in 1992 and were designed to address the public health needs of reconstruction and revision patients. With the approval of the Mentor PMA P030053 and Inamed PMA P020056, no new patients can be enrolled in the Adjunct Studies. However, both companies will continue to follow all currently-enrolled Adjunct Study patients for five years.

A. Early Concerns About Silicone Gel-Filled Breast Implants

At the time FDA restricted the availability of silicone implants to patients enrolled in the adjunct studies, few valid studies had been conducted assessing the long-term, systemic risks of silicone gel-filled breast implants. Particular concerns existed about connective tissue diseases (CTD) and cancer. CTDs include diseases such as lupus, scleroderma, rheumatoid arthritis, and fibromyalgia.

In the past decade, there have been a number of published epidemiological studies that have examined whether silicone gel-filled breast implants are associated with having a typical or defined CTD. Although only a very large study could conclusively rule out any risk of connective tissue disease among women with silicone gel-filled breast implants, the published studies have not found an increased risk of developing a typical or defined CTD in such women.[3,4,5,6,7]

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[1] 53 *Federal Register* 23874 (June 24, 1988)

[2] 56 *Federal Register* 14620 (April 10, 1991).

[3] Bondurant, S., V.L. Ernster and R. Herdman, Eds. 2000. Safety of silicone breast implants. Committee on the Safety of Silicone Breast Implants, Division of Health Promotion and Disease Prevention, Institute of Medicine. Washington, D.C.: National Academy Press.

Some literature reports have suggested an association between silicone breast implants and various rheumatological signs and symptoms such as fatigue, exhaustion, joint pain and swelling, muscle pain and cramping, tingling, numbness, weakness, and skin rashes. However, expert scientific panels and analyses of the literature have found no evidence of a consistent pattern of signs and symptoms in women with silicone gel-filled breast implants.[8,9,10,11,12] Several studies have also assessed the risk of cancer in women with silicone breast implants and have not found an elevated risk.[13,14,15,16,17]

B. Mentor's PMA

In August 2000, Mentor received FDA approval under section 520(g) of the Act for its Investigational Device Exemption (IDE) for silicone gel-filled breast implants. The study conducted under the IDE, also known as Mentor's Core Study, allowed enrollment of a limited number of augmentation, revision, and reconstruction patients. Mentor submitted a PMA on December 12, 2003, under section 515(c) of the Act and 21 C.F.R. 814.20, for the Mentor Silicone Gel-Filled Breast Implants. The Mentor PMA included extensive preclinical and clinical data. FDA issued a major deficiency letter on April 14, 2004, describing the additional information that needed to be submitted before the application could be approved.

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[4] Janowsky, E.C., et al. 2000. Meta-Analyses of the Relation Between Silicone Breast Implants and the Risk of Connective-Tissue Diseases. N. Engl. J. Med. 342(11):781-90.

[5] Lipworth, L.R.E., et al. 2004. Silicone breast implants and connective tissue disease: An updated review of the epidemiologic evidence. Ann. Plast. Surg. 52:598-601.

[6] Tugwell, P., et al. 2001. Do silicone breast implants cause rheumatologic disorders? A systematic review for a court-appointed national science panel. Arthritis Rheum. (11):2477-84.

[7] These studies do not distinguish between women with intact and ruptured implants. Only one study evaluated specific connective tissue disease diagnoses and symptoms in women with silent ruptured versus intact implants, but it was too small to rule out a small risk. *See* Hölmich, L.R., et al. 2003b. Self-reported diseases and symptoms by rupture status among unselected Danish women with cosmetic silicone breast implants. Plast. Reconstr. Surg. 111:723-732.

[8] Berner, L., M., et al. 2002. Comparative examination of complaints of patients with breast-cancer with and without silicone implants. Eur. J Obstet. Gynecol. Reprod. Biol. 102:61-66.

[9] Bondurant, S., V.L. Ernster and R. Herdman, Eds. 2000. Safety of silicone breast implants. Committee on the Safety of Silicone Breast Implants, Division of Health Promotion and Disease Prevention, Institute of Medicine. Washington, D.C.: National Academy Press.

[10] Breiting, V.B., et al. 2004. Long-term health status of Danish women with silicone breast implants. Plast. Reconstr. Surg. 114:217-26.

[11] Fryzek, J.P., et al. 2001. Self-reported symptoms among women after cosmetic breast implant and breast reduction surgery. Plast. Reconstr. Surg. 107:206-13.

[12] Kjøller, K., et al. 2004. Self-reported musculoskeletal symptoms among Danish women with cosmetic breast implants. Ann Plast Surg. 52(1):1-7.

[13] Brinton, L.A., et al. 2000. Breast cancer following augmentation mammoplasty (United States). Cancer Causes Control. 11(9):819-27. J. Long Term Eff. Med. Implants. 12(4):271-9.

[14] Bryant, H., and Brasher, P. 1995. Breast implants and breast cancer--reanalysis of a linkage study. N. Engl. J. Med. 332(23):1535-9.

[15] Deapen, D.M., et al. 1997. Are breast implants anticarcinogenic? A 14-year follow-up of the Los Angeles Study. Plast. Reconstr. Surg. 1997 99(5):1346-53.

[16] Herdman, R.C., et al. 2001. Silicone breast implants and cancer. Cancer Invest. 2001;19(8):821-32.

[17] Pukkala, E., et al. 2002. Incidence of breast and other cancers among Finnish women with cosmetic breast implants, 1970-1999. J. Long Term Eff. Med. Implants 12(4):271-9.

In August 2004, Mentor responded to that major deficiency letter with additional data. The Mentor PMA was then presented at a General and Plastic Surgery Devices Advisory Panel (the Panel) meeting held on April 11-13, 2005. The Panel determined that the preclinical and clinical data were adequate to demonstrate a reasonable assurance of safety and effectiveness, and recommended, by a seven to two vote, that Mentor's PMA be approved subject to specific conditions. Information concerning this Panel meeting, including a transcript, can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=593. After the April 2005 Panel meeting, Mentor provided additional information to FDA. After considering the Panel deliberations and the additional information received from Mentor, FDA issued a letter to Mentor on July 28, 2005, advising that its PMA was approvable subject to Mentor addressing issues related to post-approval conditions and labeling.

Mentor submitted a response to the approvable letter on August 16, 2005, after which FDA continued to develop the post-approval plans and labeling with the sponsor. On November 17, 2006, the Mentor Silicone Gel-Filled Breast Implants were approved for use in augmentation patients who are at least 22 years old and in reconstruction patients of any age.

C. Inamed's PMA

In June 1998, Inamed received FDA approval under section 520(g) of the Act for its Investigational Device Exemption (IDE) for silicone gel-filled breast implants. This study, like Mentor's Core Study, permitted enrollment of limited numbers of augmentation, revision, and reconstruction patients. Inamed submitted a PMA on December 30, 2002, under section 515(c) of the Act and 21 C.F.R. 814.20, for the Inamed Silicone-Filled Breast Implants. The Inamed PMA included extensive preclinical and clinical data. FDA issued a major deficiency letter on March 21, 2003.

In amendments submitted in March through July 2003, Inamed responded to that major deficiency letter with additional data. Inamed's PMA was first presented at a Panel meeting held on October 14-15, 2003. The Panel recommended, in a 9 to 6 vote, that Inamed's PMA be approvable subject to certain conditions. Information concerning this Panel meeting, including the transcript, can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=388. On January 7, 2004, FDA issued a not approvable letter based on safety issues raised during the Panel deliberations.

On August 20, 2004, Inamed provided a response to the not approvable letter. Inamed's PMA was then presented at a second Panel meeting held on April 11-13, 2005. The Panel recommended, in a 5 to 4 vote, that Inamed's PMA be found not approvable. The major concerns that the Panel had with the Inamed data were the relatively high rupture rate seen with the Style 153[18] and the lack of long-term data to characterize rupture rate. The Panel also had concerns

[18] Inamed Style 153 was a double-lumen device consisting of an inner bladder within the outer lumen, both filled with silicone gel. The inner bladder was located at the lower pole of the breast implant and its function was to maintain the curved profile of the style. Style 153 was withdrawn by Inamed based on discussions with FDA regarding the Core Study rupture rates and Style 153 failure modes shown in the retrieval studies.

about the gel bleed testing, the connective tissue disease (CTD) analyses, and the modes and causes of rupture studies. Information concerning this Panel meeting, including the transcript, can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=593.

After the April 2005 Panel meeting, Inamed addressed the Panel's first major concern by removing the Style 153 from the PMA and providing a revised analysis of the data without the Style 153 data. Inamed addressed the Panel's major concern about the lack of long-term data to characterize rupture by submitting the results from an International MRI Study and a new lifetime estimate based on cyclic fatigue data. Inamed addressed the Panel's remaining issues by providing additional information regarding the gel bleed testing and new CTD signs and symptoms data analyses. FDA determined that the updated data provided by Inamed about retrieved implants that had been explanted were adequate to characterize the modes and causes of rupture up to approximately 10 years following implantation, with additional data to be collected in a large post-approval study. After considering this additional information and the Panel deliberations, FDA issued a letter to Inamed on September 20, 2005, advising that its PMA was approvable subject to Inamed addressing issues related to post-approval conditions and labeling.

Inamed submitted a response to the approvable letter on November 1, 2005, after which FDA continued to develop the post-approval plans with the sponsor. On November 17, 2006, the Inamed Silicone-Filled Breast Implants were approved for use in augmentation patients who are at least 22 years old and in reconstruction patients of any age.

II. DATA DEMONSTRATING A REASONABLE ASSURANCE OF SAFETY AND EFFECTIVENESS SUPPORT THE MENTOR AND INAMED APPROVALS

The Petition's central argument is that FDA may not approve the Mentor and Inamed PMAs because the applications do not contain data to demonstrate a reasonable assurance of safety and effectiveness, the statutory standard for PMA approval. The Petition argues that data submitted by the companies since the Mentor major deficiency letter and the Inamed not approvable letter could not be sufficient to permit approval and that FDA should not follow the recommendation of the April 2005 Panel that FDA find the Mentor PMA to be approvable with conditions. The Petition also argues that FDA has shifted the pre-approval burden for these PMAs to post-approval commitments and that, for all of these reasons, approval would constitute arbitrary and capricious agency action, in violation of the Administrative Procedure Act. FDA rejects these arguments.

A. The Statutory Standard For Device Approval Is A Reasonable Assurance Of Safety And Effectiveness

The Petition's arguments rely on a reading of the standard for device approval contrary to the statutory language and inconsistent with FDA's longstanding interpretation of the language. This interpretation has governed FDA's PMA approval program since its inception and was implemented in regulations issued shortly after the program's inception. The Medical Device Amendments of 1976 created the classification system for devices and the requirement that FDA

review PMAs for class III devices, such as silicone gel-filled breast implants. The legislation specifies that the review standard for PMAs is reasonable assurance of safety and effectiveness for the labeled indications,[19] a standard "predicated upon the recognition that no regulatory mechanisms can guarantee that a product will never cause injury, or will always produce effective results."[20] The statute directs FDA to evaluate whether a PMA meets the standard,

> (A) with respect to the persons for whose use the device is represented or intended,
> (B) with respect to the conditions of use prescribed, recommended, or suggested in the labeling of a device, and
> (C) weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.

FDC Act § 513(a)(2). The FDC Act makes clear that devices subject to PMA approval raise particular concerns[21] requiring a substantial premarket showing, especially regarding the safety of a device. Congress was equally clear that the standard incorporates a degree of flexibility in that the showing must be "reasonable" rather than absolute, evaluated in relation to the intended population for the device and the labeling, and that the benefits of a device, as well as the device's risks, must factor into approval decisions.

1. Safety

FDA interpreted the statutory PMA approval standard in regulations issued in 1978, which state that a reasonable assurance of a device's safety exists when:

> it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with use of the device for its intended uses and conditions of use.

21 C.F.R. § 860.7(d)(1). The regulation notes that clinical, nonclinical *in vitro*, animal, or some combination of these data types might be appropriate to demonstrate a reasonable assurance of safety, but also notes that what constitutes valid scientific evidence "may vary according to the

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[19] *See generally* FDC Act §§ 513, 514, 515.

[20] H.R. Rept. 94-853 at 15 (February 29, 1976).

[21] Section 513(a)(1)(C) provides that a device shall be classified into class III under the following circumstances:
(i) it (I) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and (II) cannot be classified as a class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide reasonable assurance of its safety and effectiveness, and
(ii) (I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or (II) presents a potential unreasonable risk of illness or injury.

characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use." 21 C.F.R. 860.7(c)(2),(d)(2).

2. Effectiveness

The regulation defines the standard for device effectiveness in similar terms, stating that:

> [t]here is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

The regulatory language defining valid scientific evidence in relation to the device, conditions of use, labeling, and experience with the device applies also to effectiveness data; however, the statute and the regulation contain unique provisions that allow additional flexibility in supporting the effectiveness determination. Section 513(a)(3) of the Act provides that device effectiveness shall be determined on the basis of well-controlled investigations, including one or more clinical investigations, unless FDA determines other valid scientific evidence exists,

(i) which is sufficient to determine the effectiveness of a device, and
(ii) from which it can fairly and responsibly be concluded by qualified experts that the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device.

Similar language appears in the regulation, authorizing FDA to consider alternatives to well controlled investigations in assessing effectiveness where the requirement to conduct such investigations "is not reasonably applicable to the device." 21 C.F.R. 860.7(e)(2).

B. The Mentor And Inamed PMAs Provided Data Supporting A Reasonable Assurance Of Safety

The Mentor and Inamed PMAs contain a substantial amount of data demonstrating a reasonable assurance of the safety of the devices. A summary of the data is provided in the Summary of Safety and Effectiveness Data (SSED) for each PMA.[22] The primary data FDA relied on in approving the PMAs were the Core Studies (clinical studies conducted by the companies to support approval of the devices) and preclinical data, including chemistry testing, toxicology testing, mechanical testing (i.e., fatigue testing, gel cohesion testing, gel bleed testing), shelf life testing, and modes and causes of rupture studies. Supporting clinical data for each PMA included the European studies (Mentor's Sharpe/Collis Study and Inamed's

[22] Mentor SSED - http://www.fda.gov/cdrh/pdf/p030053.html.
Inamed SSED - http://www.fda.gov/cdrh/pdf/p020056.html.

International MRI Study), Adjunct Studies (open access studies for reconstruction and revision patients), and studies published in the scientific literature.

The Petition argues that these data do not overcome safety concerns about silicone gel-filled breast implants, particularly those related to rupture and gel bleed. In support of its argument, the Petition relies on interim analyses of the data in the PMAs and an incomplete record. We address each of these issues below.

1. Rupture

As the Petition states, the rate at which silicone gel-filled breast implants rupture is one of the primary issues FDA was concerned about in determining whether these devices are safe. However, FDA's view of what needed to be shown with respect to rupture in order to find that the devices are reasonably safe has changed over time, reflecting the agency's consideration of the data submitted and the deliberations of the Panel.[23] Initially, FDA expected that a combination of preclinical testing and several years of clinical data would be adequate to provide reasonable assurance of the safety of the devices,[24] information similar to what the agency generally relies upon in evaluating most implantable devices (e.g., prosthetic heart valves, orthopedic implants). Indeed, the approval of saline-filled breast implants was based, in part, on a combination of preclinical testing and two years of clinical data establishing the safety of those devices. However, based on input from the October 2003 Advisory Panel, FDA issued letters notifying Mentor and Inamed that long-term Core Study data that measured or reasonably estimated the rupture profiles of the devices over their expected lifetimes were needed before the devices could be approved.

In August 2004, Mentor and Inamed responded to the letters. Mentor provided, among other things, updated Core Study data (partial 3-year data rather than the 2-year data previously submitted), the Sharpe/Collis Study to address the long-term rupture rate, extensive modes and causes of rupture studies that examined the causes of rupture for explanted devices, and an estimated lifetime of the device based on cyclic fatigue testing. Inamed provided, among other things, updated Core Study data (partial 4-year data rather than the 3-year data previously submitted), extrapolated Core Study data analysis to address long-term rupture rate, and extensive modes and causes of rupture studies examining the known causes of rupture for explanted devices.

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[23] This evolution in thinking is documented in review memoranda in the PMA records for each company.

[24] In the *Draft Guidance for Industry and FDA Staff: Saline, Silicone-Gel, and Alternative Breast Implants* (January 2004) (Draft Guidance), FDA noted:

> 2 years of premarket clinical data may not be sufficient to evaluate the safety and effectiveness of [breast implants]. For example, because of the difficulty in detecting rupture and the risk of extracapsular and migrated silicone gel, additional years of premarket follow-up has been recommended for silicone gel-filled implants.[a]

Thus, the Draft Guidance did not specify the number of years of premarket data necessary to evaluate a PMA, but suggested the number could be greater than two.

Based on our preliminary review of these responses, and as noted in the FDA Panel memoranda[25], FDA found that Mentor's Sharpe/Collis Study and Inamed's extrapolation of its Core Study data had significant limitations, involving the generalizability of the results and the way in which the data were collected and analyzed, that did not allow for precise estimation of long-term rupture rates.[26,27] However, because this was the first time FDA had requested this amount of long-term data for an implantable device, we sought the Panel's input in assessing the data. FDA presented both PMAs to the Panel in April 2005.

With respect to Mentor's PMA, the discussions that occurred during the April 2005 Panel meeting provided FDA with a different framework for evaluating rupture rate. In recommending that FDA find the Mentor PMA to be approvable, the Panel determined that the PMA contained sufficient data to provide reasonable assurance about the rupture rate out to 10 years despite the lack of a precise estimation of rupture rate over the life of the device. FDA considered these discussions in a subsequent review of the data and concluded that, in the absence of long term clinical data showing an unreasonable risk of illness or injury, clinical data showing a low rupture rate in the short-term and preclinical data showing no expected increase in rupture rate due to inherent material or design flaws through 10 years were sufficient to support approval of the Mentor PMA.[28]

With respect to Inamed's PMA, the Panel recommended that the PMA not be approved. Two of the principal reasons the Panel cited to explain its recommendation were that the rupture rates for one of the styles of Inamed's device, Style 153, were unacceptably high and that the data in Inamed's PMA were insufficient to characterize long-term rupture rate. In response to these concerns, Inamed submitted a revised dataset with Style 153 removed, an MRI International Study addressing the long-term rupture rate, and an estimated lifetime of the device based on cyclic fatigue testing. FDA determined, as it did in approving the Mentor PMA, that, in the absence of long term clinical data showing an unreasonable risk of illness or injury, clinical data showing a low rupture rate in the short-term and preclinical data showing no expected increase in rupture rate due to inherent material or design flaws through 10 years were sufficient to support approval of the Inamed PMA.[29]

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[25] FDA Panel memos for Mentor and Inamed's PMAs - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=593

[26] The Petition states that the Mentor Core Study is flawed because it only included rupture rate data through 3 years, with MRIs at years 1 and 2 and that these data were of limited value to characterize the rupture rate over time (Petition at 18). FDA agrees that it is not scientifically sound to extrapolate short-term Core Study data out to 10 years. Nonetheless, the short-term data is robust and, considered with other sources of data contained in Mentor's PMA, support the finding that the PMA provides a reasonable assurance of device safety.

[27] The Petition states that FDA found the Mentor data to be flawed because Mentor, unlike Inamed, did not use the Core Study data to address the rupture rate over the lifetime of the device (Petition at 18). In our Panel memo for Mentor's PMA, we simply pointed out that Mentor did not attempt to extrapolate Core Study data (in any fashion). FDA did not request an extrapolation over time because the agency did not believe such an evaluation would be useful. Further, the agency determined that such data were not necessary to show a reasonable assurance of safety.

[28] Additional data from the post-approval studies will be used to quantify long-term rupture rates, and the labeling will be updated as additional data becomes available.

[29] Additional data from the post-approval studies will be used to quantify long-term rupture rates, and the labeling will be updated as additional data becomes available.

The major sources of data FDA reviewed in characterizing the rupture rate and the consequences of rupture[30] are described below.

a. *Core Studies.* The Core Study for each PMA provided the most complete assessment of the rupture rates for these devices. For each Core Study, rupture was assessed for patients who had scheduled MRIs to screen for non-symptomatic, or silent, rupture (the MRI cohort), as well as for those who did not have scheduled MRIs to screen for silent rupture (the non-MRI cohort).

Mentor's Core Study included rupture rate data from the non-MRI cohort (original sample size of 587) at years 1, 2, and 3, and from the MRI cohort (original sample size of 420) at years 1 and 2. There were a total of 8 ruptured/suspected ruptured implants in 6 patients through 3 years, all of which were from patients in the MRI cohort. The rupture rates in the MRI cohort were 0.5% for primary augmentation patients (augmentation patients receiving their first implants), 7.7% for revision-augmentation patients (augmentation patients whose implants were removed and replaced), 0.9% for primary reconstruction (reconstruction patients receiving their first implants), and 0% for revision-reconstruction (reconstruction patients whose implants were removed and replaced). Two of the implants were explanted and confirmed to be ruptured; the remaining 6 implants were considered suspected ruptures based on MRI evaluation. Of the 8 ruptured/suspected ruptured implants, 4 showed intracapsular gel and 4 showed extracapsular gel. There were no cases of migrated gel.[31]

Inamed's Core Study included rupture rate data from the non-MRI cohort (original sample size of 451) at years 1, 2, 3, and 4, and from the MRI cohort (original sample size of 264) at years 1 and 3. There were a total of 9 ruptured/suspected ruptured implants in 9 patients through 4 years, from patients in both the MRI and the non-MRI cohorts. The rupture rates in the MRI cohort were 2.7% for primary augmentation patients, 4.0% for revision-augmentation patients, 0% for primary reconstruction patients, and 0% for revision-reconstruction patients. Five of the implants were explanted and confirmed to have ruptured; the remaining 4 were considered suspected ruptures based on physical or MRI evaluation. All 9 ruptured/suspected ruptured implants showed intracapsular gel, and one intracapsular gel rupture progressed into an extracapsular gel rupture following exploratory surgery to confirm the rupture. As with Mentor's Core Study, there were no cases of migrated gel.[32] In summary, the Core Studies, which were the primary source of rupture rate data for the Mentor and Inamed devices, provided compelling data demonstrating low rates of rupture through 3 and 4 years, respectively.

b. *Preclinical Testing.* Inamed and Mentor both provided extensive data to characterize the modes and causes of rupture of their specific devices to show how the devices may fail in the clinical setting. The primary source of information regarding the modes and causes of rupture are the studies of explanted devices referred to as retrieval studies. Additional

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[30] Consequences of rupture include intracapsular rupture (when the gel remains within the scar tissue capsule surrounding the implant), extracapsular gel (when the gel moves outside the capsule but remains within the breast tissue), migrated gel (when the gel moves beyond the breast), and clinical consequences.

[31] Mentor SSED; http://www.fda.gov/cdrh/breastimplants/.

[32] Inamed SSED; http://www.fda.gov/cdrh/breastimplants/.

sources of modes and causes of rupture information include physical property testing, assessment of manufacturing processes and surgical techniques that may impact rupture, and a review of the literature on the durability of explanted devices.

The retrieval studies showed that, through approximately 10 years, devices are not rupturing from pure cyclic fatigue (e.g., normal wear and tear). Rather, the data showed that the majority of device ruptures were surgically related and, thus, should be minimized by adequate surgeon training. Coupled with fatigue testing, discussed below, showing that failure from pure cyclic fatigue is not expected for several decades, the retrieval studies provide additional assurances of safety, with no unexpected increase in failure rate due to design or materials defects through approximately 10 years.[33]

Mentor and Inamed performed fatigue testing to assess the mechanical durability of their devices in order to characterize the long-term rupture rate. Inamed and Mentor used the raw data from their fatigue testing in mathematical models that adjusted for the load/stress from walking, jogging, running, lying face down, and shell wrinkling. The results from these models demonstrated that the devices can withstand lengthy cyclic loading for decades without failure caused by inherent design or material flaws.[34]

c. *Supportive Data.* In addition to the Core Studies and the preclinical testing, FDA considered numerous sources of clinical information about the specific devices under review and about silicone gel-filled breast implants generally. Although these data sources have limitations, they were nonetheless useful as supporting information. Specifically, FDA considered these sources in determining whether the devices present an unreasonable risk of illness or injury.

Mentor and Inamed each submitted European studies to further characterize rupture rate and to provide information about the consequences of rupture. As stated previously, Mentor submitted the Sharpe/Collis Study and Inamed submitted the International MRI Studies.

The Sharpe/Collis Study submitted by Mentor was intended to provide information about the rupture rate over a longer period of time than had been evaluated in the Core Study, as well as to provide supplemental information on the consequences of rupture. Silent rupture was assessed by a single MRI on 101 augmentation patients. The average age of the implants was approximately 9 years. Silent rupture was found in approximately 10% of these patients. All ruptures were intracapsular; there were no cases of extracapsular rupture or migrated gel.[35]

Like Mentor's Sharpe/Collis Study, Inamed's International MRI Study[36] was intended to provide information about the rupture rate over a longer period of time than had been evaluated in the Core Study, as well as to provide supplemental information on the consequences of

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[33] Mentor and Inamed SSEDs; http://www.fda.gov/cdrh/breastimplants/.
[34] Mentor and Inamed SSEDs; http://www.fda.gov/cdrh/breastimplants/.
[35] Mentor SSED; http://www.fda.gov/cdrh/breastimplants/.
[36] Hedén, P., et al. 2006. Prevalence of rupture in Inamed silicone breast implants. Plast. Reconstr. Surg. 118:303-308.

rupture. Excluding 5 patients with Style 153 implants, silent rupture data were collected in a single MRI on 106 patients (77 augmentation, 11 reconstruction, and 18 revision). The average age of the implants was 11 years. Silent rupture was found in approximately 15% of the combined group of augmentation, reconstruction, and revision patients. There was one possible case of extracapsular rupture, with the remainder of the cases classified as intracapsular ruptures. No cases of migrated gel were found.[37]

The Petition objects that the Sharpe/Collis Study is of limited value for several reasons (Petition at 18-19). FDA acknowledges that the Sharpe/Collis Study and the International MRI study are of limited value in providing a precise estimate of the long-term rupture rate. However, using the same framework discussed by the April 2005 Panel in assessing rupture, we determined that these studies, which involved the specific devices for which approval was sought, provided supportive information about the long term risk of rupture and the consequences of rupture. The studies provided additional assurances, when considered with the short-term data from the Core Studies, the modes and causes of rupture studies, and the fatigue testing, that the long term risks associated with the devices are not unreasonable. As with the Core Studies, the relatively few ruptures that occurred limited our ability to assess the consequences of rupture. However, the data we do have suggest that, when rupture does occur, there is no gel migration.

FDA also conducted an extensive review of the scientific literature on breast implants. The studies from the scientific literature collectively reported a large number of ruptures. Because these studies did not report device-specific rupture rates, FDA did not rely upon them for information about the rupture rates of the devices under review.[38] However, these studies are useful in assessing the clinical consequences of rupture. The local complications reported in studies of Danish women evaluated with MRI that were associated with rupture included breast hardness, a change in breast shape or size, and breast pain. These are common local

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[37] Inamed SSED; http://www.fda.gov/cdrh/breastimplants/.

[38] The Petition refers to data reported in the literature predating the Mentor and Inamed studies indicating a significant risk of implant rupture overall, and an increased risk over time (Petition at 8-9, 15-16). The published articles the Petition refers to, such as the Holmich, Marotta, and Brown studies, included a wide variety of manufacturers and implant styles, and demonstrated a wide range in results. *See* Holmich, L.R. *et al.*, Incidence of silicone breast implants rupture, Arch. Surg. 2003; 138; Holmich L.R., et al., Self-Reported disease and symptoms by rupture status among unselected Danish women with cosmetic silicone breast implants, Plast. Reconstr. Surg. 2003; 111(2); Holmich, L.R. *et al.*, Untreated silicone breast implant rupture, Plast. Reconstr. Surg. 2004; 114(1); Marotta, *et al.*, "Silicone Gel Breast Implant Failure and Frequency of Additional Surgeries: Analysis of 36 Studies Reporting Examination of More than 8000 Explants," J. Biomed. Materials -- Applied Biomaterials 1999:48(3):354-364; Brown, S.L., *et al.*, "Prevalence of rupture of silicone breast implants revealed on MR imaging in a population of women in Birmingham, Alabama," Am. J. Roentgen. 2000; 175(4). The same is true of the IOM Report and FDA Rupture Study discussed in the Petition. *See* "Safety of Silicone Breast Implants," Institute of Medicine (National Academy Press (2000); "Study of Rupture of Silicone Gel-Filled Breast Implants (MRI Component)," FDA (2000). FDA thoroughly reviewed this literature and concluded that rupture rate is device-dependent. For this reason, we determined that it was not appropriate to extrapolate the results reported in this literature to the Mentor and Inamed implants for which approval was sought. FDA believes that the Core and European studies, which are device-specific, in conjunction with the preclinical tests supplied by the companies, provide the strongest rupture rate data for the Mentor and Inamed products.

complications observed, not only in women with intact silicone gel-filled breast implants, but also in women with intact saline-filled breast implants.[39]

Although rare reports appear in the literature of gel movement to nearby tissues (such as the chest wall, armpit, or upper abdominal wall), and to more distant locations down the arm or into the groin, a number of epidemiology studies that have evaluated large populations of women with breast implants have not shown an association with the development of connective tissue or rheumatic diseases and/or symptoms.[40,41,42,43]

Although the Adjunct Studies were neither designed nor intended to be the main set of clinical data to support the PMAs, they provided useful data assessing local complications associated with the devices, such as reoperation, capsular contracture, and breast pain. The studies showed that the local complications reported for women with ruptured implants were similar both in type and in complication rate to those reported for women with intact implants.[44]

In conclusion, FDA's determination that the Mentor and Inamed PMAs have demonstrated a reasonable assurance of safety reflects the agency's review of extensive clinical and preclinical data. Although our perspective on the type of rupture data needed has changed over time, the standard of review has remained constant. In some cases, the questions we originally had were addressed when the sponsors provided clarification or additional data. In other cases, our assessment of the data changed based on input from the Advisory Panel. In the final analysis, FDA determined that, when the totality of the rupture data are considered, both Mentor and Inamed have provided sufficient valid scientific evidence to demonstrate a reasonable assurance of the safety of their devices.

2. Gel Bleed

Mentor and Inamed conducted gel bleed testing to assess the amounts of gel constituents that bleed through the shell of intact implants. FDA worked with the companies to develop gel bleed testing methodology that mimicked conditions in the body. The testing focused on low molecular weight (LMW) silicones and platinum, a metal used as a catalyst (a substance that increases the rate of a chemical reaction) in the manufacture of the shell and gel components of silicone gel-filled breast implants. The results from this testing showed that very small amounts of gel constituents bleed through the intact implant shell.

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[39] http://www.fda.gov/cdrh/breastimplants/labeling/mentor_patient_labeling_5900.html; http://www.fda.gov/cdrh/breastimplants/labeling/inamed_patient_labeling_5900.html

[40] Berner, I., et al. 2002. Comparative examination of complaints of patients with breast-cancer with and without silicone implants. Eur. J. Obstet. Gynecol. Reprod. Biol. 102:61-6.

[41] Brown, S.L., et al. 2001. Silicone gel breast implant rupture, extracapsular silicone, and health status in a population of women. J. Rheumatol. 28:996-1003.

[42] Hölmich, L.R., et al. 2003b. Self-reported diseases and symptoms by rupture status among unselected Danish women with cosmetic silicone breast implants. Plast. Reconstr. Surg. 111:723-32.

[43] Wolfe, F. and Anderson, J. 1999. Silicone filled breast implants and the risk of fibromyalgia and rheumatoid arthritis. J. Rheumatol. 26:2025-28.

[44] Mentor and Inamed SSEDs; http://www.fda.gov/cdrh/breastimplants/.

Mentor's gel bleed testing was presented at the April 2005 Panel meeting. Although FDA believed that the overall methodology used by Mentor was appropriate, at the time of the Panel meeting FDA believed that Mentor needed to provide additional technical details and explanations of the observed results in order to perform a complete analysis of the data. Mentor provided this additional information after the Panel meeting, and the results showed that approximately 1% of the LMW silicones and platinum bled through the shell over the course of the experiment.[45]

At the time of the April 2005 Panel meeting, Inamed had not yet conducted gel bleed testing that mimicked the conditions in the body. Subsequent to that Panel meeting, Inamed did conduct such testing and provided the results to FDA. The Inamed results were comparable to Mentor's and showed that approximately 1% of the LMW silicones and platinum bled through the shell.

To determine the clinical consequences of gel bleed, FDA performed a thorough review of the scientific literature. Although some studies on breast implants that have been implanted for a long time have suggested that gel bleed may be a contributing factor in the development of capsular contracture[46] and lymphadenopathy,[47] the rates of complications reported in these studies are actually lower for silicone gel-filled implants than for saline-filled implants. Because saline-filled breast implants do not contain silicone gel, this suggests that the observed complications are not due to bleeding of silicone gel. Furthermore, toxicology testing performed by each company indicates that the silicone material used in the Mentor and Inamed implants does not cause toxic reactions when large amounts are administered to test animals.[48]

There has been some question concerning the safety of platinum. The small amounts of platinum remaining in the product following its manufacture may enter the body, either by diffusing through the intact shell (i.e., through gel bleed) or through an implant rupture. As noted above, gel bleed testing performed by both Mentor and Inamed showed that over 99% of the platinum stayed within the implant. Based on FDA's review of the gel bleed testing, the published literature on this topic[49], as well as the biocompatibility testing and clinical data on the device, FDA concluded that the low concentration of platinum contained in breast implants is in

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[45] The Petition argues that the Panel failed to consider that the patch covering the manufacturing port of the implant is not made of low bleed material and, thus, may have affected the gel bleed results for the Mentor implant. However, the Panel was aware that, although the majority of the shell is made with low bleed material, the patch is not. In fact, the information provided to the Panel clearly stated that the devices used in all preclinical testing, including the gel bleed testing, were the final finished product that included the non-low bleed patch. The Panel based its recommendation that the device be approved on the data obtained from clinical and preclinical studies performed on the final finished product.

[46] Bondurant, S., V.L. Ernster and R. Herdman, Eds. 2000. Safety of silicone breast implants. Committee on the Safety of Silicone Breast Implants, Division of Health Promotion and Disease Prevention, Institute of Medicine. Washington, D.C.: National Academy Press.

[47] Katzin, W.E., et al. 2005. Pathology of lymph nodes from patients with breast implants: a histologic and spectroscopic evaluation. Am J Surg Pathol.29(4):506-11.

[48] Mentor SSED - http://www.fda.gov/cdrh/pdf/p030053.html.
Inamed SSED - http://www.fda.gov/cdrh/pdf/p020056.html.

[49] In June 2006, FDA posted a Backgrounder on its website (http://www.fda.gov/cdrh/breastimplants), which provides a brief summary of some of the key scientific studies on platinum and silicone gel-filled breast implants.

the zero oxidation state, or the state associated with the lowest toxicity, and, thus, does not pose a significant risk to women with silicone gel-filled breast implants.[50]

In conclusion, the data from Mentor's and Inamed's PMAs provided reasonable assurance that only a small amount of LMW silicones and platinum bleeds from these devices. Toxicology studies, along with the studies in the scientific literature, reveal that this small amount of gel bleed is not associated with clinical consequences. Thus, FDA appropriately determined that there was reasonable assurance that the devices are safe.

3. Other Issues

a. *Inamed's Style 153.* Inamed's original PMA included various styles of silicone gel-filled breast implants. All of the styles were round, single-lumen (single shell) devices, except for Style 153. Style 153 had a significantly different design in that it was a contoured-shaped device with double lumens (a shell filled with silicone gel within a shell filled with silicone gel).

Inamed's modes and causes of rupture studies indicated that Style 153 had unique types of failure and the clinical data from the Core Study showed that the rupture rate for Style 153 was higher than for the other styles. Concern about Style 153 was one of the major reasons why the April 2005 Panel recommended that the Inamed PMA be found not approvable. After the April 2005 Panel meeting, Inamed withdrew Style 153 from its PMA and submitted a new dataset with Style 153 removed.

The Petition objects that removal of the data on Style 153 raises questions about the adequacy of the sample size and the generalizability of the data in Inamed's PMA (Petition Supplement 2 at 3). FDA addressed these issues when the revised dataset was submitted, recognizing that the largest loss of patients occurred in the reconstruction and revision patient cohorts. FDA determined that, even with removal of the Style 153 data, the sample size was adequate to estimate the complication rates in the reconstruction and revision patient cohorts with sufficient precision and, therefore, to provide adequate information on the safety of the remaining device styles.

FDA also disagrees with the objection in the Petition that, with the removal of Style 153, the sample size available for the 5-year and 10-year follow-up timepoints is significantly reduced (Petition Supplement 2 at 9). Inamed is required, as a condition of approval, to perform biennial MRIs on all patients in the Core Study (not only on patients who were originally in the MRI cohort) to assess for silent rupture (as is Mentor). Therefore, we believe the sample size will be adequate for the 5-year and 10-year follow-up timepoints.

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[50] Stein, J., et al. 1999. In situ determination of the active catalyst in hydrosilylation reactions using highly reactive Pt(0) catalyst precursors. J. Am. Chem. Soc. 121(15):3693-3703. Chandra, G., et al. 1987. A convenient and novel route to bis(alkyne)platinum(0) and other platinum(0) complexes from Speier's hydrosilylation catalyst. Organometallics. 6:191-2. Lappert, M.F. and Scott, F.P.A. 1995. The reaction pathway from Speier's to Karstedt's hydrosilylation catalyst. J. Organomet. Chem. 492(2):C11-C13. Lewis, L.N., et al. 1995. Mechanism of formation of platinum(0) complexes containing silicon-vinyl ligands. Organometallics. 14:2202-13.

Finally, the Petition also objects that Inamed manipulated the data in its PMA by removing the Style 153 data. As already discussed, the Style 153 device was very different from the other devices in the PMA. Because of these significant differences, FDA determined that it was appropriate to exclude the data on that style when Inamed decided not to pursue approval of the Style 153 device. Submission of a revised analysis without the Style 153 data, therefore, was not a manipulation of the data.

b. *Clinical Data per Style.* FDA also disagrees with the argument in the Petition that the data in the Mentor Core Study were flawed because only two of the six styles under review were part of the Core Study (Petition at 18). It is true that only two of the six styles were part of the Mentor Core Study and, similarly, only four of the eight styles under review (now approved) were part of the Inamed Core Study (excluding Style 153). However, additional information is not always necessary when a company adds a new style or model to its PMA. FDA determines, on a case-by-case basis, what additional data are necessary when a new style or model is added to a PMA.[51]

All of the approved styles of both Mentor's and Inamed's devices were single-lumen, round devices manufactured using the same method, materials, and specifications, with some variance in height, width, and/or projection. FDA determined that the differences between the styles included in the clinical studies and the new styles were minor and, therefore, that the Core Study data were relevant across all the styles under consideration in each company's PMA.[52] Accordingly, FDA determined that the data in each PMA provided a reasonable assurance of the safety and effectiveness of the styles under review in the PMA.

In conclusion, FDA's decisions approving the Inamed and Mentor PMAs were consistent with the statutory standard for device approval. Valid scientific evidence adequately demonstrated that the regulatory requirement of absence of unreasonable risk of illness or injury associated with use of the devices was met. Thus, FDA appropriately concluded that the PMAs provided a reasonable assurance of safety.

C. The Mentor And Inamed PMAs Provided Data Supporting A Reasonable Assurance Of Effectiveness

Similarly, FDA has adhered to the statutory standard for effectiveness in approving the Inamed and Mentor PMAs. The Petition contests the effectiveness of the products on several grounds, arguing that the literature does not show gains in Quality of Life (QoL) for either reconstruction or augmentation patients, that QoL measures are an inappropriate source of effectiveness data for silicone gel-filled breast implants, and that use of such measures to gauge

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[51] It is also standard practice that preclinical testing itself (e.g., chemistry, toxicology, mechanical) be performed on representative styles rather than on every device for which a sponsor is seeking PMA approval.

[52] We also disagree with the Petition that Inamed's rupture data should be stratified by style because of the differences in rupture rate found with Inamed's Style 153 (Petition Supplement 2 at 5-8). As described above, Style 153 had a significantly different design than the other Inamed styles, while all remaining models are similar in design.

effectiveness amounts to an abdication of FDA's responsibility to protect the public from unknown health risks in favor of increasing consumer choice. The Petition has ignored other sources of data considered by FDA and mischaracterized the basis for the agency's determination of effectiveness.

1. Effectiveness Data

As with the determination of device safety, the statute directs FDA to evaluate a device's effectiveness in light of the device's labeled indications. Section 515(d)(1)(A) provides:

> In making a determination whether to approve or deny [a PMA, FDA] shall rely on the conditions of use included in the proposed labeling as the basis for determining whether or not there is a reasonable assurance of safety and effectiveness.

Coupled with the regulatory language directing FDA to evaluate effectiveness in the target population, according to the labeled indications and conditions of use, this provision requires FDA to evaluate whether data in a PMA show that the device performs the function purported in the labeling. *See* 21 C.F.R. 860.7(e)(1).

The Mentor and Inamed products are indicated for breast augmentation and breast reconstruction. The obvious question in assessing their effectiveness, then, is whether the products perform as intended by increasing breast size or returning a breast to its former size following surgery in significant portions of the target populations. Thus, in addition to QoL data, both PMAs included data assessing the anatomical effect of the implants. The Inamed PMA included anatomical effect data only for augmentation patients, reporting an increase in cup size for 94 % of the augmentation population measured at 18 months after surgery. The Mentor PMA reported an increase of one cup size or more for 97 % of augmentation patients measured at three years after surgery and an average increase of 2.4, 1.3, and .9 inches for the revision-augmentation, primary reconstruction, and revision-reconstruction patients measured. Data submitted by Inamed and Mentor show that these implants are effective in augmenting the breast. Mentor's data from patients other than primary augmentation patients also support the effectiveness of the Mentor device in restoring breast size in reconstruction and revision patients.

In addition to QoL and anatomical effect, FDA also considers patient satisfaction in evaluating the effectiveness of breast implants. Inamed provided patient satisfaction data that showed high rates of satisfaction in all patient groups at four years after surgery.[53] Mentor assessed satisfaction by asking patients three years after implantation whether they would have breast implant surgery again and reported similarly high rates of patient satisfaction.[54] Thus, the PMAs also support the effectiveness of the devices in terms of patient satisfaction.

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[53] The percentages of patients who reported being satisfied with their Inamed silicone breast implants at four years were 95% of augmentation patients (346 individuals), 96% of revision-augmentation patients (96 individuals), 94% of primary reconstruction patients (63 individuals), and 92% of revision-reconstruction patients (12 individuals).

[54] The percentages of patients who reported they would have breast implants surgery again at three years were 98% of augmentation patients (445 individuals), 94% of revision-augmentation patients (111 individuals), 98% of primary reconstruction patients (185 individuals), and 98% of revision-reconstruction patients (47 individuals).

The QoL data that the Petition argues are inadequate to support an effectiveness showing were but one of three primary sources of data considered by FDA in reviewing the effectiveness of the Mentor and Inamed silicone gel-filled breast implants. The Petition seems to argue, however, that no effectiveness showing that relies, even if only partially, on the psychosocial benefit of implants could justify FDA's approval of the PMAs given the "uncertain safety" of these devices and the availability of saline breast implants. FDA acknowledges that assessing the psychological benefits attributable to a medical product poses challenges different from those posed by common endpoints in device studies, such as changes in physical functioning and body structures, but rejects the suggestion that such benefits provide inappropriate support for approval. FDA uses data from psychological assessments in considering the effectiveness of oncological drugs, cardiac devices, and other products; such assessments provide context to data regarding the utility of a product in, for example, diminishing tumor size or replicating a bodily function. Further, as discussed above, the agency reviewed extensive data related to the safety of silicone gel-filled breast implants and concluded that the data provide a reasonable assurance of device safety. For these reasons, the agency disagrees with the Petition's argument that safety deficiencies exist in the PMAs or that such deficiencies can only be overcome with an enhanced showing of effectiveness.

2. Risk-Benefit

The agency further disagrees with the Petition's argument that the availability of saline-filled implants undermines the approval determination for silicone implants. The availability of alternative products may affect review decisions in certain instances; in particular, section 520(m)(2)(B) directs FDA to approve a Humanitarian Use Device for limited populations only if "there is no comparable device, other than under this exemption, available to treat or diagnose such disease or condition." In the absence of corollary language in the PMA approval provisions, the availability of an alternative product does not preclude approval of a product that meets the statutory requirement for safety.

Rather, the availability of saline-filled implants is one factor among several FDA considered in the "weighing [of] probable benefit . . . against any probable risk of injury or illness" associated with silicone gel-filled breast implants. In making this assessment, FDA considered not only the scientific evidence submitted by Inamed and Mentor to support effectiveness, but other information concerning the relative benefit of silicone implants over saline-filled implants and the relative risks. These risks and benefits differ somewhat among patient groups and particularly between reconstruction and augmentation patients.

The risks of silicone gel-filled breast implants for both of these groups are those generally for silicone gel-filled breast implants; however, features of each of these groups may determine the likelihood that members of the group will be affected by the risks that have been discussed in this Response. On the one hand, reconstruction patients are likely to receive ongoing medical care, and problems such as implant rupture are arguably more likely to be detected. On the other hand, the data considered by FDA found generally fewer incidents of rupture and other complications in the augmentation group, which comprised younger, generally healthier

patients.[55] The risk profile for the two groups, then, was different, but did not clearly point to greater risks for one group or the other.

For both reconstruction and augmentation patients, the probable benefits of silicone implants are those reflected in the effectiveness data considered in the Inamed and Mentor PMAs, namely, increased cup size or chest circumference and patient satisfaction. In addition, FDA heard from surgeons and patients during the open public sessions of the October 2003 and April 2005 Panel meetings that silicone implants provide a more natural and cosmetically-appealing result than saline-filled implants, an important consideration for reconstruction and augmentation patients alike. For reconstruction patients, however, silicone implants provide a unique advantage over alternatives because some individuals in this group may lack sufficient native tissue following surgery to allow a natural result with saline-filled implants.

FDA concluded that the risk-benefit calculation favored approval for both patient groups. Although the lack of an alternative product for some reconstruction patients may suggest that the calculation should favor this group, FDA believes silicone gel-filled implants also provide a benefit over saline-filled implants for some augmentation patients as well because of the aesthetically superior results reported by patients and physicians. Further, the agency disagrees with the Petition's contention that the aesthetic and psychosocial nature of the benefit diminish its significance and that the benefit amounts to one of consumer choice. Aesthetic, psychosocial considerations are critical to assessing the benefits of breast implants, whether used for breast reconstruction or cosmetic augmentation and appropriately factored into FDA's assessment of the benefits of the Mentor and Inamed products.

D. Consistent with FDA's authority to require post-approval commitments concerning approved devices, the post-approval conditions imposed on Mentor and Inamed appropriately supplement the premarket showing

The Petition argues that FDA has attempted to compensate for deficiencies in the extensive data considered pre-approval by imposing post-approval conditions on Mentor and Inamed silicone gel-filled breast implants and notes that the FDC Act does not permit the substitution of post-approval conditions for a pre-approval showing of reasonable assurance of safety and effectiveness. The Petition argues further that a history of companies neglecting post-approval commitments, FDA's failure to take enforcement action against such companies, and the nature of the particular commitments for silicone gel-filled breast implants render such commitments ineffective. These arguments reflect a misunderstanding of FDA's authority to impose post-approval requirements on devices.

1. FDA's Post-Approval Authority

FDA's premarket authority over devices is one critical component of an entire regulatory scheme, a scheme that includes authority over trials involving investigational devices, premarket

[55] *See* SSED, Mentor at 18; SSED, Inamed at 15. For Mentor, only the primary augmentation group had lower rates of rupture and other complications than the other groups.

review, and an extensive system of post-market controls tied to the level of risk a device poses and the degree to which risks are understood and can be controlled. Demonstrating the relevant premarket showing suffices only for entry to market, but FDA's regulatory authority extends to the continued safety and effectiveness of marketed products. For class III devices, postmarket controls include not only general controls such as good manufacturing practices (GMPs), adverse event reporting, and registration and listing requirements, but also post-approval conditions imposed by PMA order.

FDA has imposed post-approval conditions in PMA orders since enactment of the Medical Device Amendments of 1976.[56] Several provisions of the FDC Act, including sections 515, 519, and 520, support this authority, which FDA formalized with regulations in 1986.[57] Under these regulations, FDA may require periodic reports, recordkeeping, and continued evaluation of the safety, effectiveness, and reliability of the device.[58] Regardless of the safety data considered in the PMA, FDA imposes post-approval conditions on all approved devices and post-approval studies on approximately one-third of all approved devices. The nature of the conditions imposed will reflect the types of safety and effectiveness issues that may arise postmarket.

The Food and Drug Administration Modernization Act of 1997 (FDAMA) affected FDA's post-approval authority by adding section 513(a)(3)(C) to the FDC Act, authorizing the agency to consider available postmarket controls in reviewing effectiveness data in a PMA. Section 513(a)(3)(C) provides:

> In making a determination of a reasonable assurance of the effectiveness of a device for which an application under section 515 has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls.

The provision authorizes the agency, in its discretion, to evaluate whether postmarket controls, such as long-term post-approval studies of effectiveness, can be used to supplement premarket effectiveness data in meeting the statutory standard of reasonable assurance of effectiveness. The provision does not, however, affect the requirement that PMA sponsors demonstrate a reasonable assurance of safety prior to PMA approval.

FDA has noted that "the primary purpose" of post-approval evaluations is "to obtain information on the long-term safety, effectiveness, or reliability of certain devices when, for example, long-term data are unavailable when the PMA is submitted."[59] The concept of "reasonable assurance" reflects the Congressional judgment that devices subject to approval should reach the market only after concerns about safety and effectiveness have been addressed

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[56] *See* 51 *Federal Register* 26342, 26360 (July 22, 1986).
[57] *See* 21 C.F.R. §§ 814.82 and 814.84.
[58] *See* 21 C.F.R. § 814.82; *see also* Draft Guidance for Industry and FDA Staff Procedures for Handling Post-Approval Studies Imposed by PMA Order (September 12, 1995).
[59] *See* 51 *Federal Register* at 26359.

and substantially alleviated, but does not assume that approval may occur only after concerns about all potential risks have been eliminated. The agency, therefore, may require post-approval evaluations when the approval standard has been met but questions about the long-term safety and performance of the device remain. By providing a mechanism for the agency to require additional data beyond that needed to establish a reasonable assurance of safety, including data collected over several years, post-approval commitments serve as an important complement to the preapproval showing of reasonable assurance of safety and effectiveness.

2. The Mentor and Inamed Post-Approval Requirements

Consistent with the agency's established authority, FDA included several post-approval conditions in the approval orders for the Mentor and Inamed silicone gel-filled breast implants. The basic conditions were the same for both devices and include the following:

- continuation of the Core Studies to 10 years. All patients in the non-MRI group during the pre-approval stage will have MRIs during the post-approval stage and patients explanted without replacement will be evaluated through ten years. The patient and physician labeling will be updated to reflect five and ten-year study findings, as well as any other time point deemed necessary by FDA;

- continuation of preclinical studies to further characterize modes and causes of rupture past 10 years. The patient and physician labeling will be updated to reflect any relevant findings;

- continued follow up of Adjunct Study patients through five years (although enrollment in the Adjunct Studies will cease);

- within 90 days, initiation of enrollment in a large 10-year study with endpoints including long-term local complications; diagnoses of connective tissue disease, signs, and symptoms; diagnoses of neurological disease, signs, and symptoms; potential interference of silicone gel implants with mammography; potential impact of silicone gel implants on reproduction, lactation, and offspring; rates of suicide; and compliance of women with implants with MRI screening recommendations. The patient and physician labeling will be updated to reflect five and ten-year study findings, as well as any other time point deemed necessary by FDA;

- reporting on a patient labeling focus group study, with information from the report to be used to update patient labeling;

- annual monitoring of the patient informed decision process, which includes an expectation that patients and their physicians sign forms in advance of surgery stating they have read and understand labeling and other information; and

- restricting access to the implants to physicians who have participated in the approved physician training program.

In addition, FDA has ordered tracking for these implants under section 519(e) of the FDC Act.

The Petition argues that the Panel's 2005 recommendation that Mentor undertake postmarket commitments similar to several of the ones imposed and, according to the Petition, similar to the types of studies required for an IDE, demonstrates deficiencies in the premarket showing in that such postmarket requirements would be unnecessary had the PMAs included long-term safety data, and argues that FDA in the past required such long-term studies for silicone gel-filled breast implants. The *Draft Guidance for Industry and FDA Staff, Saline, Silicone Gel, and Alternative Breast Implants* (January 13, 2004) (Draft Guidance) recommended that the Core Studies be designed for 10 years of follow-up, and suggested that more than two years of premarket data would be needed to support a reasonable assurance of safety and effectiveness for silicone gel-filled implants,[60] a suggestion followed by the Mentor and Inamed PMAs. More importantly, as discussed above, the safety information included in the Inamed and Mentor PMAs supports a reasonable assurance of safety (and is consistent with the types of data considered by the agency in evaluating PMAs for other implants). The comparison of the studies ordered by FDA as postmarket commitments to IDE trials overlooks the critical distinction that FDA has reviewed extensive premarket data establishing the safety and effectiveness of the devices that are the subject of the postmarket commitments.

The availability of post-approval conditions did not affect FDA's finding that the safety information included in the PMAs meets the required standard; instead, the post-approval conditions imposed by FDA on the Inamed and Mentor products appropriately supplement the premarket safety data by providing information on the long-term performance and safety of these products. FDA anticipates that data from these long-term commitments will provide important information for patients and physicians and may lead to improvements in device labeling.

3. Effectiveness of Post-Approval Requirements

The Petition argues further that FDA cannot rely on the post-approval requirements because the studies will not produce meaningful data and compliance with post-approval commitments has been poor. Specifically, the Petition refers to Mentor's "poor track record with post-approval studies" and deficiencies in FDA's oversight of these studies. The particular concern raised by the Petition regarding the Panel's recommendation for a patient registry is moot because the agency has decided to impose a large post-approval study instead of a patient registry requirement. Further, although, as the Petition notes, FDA expressed concerns at the April 2005 Panel meeting that Mentor's proposal for physician training lacked certain information related to rupture screening and implant removal, Mentor subsequently provide a revised physician training program, independent of any professional society overview, which was consistent with the labeling and addressed all of FDA's concerns.

Concerning FDA's oversight and enforcement of device post-approval commitments, the agency has acknowledged past problems and undertaken significant changes. These changes

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[60] *See supra* fn. 24.

include transferring primary responsibility for the program to the Office of Surveillance and Biometrics, the CDRH component charged with monitoring and assessing the significance of postmarket events involving devices, greater involvement of epidemiologists in the design of post-approval studies, and electronic tracking and monitoring of the progress of post-approval studies. The agency has committed itself to improving its postmarket system of controls and expects this enhanced commitment to result in improved compliance with, and better data from, all postmarket studies, including those imposed in the Mentor and Inamed PMAs.

The Petition also questions the effectiveness of the labeling recommendation advising implant patients to undergo periodic MRIs, noting the high cost of MRIs and the possibility that some silicone gel-filled breast implant recipients may not have medical insurance.[61] The Petition characterizes the recommendation as a post-approval commitment; however, FDA reviews proposed labeling as part of the premarket approval determination. The MRI recommendation is similar to other recommendations, warnings, and contraindications that appear in the labeling of approved devices and drugs in that FDA considers the recommendation important information for the safe and effective use of the product but the possibility or even the likelihood that some patients will not follow the labeling does not provide a valid ground to deny approval. Approved labeling for endovascular grafts recommends that recipients receive follow-up screening, including CT scans and X-rays, on an annual basis. The fact that some recipients may not comply with this recommendation does not negate a finding of reasonable assurance of safety and effectiveness for the device when used in accordance with the approved labeling.

Indeed, section 515(d)(1)(A)(i) of the Act directs FDA to approve a PMA unless, among other things, "there is a lack of a showing of reasonable assurance that such device is safe under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." FDC Act § 515(d)(2). The statute makes clear that FDA must rely upon "the conditions of use included in the proposed labeling" in determining whether a reasonable assurance of safety and effectiveness has been shown, so long as the proposed labeling is neither false nor misleading. FDC Act § 515(d)(1)(A). In some instances, the likelihood of compliance with a labeling recommendation may be so remote that tying a finding of safety and effectiveness to such a recommendation would be misleading. In arriving at its determination, the agency considers the importance of the recommendation to the safety and effectiveness finding and the likelihood that the recommendation will be followed. Concerning the MRI recommendation in silicone gel-filled breast implant labeling, FDA determined that the recommendation, coupled with labeling disclosures noting that most ruptures are silent and that MRI is the only reliable means of detecting a silent rupture, enhances the safety of the device by encouraging women to undergo

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[61] The patient labeling provides the following disclosure concerning the importance of MRI in detecting silent rupture and the cost of the procedure:
Rupture of silicone gel-filled breast implants is most often silent. This means that neither you nor your surgeon will know that your implants have a rupture most of the time. In fact, the ability of a physical examination by a plastic surgeon who is familiar with beast implants to detect silicone gel-filled breast implant rupture is 30% compared to 89% for MRI. You will need to have regular screening MRI examinations over your lifetime in order to determine if silent rupture is present. You should have your first MRI at 3 years after your initial implant surgery and then every two years, thereafter. The cost of MRI screening may exceed the cost of your initial surgery over your lifetime. This cost, which may not be covered by your insurance, should be considered in making your decision. (citations omitted)

periodic MRIs. Further, FDA believes that the physician training, extensive labeling, and enhanced informed decision making requirements for these devices will encourage prospective patients to carefully consider all of the consequences of silicone gel-filled breast implants, including the future costs, before implantation.

E. Approval of the Mentor And Inamed PMAs Is Consistent with the APA's Requirement of Reasoned Decision-making

By carefully considering the data contained in the Mentor and Inamed PMAs, evaluating the data against the statutory standard for premarket approval of a reasonable assurance of safety and effectiveness, and tailoring post-approval studies to long-term questions about marketed silicone gel-filled breast implants, FDA has met its responsibilities under the Administrative Procedure Act, 5 U.S.C. § 553, *et seq.* (APA) to engage in a reasoned process and reach decisions on the silicone gel-filled breast implants PMAs supported by the evidence. The Petition argues, however, that the approvals represent a significant departure from FDA's past precedents concerning these products; the Petition further argues that in the absence of an adequate explanation, the departure is arbitrary and capricious under the APA. The administrative record provides comprehensive information explaining how the agency arrived at its approval decisions and addressing circumstances that have affected the agency's approach and, in some instances, supported changes from past agency statements. The record demonstrates a reasoned process of decision-making consistent with the APA.

1. Past Policies and Decisions Concerning Silicone Gel-Filled Breast Implants

FDA acknowledges that its approach to silicone gel-filled breast implants has evolved, reflecting the agency's review of extensive clinical data collected in the years since FDA acquired regulatory authority over breast implants, several decades of experience with these devices and, in some instances, reevaluation of past approaches in light of this data and experience. A significant development that has occurred since FDA's 1992 decision restricting silicone implants is the volume of data failing to show a correlation between silicone gel-filled breast implants and systemic consequences. This development has appropriately affected FDA's thinking about these devices.[62] Since early 2004, when FDA published its draft guidance on breast implants and issued the Inamed not approvable and Mentor major deficiency decisions, additional developments have affected FDA's review of the two PMAs. In particular, each sponsor has submitted an additional year of Core data, long-term data from European studies, and extensive modes and causes of rupture studies. Mentor has also submitted a fatigue lifetime analysis. That the new data submitted by Mentor and Inamed does not include estimated rupture rates at ten years as recommended in the Draft Guidance reflects FDA's consideration of the new data in light of the April 2005 Panel discussion, a discussion that encouraged FDA to assess whether the PMAs demonstrated safety and the absence of an unreasonable long-term risk.

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[62] Discussions in the proposed and final rules requiring PMAs for silicone breast implants emphasized the systemic risks of silicone breast implants. *See* 55 *Federal Register* 20568 (May 17, 1990); 56 *Federal Register* 14620 (April 10, 1991).

The Petition argues that the APA disallows this evolution in FDA's thinking about silicone gel-filled breast implants, relying on several cases that have found agency action to be arbitrary and capricious under section 706 of the APA because the agency failed to explain changes from precedent using "reasoned decision-making." These cases considered departures from final agency requirements or positions, *see Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29 (*safety restraint requirements*); *Wisconsin Valley Imp. Co. v. FERC*, 236 F. 3d 738 (D.C. Cir. 2001) (*license renewal*); *Puerto Rico Higher Educ Assistance Corp. v. Riley*, 10 F.3d 847 (D.C. Cir. 1993) (*waiver of funds recovery provision of Higher Education Act*); *Dart v. US*, 848 F.2d 217 (D.C. Cir. 1988) (*imposition of civil sanctions*). The major deficiency and not approvable letters, however, represented FDA's interim reviews of the Mentor and Inamed PMAs. Importantly, both of these letters solicited additional information, demonstrating that the decision process remained open.[63]

Similarly, the Petition challenges changes in FDA's data recommendations from those articulated in the Draft Guidance. The agency issues draft guidance documents for the express purpose of soliciting comments that may result in changes to the agency's position in the final guidance.[64] Since issuance of the Draft Guidance, FDA has re-evaluated previous recommendations, notably the recommendation that PMAs for silicone gel-filled breast implants contain data supporting an estimated rupture rate over the life of the device, in light of information submitted by Mentor and Inamed and the discussion of the April 2005 Panel. FDA determined that, in the absence of long-term clinical data showing an unreasonable risk of illness or injury, clinical data showing a low rupture rate in the short term and preclinical data showing no failure due to inherent material or design flaws through approximately ten years were sufficient to support approval. FDA documented this evolution in thinking in review memoranda in the record.[65] This record demonstrates that, in amending its data expectations from those contained in the Draft Guidance, FDA engaged in "a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored." *Springfield v. Buckles*, 292 F.3d 813 (D.C. Cir. 2002) *quoting Great Boston Television Corp. v. FCC*, 444 F.2d 841, 852 (D.C. Cir.), *cert. denied*, 403 U.S. 923 (1971); *see also Alpharma v. Leavitt*, 460 F.3d 1, 11 (D.C. Cir. 2006) (*discussing the standard of reasoned decision-making in the context of an FDA approval decision*).

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[63] The Petition argues that the data provided by Mentor and Inamed just months after the issuance of the January 2004 guidance could not be adequate because it was submitted so soon after the guidance was released (Petition at 10, 12-14). FDA does not communicate outstanding issues to a PMA sponsor via guidance documents. FDA communicates outstanding issues via direct informal and formal communication. For the Mentor and Inamed PMAs, FDA communicated directly with the sponsors, often requesting and receiving additional information. Thus, the sponsors were aware of many of the outstanding issues FDA had with the PMAs before issuing the deficiency letters and the guidance document. Apart from data used to characterize rupture rate, data necessary to respond to these letters, such as additional information to address outstanding issues with regard to the preclinical testing, should have been readily available to or developed in a reasonable timeframe by the sponsors. Concerning rupture rate, the combination of additional data and the agency's re-evaluation of its earlier approach sufficed to address FDA's concerns.

[64] *See* 21 C.F.R. 10.115 for a description of FDA's good guidance practices.

[65] *See* Memorandum of the Director of the Office of Device Evaluation, Mentor review, Inamed Review [11/15/06]

2. April 2005 Panel Meeting

The discussion during the April 2005 Panel meeting figured prominently in FDA's review of both PMAs. The Petition argues that the recommendations of the April 2005 Panel of approvable for the Mentor PMA and not approvable for the Inamed PMA are inconsistent and that only the recommendation concerning Inamed comports with FDA's past treatment of silicone gel-filled breast implants. In light of new data and other changes to the Inamed PMA following the April 2005 Panel, FDA's decisions to approve both PMAs are appropriate and consistent with discussions of the Panel.

3. Inamed's Post-Panel Submissions

As explained above, discussions during the April 2005 Panel meeting showed that a significant concern of many members was the inclusion of the Style 153 implant in Inamed's PMA, reflecting in part the higher rupture rate associated with this model. FDA shared the Panel's concerns about the Style 153; however, Inamed addressed these concerns by excluding the Style 153 implant from consideration. Inamed addressed other concerns of the Panel by submitting long-term data from the company's International MRI study and nonclinical data. FDA's approval decision, then, does not reflect a failure to consider the Panel's recommendation that FDA deny approval to Inamed but an evaluation of that recommendation in light of significant changes in Inamed's submission to address the concerns of the Panel and FDA.

FDA's consideration of information submitted by Inamed after the April 2005 Panel meeting is proper. Petition Supplement 2, however, suggests FDA's history of openness in decision-making about breast implants binds the agency to public processes with heightened review requirements in evaluating the new Inamed data. Important components of FDA's decision to approve the Inamed PMA were public in that the April 2005 Panel discussions provided the framework for FDA's reevaluation of the rupture data needed to assess the safety of Inamed's product and specified the types of additional data necessary to make that assessment. Similarly, FDA issued its major deficiency letter to Mentor on April 14, 2004 without bringing the PMA to Panel because we determined that the issues most relevant to that review decision were not unique to the Mentor PMA and had been discussed at the 2003 Panel meeting. In any case, neither the APA nor the FDC Act require the agency to withhold a decision reflecting new information about a product until a new Panel can consider the information; indeed, the decision whether to present a PMA to a single Panel is generally within FDA's discretion, see FDC Act 515(c)(3), and Panel recommendations may result in the submission of additional data and information that the agency considers without seeking additional Panel input. Nor do these authorities require FDA to solicit public comment on review decisions, which remain confidential during review under FDA's regulations.[66] The only requirement these authorities impose is that FDA consider recommendations of that Panel in a reasoned approach to evaluating the PMA, a requirement FDA complied with by carefully evaluating the panel's recommendations for each PMA as part of the reasoned decision-making process that led to the approval of both PMAs.

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[66] *See* 21 C.F.R. § 814.9; 21 C.F.R. Part 20.

III. CONCLUSION

In conclusion, the Mentor and Inamed PMAs contain adequate data to support approval. The approvals reflect FDA's careful consideration of this data in light of the agency's extensive review experience with these devices. Although FDA's views of the types of data needed to meet the statutory standard for approval have evolved in response to new data and new approaches to evaluating the data, the agency has consistently adhered to the standard of reasonable assurance of safety and effectiveness and to a reasoned process of decision-making in determining whether the standard has been met. Accordingly, the approvals are consistent with the requirements of the FDC Act and the APA. For all the reasons discussed above, your Petition and Petition Supplements 1 and 2 are denied.

If you have any questions about this response, please contact Ms. Myrna Hanna of our Regulations Staff at (240) 276-2347.

Sincerely yours,

Linda S. Kahan

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Center for Devices and Radiological Health