FDA Executive Summary

Breast Implant Special Topics

Prepared for the Meeting of the

General and Plastic Surgery Devices

Advisory Panel

March 25 and 26, 2019

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I. Purpose of Meeting

As required by section 513(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Food and Drug Administration (FDA) is convening the General and Plastic Surgery Devices Advisory Panel (the Panel) for the purposes of discussing the long-term benefits and risks of breast implants for achieving breast augmentation and reconstruction.

II. Structure of Meeting

The panel meeting will be held over a period of two consecutive days and includes time for open public comment, questions by the panel, and panel deliberation.

The first day of the panel meeting will focus on the currently available information regarding Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) and systemic symptoms which are described as Breast Implant Illness (BII) and how best to leverage registries to improve understanding of BIA-ALCL and BII.

The second day of the panel meeting will focus on the use of surgical mesh in breast reconstruction and mastopexy, the utility of MRI screening in breast implant silent rupture, and how all stakeholders can work together to improve breast implant patient education and informed consent.

III. Introduction

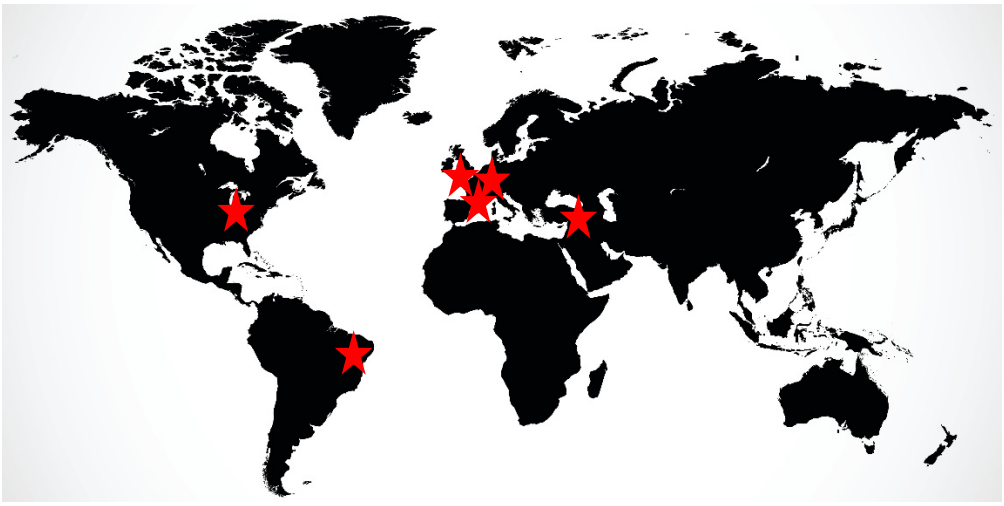
While the benefits of breast implants for reconstruction following mastectomy and for augmentation are generally recognized, there is patient concern related to incomplete or absent discussions around breast implant risk. Things that they may not know are that:

- Breast implants are not lifetime devices and the longer a patient has the implants, the more likely they are to experience local complications and adverse outcomes requiring breast implant removal.
- Local complications and adverse outcomes include capsular contracture, reoperation, removal, and implant rupture. Many patients also experience breast pain, wrinkling, asymmetry, scarring and infection.
- Breast implants are associated with BIA-ALCL, a cancer of the immune system. While most patients with BIA-ALCL may be treated only with breast implant removal, some patients have required radiation therapy, chemotherapy or both, and some patients have died from BIA-ALCL.
- At the present time, there is not sufficient evidence to show an association between breast implants and rheumatologic or connective tissue disease diagnoses. However, there are numerous breast implant patients convening on social media to discuss a wide variety of symptoms that they are experiencing--symptoms which may or may not meet the diagnostic criteria to be categorized as a disease. These patients refer to their symptoms collectively as “breast implant illness (BII)”.
- Breast reconstruction often involves the implantation of not only a breast implant device but also a surgical mesh device. The benefit of implanting a surgical mesh as part of the breast reconstruction operation has not been characterized.

In light of the growing science around these issues regarding breast implants, we are holding a public meeting of the General and Plastic Surgery Devices Panel of our Medical Devices Advisory Committee to ensure that patients and health care providers continue to have accurate, scientifically sound information.

The timing of this meeting occurs against the backdrop of several notable regulatory actions taken by governments worldwide over this past year.

Figure 1: Worldwide regulatory activities



In July 2018 the Medicines and Healthcare Products Regulatory Agency (MHRA) in the **United Kingdom** indicated that they had established an independent expert advisory group, the Plastic, Reconstructive and Aesthetic Surgery Expert Advisory Group (PRASEAG).

In December 2018, Allergan Corporation was denied 5-year renewal of their CE Mark for distribution of textured implants. Their Biocell textured implants have now been recalled in all **33 countries of Europe**, as well as **Israel** and **Brazil**.

In response to recalls in Europe, the **French** National Agency for Medicines and Health Products Safety convened international experts and regulators a 2-day public conference in February 2019 to discuss the safety of textured breast implants and released their conclusions in a public statement.

In March 2019, the **United States** issued warning letters to Mentor Worldwide and Sientra because of their failure to fulfill their breast implant post-approval study requirements.

The FDA is committed to thoughtful, scientific, transparent, public dialogue concerning breast implant safety and effectiveness and looks forward to a productive discussion.

IV. Background

A. Description of Approved Breast Implants

Breast implants are medical devices that are implanted under the breast tissue or under the chest muscle to increase breast size (augmentation) or to replace breast tissue that has been removed due to cancer or trauma or that has failed to develop properly due to a severe breast abnormality (reconstruction). They are also used in revision surgeries, which correct or improve the result of an original surgery. For both augmentation and reconstruction, breast implants can either be placed on top of the chest muscle (subglandular or pre-pectoral placement) or underneath part or all of the chest muscle (submuscular placement).

There are two types of breast implants currently approved for sale in the United States: saline-filled and silicone gel-filled. The shell for both types of implants is manufactured from polysiloxane silicone rubber and may vary in shell surface, shape, profile, volume, and shell thickness.

A saline-filled breast implant is inflated to the desired size with sterile isotonic saline. There are currently three designs for saline-filled breast implants: (1) a fixed volume implant with a single lumen that is intraoperatively filled with the entire volume of saline via a valve; (2) an adjustable volume implant with a single lumen that is intraoperatively filled with saline via a valve and has the potential for further postoperative adjustment of the saline volume; and (3) a device composed of several shells including an inner shell that is pre-filled, and outer shell(s) that are filled intraoperatively. There is currently a single design for silicone gel-filled breast implants: a single lumen containing a fixed volume of silicone gel. Silicone gel viscosity differs among implants and manufacturers.

Breast implants are manufactured with smooth and textured surfaces. Each breast implant company utilizes a proprietary manufacturing process to create the textured surface. In general terms, the surface texture is added to the smooth surface by either a stamping process or by introducing a layer of salt on the implant and then dissolving the salt leaving a textured surface (Webb et al., 2017). The different manufacturing methods create differences in the degree of porosity, complexity and depth of texturing at the surface of the implant. There are hypotheses that propose a link between breast implant texturing and BIA-ALCL. Additional hypothesized risk factors include genetic predisposition, and chronic inflammation and biofilm formation around the breast implant. Although the pathogenic mechanism of BIA-ALCL has not been determined, some regulatory bodies, plastic surgery societies, plastic surgeons and patients are advising against the use of textured breast implants and in some cases specifically textured breast implants using the salt loss process. Some surgeons advocate for the use of a multi-point plan designed to reduce biofilm formation (Adams et al., 2017).

Currently eight breast implants have been approved by the FDA through the premarket approval (PMA) application process: three saline-filled breast implants and five silicone gel-filled breast implants. Breast implants approved by the FDA are listed in Table 1.

Table 1: Breast implants approved by the FDA

PMA Number	Date of PMA Approval	Device Name	Implant Fill and surface type	SSED link
Allergan P990074	5/10/00	Natrelle Saline- Filled Breast Implants	Saline Smooth and Textured – Allergan BIOCELL® using Salt Loss Process	https://www.accessdata.fda.gov/cdrh_docs/pdf/P990074B.pdf
Mentor P990075	5/10/00	Mentor Saline- Filled and Spectrum Breast Implants	Saline Smooth and Textured – Mentor SILTEX® using Stamping Process	https://www.accessdata.fda.gov/cdrh_docs/pdf/P990075B.pdf
Allergan P020056	11/17/06	Natrelle Silicone-Filled Breast Implants	Silicone Gel Smooth and Textured – Allergan BIOCELL® using Salt Loss Process	https://www.accessdata.fda.gov/cdrh_docs/pdf2/P020056B.pdf
Mentor P030053	11/17/06	Mentor MemoryGel Breast Implants	Silicone Gel Smooth and Textured – Mentor SILTEX® using Stamping Process	https://www.accessdata.fda.gov/cdrh_docs/pdf3/P030053B.pdf
Allergan P040046	2/20/13	Natrelle® 410 Highly Cohesive Anatomically Shaped Silicone- Filled Breast Implants	Silicone Gel Textured – Allergan BIOCELL® using Salt Loss Process	https://www.accessdata.fda.gov/cdrh_docs/pdf4/P040046B.pdf
Mentor P060028	6/14/13	Mentor MemoryShape Breast Implants	Silicone Gel Textured – Mentor SILTEX® using Stamping Process	https://www.accessdata.fda.gov/cdrh_docs/pdf6/P060028B.pdf
Sientra P070004	3/9/12	Sientra OPUS™ Silicone Gel Breast Implants	Silicone Gel Smooth and Textured – Using Salt Loss Process	https://www.accessdata.fda.gov/cdrh_docs/pdf7/P070004B.pdf
IDEAL P120011	11/14/14	IDEAL IMPLANT® Structured Breast Implant	Saline smooth	https://www.accessdata.fda.gov/cdrh_docs/pdf12/P120011B.pdf

B. Status update on Breast Implant Post-Approval Studies since the 2011 Breast Implant-Advisory Committee

In 2011 the FDA held a meeting of the General and Plastic Surgery Devices Panel of the Medical Devices to discuss the postmarket experience with the silicone gel-filled breast implants and the limitations of these studies. At that time, most of the postmarket Conditions of Approval from the 2006 silicone gel-filled breast implant approvals were fulfilled with the exception of the *Large Studies, Case Control* and the *Device Failure Analyses*.

Due to low patient follow-up (60.5% at 2 years for Allergan and 21.1% at 3 years for Mentor) for the Large Studies, the Panel recommended re-designing the studies with more efficient methodologies and to assess rare outcomes using a systematic literature review to summarize the state of the literature on specific safety outcomes in women with silicone gel-filled breast implants.

FDA participated in an advisory panel that helped develop the protocol used to conduct the Tufts systematic literature review. This review included 32 studies from 58 publications encompassing patients from 1964 to 2003 with up to 27-year follow up (Balk et al., 2016). The review showed inconclusive evidence of an association between silicone breast implants and lymphoma, brain cancer, cervical cancer, rare connective tissue diseases (CTDs), or rare neurological events. The 2016 Tufts review findings were consistent with both the 1999 Institute of Medicine's comprehensive report (IOM, 1999) and the Judge Pointer report (Tugwell et al., 2001).

Table 2 shows the original and redesigned post-approval studies (PAS) for all breast implants which have not completely fulfilled the PAS requirements of their PMAs. In several instances, the original PAS was subsequently redesigned. In the table below, the PMA numbers for studies which required redesign are flagged with an "**X**". The PMA numbers of studies which are out of compliance are in ***bold italics***.

Table 2: Summary of breast implant post-approval studies

Original PAS Requirements*	**Objective**	**Manufacturer / PMA Number**	**Status**	**Redesigned Studies**
Case Control	Determine whether there is an association between rare diseases and breast implants	Allergan P040046 Mentor P060028 Sientra P070004	Study terminated based on Tufts Literature Review	
Large PAS	Collect long term safety data on the following endpoints: local complications, CTD, CTD signs and symptoms, neurological disease, neurological signs and symptoms, reproductive complications, cancer, suicide	Allergan P020056 **X** Mentor P030053 **X**	Replaced by Allergan Breast Implant Follow-up and Re-Op Studies / Mentor Glow and Re-Op Studies	**Breast Implant Follow Up** Allergan P020056 Allergan P040046
				Glow ***Mentor P030053*** ***Mentor P060028***
				Re-Operation Allergan P020056 Mentor P030053
Continued Access	Continue collecting safety data on all pre-market safety and effectiveness endpoints	Allergan P040046 Mentor P060028 Sientra P070004	Complete – safety and effectiveness data added to labeling	

Original PAS Requirements*	Objective	Manufacturer / PMA Number	Status	Redesigned Studies
Adjunct	Collect data on the following complications: device rupture, capsular contracture, reoperations involving the breast/chest area (e.g., implant replacement/removal)	Allergan P020056 Mentor P030053	Complete – safety and effectiveness data	
Focus Group studies	Evaluate patient comprehension of information the patient labeling	Allergan P020056 Allergan P040046 Mentor P030053 Mentor P060028 Sientra P070004	Complete – P020056 and P030053 labeling revised based on study findings, no updates recommended for P040046, P060028 and P070004	
Informed decision process	Evaluate the success of the Informed Decision Process.	Allergan P020056 Mentor P030053	Complete – patient informed consent survey no longer required	
Core Study 10-year follow-up	Continued to evaluate the effectiveness endpoints including chest size change, patient satisfaction, and quality of life; and safety endpoints includes complication rates, reasons for re-operation and implant removal	Allergan P020056 Allergan P040046 Mentor P030053 Mentor P060028 Sientra P070004	Complete – labeling revised based on study findings	
		IDEAL P120011	Ongoing	
US-PAS	Evaluate the long-term clinical performance of breast implants under the general conditions of use in the post-market environment including patient satisfaction, quality of life and the following safety endpoints: connective tissue diseases (CTDs), rheumatologic and neurologic signs and symptoms, cancer, suicide/attempted suicide, local complications, reoperation and implant removal, reproductive complications	***Sientra P070004***	Ongoing	
Device Failure	To better understand possible modes of gel implant failure in vivo	Allergan P020056 Allergan P040046 Mentor P030053 Mentor P060028 Sientra P070004	Ongoing	

*2006 Requirements for Allegan and Mentor, 2012 Requirements for Sientra, 2014 Requirements for IDEAL

C. Additional Breast Implant Data Collection

Breast implant post-approval studies designed at the time of device premarket approval to follow patients longitudinally and answer our long-term questions have been unreliable. Poor compliance and changes in surgical practice over time have produced results difficult to interpret in a generalized manner much less with the precision needed to deliver personalized patient care.

Table 3 describes existing data collection methods available in the U.S. which may over time prove suitable to supplement and possibly replace postapproval studies.

D. For Panel Deliberation

The Panel will be asked to discuss how best to modify and utilize breast implant registries for data generation characterizing longitudinal outcomes to better inform patient care.

Table 3: Existing Data Collection Methods Related to Breast Implants in the U.S.

	The National Breast Implant Registry (NBIR)	The Patient Registry and Outcomes For Breast Implants and anaplastic large cell Lymphoma (ALCL) etiology and Epidemiology (PROFILE)	Medical Device Reports (MDRs)	ICOR International Collaboration of Breast Registry activities (ICOBRA)
Website	https://www.thepsf.org/research/registries/nbir	https://www.thepsf.org/research/registries/profile	https://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm	http://www.plasticsurgeryfoundation.org.au/news/
Initiated	September 2018	August 2012	1976	2012
Coordinating Center	The Plastic Surgery Foundation	The Plastic Surgery Foundation	U.S. FDA	Australasian Foundation for Plastic Surgery
Collaborating Groups	U.S. FDA Breast implant device manufacturers	U.S. FDA American Society of Plastic Surgeons	N/A	Governments, Notified Bodies and other Stakeholders across 15 countries
Principal Investigators	Andrea Pusic, MD, MS Charles N. Verheyden, MD, PhD	Colleen McCarthy, MD Benjamin Eloff, PhD Nilsa Loyo-Berrios, PhD	N/A	N/A
Participating Sites	Any site performing breast implant procedures is invited	Any physicians whose patient with breast implants has a suspected or confirmed case of BIA-ALCL	N/A	N/A
Data entered by	Plastic Surgeons	Any physician in the US	Anyone including, but not limited to, manufacturers, importers, health care professionals, patients and consumers	N/A
Data collected	Clinical, procedural, and outcomes data from initial breast implant operation and any subsequent breast implant reoperations	Demographic, and clinical characteristics of patients diagnosed with BIA-ALCL	Suspected medical device-associated deaths, serious injuries, and malfunctions	Data collection, analysis and governance best practices for breast implant registries
Voluntary/ Mandatory	Voluntary	Voluntary	Mandatory for manufactures, importers and device user facilities; Voluntary for everyone else	N/A
Data Analysis	Plastic Surgeons that enter the data into NBIR are able to compare their practice performance and outcomes to the registry aggregate	Enumeration and descriptive analysis of BIA-ALCL epidemiology	Monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products.	N/A
Countries	United States	United States	Required for mandatory reporters in the United States. MDRs for outside US events are required if the event involves a device that is the same or similar to a device that has been cleared or approved for marketing in the U.S.	15 countries including the United States

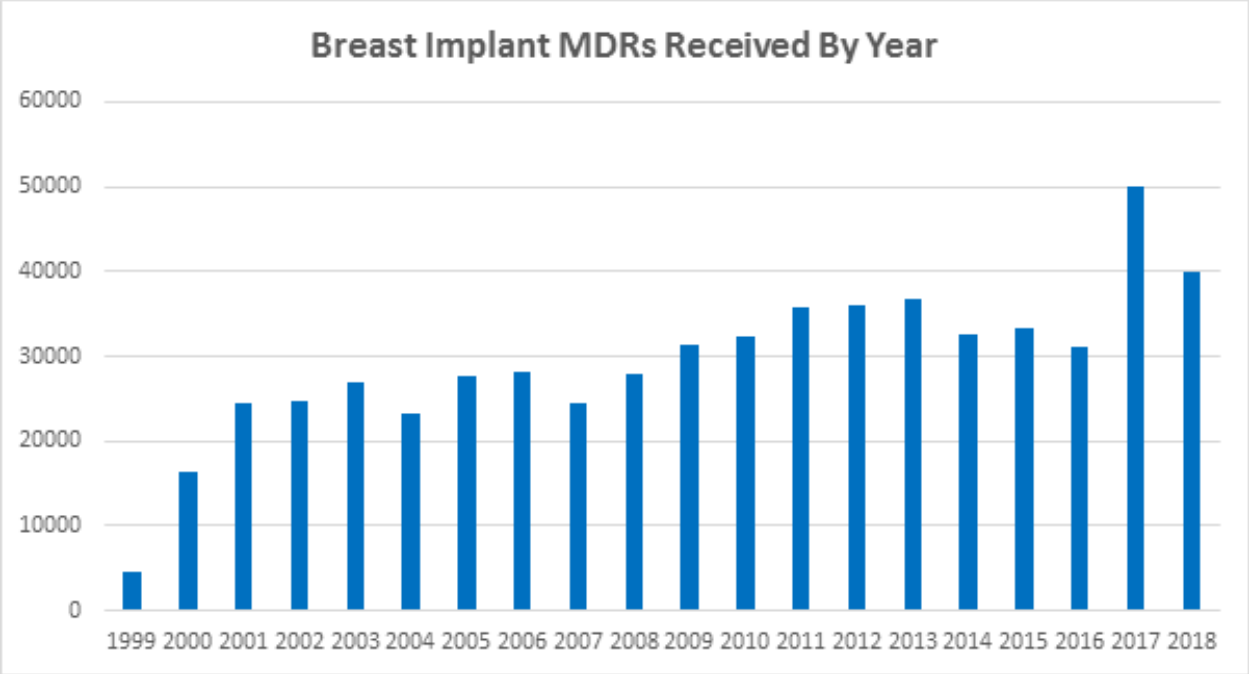
V. Current Concerns About Breast Implants

A. Medical Device Reports (MDR)

The MDR system provides FDA with timely information on medical device performance from patients, providers, and manufacturers. The FDA uses MDRs to monitor postmarket device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of devices. While the MDR system is a valuable source of information, this passive surveillance system has limitations, including incomplete, inaccurate, untimely, unverified, or biased data in the reports.

In recent years, the number of Breast Implant MDRs have increased. This increase in reports over time and the spike noted in 2017 may be due to a combination of factors, including but not limited to better awareness of how to report device issues to FDA.

Figure 2: Total MDR Reports Received Per Year



B. Breast Implant-Associated Anaplastic Large Cell Lymphoma

Background

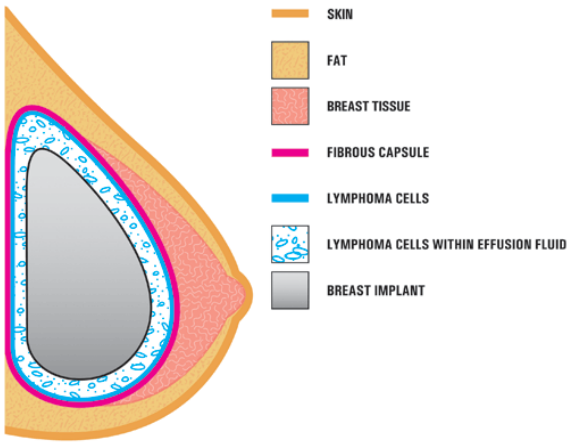
In 2011, the FDA identified a possible association between breast implants and the development of anaplastic large cell lymphoma (ALCL). At that time, the FDA knew of so few cases of ALCL that it was not possible to determine what factors increased a patient's risk. In a report summarizing the Agency's findings, we emphasized the need to gather additional information to better characterize ALCL in individuals (cis- and trans-gender women and men) with breast implants.

Over time, we have strengthened our understanding of this condition. In 2016, the World Health Organization (WHO) designated breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) as a T-cell lymphoma that can develop following breast implants (Swerdlow et al., 2016). The exact

number of cases remains difficult to determine due to significant limitations in world-wide reporting and lack of global breast implant sales data (de Boer et al., 2018).

Clinically, BIA-ALCL typically originates in the capsule around breast implants and presents as a fluid collection or tumor adjacent to the implant surface.

Figure 3: BIA-ALCL illustration



The National Comprehensive Cancer Network established BIA-ALCL diagnosis and treatment guidelines in 2017 and recommends ultrasound and peri-prosthetic fluid collection by needle aspiration for diagnostic work up. Treatment includes surgical implant removal with excision of the fibrous implant capsule and any fluid or tumor present. Some patients additionally require radiation or chemotherapy, and targeted immunotherapy has been reported.

The American Society of Plastic Surgeons reports that there are 673 worldwide cases of BIA-ALCL as of January 16, 2019 (ASPS, 2019), with 16 disease-related deaths (ASPS, 2018). Incidence estimates are highly variable but range from roughly 1:3,000 to 1:30,000 patients with textured implants (Clemens et al., 2017; de Boer et al., 2018; Loch-Wilkinson et al., 2017). While the majority of cases have been reported around textured implants, case reports exist in women with smooth implants, and much of the data in MDR reports is incomplete. BIA-ALCL may occur around saline or silicone breast implants.

Table 4 presents MDR data as originally received and tabulated as of September 30, 2018. Since September 30, 2017, 246 new MDRs were received, resulting in a cumulative total of 660 MDRs for BIA-ALCL.

To further analyze these data, FDA staff carefully reviewed any MDR with mention of “ALCL” or other spelling variations (e.g. anaplastic lymphoma, large cell lymphoma) in the event narrative to identify potential BIA-ALCL cases. Duplicate reports were removed, and reports were included as a report of BIA-ALCL only if they met one of the following criteria: diagnosis confirmed by a physician, diagnosis confirmed by positive pathology/cytology test results, or diagnosis confirmed as positive for biomarker CD30 and negative for biomarker ALK. The resulting dataset is presented in Table 5.

These data reflect a total of 457 distinct MDRs for BIA-ALCL. There were 9 deaths identified from 12 individual MDRs (i.e., three women had bilateral implants). FDA staff identified 334 reports that

provided information on the implant surface. Of these, 310 concerned textured implants and 24 concerned smooth implants. All 457 reports included the implant fill type. There were 274 reports on silicone gel-filled implants, and 183 reports on saline-filled implants.

Due to missing data, it is not possible to be confident of the distribution of patient and device characteristics in either data set. However, the FDA believes that the data in Table 5 more accurately reflect the number of MDR reports of BIA-ALCL cases (457) and deaths (9). It is crucial to understand that we do not know whether this dataset reflects the distribution of BIA-ALCL cases. In most of these reports the full patient history of prior implants, including the implant surface type and the tissue expander surface type, is unknown. Information on the numbers of implants with each surface type that have been implanted is not available, so it is not possible to calculate and compare rates of BIA-ALCL in smooth surface versus textured surface implants. MDR is a method of **passive** surveillance, because it accepts reports, but does not actively interview every patient and manufacturer for information. Therefore, FDA cannot use MDR data to state with certainty how many patients have been diagnosed with BIA-ALCL. Secondly, it is impossible to determine what percentage of patients who have received a breast implant have been diagnosed with BIA-ALCL, because there is no definitive accounting of the total number of breast implants. This is why MDRs comprise only one of FDA's **current postmarket surveillance efforts.**

Table 4: Summary of Originally Received MDR Data as of September 30, 2018 (N = 660)

		n	%[a]
Age at time of diagnosis (years)	Median	53	-
	Range	24 - 90	-
	Not specified (# of reports)	240	36
Time from the last implant to diagnosis[b] (years)	Median	8.5	-
	Range	0 - 44	-
	Not specified (# of reports)	231	35
Implant Surface	Textured	425	64
	Smooth	39	6
	Not specified	196	30
Implant Fill	Silicone	399	60
	Saline	260	39
	Not specified	1	0
Reason for Implant	Reconstruction	119	18
	Augmentation	125	19
	Not specified	416	63
Clinical presentation (breast)[c]	Seroma	350	53
	Breast swelling/pain	188	28
	Capsular contracture	75	11
	Peri-implant mass/lump	85	13
	Others	226	34
	Not specified	187	28
Anaplastic lymphoma kinase (ALK)	Positive	0	0
	Negative	239	36
	Not specified	421	64
CD30 Status	Positive	239	36
	Negative	0	0
	Not specified	421	64

[a] Percentage in terms of the total 660 MDRs

[b] Includes physician- pathology-, or biomarker-confirmed diagnosis

[c] MDRs sometimes list more than one clinical presentation, e.g. seroma and peri-implant mass/lump, in which case two presentations were counted.

Table 5: Summary of Filtered MDR Data as of September 30, 2018 (N=457)

		n	%[a]
Age at time of diagnosis (yrs)	Median	53	-
	Range	27-90	-
	Not specified (# of reports)	111	24
Time from the last implant to diagnosis[b] (yrs)	Median	9.0	-
	Range	0-34	-
	Not specified (# of reports)	110	24
Implant Surface	Textured	310	68
	Smooth	24	5
	Not specified	123	27
Implant Fill	Silicone	274	60
	Saline	183	40
	Not specified	0	0
Reason for Implant	Reconstruction	108	24
	Augmentation	104	23
	Not specified	245	54
Clinical presentation (breast)[d]	Seroma	266	58
	Breast swelling/pain	135	30
	Capsular contracture	69	15
	Peri-implant mass/lump	82	18
	Rupture/deflated	54	12
	Others	43	9
	Not specified	105	23
Anaplastic lymphoma kinase (ALK)	Positive	0	0
	Negative	229	50
	Not specified	228	50
CD30 Status	Positive	215	47
	Negative	0	-
	Not specified	242	53

[a] Percentage in terms of the total 457 MDRs

[b] Includes physician- pathology-, or biomarker-confirmed diagnosis

[c] MDRs sometimes list more than one clinical presentation, e.g. seroma and peri-implant mass/lump, in which case two presentations were counted.

PROFILE registry reports

From August 2012 to March 2018, a total of 186 distinct cases of BIA-ALCL in the United States were reported to PROFILE. At the time of this present analysis, complete initial detailed case report forms have only been received for 89 (48%) cases. Efforts to collect data on the remaining 97 (52%) reported cases are ongoing. Of the 89 cases with available data, implant filler was reported as saline in 39 women (44%) and silicone in 46 (52%). One patient had a combined saline/silicone implant. In 3 patients, fill type was not reported. At the time of diagnosis, 69 patients (78%) had an implant with a textured shell; in 5 cases (6%) the implant type was smooth. In 15 (16%) cases the texture of the device was not reported (Colleen M. McCarthy et al., 2019).

C. For Panel Deliberation

The panel will be asked to make recommendations regarding next steps for the characterization of BIA-ALCL incidence and its risk factors

D. Systemic Symptoms – Breast Implant Illness

Background

Reports have been published that suggest an association between breast implants and rheumatologic conditions. Recently, Watad et al. (Watad, Rosenberg, et al., 2018) examined electronic health records from 20 years of data involving 2 million patients and detected a significant increase in rheumatologic conditions in women with silicone breast implants compared to age and socio-economic status matched controls. Similarly, symptoms and diagnoses related to rheumatologic conditions and connective tissue disorder have been referred to as breast implant illness (BII) by breast implant patients and the public (Tang et al., 2017). While there is limited use of this term in literature, it is more commonly used by breast implant patients and used during reporting of adverse events through FDA's Medical Device Reporting (MDR) system, as described below.

MDRs

FDA conducted a query of the MDR database for all reports posted between January 1, 2008 and October 31, 2018 referring to a saline- or silicone-filled breast prosthesis with the search terms listed in Table 6. The search terms used represent the various symptoms patient groups refer to as "Breast Implant Illness (BII)". It is important to note that, while the MDR system is a valuable source of information, this passive surveillance system has limitations, including incomplete, inaccurate, untimely, unverified, or biased data in the reports. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting, duplicate reporting of events, and the lack of information about the total number of breast implants. These data provide insights into the extent of patient-reported BII symptoms, especially considering that some symptoms are not MDR reportable events.

Table 6: Search Terms Relevant to BII

acid reflux	easy bruising	inflammation	premature aging
adrenal	EBV	Insomnia	rash
allergy	fibromyalgia	intoleran*[a]	Raynaud
allergies	fog	joint	reflux
anxiety	frequent urination	joint pain	rheumatoid arthritis
arthritis	gallbladder	kidney	scleroderma
autoimmune	gastritis	leaky gut	shortness of breath
candida	Fatigue	libido	SIBO
chest discomfort	fever	liver	sick
choking	gastrointestinal issues	lupus	sinus
cold		Lyme disease	Sjogren
connective tissue	GERD	memory loss	sleep
cough	GI issues	menopause	slow healing
dehydration	hair loss	metallic taste	slow muscle recovery
depression	Hashimoto	migraine	throat clearing
difficulty swallowing	headaches	multiple sclerosis	thyroid
	heart pain		tingling
dry eyes	heart palpitations	muscle pain	toxic
dry hair	heart rate	night sweats	toxic shock
dry skin	hormone	numbness	urinary tract
dying	hysterectomy	pancreatitis	vertigo
ear ringing	IBS	panic attack	weight
early menopause	illness	parathyroid	yeast

[a] Use of the * wildcard will capture all words that begin with "intoleran," including intolerance and intolerant

This search resulted in 1,328 related MDRs, the majority of which were reported by voluntary reporters (n=851, 62%) rather than manufacturers. The reports concerned health issues in both breast implant patients and children born to them. A total of 765 MDRs reported patient ages ranging from 9 years to 76 years, with an average of 43 years. Only 969 MDRs provide sufficient information to determine the time interval between implantation and the development of symptoms. This time ranged from <1 month to 38 years, 9 months, with an average of 5 years, 2 months.

Implant and explant dates are provided in 565 MDRs. The time to explant ranges from <1 month to 40 years, 10 months, with an average of 9 years, 7 months. There are 101 MDRs reporting improvement in symptoms after explant. However, incomplete information provided in MDRs regarding what patients perceived as improvement in symptoms or the time course for improvement made further analysis impossible.

Table 7: Summary of "BII" MDR reports

N = 1328	
Deaths	8 reports (4 deaths)
Injuries	1311
Silicone gel filled breast implant	693
Saline filled breast implant	624
Both saline and silicone gel filled breast implant	11
Explant and implant dates provided	565
Time to explant	Range: <1 month to 40 years, 10 months Mean: 9 years, 7 months

Table 8: Top 5 reported symptoms of BII.

BII Symptoms	#MDRs
Fatigue	630
Brain Fog	305
Rash	266
Joint Pain	256
Memory Loss	149

Rheumatologic Signs and Symptoms from Post-Approval Studies

The mandatory manufacturer-led post-approval studies were designed to evaluate the long-term safety of breast implants, including the possible association with rheumatologic conditions. To evaluate the association of breast implants with symptoms of breast implant illness, FDA requested that each manufacturer provide data from their post-approval studies describing patient reports of the numerous symptoms being reported as breast implant illness. It is important to note that study protocols were different for each manufacturer, and therefore, the results are not comparable across studies. The results from each post-approval study are presented below along with a summary of the protocols, but a brief comparison is provided here to highlight the unique features and limitations of each study.

- Allergan referenced the Breast Implant Follow Up Study, which follows a 2,257-patient subset of the original Large Post Approval study cohort of >40,000 patients
- Mentor referenced their Large Post Approval Study cohort with 14.6% follow up rate.
- Sientra referenced the final 10-year results from their premarket core study with 51% follow up rate.
- IDEAL referenced their ongoing core study postmarket continuation, which does not require reporting of symptoms, but requires reporting of all patients referred to a rheumatologist.

For all of the studies, in the case that a single patient reported more than one symptom, each symptom was counted individually in the tables below.

Allergan Reporting of Signs and Symptoms

The following limitations apply to the Allergan Large Post-Approval Study (LPAS): The redesigned Allergan post-approval study, Breast Implant Follow up Study (BIFS) selected 2000 silicone and 257 saline patients from the original cohort of >40,000. These patients were selected because they had been compliant with annual patient questionnaires by year 4 and may represent a biased sample of the original cohort. Every patient has now surpassed 7 years of follow up, with an overall 78% follow up rate. The original study cohort is used as the denominator, regardless of follow-up, because of the reporting method used. Table 9 provides data through 10 years with occurrence expressed as percentage of patient reports at any time period after implantation but not present at baseline. Symptoms listed here are the subset of 19, from the original 95 questions, that are most similar to the BII symptoms from MDR reports.

Table 9: Allergan patient reports of symptoms (P020056)

	Primary Augmentation		Revision Augmentation		Primary Reconstruction		Revision Reconstruction	
Changes in Signs and Symptoms	RR* **n = 1519**	S* **n = 218**	RR **n = 209**	S **n = 20**	RR **n = 250**	S **n = 12**	RR **n = 22**	S **n = 7**
Aching of the arms and legs and arthritis in the hands and wrists	9.2%	7.3%	19.1%	30.0%	17.6%	41.7%	18.2%	0
Achy joints arthralgia	10.1%	9.6%	16.7%	10.0%	25.6%	25.0%	22.7%	57.1%
Arthritis	5.3%	4.1%	12.9%	10.0%	18.8%	33.3%	9.1%	14.3%
Burning, tingling, or numbness in the fingers, toes, hands or feet	11.7%	8.7%	20.1%	15.0%	18.8%	25.0%	13.6%	14.3%
Changes in ability to think or learn	5.3%	2.8%	8.6%	5.0%	7.2%	16.7%	18.2%	14.3%
Confusion	2.2%	0	3.8%	5.0%	2.4%	0	9.1%	0
Difficulty Concentrating	8.9%	6.4%	9.1%	5.0%	11.2%	16.7%	22.7%	14.3%
Difficulty speaking or understanding what is being said	1.9%	0.9%	3.8%	0	2.4%	0	18.2%	14.3%
Difficulty walking or manipulating small objects	1.0%	0	1.0%	5.0%	2.4%	0	4.5%	14.3%
Dry Eyes	10.3%	8.3%	17.7%	10.0%	20.0%	33.3%	9.1%	42.9%
Dry Mouth	4.2%	4.1%	7.2%	5.0%	10.8%	16.7%	4.5%	0
Extreme Muscle Weakness	2.0%	0.9%	3.3%	5.0%	3.6%	8.3%	4.5%	0
Generalized aching or stiffness of the joints and muscles, especially after sleep or after periods of rest	10.7%	8.7%	14.8%	15.0%	21.6%	33.3%	36.4%	28.6%
Insomnia	8.2%	8.7%	12.9%	10.0%	13.2%	16.7%	22.7%	14.3%
Memory Loss	6.8%	4.1%	8.6%	10.0%	11.2%	25.0%	13.6%	0
Raynaud's phenomenon	4.8%	5.5%	5.3%	15.0%	2.8%	16.7%	9.1%	14.3%

	Primary Augmentation		Revision Augmentation		Primary Reconstruction		Revision Reconstruction	
Swelling of Muscles	0.9%	1.4%	1.9%	0	4.8%	16.7%	0	0
Weakness	3.5%	1.8%	5.3%	0	4.4%	0	18.2%	0

**RR* – Round responsive (Silicone) Implants P020056, *S* – Saline Implants P990074

Mentor's Reporting of Signs and Symptoms

The following limitations apply to the Mentor LPAS: The sample size of patients providing reports is small (6063/41,452; 14.6% follow up rate) as provided in Table 10 for each cohort due to low follow-up rates [although original number of patients for each cohort were: primary augmentation (n=26,173), revision augmentation (n=8,382), primary reconstruction (n=5,023), revision reconstruction (n=1,761), and unknown indication (n=113)]. All patients have surpassed a 7-year collection period. Table 10 provides data for 12 symptoms, from the original set of 28 questions, most similar to the BII symptoms described in MDR reports.

Table 10: Mentor patient reports of symptoms (P030053)

Changes in Signs and Symptoms	Primary Augmentation (n=3,633)	Revision Augmentation (n=1,115)	Primary Reconstruction (n=994)	Revision Reconstruction (n=301)
Persistent joint stiffness that lasts at least one hour, over a period of two weeks or longer	274 (7.7%)	121 (11.1%)	137 (14.1%)	50 (17.2%)
Persistent non-traumatic joint pain	370 (10.4%)	138 (12.7%)	157 (16.2%)	56 (19.3%)
Persistent joint swelling (more than 1 week)	133 (3.7%)	68 (6.3%)	62 (6.4%)	27 (9.3%)
Persistent muscle pain	244 (6.9%)	102 (9.4%)	82 (8.5%)	38 (13.1%)
Persistent sleep disorders at night, for example, waking up too early, not falling asleep for a long time, or awakening frequently	717 (20.1%)	313 (28.8%)	286 (29.4%)	94 (32.3%)
Persistent fatigue that kept you from working inside or outside the home	136 (3.8%)	69 (6.3%)	48 (4.9%)	23 (7.9%)
Fingers becoming unusually pale, numb, or uncomfortable in the cold	369 (10.3%)	128 (11.8%)	116 (11.9%)	28 (9.7%)
Excessively dry eyes or mouth	233 (6.5%)	130 (11.9%)	131 (13.5%)	47 (16.1%)
Persistent or recurrent tingling or numbness lasting at least several weeks	156 (4.4%)	65 (6.8%)	64 (6.6%)	24 (8.3%)

Changes in Signs and Symptoms	Primary Augmentation (n=3,633)	Revision Augmentation (n=1,115)	Primary Reconstruction (n=994)	Revision Reconstruction (n=301)
Episode of sudden visual loss or double vision	71 (2.0%)	15 (1.4%)	23 (2.4%)	1 (5.0%)
Persistent memory problems, difficulty concentrating on simple tasks, such as reading, television, etc. for at least 3 months.	185 (5.2%)	59 (5.4%)	41 (4.3%)	14 (4.9%)
Persistent weakness in your muscles lasting at least several weeks	44 (1.2%)	27 (2.5%)	18 (1.9%)	9 (3.1%)

Sientra Reporting of Signs and Symptoms

The following limitations apply to the Sientra data: Sientra has referenced the completed 10-year follow-up data from the core study (called the PACS, or Post-Approval PMA Cohort Study). The patient reports are from an initial study cohort of 1479 augmentation and 309 reconstruction patients (51% follow up rate). Table 11 provides data for 13 symptoms, from the original 45 questions, that are most similar to the symptoms seen in MDR reports.

Table 11: Sientra patient reports of symptoms (P070004)

Changes in Signs and Symptoms	Augmentation Cohort (Primary and Revision) (**n=827**)	Reconstruction Cohort (Primary and Revision) (**n=86**)
Muscle: muscle weakness/tenderness	18 (2.2%)	1 (1.2%)
Myalgias	3 (0.4%)	0 (0.0%)
Morning stiffness > 30 minutes	27 (3.3%)	2 (2.3%)
Rheumatoid Arthritis	14 (1.7%)	0 (0.0%)
Abnormal mental status	2 (0.2%)	0 (0.0%)
Pain: muscle weakness/tenderness	18 (2.2%)	1 (1.2%)
Chronic fatigue syndrome	6 (0.7%)	0 (0.0%)
Chronic malaise	0 (0.0%)	0 (0.0%)
Fibromyalgia: muscle weakness/tenderness	18 (2.2%)	1 (1.2%)
Dry eyes	45 (5.4%)	5 (5.8%)
Dry mouth	14 (1.7%)	3 (3.5%)
Sjögren’s Syndrome	0 (0.0%)	0 (0.0%)
Raynaud’s phenomenon	30 (3.6%)	0 (0.0%)

IDEAL™ IMPLANT Reporting of Signs and Symptoms

The IDEAL™ IMPLANT Post-Approval study was a prospective multi-center continuation of the premarket core study to extend out to 10-year follow up. Only saline implant augmentation patients are evaluated in this study because Ideal does not manufacture silicone implants and is not indicated for reconstruction. This study included 502 patients (399 primary augmentation and 103 revision augmentation). All patients in the study have passed 8 years, with an overall follow up rate of 93.8%. The study was not designed to assess rheumatologic signs and symptoms specifically but required reporting of all patients referred to a rheumatologist during the study period.

Table 12: IDEAL™ IMPLANT (P120011) patient reporting of symptoms

Cohort	CTD Sign/Symptom	1 Yr	2 Yrs	3Yrs	4 Yrs	7 Yrs	Cumulative rate [2]
Primary Augmentation	Referral to board-certified Rheumatologist[1]	0.8% (3/382)	1.3% (5/378)	3.0% (11/371)	3.6% (13/365)	1.7% (6/344)	**7.8% (31/399)**
Revision Augmentation	Referral to board-certified Rheumatologist[1]	2.1% (2/96)	5.3% (5/94)	3.2% (3/94)	3.3% (3/91)	2.4% (2/83)	**9.7% (10/103)**

Number are Percent (Count/N)

Signs and symptoms were only collected at certain visits. Only new signs and symptoms not present at baseline are summarized

[1] This does not include subjects who have already been seen by a board-certified Rheumatologist

[2] Subjects referred to a rheumatologist through 8 years of follow up

E. Inflammatory Response to Implant Materials and the "Auto-immune/Anti-inflammatory Syndrome Induced by Adjuvants (ASIA)"

Clinical Characteristics

For decades, some breast implant patients have described systemic signs or symptoms that they attribute to their implants as discussed in Section D. Despite overlap in clinical manifestations, conflicting research outcomes have failed to provide definitive evidence that silicone breast implants are associated with the development of a defined autoimmune or connective tissue disease.

It is known, however, that materials used in medical implants have the ability to produce an inflammatory and immunological response after implantation. The type, magnitude, and duration of the response may vary significantly from patient to patient and is likely to be impacted by factors including, but not limited to, genetics, clinical comorbidities, concurrent therapies/medications, and lifestyle behaviors (e.g., smoking). It is also possible that the composition of the material, the anatomical location of the implant, and the duration of the implant may all influence whether symptoms are observed and whether an acute or chronic response occurs.

One clinical entity that attempts to explain this type of response was first described in 2011 and is called "Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants (ASIA)" (Shoenfeld & Agmon-Levin, 2011) The researchers defined an adjuvant as a substance that enhances antigen-specific immune responses.

Based on their evaluations, the authors proposed assigning a diagnosis of ASIA based on the presence of at least two major criteria [Table 13]. The presence of one major criterion and two minor criteria would be suggestive of the condition. While somewhat imprecise, such an approach serves as a potential framework for characterizing ASIA.

Table 13: Criteria for ASIA diagnosis

Major Criteria	Minor Criteria
• Exposure to external stimulus prior to clinical manifestations. • The appearance of 'typical' clinical symptoms: o Myalgia, Myositis or muscle weakness o Arthralgia and/or arthritis o Chronic fatigue, un-refreshing sleep or sleep disturbances o Neurological manifestations (especially associated with demyelination) o Cognitive impairment, memory loss o Pyrexia, dry mouth • Removal of inciting agent induces improvement • Typical biopsy of involved organs	• The appearance of autoantibodies or antibodies directed at the suspected adjuvant • Other clinical manifestations (i.e. irritable bowel syn.) • Specific human lymphocytic antigens (HLA) (i.e. HLA DRB1, HLA DQB1) • Evolvement of an autoimmune disease (i.e.multiple sclerosis, scleroderma and systemic sclerosis (SSc))

Theorized potential adjuvants include aluminum salts, mineral oils, collagen, hyaluronic acid, metals, and silicones, among others.

Recent publications have described two patient series suspected of having ASIA associated with implanted medical devices including silicone breast implants, skin fillers, and metal implants. Alijotas-Reig et al. (Alijotas-Reig et al., 2018) performed a retrospective analysis of 45 subjects and reported a 6-year average latency from implantation to symptoms. Eighty percent (80%) of these subjects tested positive for the production of antinuclear antibody (ANA), a biomarker often associated with connective tissue autoimmune disorders. The authors also noted that 40% of the studied patients expressed the HLA-B*8/HLA-DRB1*03 haplotype and proposed that this may be a risk marker for ASIA. In addition, the authors reported that 70% of subjects clinically responded to anti-inflammatory and/or immunomodulation drugs. Watad and colleagues (Watad, Quaresma, et al., 2018) reviewed data for 300 patients enrolled in an international ASIA registry. The clinical signs and symptoms for patients in this registry were similar to other reports, and more than 50% of subjects were ANA positive. The mean time from implantation to the onset of clinical symptoms was 2.5 years.

Several publications have focused specifically on an association between suspected ASIA cases and breast implants. Reported symptom were consistent with the symptoms reported in breast implant MDRs (Section C). In addition, the mean time from implantation to initiation of symptoms ranged from 4 to 10 years in 3 different cohorts, suggesting a "delayed" presentation (Cohen Tervaert & Kappel, 2013) (Colaris et al., 2017) (Maijers et al., 2013). A personal history of allergies (e.g., pollen, drug allergies, etc.) prior to implantation has been suggested as a predisposing factor (Maijers et al., 2013) (Goren et al., 2015) (Cohen Tervaert, 2018), as has deficiency or insufficiency of Vitamin D (Colaris et al., 2017). However, no control groups were included in these studies. A review was conducted of the medical

literature for changes in ASIA-associated symptoms following breast implant removal (de Boer et al., 2017). The review included a total of 622 women by pooling case reports and series. Of these patients, 469 (75.4%) reported symptom improvement after explantation. Among women who had developed a specific autoimmune diagnosis, only 56% improved after removal, with many requiring immunosuppression to achieve improvement. The results may be difficult to interpret as the definition and degree of improvement may have varied significantly among the included studies.

Current information suggests that implanted materials, including silicone, may interact with cells of the innate and adaptive immune systems, possibly through Toll-Like Receptors (TLRs) and inflammasomes, to induce a pro-inflammatory response and that, in some predisposed subjects, it is possible that this response is not appropriately down-regulated (McKee & Marrack, 2017; Auquit-Auckbur, 2011; Segretol, 2016; Wolfram, 2012; Bassetto, 2012; Szordoray, 2013; Nakken, 2015). Furthermore, this inappropriately regulated response may be perpetuated over months/years by the continued presence of the material. Although additional data are needed, it appears possible and plausible that this exaggerated and persistent response, for some patients, may produce local and systemic signs and symptoms which closely mimic, but do not meet the formal criteria for, an established connective tissue, autoinflammatory or autoimmune disease. If this is true, additional study of several factors is warranted, including the ability to identify the higher-risk individual prior to implantation based on characteristics such as genetic markers or comorbidities; the natural history of progression and resolution; and the effectiveness of treatment modalities such as device removal and immunomodulation.

F. For Panel Deliberation

The panel will be asked to discuss methods for assessing and addressing breast implant illness symptoms.

G. Breast Implant Rupture

Rupture is a tear or hole in the outer shell of the breast implant and is not always noticeable to the patient. Rupture is one of the most reported device problems for breast implants in MDRs.

Some cases of rupture are noticeable with lumps or changes to appearance. Such changes are more likely when a saline filled breast implant ruptures because the breast deflates as the saline is absorbed by the body. In other cases, there is "silent" rupture of a silicone-gel filled breast implant which occurs in the absence of noticeable changes. Silicone gel-filled breast implant rupture may be intracapsular (the gel remains in the shell or within the scar tissue that forms around the implant), extracapsular (gel moves outside the scar tissue, or may migrate (gel moves beyond the vicinity of the augmented or reconstructed breast.

For silicone gel-filled breast implants, MRI has been the most effective imaging method for detecting silent rupture of silicone gel-filled breast implants. Other modalities that have been used include mammography, ultrasonography, and computed tomography.

Based on Advisory Committee input regarding the first PMAs for silicone gel-filled breast implants approved in 2006, the FDA has recommended that labeling for all approved silicone gel-filled breast implants include the recommendation of MRI screening at 3 years and every 2 years thereafter to detect silent rupture. In 2011, FDA held an Advisory Panel meeting to discuss breast implant post-approval studies. FDA sought Advisory Panel recommendations on improving the design and implementation of silicone gel-filled breast implant post-approval studies including panel input on MRI imaging of implant

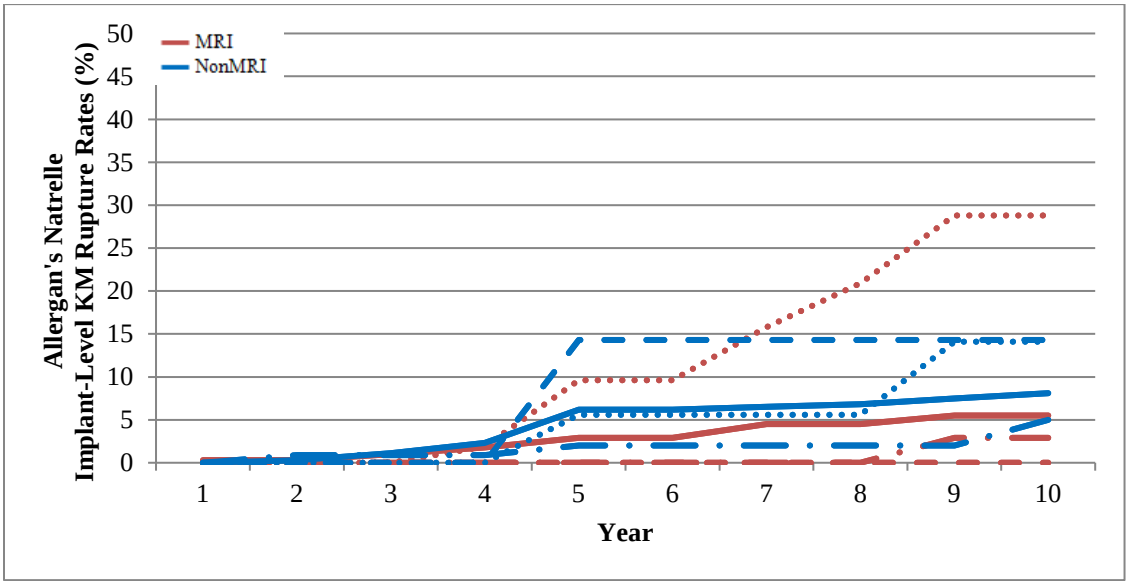
rupture. The Advisory Panel did not provide definitive recommendations on the use of MRI screening; however, Advisory Panel members did express reservations about FDA's labeling recommendations. In preparation for the current meeting, FDA has conducted additional analyses of breast implant rupture reports and is seeking Advisory Panel recommendations on the labeling recommendations for silent breast implant rupture screening.

In each of the premarket silicone gel filled implant "Core" studies patients were followed for a total of 10 years post-implant placement and a cohort of subjects were regularly screened for silent silicone gel filled breast implant rupture with MRI at three years post implant placement and every other year thereafter.

To assess the current MRI screening frequency recommendation, 10-year Core study rupture data from Allergan, Mentor, and Sientra for silicone implants were analyzed. Due to the differences in the methods in which ruptures were detected and confirmed, the types of data that were collected, length and frequency of patient follow-up, and the methods for analyzing and presenting the data greatly limited the comparisons that can be made between manufacturers. The results of the completed Allergan and Mentor Core studies indicated that comparable numbers of silent and symptomatic rupture were found in the MRI and non-MRI cohorts. Due to the design of the Sientra study it was not possible to determine the comparative number of silent and symptomatic ruptures in the MRI and non-MRI cohorts.

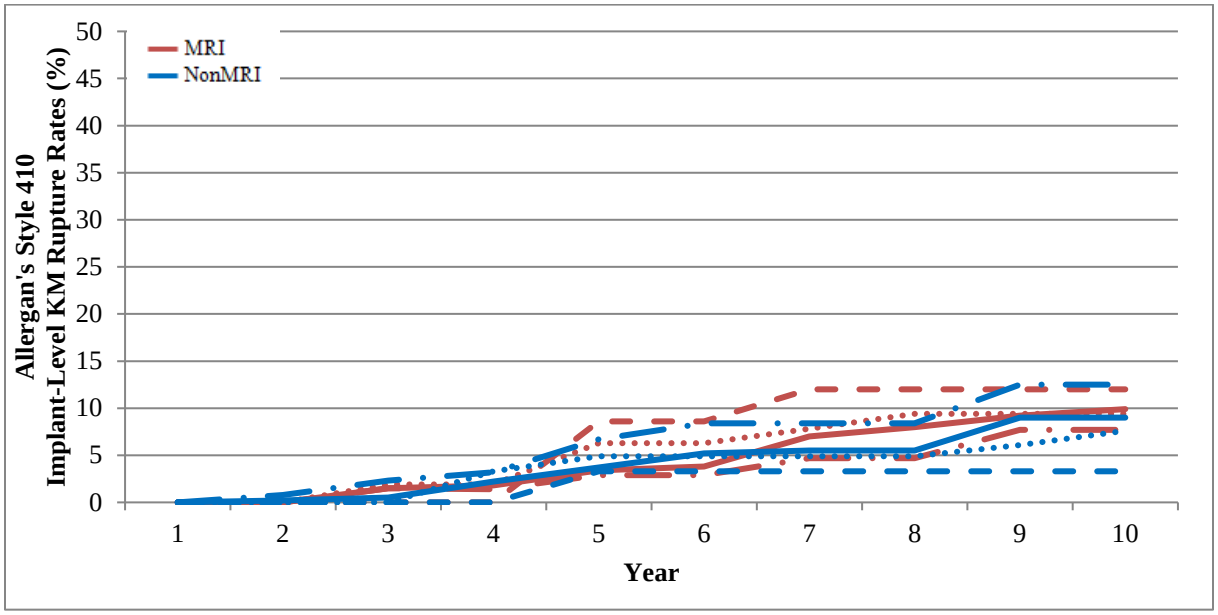
Rupture-related data presented in the following tables 14-16 and figures 4-8 were obtained from the approved breast implant Core studies for Allergan, Mentor and Sientra. In the graphs below, MRI cohort data is in red and non-MRI cohort data is in blue. Each main cohort was separated into 4 sub-cohorts, Augmentation (Aug, solid line), Reconstruction (Recon, dotted line), Revision-Augmentation (Rev-Aug, dash-dot line) and Revision-Reconstruction (Rev-Recon, dashed line).

Figure 4: Allergan Natrelle (P020056) Implant-Level Kaplan-Meier Rupture Rate Curve



Augmentation (solid line), Reconstruction (dotted line), Revision-Augmentation (dash-dot line) Revision-Reconstruction (dashed line)

Figure 5: Allergan Style 410 (P040046) Implant-Level Kaplan-Meier Rupture Rate Curve

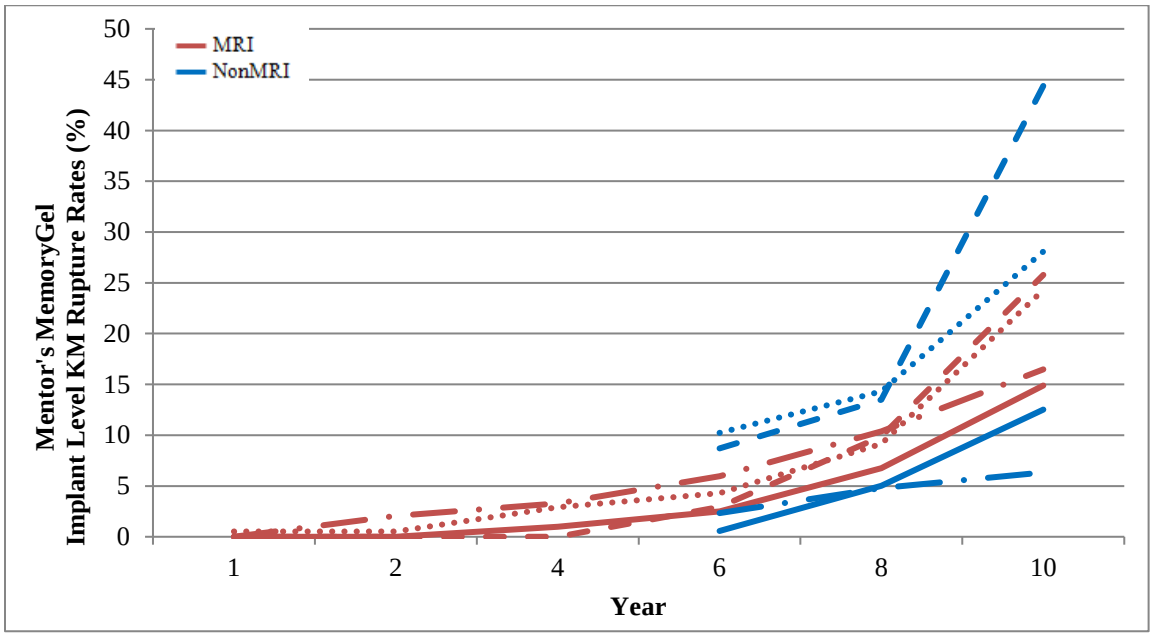


Augmentation (solid line), Reconstruction (dotted line), Revision-Augmentation (dash-dot line) Revision-Reconstruction (dashed line)

Table 14: Allergan Patient-Level Kaplan Meier Rupture Rates (RR, %) with 95% Confidence Intervals (CIs, %)

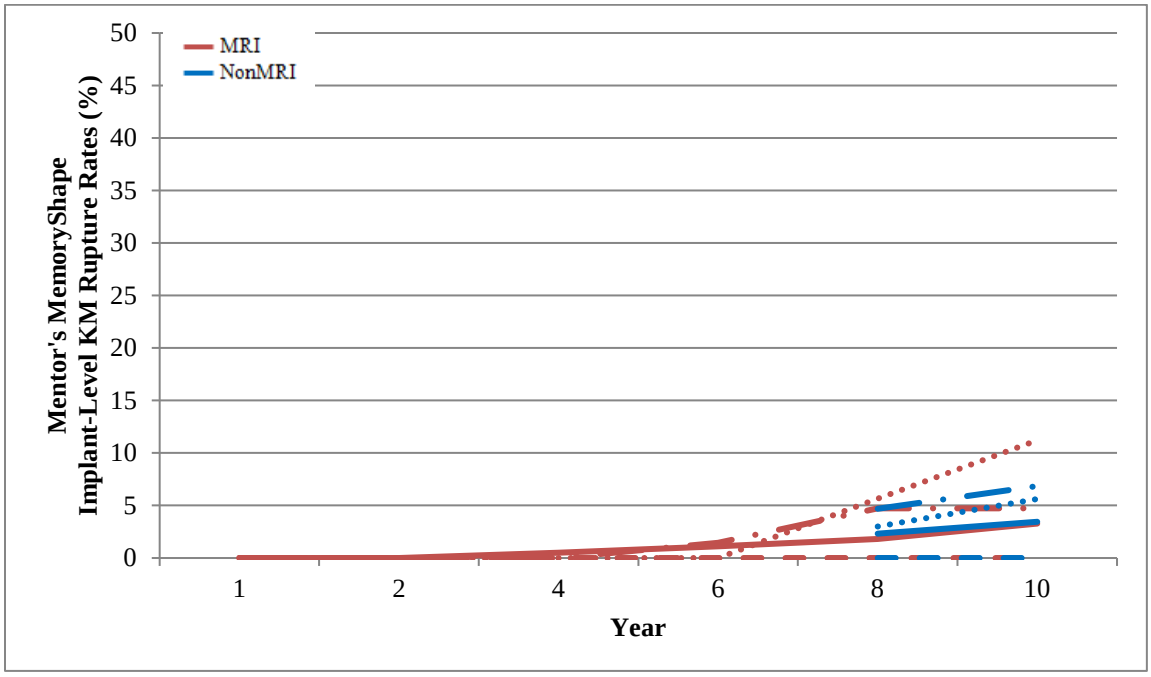
Device	Cohort	Indication	n	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Allergan Natrelle P020056	MRI	Aug	158	0.7 (0.1,4.5)	0.7 (0.1,4.5)	2.0 (0.7,6.1)	2.8 (1.0,7.2)	5.0 (2.4,10.1)	5.0 (2.4,10.1)	7.4 (4.0,13.2)	7.4 (4.0,13.2)	9.3 (5.3,15.8)	9.3 (5.3,15.8)
		Rev-Aug	50	0	0	0	0	0	0	0	0	5.4 (1.4,20.0)	5.4 (1.4,20.0)
		Recon	51	0	0	0	2.3 (0.3, 15.4)	11.9 (5.1,26.2)	11.9 (5.1,26.2)	19.4 (10.2,35.1)	25.7 (14.6,42.9)	35.4 (22.1,53.6)	35.4 (22.1,53.6)
		Rev- Recon	5	0	0	0	0	0	0	0	0	0	0
	Non MRI	Aug	297	0	0.6 (0.1,3.8)	2.2 0.8,5.8)	4.6 (2.3,8.9)	10.5 (6.7,16.1)	10.5 (6.7,16.1)	11.1 (7.2,16.9)	11.7 (7.7,17.6)	12.3 (8.2,18.3)	13.7 (9.3,19.9)
		Rev-Aug	97	0	1.8 (0.2,11.8)	1.8 (0.2,11.8)	3.9 (1.0,4.8)	3.9 (1.0,4.8)	3.9 (1.0,4.8)	3.9 (1.0,4.8)	3.9 (1.0,4.8)	3.9 (1.0,14.8)	10.1 (3.8,25.4)
		Recon	47	0	0	0	0	6.7 (1.0,38.7)	6.7 (1.0,38.7)	6.7 (1.0,38.7)	6.7 (1.0,38.7)	6.7 (1.0,38.7)	6.7 (1.0,38.7)
		Rev- Recon	10	0	0	0	0	20.0 (3.1, 79.6)	20.0 (3.1, 79.6)	20.0 (3.1, 79.6)	20.0 (3.1, 79.6)	20.0 (3.1, 79.6)	20.0 (3.1, 79.6)
Allergan Natrelle Style 410 P040046	MRI	Aug	150	0	0	2.2 (0.7,6.6)	2.9 (1.1,7.5)	6.0 (3.0,11.7)	6.0 (3.0,11.7)	12.2 (7.5,19.5)	14.2 (9.0,21.9)	16.4 (10.7,240.6)	17.7 (11.7,26.4)
		Rev-Aug	45	0	0	2.7 (0.4,17.7)	2.7 (0.4,17.7)	5.7 (1.4,20.8)	5.7 (1.4,20.8)	9.0 (3.0,25.6)	9.0 (3.0,25.6)	14.7 (5.4,36.4)	14.7 (5.4,36.4)
		Recon	86	0	0	3.1 (0.8,11.1)	3.1 (0.8,11.1)	10.1 (4.07,21.2)	10.1 (4.07,21.2)	12.4 (6.0,24.4)	12.4 (6.0,24.4)	12.4 (6.0,24.4)	12.4 (6.0,24.4)
		Rev- Recon	25	0	0	0	0	14.3 (4.8,38.0)	14.3 (4.8,38.0)	19.6 (7.8,44.4)	19.6 (7.8,44.4)	19.6 (7.8,44.4)	19.6 (7.8,44.4)
	Non-MRI	Aug	343	0	0.5 (0.1,3.3)	1.0 (0.2,3.7)	3.9 (1.9,7.6)	5.8 (3.3,10.0)	8.8 (5.6,13.6)	9.3 (6.0,14.2)	9.3 (6.0,14.2)	14.8 (10.3,20.9)	14.8 (10.3,20.9)
		Rev-Aug	111	0	1.5 (0.2,10.0)	3.0 (0.8,11.5)	4.6 (1.5,13.7)	11.4 (5.6,22.4)	14.8 (8.0,26.5)	14.8 (8.0,26.5)	14.8 (8.0,26.5)	19.8 (11.3,33.4)	19.8 (11.3,33.4)
		Recon	139	0	0	0	4.9 (1.9,12.5)	6.1 (2.6,14.0)	6.1 (2.6,14.0)	6.1 (2.6,14.0)	6.1 (2.6,14.0)	7.9 (3.6,17.1)	10.1 (4.8,20.6)
		Rev- Recon	43	0	0	0	0	5.0 (0.7,30.5)	5.0 (0.7,30.5)	5.0 (0.7,30.5)	5.0 (0.7,30.5)	5.0 (0.7,30.5)	5.0 (0.7,30.5)

Figure 6: Mentor MemoryGel (P030053) Implant-Level Kaplan-Meier Rupture Rate Curves



Augmentation (solid line), Reconstruction (dotted line), Revision-Augmentation (dash-dot line) Revision-Reconstruction (dashed line)

Figure 7: Mentor MemoryShape (P060028) Implant-Level Kaplan-Meier Rupture Rate Curve



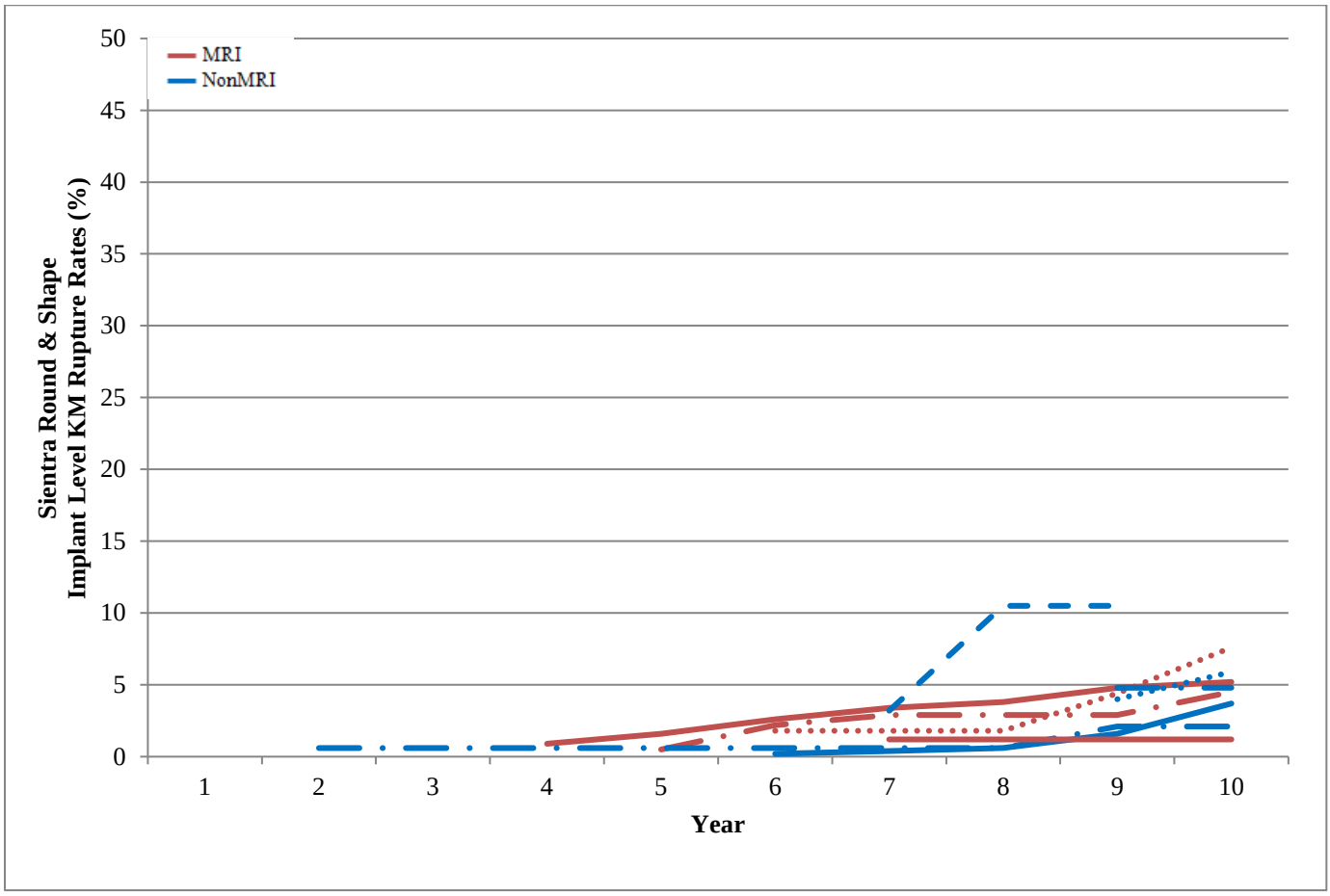
Augmentation (solid line), Reconstruction (dotted line), Revision-Augmentation (dash-dot line) Revision-Reconstruction (dashed line)

Table 15: Mentor Patient-Level Kaplan-Meier Rupture Rates (RR, %) with 95% Confidence Intervals (CIs, %)

Device	Cohort	Indication	n	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
MemoryGel P030053	MRI	Aug	202	0	0	NR	1.33 (0.34,5.23)	NR	3.66 (1.54,8.60)	NR	10.34 (5.97,17.60)	NR	24.22 (16.97,33.87)
		Rev-Aug	56	0	1.96 (0.28,13.11)	NR	4.24 (1.07,15.98)	NR	9.42 (3.61,23.35)	NR	12.25 (5.24,29.19)	NR	23.69 (12.27,42.80)
		Recon	134	0.82 (0.12,5.68)	0.82 (0.12,5.68)	NR	4.67 (1.97,10.88)	NR	6.91 (3.34,14.02)	NR	14.78 (8.78,24.29)	NR	32.72 (23.22,44.82)
		Rev-Recon	28	0	0	NR	0	NR	4.55 (0.65,28.13)	NR	15.78 (5.33,41.60)	NR	38.75 (19.08,67.86)
	Non-MRI	Aug	350	NR	NR	NR	NR	NR	1.15, (0.29,4.52)	NR	8.85, (5.34,14.50)	NR	21.39 (15.30,29.45)
		Rev-Aug	89	NR	NR	NR	NR	NR	2.38 (0.34,15.72)	NR	7.52 (2.49,21.55)	NR	7.52 (2.29,21.55)
		Recon	117	NR	NR	NR	NR	NR	16.07 (8.71,28.61)	NR	20.17, (11.68,33.52)	NR	36.13 (24.33,51.38)
		Rev-Recon	32	NR	NR	NR	NR	NR	5.56 (0.80,33.36)	NR	11.85 (3.09,39.81)	NR	43.91 (22.28,73.45)
MemoryShape P060028	MRI	Aug	252	0	0	NR	1.04 (0.26,4.08)	NR	2.23 (0.84,5.84)	NR	3.63 (1.63,7.94)	NR	6.55 (3.38,12.47)
		Rev-Aug	38	0	0	NR	0	NR	2.94 (0.42,19.10)	NR	9.63 (3.20,27.05)	NR	9.63 (3.20,27.05)
		Recon	73	0	0	NR	0	NR	0	NR	9.38 (3.12,26.31)	NR	18.91 (8.11,40.52)
		Rev- Recon	56	0	0	NR	0	NR	0	NR	0	NR	0
	Non-MRI	Aug	320	NR	NR	NR	NR	NR	NR	NR	4.11 (1.98,8.43)	NR	6.39 (3.47,11.62)
		Rev-Aug	31	NR	NR	NR	NR	NR	NR	NR	9.09 (3.03,25.59)	NR	13.22 (5.10,31.89)
		Recon	117	NR	NR	NR	NR	NR	NR	NR	5.08 (1.67,14.94)	NR	7.19 (2.74,18.15)
		Rev- Recon	68	NR	NR	NR	NR	NR	NR	NR	0	NR	0

NR= Not Reported, MRIs not required at time point

Figure 8: Sientra Round and Shape (P070004) Implant-Level Kaplan-Meier Rupture Rate Curves



Augmentation (solid line), Reconstruction (dotted line), Revision-Augmentation (dash-dot line) Revision-Reconstruction (dashed line)

Table 16: Sientra P070004 10-Year Results: Patient-Level Kaplan-Meier Rupture Rates (RR, %) with 95% Confidence Intervals (CI, %)

Device	Cohort	Indication	n	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Round implants Sientra OPUS High Strength Cohesive Silicone Gel Breast Implants	MRI	Aug	343	--	--	--	1.5 (0.6,3.6)	2.8 (1.5,5.3)	4.9 (3.0,8.0)	6.4 (4.1,9.9)	6.9 (4.5,10.5)	8.8 (5.9,12.9)	9.5 (6.4,13.9)
		Rev-Aug	100	--	--	--	--	1.1 (0.2,7.2)	3.3 (1.1,9.9)	4.5 (1.7,11.7)	4.5 (1.7,11.7)	4.5 (1.7,11.7)	7.6 (3.5,16.4)
		Recon	40	--	--	--	--	--	3.3 (0.5,21.4)	3.3 (0.5,21.4)	3.3 (0.5,21.4)	8.2 (2.1,29.6)	NR-
		Rev-Recon	8	--	--	--	--	--	--	--	--	--	--
	Non-MRI	Aug	645	--	--	--	--	--	0.4 (0.1,2.6)	0.7 (0.2,2.9)	1.1 (0.4,3.4)	2.7 (1.3,5.5)	6.8 (4.2,10.9)
		Rev-Aug	212	--	1.1 (0.2,7.8)	1.1 (0.2,7.8)	1.1 (0.2,7.8)	1.1 (0.2,7.8)	1.1 (0.2,7.8)	1.1 (0.2,7.8)	1.1 (0.2,7.8)	2.7 (0.7,10.4)	2.7 (0.7,10.4)
		Recon	161	--	--	--	--	--	--	--	--	4.7 (1.2,17.3)	8.1 (2.6,23.4)
		Rev-Recon	65	--	--	--	--	--	--	5.6 (0.8,33.4)	17.8 (6.1,45.7)	17.8 (6.1,45.7)	NR-
Shaped Implants Sientra OPUS High Strength Cohesive Silicone Gel Breast Implants	MRI	Aug	55	--	--	--	--	--	--	2.4 (0.3,15.7)	2.4 (0.3,15.7)	2.4 (0.3,15.7)	2.4 (0.3,15.7)
		Rev-Aug	15	--	--	--	--	--	--	--	--	--	--
		Recon	9	--	--	--	--	--	--	--	--	--	NR-
		Rev-Recon	3	--	--	--	--	--	--	--	--	--	--
	Non-MRI	Aug	73	--	--	--	--	--	--	--	--	--	--
		Rev-Aug	36	--	--	--	--	--	--	--	--	9.1 (1.3,49.2)	NR-
		Recon	21	--	--	--	--	--	--	--	--	--	--
		Rev-Recon	9	--	--	--	--	--	--	--	--	--	--

NR: Some rates are not reported because the number of remaining patients/implants at timepoint is < 10.

FDA surveyed scientific literature published between January 1, 2006, and May 15, 2017 for references to silicone gel-filled breast implants, MRI, and rupture. The findings generally support MRI as the gold standard imaging modality for assessing silicone implant integrity. However, several reports have challenged the role of MRI as a screening tool for the evaluation of silent rupture citing concerns related to compliance, cost and reimbursement (Adams et al., 2017; Bengtson & Eaves, 2012; Juanpere et al., 2011; Lindenblatt et al., 2014; Lourenco et al., 2018; C. M. McCarthy et al., 2008; Paetau et al., 2010; Sardanelli et al., 2010; Song et al., 2011).

In April 2018, the American College of Radiology (ACR) published new Appropriateness Criteria for breast implant imaging evaluation. These are evidence-based guidelines for specific clinical conditions that are reviewed periodically by a multidisciplinary expert panel. The ACR concluded that as there is currently no consensus on whether ruptured silicone implants require surgery in asymptomatic patients, and the benefits of screening for implant rupture are controversial, that breast MRI is not indicated for implant evaluation in asymptomatic women at any age. (Lourenco et al., 2018)

Summary of Findings

- Rupture rates increase the longer implants are in place. Overall, premarket patient-level rupture rates generally are less than 5% before Year 4 and then increase around 4-6 years post-implantation. After Year 6, the rupture rates continue to increase at variable rates. Implant-level rupture rates generally follow the same trend as patient-level rupture rates.

- There does not appear to be a difference in 10-year rupture rates between MRI screening and Non-MRI screening cohorts in premarket studies. The confidence intervals (CIs) for the MRI and Non-MRI data are wide and generally overlap, and as such, statistical significance of any observed differences has not been seen. The wide CIs also restrict comparison of rupture rates based on manufacturer, cohort, indication, and gel cohesivity.

- The majority of rupture events in premarket studies were silent and intracapsular in nature regardless of cohort MRI schedule. In general, the proportion of silent ruptures first identified by MRI ranged from 40 to 100%.

H. For Panel Deliberation

The panel will be asked to discuss the MRI screening recommendations for silent silicone gel-filled breast implant rupture.

VI. Emerging Concerns Related to Breast Implants

A. Use of Surgical Mesh

Mesh Products

Surgical mesh is a sheet of porous material used to reinforce soft tissue where weakness exists and is cleared for hernia repair. Synthetic surgical mesh is typically a woven or knitted implanted device composed of nonbiodegradable plastics such as polypropylene or polyester, or from biodegradable plastics such as Dexon or Vicryl. Biological meshes are biodegradable and are formed by processing and sterilizing human, cow, or pig tissue to remove cells, resulting in a collagen, acellular dermal matrix (ADM).

Breast Reconstruction

Breast reconstruction is intended to reconstruct the breast mounds after an oncologic mastectomy or reconstruct congenitally deformed or traumatically injured breasts. In the past decade, surgeons have begun utilizing surgical mesh products to assist with these reconstructive procedures, and ADM mesh products are now used in the majority of implant-based breast reconstruction procedures in the United States (Sorkin et al., 2017) .

The diversity of options for breast reconstruction are presented in Figure 9. Options involving implantation of surgical mesh are highlighted in yellow.

Figure 9: Breast reconstruction procedures

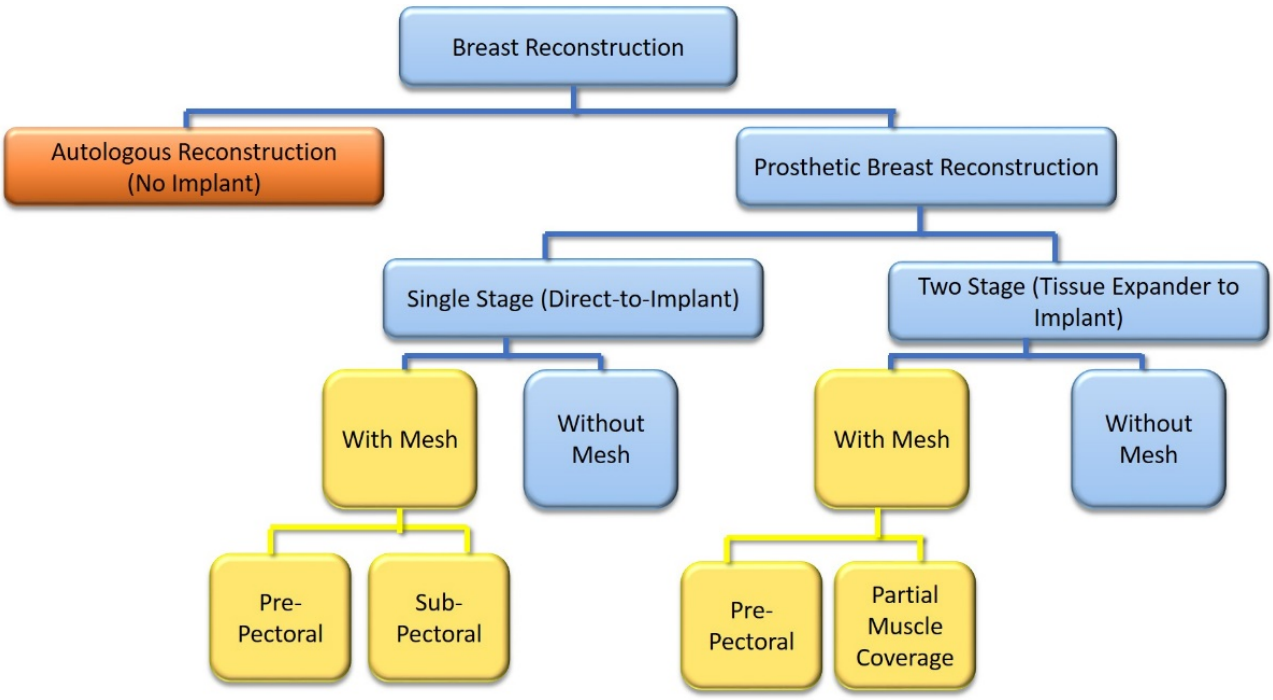
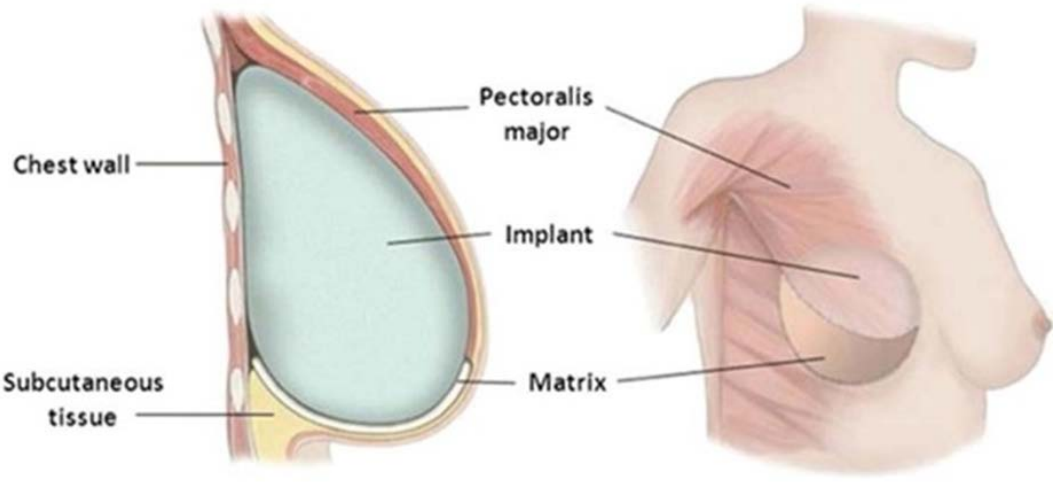


Figure 10: Breast reconstruction using mesh and partial muscle coverage



There are numerous variables that may affect the outcomes of mesh in breast reconstruction. Designing a clinical trial in support of a potential marketing application may require identifying specific patient populations and surgical procedures that demonstrate an appropriate balance of safety and effectiveness. Surgical variables include, but are not limited to:

Type of procedure: For example, skin sparing mastectomy vs nipple sparing mastectomy.

Direct-to-implant versus tissue expander-to-implant reconstruction: One approach to reconstruction involves placement of a permanent breast implant as a complete reconstruction in one stage (direct-to-implant reconstruction). Alternatively, a tissue expander device may be placed as a temporary implant (not to exceed 6 months), which is serially inflated non-surgically over a period of months to expand the overlying tissues (tissue expander-to-implant reconstruction). This expander is then replaced with a permanent breast implant at a second staged surgery. The expander approach may be selected depending on the desired final size of the reconstruction, the amount of patient skin removed during the mastectomy, and surgeon judgement. Of note, tissue expander surfaces may be textured or smooth, and most are unclassified devices cleared through the 510(k) pathway.

Immediate vs. delayed reconstruction: Breast reconstruction can be performed during the same operation as the mastectomy or at a later surgery. Placement of a tissue expander or a permanent implant during the same surgery as the mastectomy is considered an immediate reconstruction.

Implant type: There are several implant characteristics that may influence the outcome of a breast reconstruction including implant manufacturer, implant size, saline or silicone gel filling, round versus anatomically shaped implant, and surface texturing versus smooth shell.

Pre-pectoral vs submuscular: When performing implant-based breast reconstruction, the breast implant or tissue expander can be placed directly into the subcutaneous pocket to replace the breast tissue (pre-

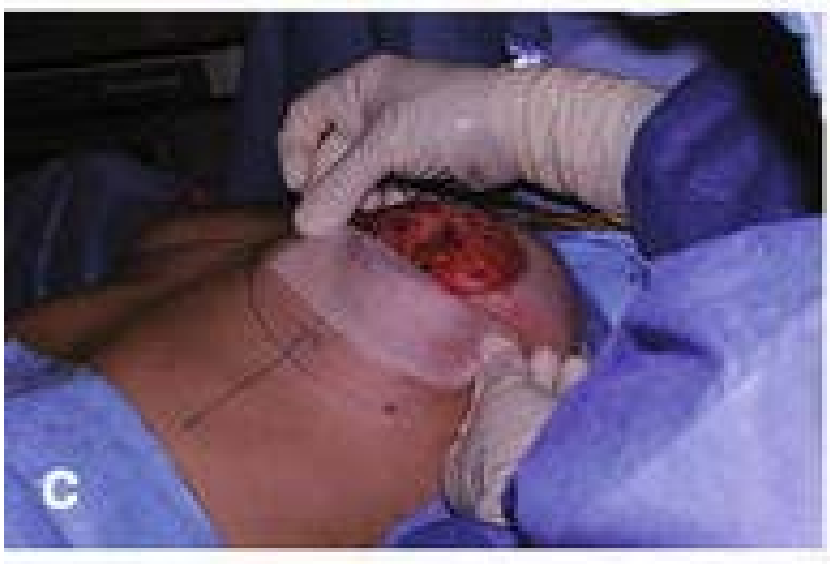
pectoral) or can be placed under the pectoralis muscle (submuscular) to provide an additional barrier of vascularized tissue.

Use of Surgical Mesh in Mastopexy

Roughly 175,000 patients per year undergo reduction mammaplasty (breast reduction) and cosmetic mastopexy (breast lift) procedures (ASPS, 2017). The use of synthetic and biologic mesh products during these procedures has not been FDA approved although anecdotal experience for this emerging use has been described in the literature. The mesh products are typically implanted in the inferior segment of the breast tissue as illustrated in Figure 11.

FDA has experienced challenges developing clinical trials designed to appropriately characterize the overall benefit and risk profile justifying surgical mesh for mastopexy.

Figure 11: Mastopexy (breast lift) using a mesh device



Surgical Mesh Regulatory History

FDA has not cleared or approved any surgical mesh device—whether synthetic, animal collagen derived, or human collagen derived--specifically indicated for use in breast surgery. The indication of surgical mesh for general use in "Plastic and reconstructive surgery" was cleared by CDRH for synthetic and animal-derived mesh products before surgical mesh was described for breast reconstruction in 2005 (Breuing & Warren, 2005). At the time of CDRH's initial clearance, mesh devices were not used in breast reconstruction, and that specific indication was not considered in the review and evaluation of the "plastic and reconstructive surgery" indication.

CDRH has informed sponsors seeking to claim substantial equivalence between surgical mesh indicated for "Plastic and reconstructive surgery" and "breast reconstruction or mastopexy" that a substantial equivalence evaluation via 510(k) review is not appropriate and that PMA evaluation is required. In determining that 510(k) is not appropriate, CDRH has relied on the General to Specific Guidance ("General/Specific Intended Use - Guidance for Industry," 2019) which cites several decision making criteria for determining whether a new specific indication changes the cleared, general intended use of a medical device and therefore represents a new intended use. In this case, CDRH considers that the

specific use of surgical mesh in breast procedures represents a new intended use due to differences in the following criteria:

Risk: New risks associated with concurrent use of surgical mesh with a breast implant (e.g., capsular contracture, explantation, reconstructive failure and implant rupture) and in the case of mastopexy without breast implant, risk of altering breast physiology and imaging which cannot be extrapolated from the general indication for plastic and reconstructive surgery.

Public Health Impact: Significant public health impact affecting patients who are undergoing mastectomy either as breast cancer treatment or to prevent breast cancer when there is high risk, and patients who are undergoing mastopexy who may later go on to breast feed.

Endpoints: Different endpoints needed to assess clinical benefit (aesthetic versus functional).

Knowledge Base: Inability to use data from general surgical mesh indications to assess benefit and risk justifying implantation either adjacent to a breast implant or breast tissue.

Clinical Trial Considerations

Recognizing the mismatch between widespread clinical use of surgical mesh in breast reconstruction and the lack of data or FDA approval justifying its use, CDRH has proactively worked to determine the least burdensome clinical evidentiary requirements assessing surgical mesh benefit versus risk in breast reconstruction.

Trial design considerations identified by FDA as critical to a successful determination of device safety and effectiveness include, but are not limited to:

- A comparison of patients treated with the subject device to a breast reconstruction control group that does not receive mesh.
- Assessment of the effectiveness of mesh for breast reconstruction compared to the no-mesh control in at least one effectiveness outcome assessing patient benefit.
- Inclusion and evaluation of relevant adverse events for both the treatment and control arms. These adverse events would be those that are reasonably likely to occur with the combined use of a mesh implant immediately adjacent to a tissue expander or permanent breast prosthesis including but not limited to: hematoma, explantation, reoperation, capsular contracture, infection, dehiscence, tissue necrosis, implant rupture, seroma.
- An analysis comparing treatment and control on both a per-breast and per-patient basis, where feasible and appropriate.
- Pre-specified statistical analysis accounting for reasonably obtainable relevant confounding variables including but not limited to: radiation, chemotherapy, patient demographics and medical history, type of reconstruction, type of mastectomy, type of breast implant.
- Premarket clinical follow-up to a minimum of 12 months post-implantation. If time to mesh resorption or time to quiescence of the inflammatory response of the tissue surrounding the mesh exceeds 12 months, then longer duration follow-up may be necessary. Postmarket follow-up for longer term outcomes may be necessary.
- Evidence of a favorable benefit-risk profile for breast reconstruction with the subject device compared to breast reconstruction without the use of mesh.

B. For Panel Deliberation

The panel will be asked to discuss the evidentiary requirements for assessing the safety/effectiveness and benefit/risk for the implantation of surgical mesh for breast reconstruction and mastopexy procedures.

VII. Patient Perspectives

Medical devices are required to include labeling that identifies the indications, directions for use, contraindications, warnings, precautions and adverse events. Breast implants are approved with both physician and patient-specific labeling. The patient-specific labeling was developed to help patients make an informed decision about the use of breast implants.

See this link for access to all US FDA approved breast implant labeling. Additionally, FDA first provided information on its website regarding the association of ALCL with breast implants in 2011, and the FDA website and breast implant labeling contain information on breast implant risk.

As described in the Post-approval study section above, breast implant manufactures conducted post-approval studies to evaluate their patient labeling and informed consent procedures. FDA has become aware that some patients do not believe they were adequately informed about all of the risks posed by breast implants, including risks related to implant rupture, BIA-ALCL and systemic symptoms commonly referred to as breast implant illness. CDRH recognizes the importance of communicating the benefits and risks of medical devices to patients, and the importance of incorporating the patient's unique perspective into communication efforts. CDRH is working toward being more patient-centered in our work, and we are working towards including how patients evaluate benefits and risks. As part of that effort, FDA is seeking Advisory Panel input what additional steps FDA and other stakeholders can take to ensure that patients are better informed about the benefits and risks of breast implants, and that the patient perspective is fully considered in this effort.

A. For Panel Deliberation

The panel will be asked to discuss the role and responsibility of all stakeholders for communicating breast implant related risks and benefits to patients.

VIII. References

Adams, W. P., Jr., Culbertson, E. J., Deva, A. K., M, R. M., Layt, C., Jewell, M. L., Mallucci, P., & Heden, P. (2017). Macrotextured Breast Implants with Defined Steps to Minimize Bacterial Contamination around the Device: Experience in 42,000 Implants. *Plast Reconstr Surg, 140*(3), 427-431. doi:10.1097/prs.0000000000003575

Alijotas-Reig, J., Esteve-Valverde, E., Gil-Aliberas, N., & Garcia-Gimenez, V. (2018). Autoimmune/inflammatory syndrome induced by adjuvants-ASIA-related to biomaterials: analysis of 45 cases and comprehensive review of the literature. *Immunol Res, 66*(1), 120-140. doi:10.1007/s12026-017-8980-5

ASPS. (2017). *Plastic Surgery Statistics Report*. Retrieved from https://www.plasticsurgery.org/documents/News/Statistics/2017/plastic-surgery-statistics-report-2017.pdf

ASPS. (2018). BIA-ALCL by the Numbers. Retrieved from https://www.plasticsurgery.org/for-medical-professionals/health-policy/bia-alcl-physician-resources/by-the-numbers

ASPS. (2019). BIA-ALCL Physician Reseources. Retrieved from https://www.plasticsurgery.org/for-medical-professionals/health-policy/bia-alcl-physician-resources

Balk, E. M., Earley, A., Avendano, E. A., & Raman, G. (2016). Long-Term Health Outcomes in Women With Silicone Gel Breast Implants: A Systematic Review. *Ann Intern Med, 164*(3), 164-175. doi:10.7326/m15-1169

Bengtson, B. P., & Eaves, F. F., 3rd. (2012). High-resolution ultrasound in the detection of silicone gel breast implant shell failure: background, in vitro studies, and early clinical results. *Aesthet Surg J, 32*(2), 157-174. doi:10.1177/1090820x11434507

Breuing, K. H., & Warren, S. M. (2005). Immediate bilateral breast reconstruction with implants and inferolateral AlloDerm slings. *Ann Plast Surg, 55*(3), 232-239.

Clemens, M. W., Nava, M. B., Rocco, N., & Miranda, R. N. (2017). Understanding rare adverse sequelae of breast implants: anaplastic large-cell lymphoma, late seromas, and double capsules. *Gland Surg, 6*(2), 169-184. doi:10.21037/gs.2016.11.03

Cohen Tervaert, J. W. (2018). Autoinflammatory/autoimmunity syndrome induced by adjuvants (ASIA; Shoenfeld's syndrome): A new flame. *Autoimmun Rev, 17*(12), 1259-1264. doi:10.1016/j.autrev.2018.07.003

Cohen Tervaert, J. W., & Kappel, R. M. (2013). Silicone implant incompatibility syndrome (SIIS): a frequent cause of ASIA (Shoenfeld's syndrome). *Immunol Res, 56*(2-3), 293-298. doi:10.1007/s12026-013-8401-3

Colaris, M. J. L., de Boer, M., van der Hulst, R. R., & Cohen Tervaert, J. W. (2017). Two hundreds cases of ASIA syndrome following silicone implants: a comparative study of 30 years and a review of current literature. *Immunol Res, 65*(1), 120-128. doi:10.1007/s12026-016-8821-y

de Boer, M., Colaris, M., van der Hulst, R., & Cohen Tervaert, J. W. (2017). Is explantation of silicone breast implants useful in patients with complaints? *Immunol Res, 65*(1), 25-36. doi:10.1007/s12026-016-8813-y

de Boer, M., van Leeuwen, F. E., Hauptmann, M., Overbeek, L. I. H., de Boer, J. P., Hijmering, N. J., Sernee, A.,

Klazen, C. A. H., Lobbes, M. B. I., van der Hulst, R., Rakhorst, H. A., & de Jong, D. (2018). Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast. *JAMA Oncol, 4*(3), 335-341. doi:10.1001/jamaoncol.2017.4510

General/Specific Intended Use - Guidance for Industry. (2019). Retrieved from https://www.fda.gov/RegulatoryInformation/Guidances/ucm073944.htm

Goren, I., Segal, G., & Shoenfeld, Y. (2015). Autoimmune/inflammatory syndrome induced by adjuvant (ASIA) evolution after silicone implants. Who is at risk? *Clin Rheumatol, 34*(10), 1661-1666. doi:10.1007/s10067-015-2931-0

IOM. (1999). *Safety of Silicone Breast Implants* E. V. Bondurant S, Herdman R (Ed.)

Juanpere, S., Perez, E., Huc, O., Motos, N., Pont, J., & Pedraza, S. (2011). Imaging of breast implants-a pictorial review. *Insights Imaging, 2*(6), 653-670. doi:10.1007/s13244-011-0122-3

Lindenblatt, N., El-Rabadi, K., Helbich, T. H., Czembirek, H., Deutinger, M., & Benditte-Klepetko, H. (2014). Correlation between MRI results and intraoperative findings in patients with silicone breast implants. *Int J Womens Health, 6*, 703-709. doi:10.2147/ijwh.s58493

Loch-Wilkinson, A., Beath, K. J., Knight, R. J. W., Wessels, W. L. F., Magnusson, M., Papadopoulos, T., Connell, T., Lofts, J., Locke, M., Hopper, I., Cooter, R., Vickery, K., Joshi, P. A., Prince, H. M., & Deva, A. K. (2017). Breast Implant-Associated Anaplastic Large Cell Lymphoma in Australia and New Zealand: High-Surface-Area Textured Implants Are Associated with Increased Risk. *Plast Reconstr Surg, 140*(4), 645-654. doi:10.1097/prs.0000000000003654

Lourenco, A. P., Moy, L., Baron, P., Didwania, A. D., diFlorio, R. M., Heller, S. L., Holbrook, A. I., Lewin, A. A., Mehta, T. S., Niell, B. L., Slanetz, P. J., Stuckey, A. R., Tuscano, D. S., Vincoff, N. S., Weinstein, S. P., & Newell, M. S. (2018). ACR Appropriateness Criteria® Breast Implant Evaluation. *Journal of the American College of Radiology, 15*(5, Supplement), S13-S25. doi:https://doi.org/10.1016/j.jacr.2018.03.009

Maijers, M. C., de Blok, C. J., Niessen, F. B., van der Veldt, A. A., Ritt, M. J., Winters, H. A., Kramer, M. H., & Nanayakkara, P. W. (2013). Women with silicone breast implants and unexplained systemic symptoms: a descriptive cohort study. *Neth J Med, 71*(10), 534-540.

McCarthy, C. M., Loyo-Berríos, N., Qureshi, A. A., Mullen, E., Gordillo, G., Pusic, A. L., Ashar, B. S., Sommers, K., & Clemens, M. W. (2019). Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (PROFILE): Initial Report of Findings, 2012–2018. *Plastic and Reconstructive Surgery, 143*(3S), 65S-73S. doi:10.1097/prs.0000000000005571

McCarthy, C. M., Pusic, A. L., & Kerrigan, C. L. (2008). Silicone breast implants and magnetic resonance imaging screening for rupture: do U.S. Food and Drug Administration recommendations reflect an evidence-based practice approach to patient care? *Plast Reconstr Surg, 121*(4), 1127-1134. doi:10.1097/01.prs.0000302498.44244.52

Paetau, A. A., McLaughlin, S. A., McNeil, R. B., Sternberg, E., TerKonda, S. P., Waldorf, J. C., & Perdikis, G. (2010). Capsular contracture and possible implant rupture: is magnetic resonance imaging useful? *Plast Reconstr Surg, 125*(3), 830-835. doi:10.1097/PRS.0b013e3181cb6066

Sardanelli, F., Boetes, C., Borisch, B., Decker, T., Federico, M., Gilbert, F. J., Helbich, T., Heywang-Kobrunner,

S. H., Kaiser, W. A., Kerin, M. J., Mansel, R. E., Marotti, L., Martincich, L., Mauriac, L., Meijers-Heijboer, H., Orecchia, R., Panizza, P., Ponti, A., Purushotham, A. D., Regitnig, P., Del Turco, M. R., Thibault, F., & Wilson, R. (2010). Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. *Eur J Cancer, 46*(8), 1296-1316. doi:10.1016/j.ejca.2010.02.015

Shoenfeld, Y., & Agmon-Levin, N. (2011). 'ASIA' - autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun, 36*(1), 4-8. doi:10.1016/j.jaut.2010.07.003

Song, J. W., Kim, H. M., Bellfi, L. T., & Chung, K. C. (2011). The effect of study design biases on the diagnostic accuracy of magnetic resonance imaging for detecting silicone breast implant ruptures: a meta-analysis. *Plast Reconstr Surg, 127*(3), 1029-1044. doi:10.1097/PRS.0b013e3182043630

Sorkin, M., Qi, J., Kim, H. M., Hamill, J. B., Kozlow, J. H., Pusic, A. L., & Wilkins, E. G. (2017). Acellular Dermal Matrix in Immediate Expander/Implant Breast Reconstruction: A Multicenter Assessment of Risks and Benefits. *Plast Reconstr Surg, 140*(6), 1091-1100. doi:10.1097/prs.0000000000003842

Swerdlow, S. H., Campo, E., Pileri, S. A., Harris, N. L., Stein, H., Siebert, R., Advani, R., Ghielmini, M., Salles, G. A., Zelenetz, A. D., & Jaffe, E. S. (2016). The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood, 127*(20), 2375-2390. doi:10.1182/blood-2016-01-643569

Tang, S. Y., Israel, J. S., & Afifi, A. M. (2017). Breast Implant Illness: Symptoms, Patient Concerns, and the Power of Social Media. *Plast Reconstr Surg*. doi:10.1097/prs.0000000000003785

Tugwell, P., Wells, G., Peterson, J., Welch, V., Page, J., Davison, C., McGowan, J., Ramroth, D., & Shea, B. (2001). Do silicone breast implants cause rheumatologic disorders? A systematic review for a court-appointed national science panel. *Arthritis Rheum, 44*(11), 2477-2484.

Watad, A., Quaresma, M., Bragazzi, N. L., Cervera, R., Tervaert, J. W. C., Amital, H., & Shoenfeld, Y. (2018). The autoimmune/inflammatory syndrome induced by adjuvants (ASIA)/Shoenfeld's syndrome: descriptive analysis of 300 patients from the international ASIA syndrome registry. *Clin Rheumatol, 37*(2), 483-493. doi:10.1007/s10067-017-3748-9

Watad, A., Rosenberg, V., Tiosano, S., Cohen Tervaert, J. W., Yavne, Y., Shoenfeld, Y., Shalev, V., Chodick, G., & Amital, H. (2018). Silicone breast implants and the risk of autoimmune/rheumatic disorders: a real-world analysis. *Int J Epidemiol, 47*(6), 1846-1854. doi:10.1093/ije/dyy217

Webb, L. H., Aime, V. L., Do, A., Mossman, K., & Mahabir, R. C. (2017). Textured Breast Implants: A Closer Look at the Surface Debris Under the Microscope. *Plast Surg (Oakv), 25*(3), 179-183. doi:10.1177/2292550317716127