A comparison of the incidence of both benign and malignant breast tumors following breast implantation in the Core Clinical Study with comparable epidemiologic data of patients without breast implants is provided below. Copies of cited literature are provided in Attachment 14.

Benign Breast Tumors

Benign breast conditions causing lumps or tumors are quite common in women (American Cancer Society 2002, Dolan 2002, Johnson 1999, Marchant 2002), with an estimated 9 out of 10 women showing benign tissue changes if tissue is examined microscopically (American Cancer Society 2002). The most prevalent benign breast diseases involving tumors or lumps are fibrocystic disease and dominant lumps. Dominant lumps are defined as clinically benign breast lesions that are distinct, persistent, and relatively unchanging, and include fibroadenomas, gross cysts, and galactoceles (Johnson 1999).

Despite the apparent widespread nature of benign breast conditions, their incidence does not appear to have been widely studied (Johnson 1999, Marchant 2002). In fact, in a review of benign breast disease, Johnson (1999) states that the subjective nature of these conditions makes accurate estimation of their incidence nearly impossible. Inamed identified data from several sources and their results were highly variable. The self-reported incidence of fibrocystic disease or other benign breast disease was found to be 30.9 per 1000 person-years (3.9%) in The Nurses' Health Study II (Webb et al. 2002). This study found that the incidence increased with age from a rate of 22.6 per 1000 person-years (2.3%) for women ages 25-29 to 35.6 per 1000 person-years (3.6%) for women ages 40-44.

Other sources estimate the incidence of fibrocystic disease alone to be as high as 60% of all women (Dolan 2002), and a recent review of benign breast disease by Marchant (2002) indicates that although the precise incidence is not known, fibrocystic changes have been identified in 54% of autopsies of clinically normal breasts, 34% of breast biopsies, and 40% of all breasts with cancer.

Reports of the incidence of dominant lumps are more rare. The incidence of fibroadenoma is highest in younger women under 30, whereas gross cysts are more common in older women (Johnson 1999, Marchant 2002), with Johnson (1999) reporting an estimate of 15% of postmenopausal women having dominant lumps.

In Inamed's Core Clinical Study, 29 of 494 augmentation patients (5.9%), 10 of 221 reconstruction patients (4.5%), and 16 of 225 revision patients (7.1%) had some type of benign breast disease (*e.g.*, fibrocystic disease, cyst, or other benign mass or lump). The proportion of women in the Core Clinical Study with benign breast tumors is far lower than the majority of rates reported in the literature among women without breast implants.

Malignant Breast Tumors

Breast cancer is the most common cancer among women in the U.S. The incidence of invasive breast cancer age-adjusted to the 2000 census is 134.1 per 100,000 women (0.13%), and the incidence of breast cancer *in situ* is 28.8 per 100,000 women (0.03%) (U.S. Cancer Statistics Working Group 2002). These data were chosen as representative of the publicly available information for the purposes of this response because they are so widely cited by other authors. No additional independent references were identified that differed substantially from the census results.

In Inamed's Core Clinical Study, 1 of 494 augmentation patients (0.2%) and 5 of 221 reconstruction patients (2.3%) had malignant breast cancer. No revision patients in Inamed's study had malignant breast cancer. The rate of malignant breast cancer in the Core Clinical Study is comparable to that reported by the United States Cancer Statistics Working Group. While the rate of breast cancer in reconstruction patients is slightly higher in Inamed's study than in the general population, the majority of women in the reconstruction cohort had breast cancer prior to the study and thus, they were likely to have been at increased risk.

References

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U.S. Cancer Statistics Working Group. 2002. United States Cancer Statistics: 1999 Incidence. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute.

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The scientific literature was surveyed to obtain information on the rates of abnormal mammograms and subsequent diagnostic procedures in the general population of women without breast implants. Copies of cited literature are provided in Attachment 14. The rates of abnormal mammograms provided for comparison to the patient population in the Core Clinical Study are from large cohort or population-based studies, including several from the Mammography Screening and Outcomes Database of the Breast Cancer Surveillance Consortium (Ballard-Barbash et al. 1997).

These studies are generally consistent in their definitions of screening and diagnostic mammograms: screening mammograms were those used to detect breast changes in women who had no signs of breast cancer, and diagnostic mammograms were those performed for a variety of reasons including diagnosis of unusual breast changes, symptoms of breast cancer, or evaluation of abnormalities detected on a screening mammogram.

The majority of these studies relied upon the Breast Imaging Reporting and Data System (BI-RADS) standardized method of mammographic interpretation. This system includes the following six assessment categories (American College of Radiology 1998):

0, "incomplete assessment, need additional imaging";
1, "negative";
2, "benign finding";
3, "probably benign finding";
4 "suspicious abnormality"; and
5 "highly suggestive of malignancy"

Despite the use of a systematic method for reporting mammography results, there is considerable variability in the interpretation of mammographic examinations (Kerlikowske et al. 1998), and indeed, the literature survey performed revealed a

relatively wide range of rates. As some of the women in the Inamed Core Clinical Study with abnormal mammograms had previously documented cases of benign and malignant tumors, abnormal rates of both diagnostic and screening mammograms are provided for comparison.

Abnormal Mammogram

The reported rates of abnormal findings (regardless of clinical diagnosis or cancer outcome) from screening mammograms ranged from 2.9% to 10.4% (Burnside et al. 2002, Dee and Sickles 2001, Kerlikowske et al. 1996, Mushlin et al. 1998, Poplack et al. 2000, Sohlich et al. 2002, Taplin et al. 2002). The rates of abnormal findings (regardless of clinical diagnosis or cancer outcome) from diagnostic mammograms ranged from 8.6% to 16.0% (Barlow et al. 2002, Burnside et al. 2002, Geller et al. 2002, Sohlich et al. 2002). These findings are detailed in Table A below. If reported by the authors, the basis for determination of an abnormal mammogram is noted.

Table A. Abnormal Mammogram Rates in Populations Without Breast Implants

Citation	Abnormal Mammogram Rate
Barlow et al. 2002	6,279/41,427 (15.2%) abnormal diagnostic mammograms
Burnside et al. 2002	1,539/38,456 (4.0%) abnormal screening mammograms (BI-RADS category 0, 4 or 5) 848/9,825 (8.6%) abnormal diagnostic mammograms (BI-RADS category 4 or 5)
Caplan et al. 1999	27,042/372,760 (7.3%) abnormal mammograms (screening or diagnostic) (BI-RADS category 0, 4 or 5)
Dee and Sickles 2001	1,925/36,850 (5.2%) abnormal screening mammograms (BI-RADS category 0, 4 or 5) 1,441/10,007 (14.4%) abnormal diagnostic mammograms (BI-RADS category 4 or 5)
Geller et al. 2002	5,096/51,673 (9.9%) abnormal diagnostic mammograms (BI-RADS category 0,4 or 5)
Mushlin et al. 1998 (with data computed from Kerlikowske et al. 1996)	1,850/26,057 (7.1%) abnormal screening mammograms
Liberman et al. 1993	1,558/14,911 (10.4%) abnormal screening mammograms
Poplack et al. 2000	1,381/47,651 (2.9%) abnormal screening mammograms (BI-RADS category 0,4 or 5)
Rosenberg et al. 2000	23,285/234,051 (9.9%) abnormal screening mammograms (BI-RADS category 0,4 or 5)
Sohlich et al. 2002	2,110/40,691 (5.2%) abnormal screening mammograms (BI-RADS category 0,4 or 5) 1,779/11,114 (16.0%) abnormal diagnostic mammograms (BI-RADS category 4 or 5)
Taplin et al. 2002	11,912/292,795 (4.1%) abnormal screening mammograms (BI-RADS category 0,4 or 5)

In Inamed's Core Clinical Study, 12 of 494 augmentation patients (2.4%), 12 of 221 reconstruction patients (5.4%), and 7 of 225 revision patients (3.1%) were reported to have

abnormal mammograms, regardless of biopsy or cancer outcome. These values have been updated since the December 2002 PMA submission, which included data available through August 30, 2002, to include more recent mammographic findings through March 27, 2003. These findings are comparable to abnormal screening mammogram rates (2.9% to 7.1%), and are lower than the abnormal diagnostic screening mammogram rates (8.6% to 16.0%) found in the literature survey for women without implants.

Additional Diagnostic Procedures Following Abnormal Mammogram

To obtain information on additional invasive or noninvasive diagnostic procedures following an abnormal mammogram in women without breast implants, the following conventions were used. For comparative purposes, reports in the literature of biopsies and fine-needle aspiration were considered by Inamed to be invasive procedures, whereas sonogram, additional follow-up mammography (such as coned mammographic views), clinical examination, and referral to surgical consult were considered to be noninvasive procedures.

Reported rates of invasive diagnostic procedures following abnormal mammograms ranged from 2.6% to 43.2% for screening mammograms (Burnside et al. 2002, Dee and Sickles 2001, Liberman et al. 1993, Poplack et al. 2000, Sohlich et al. 2002, Taplin et al. 2002) and 69.2% to 82.9% for diagnostic mammograms (Burnside et al. 2002, Dee and Sickles 2001, Geller et al. 2002, Sohlich et al. 2002). Findings for additional invasive procedures are detailed in Table B below. Reported rates of noninvasive diagnostic procedures following abnormal mammograms were 53.2% (Liberman et al. 1993), and 88.3% (Taplin et al. 2002) for screening mammograms and 17.0% (Geller et al. 2002) for diagnostic mammograms. Findings for additional noninvasive procedures are detailed in Table C below.

Table B. Additional Invasive Diagnostic Procedures Following Abnormal Mammogram in Populations Without Breast Implants

Citation	Additional Invasive Procedures
Burnside et al. 2002	472 biopsies performed out of 1,539 abnormal screening mammograms (30.7%) (BI-RADS category 0, 4, 5) 676 biopsies out of 848 abnormal diagnostic mammograms (79.7%) (BI-RADS category 4, 5)
Dee and Sickles 2001	516 biopsies performed out of 1,925 abnormal screening mammograms (26.8%) (BI-RADS category 0, 4, 5) 1,194 biopsies performed out of 1,441 abnormal diagnostic mammograms (82.9%) (BI-RADS category 4, 5)
Geller et al. 2002	2,312 patients underwent biopsy or fine-needle aspiration out of 3,339 abnormal diagnostic mammograms (69.2%) (BI-RADS category 4 or 5)
Liberman et al. 1993	40 biopsies out of 1,558 abnormal screening mammograms (2.6%)
Poplack et al. 2000	597 biopsies performed out of 1,381 abnormal screening mammograms (43.2%) (BI-RADS category 0, 4, 5)

Table B. Additional Invasive Diagnostic Procedures Following Abnormal Mammogram in Populations Without Breast Implants *(continued)*

Citation	Additional Invasive Procedures
Sohlich et al. 2002	572 biopsies performed out of 2,110 abnormal screening mammograms (27.1%) (BI-RADS category 0, 4, 5) 1,301 biopsies performed out of 1,779 abnormal diagnostic mammograms (73.1%) (BI-RADS category 4, 5)
Taplin et al. 2002	1,026 biopsies performed out of 11,912 abnormal screening mammograms (8.6%) (BI-RADS category 0,4 or 5)

Table C. Additional Noninvasive Diagnostic Procedures Following Abnormal Mammogram in Populations Without Breast Implants

Citation	Additional Noninvasive Procedures
Geller et al. 2002	567 patients underwent additional imaging or other clinical examination or surgical consult out of 3,339 abnormal diagnostic mammograms (17.0%) (BI-RADS category 4 or 5)
Liberman et al. 1993	829 noninvasive procedures performed (481 follow-up sonograms and 348 follow-up mammograms with coned views) out of 1,558 abnormal screening mammograms (53.2%)
Poplack et al. 2000	There were 1,381 abnormal screening mammograms in this study (BI-RADS category 0, 4, 5). A woman may have had more than one noninvasive procedure, thus rates were computed separately for each procedure: 229 surgical consultations (16.6%), 267 supplementary imaging procedures (19.3%), 347 ultrasound imaging procedures (25.1%), and 39 clinical breast examinations (2.8%)
Taplin et al. 2002	10,521 noninvasive procedures (10,238 additional imaging and 283 clinical exam or surgical consult) out of 11,912 abnormal screening mammograms (88.3%) (BI-RADS category 0,4 or 5)

Inamed did not prospectively collect data on additional invasive or noninvasive diagnostic procedures following an abnormal mammogram in its Core Clinical Study. These data have subsequently been obtained from the clinical sites on the 32 patients who had at least one abnormal mammogram through March 27, 2003, and they are summarized in Table D below. Although the rates of additional procedures reported in the literature vary, the data from the Core Clinical Study fall within the ranges reported in Tables B and C above.

Table D. Additional Invasive or Noninvasive Diagnostic Procedures Following Abnormal Mammogram in Inamed's Core Clinical Study

Cohort	Total in Cohort (n)	Abnormal Mammograms (n)	Invasive Diagnostic Procedure n (%)	Non-Invasive Diagnostic Procedure n (%)	No Additional Procedures (n)	No Data Available (n)
Augmentation	494	12	7* (53.8%)	2* (16.7%)	4	0
Reconstruction	221	12	6** (50.0%)	4** (33.3%)	3	1
Revision	225	7	3 (42.9%)	2 (28.6%)	1	1

* 1 augmentation patient had both additional invasive and noninvasive procedures
** 2 reconstruction patients had both additional invasive and noninvasive procedures

References

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Caplan, L.S., Blackman, D., Nadel, M., and Monticciolo, D.L. 1999. Coding mammograms using the classification "probably benign finding--short interval follow-up suggested". Am. J. Roentgenol. 172(2):339-342.

Dee, K.E. and Sickles, E.A. 2001. Medical audit of diagnostic mammography examinations: Comparison with screening outcomes obtained concurrently. Am. J. Roentgenol. 176(3):729-733.

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Kerlikowske, K., Grady, D., Barclay, J., Frankel, S.D., Ominsky, S.H., Sickles, E.A., and Ernster, V. 1998. Variability and accuracy in mammographic interpretation using the American College of Radiology Breast Imaging Reporting and Data System. J. Natl. Cancer Inst. 90(23):1801-1809.

Kerlikowske, K., Grady, D., Barclay, J., Sickles E.A., and Ernster V. 1996. Effect of age, breast density, and family history on the sensitivity of first screening mammography. JAMA 276(1):33-38.

Liberman, L., Dershaw, D.D., Deutch, B.M., Thaler, H.T., and Lippin, B.S. 1993. Screening mammography: Value in women 35-39 years old. Am. J. Roentgenol. 161(1):53-56.

Mushlin, A.I., Kouides, R.W., and Shapiro, D.E. 1998. Estimating the accuracy of screening mammography: A meta-analysis. Am. J. Prev. Med. 14(2):143-153.

Poplack, S.P., Tosteson, A.N., Grove, M.R., Wells, W.A., and Carney, P.A. 2000. Mammography in 53,803 women from the New Hampshire mammography network. Radiology 217(3):832-840.

Rosenberg, R.D., Yankaskas, B.C., Hunt, W.C., Ballard-Barbash, R., Urban, N., Ernster, V.L., Kerlikowske, K., Geller, B., Carney, P.A., and Taplin, S. 2000. Effect of variations in operational definitions on performance estimates for screening mammography. Acad. Radiol. (12):1058-1068.

Sohlich, R.E., Sickles, E.A., Burnside, E.S., and Dee, K.E. 2002. Interpreting data from audits when screening and diagnostic mammography outcomes are combined. Am. J. Roentgenol. 178(3):681-686.

Taplin, S.H., Ichikawa, L.E., Kerlikowske, K., Ernster, V.L., Rosenberg, R.D., Yankaskas, B.C., Carney, P.A., Geller, B.M., Urban, N., Dignan, M.B., Barlow, W.E., Ballard-Barbash, R., and Sickles, E.A. 2002. Concordance of breast imaging reporting and data system assessments and management recommendations in screening mammography. Radiology 222(2):529-535.

The requested information in the context of post-implant lactation problems is provided in Table 184. Although FDA did not request this same information pre-implant, the corresponding number of patients has also been added to Table 183, which addresses pre-implantation lactation problems. Specifically, a footnote, which provides the number of patients who attempted to breastfeed, was added to both tables.

In each cohort analysis, Tables 183 and 184 are provided in Attachment 2 for Core Augmentation, Attachment 3 for Core Reconstruction, and Attachment 4 for Core Revision.

From the respective tables one notices that in the Augmentation cohort, 15% of women who attempted to breast feed prior to their enrollment surgeries reported lactation complications. Following breast implantation, 16% reported complications. In the Reconstruction cohort, 22% reported pre-enrollment difficulties, while 0% reported complications post-implant. (Note: Only 2 reconstruction patients attempted to breast feed following surgery, so this sample size is extremely small.) In the Revision cohort, 20% reported lactation problems prior to enrollment in the surgery, and 44% reported problems after surgery. Inclusion in the Revision cohort was determined by the patient having had a history of at least one prior implant surgery. Therefore, patients in this category may have had multiple breast surgeries by the time they attempted to breastfeed.

In summary, the results of Inamed's study indicate that between 15% and 22% of women attempting to breast-feed prior to joining the study experienced complications. Following implantation with the study device, between 16% and 44% indicated lactation complications. Because there are no reported post-implant complications in the Reconstruction cohort, no conclusions can be drawn for this cohort. However, in the Augmentation cohort the incidence of lactation difficulties is essentially the same both pre-implant and post-implant. The percentage of lactation complications in the Revision cohort is higher post-implantation than pre-implantation. However, this is consistent with the literature[1,2] that describes a varying degree of lactation difficulties in women after breast surgery, regardless of whether or not implants are placed during the surgery.

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[1] Institute of Medicine, Committee on the Safety of Silicone Breast Implants. 2000. *Safety of Silicone Breast Implants. Effects During Lactation.* Bondurant, S., V. Ernster, and R. Herdman, editors. National Academy Press, Washington, D.C. pages 193-199. [http://books.nap.edu/books/0309065321/html/index.html]

[2] Inamed Corporation. 2002. *Interference with Breast Feeding*, PMA P020056, Module 5, Volume 11, Attachment 18, pages 26-27 (Previously submitted to FDA as part of the Literature Discussion).

Literature Discussion

Beraka (1995) cited three case reports, in which "the sequence of events was very suggestive of implant rupture during mammography. There was a unilateral rupture in two of the patients and bilateral rupture in the third. All these patients had subglandular silicone gel implants. In each of the affected breasts, there was sudden severe pain on compression during mammography, and this pain lasted several days. These patients had class II or III capsular contracture. One patient underwent augmentation 20 years ago and the other two within the last 5 years. In one patient the pain on breast compression radiated toward the twelve o'clock position, which was where the free silicone tracking in the breast tissue was seen on the mammogram."

Pickford and Webster (1994) discussed a single case report, in which the patient experienced vague discomfort within her right breast approximately two weeks after a routine screening mammography. During the routine screening of this patient, additional films had to be taken since the initial films were considered inadequate. The patient recalled "significant compression being applied to the breasts to obtain satisfactory radiographs on the second occasion, but experienced no immediate discomfort." Pickford and Webster indicated that the clinical suspicion of rupture was subsequently confirmed during surgery when the right prosthesis was found to have been ruptured. They attributed the implant rupture to be due to the compressive forces applied during mammography.

Williams (1991) described a single case report of a woman who "presented with pain and swelling over the lateral chest wall and adjacent axillary region following a mammogram a few weeks before." The patient observed that "during this procedure, when more compression than usual had been applied, she noted a 'popping' sensation at the time of the exposure." Approximately three weeks later an additional mammogram was performed. "It was noted that a number of irregular globules now appeared on the film where the previous mammogram showed implant distortion." The right implant was found, upon surgical investigation, to be "extensively ruptured, with silicon[e] lying free in the cavity and the bag collapsed within the silicon[e] gel."

Eklund (1990) described a case of 'capsulotomy' (as opposed to rupture) occurring during mammography. During the mammographic procedure, "an audible pop was heard when the compression paddle was applied in the oblique position." The breast that had been firm and erect, was "suddenly soft; it had a normal contour, but also normal droop". The breast was imaged a second time and no change was observed with respect to the first film. Eklund recognized that, since capsulotomy can occur then, "the possibility of damage to an implant by compression during mammography certainly exists, although the event must be extremely rare." However, Eklund cautioned, "Although I applaud the reporting of this event, it should not deter continued appropriate mammographic imaging of the augmented breast."

De Camara *et al.* (1993) provided the findings of a retrospective study of silicone gel breast implants in 31 women. Three patients "described severe burning pain in the breast, radiating to the axilla during mammography. Change in the contour of the breast also was noted. All three of these patients had removal of ruptured older implants ranging from 8 to 14 years." De Camara indicated that "mammograms are usually not considered traumatic and are commonly performed in the augmented and reconstructed breast." However, in light of his findings, he recommended that "mammography may need to be performed more carefully with the older silicone implant."

Although these reports consist primarily of "anecdotal" case studies, in which it is difficult to draw conclusions as to the "significance" of this event, the literature suggests that mammography can produce sufficient compressive forces to result in implant rupture. Furthermore, the literature also demonstrates that routine mammographic screening has been identified as possibly contributing to gel-filled breast implant rupture or as a potential source of damage to the implants.

References

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De Camara DL, Sheidan JM, Kammer BA, 1993. Rupture and aging of silicone gel breast implants. *Plast Reconstr Surg.* 91:828-34.

Eklund GW. 1990. Collapse of a breast implant after mammography. Reply. *AJR Am J Roentgenol.* Jun;154(6):1345-6.

Pickford MA, Webster MH. 1994. Implant rupture by mammography. *Br J Plast Surg.* Oct;47(7):512.

Williams CW. 1991. Silicone gel granuloma following compressive mammography. *Aesthetic Plast Surg.* Winter;15(1):49-51.

In the literature review previously submitted in Module 5, the topics of gel bleed and rupture were discussed on page 28 of Attachment 18 in Volume 9. The citation for the information referenced in the question above was inadvertently omitted from the text. However, the citation was provided in Table 7 of Attachment 18, on page 38 (Robinson et al. 1995), with the complete reference provided on page 115. That reference is as follows: Robinson, C.G., Bradley, E.L., and Wilson, D.S. 1995. *Analysis of explanted silicone implants: a report of 300 patients. Ann. Plast. Surg.* 34:1-7. A copy of this reference, as well as any references cited below, are provided in Attachment 14.

As indicated above, the topics of gel bleed and rupture were addressed in the literature discussion (Module 5, Attachment 18), provided on page 28. As part of that discussion, literature concerning silicone migration and extravasation and the resulting potential outcomes of lymphadenopathy and silicone granulomas were also identified and cited. However, Inamed is providing the following literature discussion to expand on the issue of the consequences of gel migration.

Silicone migration can result from either the passage of minute amounts of the gel through the intact silicone elastomer envelope ("gel bleed") or from the release of gel due to rupture of the envelope. Closed capsulotomy, which has been linked by some investigators to implant rupture and/or leakage, subsequently could result in release of extracapsular silicone. Therefore, this procedure is strongly discouraged in Inamed's product literature.

A local site of migration for silicone gel released from breast prostheses has been the breast parenchyma (Argenta, 1983) or lactiferous ductal system. Gel expressing from the nipples has been described by Holten and Barnett (1995) and commented upon by Bloomenstein (1995). Implant rupture accompanied by breaches in the capsule can allow extracapsular gel to infiltrate the breast tissue. Depending on the clinical findings, removal of the extruded gel may include the sacrifice of breast parenchyma.

One of the most commonly reported migration sites for silicone gel released from breast prostheses has been the regional (i.e. axillary) lymph nodes. As a consequence of gel migration to the lymph nodes, silicone associated lymphadenopathy (considered

generally to be any disease that affects a lymph node or nodes) and/or lymphedema (swelling as a result of an obstruction of lymphatic vessels or nodes that causes a build up of lymph in the affected region) may develop. Hausner et al. (1978 and 1981) described case reports in which a foreign body reaction to silicone gel was evident in the axillary lymph nodes eight to ten years after implantation surgery. As discussed by Brown and coworkers (1997) "Many case reports and series have described migration to the axillary nodes. Silicone lymphadenopathy in the absence of apparent rupture has also been reported". Lymphadenopathy and lymphedema were previously discussed in the literature review in Module 5 on page 36 of Attachment 18.

Additionally, the bulk movement of gel released from the breast implant to distant locations in the body has been described in the literature. "Silicone gel can also migrate from breast implants through soft tissues to a variety of sites including the antecubital fossa, the upper arm, the chest and shoulder, and along the chest and abdominal walls as far as the groin" (Travis et al. 1985). This review article by Travis and his coauthors also noted that rupture was evident in each of the cases in which distant migration of silicone occurred. This observation of distant migration of silicone gel following rupture of gel-filled prostheses has been described historically by a number of authors (Ahn and Shaw 1994, Capozzi et al. 1978, Foster et al. 1983, Goin 1978, Hirmand et al. 1994, Huang et al. 1978, Mason and Apisarnthanarax 1981, Persellin et al. 1992, Teuber et al. 1995).

Other consequences of silicone migration may include "silicone granulomas," "silicone nodules" and "siliconomas", which have been discussed in the literature (Anderson et al. 1996, Meyer et al. 1998, Teuber et al. 1999). These terms all describe soft masses of encapsulated silicone material found in tissue, and refer to a normal response of the body to foreign material; they do not represent a preneoplastic growth, nor are they associated with any type of carcinogenesis. As stated by Austad (2002), "it is particularly important to note that the formation of a granuloma is not a disease process but rather a type of foreign body reaction. The 1998 report of the Independent Review Group to the British government states this quite succinctly: 'The overall biological response to silicone is consistent with conventional forms of response to foreign materials, rather than an unusual toxic reaction.'" Previously, silicone granulomas were addressed and a frequency rate was provided in the Module 5 literature review on page 36 of Attachment 18.

Regarding the clinical significance of the outcome of gel migration (i.e., silicone granulomas and silicone lymphadenopathy), a review by Travis and coauthors (1985) generally concluded that "critical reassessment of the silicone-related complications reported to date seems to support the continued use of most of the currently available silicone-containing medical prostheses and equipment". A comment was also included by Nalbandian et al. (1983) that "the low incidence and relatively minor consequences of foreign body reactions in the synovium or regional lymph nodes do not constitute a contraindication to the use of silicone as a prosthetic implant material."

Few authors have provided frequency rates for gel migration. Two recent references, Brown et al. (2002) and Robinson et al. (1995), were previously provided in the Module 5 literature discussion and their findings are reiterated below; Nelson (1980) is provided

for historical perspective. Brown et al. (2002) reported that out of 344 women in their study, 73 women (9.6%) had extracapsular silicone detected. Robinson et al. (1995) reported 20% (60/300) of patients experienced gel bleed or migration. Nelson (1980) reported on the results of a physician survey of 756 physicians. Of the 756 physicians participating in the survey, five cases of distant migration were reported out of the estimated 114,617 silicone gel-filled breast implant augmentation procedures performed. This represents an incidence rate of approximately 0.004%.

In addition to the review of the literature provided above, information pertinent to silicone gel bleed and migration is available from the Inamed complaint system. Migration of silicone gel from silicone-filled breast prostheses has been the subject of several gel-filled breast implant Inamed complaints and MDR filings. A total of 37 MDRs for gel migration for the devices that are the subject of this PMA have been reported to FDA over the past ten years. An analysis of the Inamed complaint database indicates a 0.02% incidence rate of complaints for gel migration.

Furthermore, information pertinent to silicone gel bleed and migration is available from a review of the Inamed Core Clinical Study data. Physician evaluations of explanted devices were collected regarding the presence of *Gel on Implant Surface* and *Extracapsular Gel* in Inamed's Core Clinical Study of McGhan Silicone-Filled Breast Implants. Of the 31 explanted patients (58 implants) in the Augmentation Cohort, physicians observed 2 ruptured implants with surface gel, while no gel was observed either on the implant surface or extracapsular for the other 56 intact devices. Of the 46 explanted patients (56 implants) in the Reconstruction Cohort, physicians observed 6 ruptured implants with surface gel; no gel was observed either on the implant surface or extracapsular for the other 50 intact devices. Of the 27 explanted patients (46 implants) in the Revision Cohort, physicians observed 2 ruptured implants with surface gel, while no gel was observed either on the implant surface or extracapsular for the other 44 intact devices. Please refer to Table 175 in each cohort for physician evaluations of explanted devices in the Core Clinical Study (Attachment 2 for Core Augmentation, Attachment 3 for Core Reconstruction and Attachment 4 for Core Revision).

While a review of the literature, Inamed complaint database and Core Clinical Study data all indicate that the migration/bleed of silicone gel from silicone-filled breast implants can occur, it should also be noted that silicone-filled breast prostheses are not the only source of polydimethylsiloxanes to which individuals are exposed. The widely used antiflatulent, simethicone, is composed of polydimethylsiloxanes. Silicones are used in a variety of medical devices, including use as internal lubricants in disposable syringes. The lifelong repeated exposure to silicone associated with these other medical uses provides a useful perspective on human exposure to silicones from silicone-filled breast prostheses. There has been no evidence to indicate the accumulation of silicone from regular exposure to these other medical devices is harmful to patients.

Furthermore, the National Science Panel appointed by the Honorable Sam C. Pointer Jr. "reaffirmed the low systemic toxicity of silicone." The report reiterated that "results of this review indicate that the silicones used in SBIs [silicone breast implants] are of very

low toxicity to animals. Although there is documented evidence of local inflammatory reactions to silicone breast implant materials in animals, there is no convincing evidence for a significant systemic inflammatory response. The local reaction to silicone is similar to other 'foreign body reactions' described with other implanted materials." In its conclusion, the National Science Panel confirmed that "the preponderance of evidence from animal studies indicates little probability that silicone exposure induces or exacerbates systemic disease in humans." (Diamond et al. 1998)

In summary, as stated by the Independent Review Group (IRG) (1998), "the effects of a rupture may be local and/or regional. There are reports of silicone gel having migrated to distant parts of the body such as the arm or trunk, but these are rare." Moreover, the IRG indicated that "in the vast majority of extracapsular ruptures the gel is still in the region of the original pocket and can be removed when the ruptured implant is removed." Although silicone lymphadenopathy and granulomas do occur, their clinical significance is questionable. As stated by IRG, "The substantial risk of implants, as shown in experiments in animals and in other laboratory studies, and as borne out by the much more limited investigation of samples from women with implants, are local inflammatory and scarring reactions, and local infection, as around any foreign body in the tissues." The IRG concluded that "there has been no clinical, laboratory or pathological indication of unusual or unique types of reaction."

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