

## Literature

- 32. The literature information provided in Sections 5.1 and 8.6 did not adequately discuss the issue of potential systemic health consequences of extracapsular gel and migrated gel. Please provide a detailed summary of all reasonably available literature regarding this issue. Please provide copies of all references cited.**

32 Response:

Aside from the need for reoperations in the event of rupture, potential concerns have been raised over whether device rupture, and extracapsular and migrated silicone gel in particular, might be associated with systemic health consequences, such as the development of connective tissue diseases (“CTD”), rheumatic diseases, and/or related symptoms. The composite of well-designed, CTD and related population-based epidemiology studies that have evaluated this issue, do not support such an association (see table below for a summary of the literature related to this issue). All copies of the cited references are provided in Attachment 32.

A number of the more recent questions concerning a potential association between extracapsular and/or migrated silicone subsequent to device rupture and CTD derive from a study by Brown et al. (2001).<sup>1</sup> In this study, the potential association between breast implant rupture, extracapsular silicone, and various adverse health outcomes was evaluated among 344 MRI-assessed patients with silicone gel breast implants (687 implants) selected from a larger cohort of women in Alabama. These women underwent MRI evaluation to determine the status of their breast implants and completed a questionnaire on health status, satisfaction with implants, symptoms of connective tissue disease, and self-reported, physician-diagnosed connective tissue disease. Evidence of extracapsular gel was observed by MRI in 85 of 687 implants (12.4%) in 73 of 344 women (21.2%). It is important to note that, while not specified, it can be assumed that the extracapsular ruptures were primarily, if not entirely, first and/or second generation implants, as only one third generation implant was reported to be ruptured in this study. These authors noted a potential association between extracapsular silicone (MRI-assessed) and self-reported fibromyalgia as compared to women with intact implants and women with total ruptures (intracapsular and extracapsular), combined ( $p=0.004$ , OR = 2.7, 95% CI =1.4-5.2). No increase in the report of any symptoms was noted in the women with extracapsular silicone as compared to all other women.

This study has a number of important design and analysis issues, however, that limit the relevance of the findings to this PMA. First, because the fibromyalgia information was self-reported and not confirmed by physical examination or medical records, it is not possible to assess whether the fibromyalgia was present prior to implant surgery. Second, only when patients with intact and intracapsular ruptured devices were combined and compared to the patients with extracapsular rupture in the analysis, was a significant association noted with self-reported fibromyalgia. Comparison of patients with extracapsular rupture to patients with intact implants, showed no significant association with self-reported fibromyalgia (OR

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<sup>1</sup> Brown, S.L., et al. 2001. Silicone gel breast implant rupture, extracapsular silicone, and health status in a population of women. *J. Rheumatol.* 28:996-1003.

= 1.88, 95% CI = 0.83-4.29).<sup>2</sup> Similarly, when the incidence of self-reported fibromyalgia for any rupture was compared to intact implants, the difference was not statistically significant (OR = 0.84, 95% CI = 0.44-1.79).<sup>3</sup> Moreover, Brown et al.'s finding that the group of women with intracapsular rupture had a lower rate of fibromyalgia reports than women with either intact implants or extracapsular ruptures casts doubt on a plausible role for silicone gel in the development of fibromyalgia.<sup>4</sup> Third, the fibromyalgia report rates are high in all implant status groups in Brown et al.'s study (13.1% for all ruptures, 14.8% in intact) when compared with the estimated prevalence rate for fibromyalgia of 3.4% in U.S. women.<sup>5</sup> Last, as no significant differences were noted in any symptoms related to fibromyalgia (including joint symptoms and fatigue) between any of the groups, it is difficult to conclude that the statistical association found between self-reported fibromyalgia and extracapsular rupture is clinically meaningful.

Other studies of women with ruptured breast implants and long-term follow-up, including Malata et al. (1994), Berner et al. (2002), Contant et al. (2002), Gaubitz et al. (2002), Hölmich et al. (2003), and Hölmich et al. (2004),<sup>6</sup> do not support an association between rupture, extracapsular/migrated silicone gel, and systemic health consequences. Several of these studies (Malata et al. 1994, Berner et al. 2002, Contant et al. 2002) did not distinguish between intra- and extracapsular ruptures, but, in general, no increased incidence of systemic complaints, signs, or symptoms, blood silicon levels, laboratory indices of immune function, and/or antinuclear antibodies was noted in women with ruptured implants in these studies (see table). One exception was reported in a study by Berner et al. (2002), in which various self-reported symptoms among 96 breast cancer patients with silicone breast implants (32 patients, with an average follow-up of 7 years) and a matching control of 64 breast cancer patients with no breast implants were assessed. No physical examination or laboratory studies were conducted. The study reported that "positive correlation with implant rupture [assessed by MRI imaging] was given only for the numb feeling/tingling sensation in extremities." There was no significant difference observed for 24 other arthralgia and

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- 2: Bowling, S.J. 2001. Correspondence: Silicone gel breast implants. *J. Rheumatol.* 28(12):2760-1; Bowling, S.J. 2002. Correspondence: Silicone gel breast implants. *J. Rheumatol.* 29(11), 2468-9
- 3: *Id*
- 4: Lipworth, L., et al. 2004. Breast implants and fibromyalgia. A review of the epidemiologic evidence. *Ann Plast Surg.* 54(3):284-7; Bowling, S.J. 2001. Correspondence: Silicone gel breast implants. *J. Rheumatol.* 28(12):2760-1; Bowling, S.J. 2002. Correspondence: Silicone gel breast implants. *J. Rheumatol.* 29(11), 2468-9
- 5: Wolfe, F., et al. 1995. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum.* 38:19-28.
- 6: Malata, C.M., et al. 1994. Silicone breast implant rupture: common/serious complication? *Medical Progress through Technology* 20:251-60; Berner, I., M. et al. 2002. Comparative examination of complaints of patients with breast-cancer with and without silicone implants. *Eur. J Obstet. Gynecol. Reprod. Biol.* 102:61-66; Contant, C.M., et al. 2002. A prospective study on silicone breast implants and the silicone-related symptom complex. *Clin Rheumatol* 2:215-9; Gaubitz, M., et al. 2002. Silicone breast implants: correlation between implant ruptures, magnetic resonance spectroscopically estimated silicone presence in the liver, antibody status and clinical symptoms. *Rheumatology* 41:129-35; Hölmich, L.R., et al. 2003. Incidence of silicone breast implant rupture. *Arch. Surg.* 138:801-6; Hölmich, L.R., et al. 2004. Untreated silicone breast implant rupture. *Plast Reconstr. Surg.* 114:204-14.

myalgia symptoms. The study authors noted that “there was no correlation between silicone implants and the symptoms of the ‘chronic-fatigue syndrome’ nor any other described silicone-induced disease,” and concluded that, “according to [their] analysis, many of the symptoms examined . . . are present in middle-aged women regardless of silicone implants and underlying disease,” and that, with the possible exception of numb/tingling sensation in the extremities, the “assumption that in particular the leakage of silicone induced these complaints does not seem to be supported.”<sup>7</sup>

Vermuelen and Scholte (2003)<sup>8</sup> reported that, among 131 women who were informed that their silicone breast implants were ruptured, a statistically increased incidence of self-reported complaints of debilitating chronic fatigue, impaired short-term memory or concentration, multi-joint pain, and postexertional malaise lasting more than 24 hours was noted as compared to women with intact implants. This study also has a number of important design issues that cast doubt on the validity of the findings. The women who participated in this study were readers of the Dutch silicone breast implant support group magazine who responded to a questionnaire sent by the study authors. This highly selected population likely introduced a serious bias, because women who read this publication probably experience problems that they attribute to their breast implants. Moreover, because the implant rupture status and symptoms were self-reported, and during an unspecified period of time, it is difficult to determine whether the symptoms arose prior to or after rupture occurred.

Those studies that specifically address systemic health consequences of extracapsular and/or migrated silicone are discussed below. Gaubitz et al. (2002)<sup>9</sup> studied 90 consecutive women by MRI for implant rupture, and magnetic resonance spectroscopy (“MRS”) for the presence of silicone in the liver (mean implant duration of 9.1 years). The women also completed a questionnaire for self-reported symptoms, and underwent physical examination by a rheumatologist and antibody screening. Of the 24 women with implant defects identified by MRI, 6 were extracapsular, and in 5 patients, both intra- and extracapsular ruptures were identified. With one exception, there was no association between the presence of migrated silicone in the liver (as determined by MRS) and CTD signs and symptoms. “Tingling/numbness of the fingers” was reported at a high incidence in all women, but the incidence was significantly higher in women with silicone detected in the liver as compared to women with no silicone detected in the liver (82.1% versus 51.6%, p=0.006). The authors noted that “the increased prevalence of tingling/numbness of the fingers has not yet been correlated with an objectively measurable neuropathy.”<sup>10</sup> While a positive antinuclear

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

8. Vermeulen, R.C.W., and Scholte, H.R. 2003. Rupture of silicone gel breast implants and symptoms of pain and fatigue. *J Rheumatol* 30:2263-7.

9. Gaubitz, M., et al. 2002. Silicone breast implants: correlation between implant ruptures, magnetic resonance spectroscopically estimated silicone presence in the liver, antibody status and clinical symptoms. *Rheumatology* 41:129-35

10. The lack of an association between silicone gel breast implants and neurological disease was stated in the IOM report and further strengthened by the full publication in 2001 of an updated and expanded Danish study by Winther et al. (Winther, J.F., et al. 2001. Neurological disease among women with silicone breast

response was detected in significantly more women with silicone in the liver, the incidence of antinuclear antibody positivity did not differ significantly from that found in women of comparable age. The results of this study led the authors to conclude that “implant integrity has no major impact on rheumatic symptoms of women with [silicone breast implants],” and “there is no strong evidence of silicone-related damage in women with [silicone breast implants].”

Hölmich et al. (2003)<sup>11</sup> examined a range of self-reported diseases and symptoms, as well as antinuclear antibodies, among 238 randomly selected Danish women with cosmetic silicone breast implants. Patients in this study (with an average follow-up of 14 years) were categorized based on the rupture status (MRI-assessed) of their implants (146 patients with intact implants, 92 patients with definite rupture, of whom 23 had extracapsular rupture). Women with ruptures (both intra- and extracapsular) were more likely to have implant durations of greater than 16 years (*i.e.*, first or second generation implants) as compared to women with intact implants. After adjusting for age and implant characteristics, there was no difference in the occurrence of self-reported disease or symptoms, nor was there a difference in the presence of antinuclear antibodies between women with intact implants, and women with ruptured implants, including extracapsular ruptures. Based on their findings, the study authors concluded that “this study of unselected women with silicone breast implants could establish no association between silicone implant rupture and specific diseases or symptoms related to connective tissue disease or other rheumatic conditions . . .”

In a continuation of their earlier study, Hölmich et al. (2004)<sup>12</sup> compared the results of a second MRI examination two years later on 64 women who had at least one ruptured implant at the first MRI examination and 98 women who had intact implants at both examinations. Blood samples were also obtained from most of the women in both groups to assess antinuclear antibodies, rheumatoid factor immunoglobulin M antibodies, and cardiolipin immunoglobulin G and M antibodies. No increase in autoantibody seropositivity was

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implants in Denmark. *Acta Neurol. Scand.* 103:93-96) that found no causal association between silicone breast implants and neurological disease. Those results were consistent with the previously published large epidemiological study from Sweden (Nyrén, O.L., et al. 1998. Breast implants and risk of neurologic disease. *Neurology.* 50:956-961). In this Danish study, neurologic disorders were examined in a new cohort of 1,653 women with cosmetic breast implants from private clinics (their previous study had examined women who received cosmetic breast implants in public hospitals) in comparison with a cohort of 1,736 who underwent other cosmetic surgery at the same clinics (with a mean follow-up of 6.9 years). Data from these two cohorts were compared with the Danish National Registry of Patients. Overall, the relative risks for cohorts for any of the neurologic diseases were comparable. These investigators also conducted a further analysis in which two additional years of follow-up (with a mean follow-up of 8.9 years) were added to the public hospital cohorts. The implant cohorts were then combined (2,761 women), and compared with the combined comparison cohorts (8,787 women). No significant excess risk of overall neurologic disease was observed in the combined breast implant cohort, while a statistically significant relative risk was observed in the combined comparison cohort, leading the authors to conclude that there is no causal association between silicone breast implants and neurological disease. This expanded report more than doubled the population of Danish cosmetic breast implant patients previously studied, and provided sufficient statistical power to exclude excess relative risks of about two-fold.

11. Hölmich, L.R., et al. 2003. Incidence of silicone breast implant rupture. *Arch Surg.* 138:801-6.

12. Hölmich, L.R., et al. 2004. Untreated silicone breast implant rupture. *Plast Reconstr Surg.* 114:204-14.

observed in women with untreated ruptures, and in fact, a number of women who were seropositive for one or more antibodies two years prior became seronegative at the subsequent examination.

Overall, these studies, ranging from an average follow-up of 7 to over 16 years, and in the aggregate evaluating well over 2,500 women with silicone breast implants, provide reasonable assurance that rupture of silicone breast implants, and in particular, extracapsular and/or migrated silicone, is not associated with connective tissue or rheumatic diseases or related systemic symptoms.

**SUMMARY OF LITERATURE ON THE SYSTEMIC HEALTH CONSEQUENCES OF EXTRACAPSULAR AND MIGRATED SILICONE GEL**

CITATION	IMPLANT GENERATION/ DURATION OF IMPLANTATION	STUDY DESIGN/ENDPOINTS	RESULTS
Malata et al. 1994	Likely second generation  Mean implant duration 7 years (intact and ruptured)	Prospective study of 51 patients (83 breasts) who underwent revisional breast implant surgery (for significant capsular contracture, suspected prosthesis rupture, or unrelieved implant-induced anxiety).  Preoperative assessments included: assessment of axillary and systemic lymphadenopathy and hepatosplenomegaly; screening for autoantibodies; blood silicon levels; erythrocyte sedimentation rate; and standard biochemical and hematological screening.	Implant rupture was confirmed at surgery in 14 women (19 breasts, 23% incidence); all ruptured implants were manufactured at least 10 years prior to the study with a mean implantation duration of 12 years; the presence of extracapsular silicone was not reported.  Mean blood silicon levels were normal  Clinical exam revealed no lymphadenopathies or systemic complications; no hematological abnormalities were found; and bone biochemistry and liver function tests were normal in the patients with ruptured implants.  The mean erythrocyte sedimentation rate in the patients with ruptured implants was 6 mm/hour.  Only one patient, who had bilateral ruptured implants had elevated autoantibodies (ANA, peritidal, mitochondrial, smooth muscle, and reticulin), but this patient had pre-existing autoimmune pernicious anemia prior to breast augmentation.
Brown et al. 2001	First n=12 Second n=316 Third: n=6 Unknown: n=9 (from Brown et al. 2000)	A cohort of 344 women with 687 implants from the NCI study in Alabama underwent MRI evaluation to determine the status of their breast implants and completed a questionnaire on health status, satisfaction with implants, symptoms of connective tissue disease, and physician-diagnosed connective tissue disease ("CTD") (i.e., self-reported physician-diagnosed CTD); no physical exam or laboratory studies were conducted.	Evidence of extracapsular gel seen in 85 of 687 implants (12.4%) in 73 of 344 women (21.2%); rupture was evident in all but one of these implants; while not specified, it is assumed that these implants were primarily, if not entirely first and/or second generation as only one rupture was observed in third generation implants.  No increase in the report of any symptoms was noted in the women with extracapsular silicone as compared to all women with intact or intracapsular ruptured implants: there was a significant association between extracapsular silicone and self-reported fibromyalgia

CITATION	IMPLANT GENERATION/ DURATION OF IMPLANTATION	STUDY DESIGN/ENDPOINTS	RESULTS
			(p=0.004; OR, 2.7, 95% CI, 1.4-5.2) and other self-reported connective tissue disease, including dermatomyositis, polymyositis, Hashimoto's thyroiditis, mixed connective tissue disease, pulmonary fibrosis, eosinophilic fasciitis, and polymyalgia (p=0.008) as compared to all women with intact or intracapsular ruptured implants.
Bernier et al. 2002	Generation not reported, mean implant duration: 6.9±4.6 years	Matched-pair analysis of 96 women with breast cancer (32 with silicone breast implants from the investigators' outpatient clinic and 64 without implants selected from a cohort of over 1,100 breast cancer patients); MRI evaluation of breast implant status and self-reported symptoms/complaints (questionnaire); no physical exam or laboratory studies were conducted.	<p>An implant "defect" was identified by MRI in 41% of the women with breast implants, and 11% of the women required a second surgical procedure to remove ruptured implants; the presence of extracapsular silicone was not reported.</p> <p>While statistically significant increases in 6 of the 24 symptoms were reported by all women with implants, only "numb/tingling sensation in the extremities" was reported at a statistically significantly greater incidence in women with ruptured implants (84% versus 45%, p=0.02).</p> <p>Based on these results, with the possible exception of "numb/tingling sensation in the extremities, the investigators concluded that the leakage of silicone is not related to systemic complaints.</p>
Contant et al. 2002	Likely third generation; implant duration: 1 year	Prospective study of 57 consecutive breast cancer patients (87 implants) who underwent immediate reconstruction with silicone breast implants; MRI evaluation of implant status at 1 month and 1 year after surgery; just prior to surgery and at 1 year, sera collected for measurement of antinuclear antibodies, and screening for self-reported silicone-related symptom complex complaints (Sjögren's syndrome; rheumatoid arthritis; Raynaud's phenomenon; and	Three implants were determined to be ruptured (intracapsular) by MRI; none of these three women reported silicone-related symptom complex complaints or were antinuclear antibody positive at 1 year.

CITATION	IMPLANT GENERATION/ DURATION OF IMPLANTATION	STUDY DESIGN/ENDPOINTS	RESULTS
		undefined complaints) by questionnaire; no physical exam.	
Gaubitz et al. 2002	Mean implant duration: 9 years (40% >10 years; 60% <10 years)	90 consecutive women with silicone breast implants from investigators' outpatient gynecological clinic (142 implants, 76% reconstruction; 24% cosmetic) underwent the following assessments: MRI evaluation for implant status; questionnaire for self-reported symptoms; magnetic resonance spectroscopy to determine the presence of silicone in the liver; physical examination by a rheumatologist; and antibody screening.	<p>Implant defects identified by MRI in 24 (26.6%) of the women: 23 ruptures were intracapsular; 6 were extracapsular; and in 5 patients, both intra- and extracapsular ruptures were identified by MRI; silicone was detected in the liver in 13 (54.2%) of these women with implant defects (silicone was detected in the liver of 15 (22%) of women with intact implants)</p> <p>With the exception of "tingling/numbness of the fingers" (82.1% vs. 51.6%, p=0.006), there were no statistically significant differences in the complaints reported by women with silicone detected in the liver as compared to women with no silicone detected in the liver. Antinuclear antibody positivity was detected in 13 of 28 (46.4%) of patients with silicone in the liver as compared to 15 of 47 (24.2%) of women with no silicone in the liver (p&lt;0.033), but the incidence of antinuclear antibody positivity did not differ significantly from that found in women of comparable age.</p>
Vermuelen and Scholte 2003	No information provided.	<p>Readers of the Dutch silicone breast implant support group magazine were requested to complete a questionnaire on symptoms of chronic fatigue syndrome if they had undergone a second operation for silicone breast implants and received information from their surgeons about the integrity of their removed implants; 319 women returned the questionnaire; no physical exam or laboratory studies were conducted.</p> <p>Results from breast implant group were compared to a control group of 40 women without silicone breast implants who were diagnosed with chronic fatigue</p>	<p>For 176 women who knew the status of their implants, 131 (74%) reported defective implants; the presence of extracapsular silicone was not reported.</p> <p>The following chronic fatigue syndrome symptoms were reported at a statistically higher incidence in women with ruptured implants as compared to women with intact implants: debilitating chronic fatigue (75% vs. 51%, p=0.005, OR = 2.8, 95% CI = 1.4-5.8); impaired short-term memory or concentration (58% vs. 38%; p=0.024, OR = 2.3, 95% CI = 1.1-4.6); multi-joint pain (77% vs. 60%, p=0.033, OR = 2.2, 95% CI =</p>

CITATION	IMPLANT GENERATION/ DURATION OF IMPLANTATION	STUDY DESIGN/ENDPOINTS	RESULTS
		syndrome.	1-4.6), and postexertional malaise >24 hours (76% vs. 51%, p=0.002, OR = 3.1, 95% CI = 1.5-6.3).
Hölmich et al. 2003	First: n=62 Second: n=208 Third: n=263  (Totals from women enrolled, as reported in Hölmich et al 2001)	A total of 271 women (533 implants) who underwent implantation with silicone breast implants for cosmetic reasons and unselected for clinical course underwent MRI evaluation of their implant status and completed a questionnaire regarding their self-reported diseases and symptoms relate to connective tissue diseases or other rheumatic conditions; 238 women were included in the analyses (19 women were excluded because of a diagnosis of "possible rupture," and 14 women were excluded because they did not complete the questionnaire); blood samples were obtained from 234 of the 238 women who provided questionnaire data and analyzed for antinuclear antibodies, rheumatoid factor immunoglobulin M antibodies, and cardiolipin immunoglobulin G and M antibodies. Only diseases with an onset after breast augmentation were considered; no physical exam was conducted.	MRI determined that 146 (61%) women had intact implants; and 92 (39%) women had ruptured implants; of the women with ruptured implants 23 (10%) had evidence of extracapsular rupture.  Women with ruptures (both intra- and extracapsular) were more likely to have implant durations of >16 years as compared to women with intact implants.  After adjusting for age and implant characteristics, women with ruptured implants in general, and those with extracapsular ruptures were no more likely to report symptoms than those with intact implants (OR = 1.0, 95% CI = 0.5-2.3 and OR = 1.0, 95% CI = 0.2-4.2, respectively). No significant differences in self-reported definite connective tissue disease were found between all women with ruptured implants and women with intact implants (OR = 0.9, 95% CI = 0.1-6.7), or women with extracapsular ruptures and women with intact implants (OR = 3.8, 95% CI = 0.4-35.1).  There were no significant differences between women with intact implants, ruptured implants in general, or extracapsular ruptures with respect to the number of positive blood test results.
Hölmich et al. 2004	First: n=15 Second: n=119 Third: n=185	Continuation of MRI study cited in Hölmich et al. 2001 and 2003; comparison of MRI images from 64 women who had at least one ruptured implant at the first MRI examination and 98 women who had intact implants at both examinations for comparison; blood samples were obtained from 62 of the 64 women with untreated ruptures and 96 of the 98 women with intact ruptures and analyzed for antinuclear antibodies, rheumatoid	No increase in autoantibody seropositivity was observed in women with untreated ruptures, and in fact, a number of women who were seropositive for one or more antibodies two years prior became seronegative at this examination.

CITATION	IMPLANT GENERATION/ DURATION OF IMPLANTATION	STUDY DESIGN/ENDPOINTS	RESULTS
		factor immunoglobulin M antibodies, and cardiolipin immunoglobulin G and M antibodies; no physical exam was conducted.	

References cited in table:

- Berner, I., M. et al. 2002. Comparative examination of complaints of patients with breast-cancer with and without silicone implants. *Eur. J Obstet. Gynecol. Reprod Biol* 102:61-66.
- Brown, S.L., et al. 2000. Prevalence of rupture of silicone gel breast implants revealed on MR imaging in a population of women in Birmingham, Alabama. *AJR* 175:1057-64.
- Brown, S.L., et al. 2001. Silicone gel breast implant rupture, extracapsular silicone, and health status in a population of women. *J Rheumatol* 28:996-1003.
- Contant, C.M., et al. 2002. A prospective study on silicone breast implants and the silicone-related symptom complex. *Clin Rheumatol* 2:215-9.
- Gaubitz, M., et al. 2002. Silicone breast implants, correlation between implant ruptures, magnetic resonance spectroscopically estimated silicone presence in the liver, antibody status and clinical symptoms. *Rheumatology* 41:129-35
- Hölmich, L.R., et al. 2001. Prevalence of silicone breast implant rupture among Danish women. *Plast Reconstr Surg*. 108:848-58.
- Hölmich, L.R., et al. 2003. Incidence of silicone breast implant rupture. *Arch Surg* 138:801-6.
- Hölmich, L.R., et al. 2004. Untreated silicone breast implant rupture. *Plast Reconstr. Surg.* 114:204-14.
- Malata, C.M., et al. 1994. Silicone breast implant rupture: common/serious complication? *Medical Progress through Technology* 20:251-60.
- Vermeulen, R.C.W., and Scholte, H.R. 2003. Rupture of silicone gel breast implants and symptoms of pain and fatigue. *J. Rheumatol* 30:2263-7.

33. FDA defines silicone gel bleed as diffusion of gel constituents (e.g., low molecular weight silicones) through an intact shell. FDA believes that there are potential clinical local complications (e.g., chronic inflammation, chronic pain, capsular contracture) that may be associated with gel bleed. The literature information provided in Sections 5.1 and 8.6 did not adequately discuss this issue. Therefore, please provide a detailed summary of all reasonably available literature regarding clinical local complications associated with gel bleed. Please provide copies of all references cited.

33 Response:

It has been hypothesized that silicone gel that diffuses through intact breast implant shells might be a contributing factor to local complications, such as capsular contracture, pain, and inflammation. The available published literature addressing these potential associations is discussed below. None of the literature establishes a causal relationship between silicone gel bleed, and local complications. Moreover, as discussed above in Response 26, extensive testing of third generation implants has demonstrated that there is little gel bleed from Mentor's device. All copies of the cited references are provided in Attachment 32.

#### Capsular Contracture

The IOM Expert Panel considered the contribution of silicone gel bleed to capsular contracture, and considered it a relationship lacking definite "proof." Specifically, the Panel noted the following:<sup>13/</sup>

*"Qualitatively, silicone droplets are often visible in capsular tissue, however, and their presence has been said variously to correlate (Barker et al., 1978; Domanskis and Owlsey, 1976; Wilflingseder et al., 1974) or not correlate with capsular thickness and contracture (Gayou, 1979; Rudolph et al. 1978; Thuesen et al., 1995)."*

*"The definite proof of a relationship between tissue silicone and contracture in humans is lacking since no study of adequate power has held all other variables constant and compared actual tissue silicon measurements to contractures. There is considerable inconsistency among various reports, as noted earlier. In the reported literature, qualitative assessments of silicone droplets or a few measurements of silicon may or may not correlate with contracture severity. On the other hand, silicone fluid injected into breasts causes fibrosis and walling-off of silicone deposits, and gel implants are associated with much higher capsule and tissue silicon measurements. Saline-filled and barrier-coated implants appear to be associated with lower tissue silicone exposure and fewer and less severe contractures compared to conventional gel implants in a preponderance of the studies cited above. Fibrous capsules form around any foreign body, and*

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13/ Bondurant, S., Ernster, V., and Herdman, R., Eds. 2000. *Safety of Silicone Breast Implants*. Committee on the Safety of Silicone Breast Implants, Division of Health Promotion and Disease Prevention, Institute of Medicine (Washington, D.C., National Academy Press), pages 151, 161.

*contracture of these capsules is undoubtedly multifactorial, however. Until definitive studies are carried out, it seems reasonable to assume, based on current evidence, that silicone fluid and gel may contribute to contracture rate and severity . . . ”*

Mentor has not identified any literature published since the IOM report that evaluates the relationship between silicone gel bleed and capsular contracture. A short review of selected earlier literature is provided below.

Caffee (1986)<sup>14</sup> implanted female New Zealand white rabbits with a standard gel implant (Dow Corning Silastic I) on one side of the chest wall and a low bleed implant of identical gel composition (Dow Corning Silastic II) on the other side. The animals were sacrificed after six months, and the implants were removed with the fibrous capsule intact. Using several quantitative indices of capsular contracture (compressibility using indentation tonometry; compressibility using applanation tonometry; and comparison of surface areas), Hollis found that the low bleed implants were significantly softer than the standard implants (indentation tonometry,  $p=0.0209$ ; applanation tonometry,  $p=0.0143$ ), and the surface area of the low bleed implants was significantly larger than the standard implants ( $p=0.0048$ ). Based on these results, Hollis concluded that reduction in silicone bleed, as is seen in the “low bleed” implants, is associated with a reduced incidence and severity of capsular contracture. He noted, however, that silicone gel bleed “is not the only explanation for the contracture phenomenon, since contracture was still seen after a substantial reduction in the leakage of silicone through the implant shell.”

Asplund and colleagues<sup>15</sup> compared the contracture rate observed in women with silicone gel-filled breast implants and saline implants using subjective evaluation of firmness by blinded evaluators in a prospective randomized study of 64 breast implant recipients. They found a significantly higher capsular contracture rate in women with silicone gel-filled breast implants as compared to saline implants (surgeons’ evaluation: 54% versus 20%,  $p=0.006$ ; patients’ evaluation: 54% versus 29%,  $p=0.03$ ). Because the only difference between the implants was the filler, Asplund concluded that “the free silicone around silicone gel-filled prostheses is the major cause of contracture.” In a 6-year follow-up study of these patients, the higher incidence of capsular contracture in the silicone gel-filled breast implant group as compared to the saline implant group was maintained (surgeons evaluation: 50% versus 16%). However, this study, which was published in 1984, was not evaluating third generation devices, which exhibit minimal gel bleed.

### Pain

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14/ Caffee, H.H. 1986. The influence of silicone bleed on capsule contracture. *Ann Plast Surg.* 17(4):284-7.

15/ Asplund, O. 1984. Capsular contracture in silicone gel and saline-filled breast implants after reconstruction. *Plast Reconstr Surg.* 73(2):270-5.

Mentor found no literature that directly addressed the potential association between silicone gel bleed and breast pain.

#### Histologic Changes in Breast Tissue, Including Inflammation

The IOM Expert Panel's review determined that there was insufficient evidence to establish a relationship between the presence of silicone gel and microscopic changes in the breast. Specifically the Panel concluded the following:

*“Evidence for a relationship of tissue silicon concentrations and changes in the breast, including capsular contracture, is insufficient. Silicon levels were correlated with microscopic changes such as foamy histiocytes and vacuoles; that is, the levels were associated with microscopic signs of silicone in the tissue, but not with inflammation, giant cells, or calcification (McConnell et al., 1997). Silicone levels were also correlated with an abundance of fibroblasts and lymphocytes, silicone droplets in tissues, and sparseness of plasma cells (Thomsen et al. 1990). Thomsen's report stands alone in suggesting a direct relationship, measured by quantitative analytic techniques of silicone equivalents, between increasing silicone capsular tissue levels and increasing fibrosis.”<sup>16</sup>*

Mentor has not identified any literature published since the IOM report that evaluates the relationship between silicone gel bleed and histologic changes in the breast tissue, including inflammation. A short review of older literature referenced in the IOM report, most of which reported on findings with earlier generation implants, as well as other selected earlier literature is provided below. It can be seen that the more recent studies do not support an association between silicone gel bleed and histologic changes in the breast tissue. As noted above, and in Response 26, Mentor's gel bleed data obtained in a new *in vitro* study in porcine serum and the weight loss study, demonstrate the nominal amount of bleed in third generation implants. Thus, any local complications reported in earlier studies likely are attenuated or perhaps, no longer an issue, for third generation implants.

In an early study conducted by Barker et al.,<sup>17/</sup> 17 capsule biopsies were taken from 10 consecutive women undergoing open capsulotomy and assessed by light microscopy. Evidence of varying amounts of silicone was seen in 16 of 17 of the samples. The capsule thickness varied considerably. Mild or trace levels of acute inflammation was seen in four of the samples, whereas evidence of trace to moderate chronic inflammation (mononuclear inflammatory cells) and foamy histiocytes was seen in 16 of the 17 samples. A foreign body giant cell granulomatous reaction was observed in three of the 17 samples. Based on their results, the authors concluded that “leaked silicone, together with fibrous thickening and various degrees of

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16/ Bondurant, S., Ernster, V., and Herdman, R., Eds. 2000. *Safety of Silicone Breast Implants* Committee on the Safety of Silicone Breast Implants, Division of Health Promotion and Disease Prevention, Institute of Medicine (Washington, D.C., National Academy Press), page 157.

17/ Barker, D.E., et al. 1978. “Bleeding” of silicone from bag-gel breast implants, and its clinical relation to fibrous capsule reaction. *Plast Reconstr. Surg.* 61(6):836-41.

inflammation will be found in capsules surrounding the implants if extensive biopsies are taken and many sections are examined.”

In the study by Thomsen and colleagues cited above,<sup>18</sup> 86 biopsies from 67 breasts were taken from 55 women with silicone breast implants who were experiencing problems (capsular contracture or suspicion of a malignant tumor), and subjected to histologic analysis. A statistically significant positive relationship was found between silicone concentration in the capsule biopsies (measured by atomic absorption spectroscopy) and the following histologic indices of inflammation: fibroblasts, lymphocytes, and droplets. A significant negative relationship was found for plasma cells. Based on these results, the authors concluded that “silicone prostheses provoke an inflammatory response not only because they act as foreign bodies, but also because of silicone seepage through intact membranes.”

Evidence of capsular inflammation was not present, however, in a later study conducted by Malata et al.<sup>19</sup> In this study, histological examination of capsules removed from 51 women who underwent revision surgery because of significant capsular contracture, suspected prosthesis rupture, or unrelieved implant-induced anxiety revealed nothing remarkable. Benign fibrotic and foreign body reactions were typically observed except in two patients who had silicone granulomas. Both of these patients had implant shell disintegration with gross leakage of silicone.

McConnell et al.,<sup>20</sup> as noted above, also found no correlation between breast tissue silicon concentration and inflammation, calcification, or giant cell rating in 54 tissue samples taken from women during various breast procedures. Additionally, there was no difference in tissue silicon concentration in women who exhibited signs or symptoms of morbidity and those who did not.

Based on the information presented above, the literature does not support a relationship between local complications and gel bleed, and, moreover, there is little gel bleed in third generation devices, which further mitigates potential concern.

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- 18/ Thomsen, J.L., et al. 1990. Histologic changes and silicone concentrations in human breast tissue surrounding silicone breast prostheses. *Plast Reconstr. Surg* 85(1):38-41.
- 19/ Malata, C.M., et al. 1994. Silicone breast implant rupture: common/serious complication: *Medical Progress through Technology* 20:251-60.
- 20/ McConnell, J.P., et al. 1997. Determination of silicon in breast and capsular tissue from patients with breast implants performed by inductively coupled plasma emissions spectroscopy. Comparison with tissue histology. *Am. J. Clin. Pathol* 107(2):236-46.