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Stephen Ostroff, M.D.
Acting Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition to withdraw approval of Seprafilm Bioresorbable Membrane (P950034) and initiate a mandatory recall

Dear Dr. Ostroff:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to Sections 515 and 518 of the Federal Food, Drug, and Cosmetic Act (FDCA); 21 C.F.R. Parts 810 and 814; and 21 C.F.R. § 10.30, to withdraw approval of Seprafilm Bioresorbable Membrane (Seprafilm), premarket approval application number P950034, and initiate a mandatory recall of this product, on the grounds that the manufacturer has not demonstrated reasonable assurance that the device is safe and effective under its current conditions of use, and there is a reasonable probability that the device will cause serious adverse health consequences and death.

I. Actions Requested

We request that the FDA Commissioner, pursuant to Sections 515 and 518 of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. Parts 810 and 814:

(1) Withdraw the premarket approval of Seprafilm (P950034); and

(2) Initiate a mandatory recall of all remaining unused Seprafilm devices.

II. Statement of Grounds

a. Background on the Device and Regulatory Actions

Seprafilm is an anti-adhesion barrier device used in abdominal and pelvic surgical procedures to prevent the formation of postoperative adhesions (fibrous bands that form between tissues and organs). The device is a bioresorbable membrane composed of sodium hyaluronate and carboxymethylcellulose, which adheres to tissue surfaces and hydrates to form a viscous gel coating in one to two days.[1] Seprafilm is typically resorbed from the application site within seven days and cleared from the body within 28 days.[2] It has been postulated that Seprafilm is able to reduce postoperative adhesions by acting as a physical/mechanical barrier, separating adjacent serosal tissues during the critical stages of wound repair.[3,4] However, its precise mechanism of action remains unclear.[5,6]

The FDA approved the Seprafilm premarket approval (PMA) application on August 12, 1996. The device is indicated for use in patients undergoing abdominal or pelvic laparotomy as an adjunct intended to reduce the incidence, extent, and severity of postoperative adhesions between the abdominal wall and the underlying viscera, and between the uterus and surrounding structures.[7] At the time of approval, the FDA ordered the product's sponsor, Genzyme, to conduct a postmarket safety study, later dubbed SF97-0601 (Study 601), to address the agency's concerns with a large number of serious adverse events detected in the Seprafilm group during one of the two pivotal efficacy studies that Genzyme submitted in support of the PMA application.

Genzyme conducted Study 601 and subsequently filed two PMA supplements, Supplement 26 (August 2003)[8] and Supplement 27 (December 2004),[9] requesting updates to the Seprafilm package insert regarding the product's safety and effectiveness. As part of those updates, Genzyme asked that the label be updated to indicate that Seprafilm was effective at reducing the incidence of small bowel obstruction requiring re-operation.[10,11] The FDA reviewers raised concerns about the requested efficacy claim, which the company subsequently withdrew.[12] But

[1] Diamond MP, Burns EL, Accomando B, et al. Seprafilm adhesion barrier: (1) A review of preclinical, animal and human investigational studies. *Gynecol Surg.* 2012;9:237-245.
[2] *Ibid*.
[3] *Ibid*.
[4] Gago LA, Saed GM, Chauhan S, et al. Seprafilm (modified hyaluronic acid and carboxymethylcellulose) acts as a physical barrier. *Fertil Steril*. 2003;80(3):612-616.
[5] Sikkink C. Applications of Hyaluronan in Abdominal Surgery. Schrijen-Lippertz, 2011:p143.
[6] Reijnen MM, van Goor H, Falk P, et al. Sodium hyaluronate increases the fibrinolytic response of human peritoneal mesothelial cells exposed to tumor necrosis factor α. *Arch Surg*. 2001;136(3):291-296.
[7] Food and Drug Administration. Seprafilm Premarket Approval: P950034. 1996.
[8] Letter from Genzyme Corporation to David Berkowitz regarding PMA Supplement to P950034. August 4, 2003.
[9] Letter from Genzyme Corporation to David Berkowitz regarding PMA Supplement to P950034. December 10, 2004.
[10] Letter from Genzyme Corporation to David Berkowitz regarding PMA Supplement to P950034. August 4, 2003.
[11] Letter from Genzyme Corporation to David Berkowitz regarding PMA Supplement to P950034. December 10, 2004.
[12] Berkowitz D. Memorandum to file, Subject: P950034/S27A1 Seprafilm Adhesion Barrier, Genzyme Corporation. November 2, 2005.

the FDA eventually accepted many of the company's other proposed modifications to the product label, including changes describing adverse events and the results of the postmarket study.

b. FDA Regulatory Authority

The FDA may issue an order withdrawing a PMA if the agency determines that any of the grounds under Section 515(e)(1) of the Federal Food, Drug, and Cosmetic Act applies.[13] One of these grounds is a conclusion,

> on the basis of new information before [the FDA] with respect to [a] device, evaluated together with the evidence available to [the FDA] when the application was approved, that there is a lack of a showing of reasonable assurance that the device is safe or effective under the conditions of use prescribed, recommended, or suggested in the labeling thereof.[14]

The FDA may also issue a mandatory recall under Section 518(e) of the FDCA, upon finding "a reasonable probability that a device intended for human use would cause serious, adverse health consequences or death."[15]

c. Three Major Efficacy Studies Failed to Show Clinically Meaningful Benefits and Raised Serious Safety Concerns

Genzyme submitted to the FDA data from three randomized, controlled clinical trials — including two that were conducted prior to approval of the original PMA application — to support the efficacy claims in the Seprafilm label. Despite elaborate attempts by the company to present the data from these studies in a favorable light, the studies failed to demonstrate effectiveness at achieving a clinically meaningful endpoint and, instead, raised serious safety concerns.

The first two efficacy trials were submitted as part of the original Seprafilm PMA application: HF92-0901 (Study 901), a randomized, controlled trial assessing the safety and effectiveness of Seprafilm for preventing postoperative adhesion formation following abdominal surgery in 183 subjects, and HF92-0902 (Study 902), a randomized, controlled trial assessing the safety and effectiveness of Seprafilm for preventing postoperative adhesion formation following uterine myomectomy in 127 subjects.[16] These studies were published in medical journals by Becker et al. (1996) and Diamond (1996), respectively.[17,18]

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[13] 21 C.F.R. Sec. 814.46 (Withdrawal of approval of a PMA).
[14] Federal Food, Drug, and Cosmetics Act, Section 515(e)(1)(B), *codified as* 21 U.S.C. § 360e(e)(1)(B).
[15] Federal Food, Drug, and Cosmetics Act, Section 518(e), *codified as* 21 U.S.C. § 360h(e).
[16] In addition, Genzyme also conducted two smaller safety studies enrolling only 32 patients, combined: Food and Drug Administration. Summary of Safety and Effectiveness Data, Genzyme Corporation, Seprafilm Bioresorbable Membrane. August 12, 1996.
[17] Becker JM, Dayton MT, Fazio VW, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: A prospective, randomized, double-blind multicenter study. *J Am Coll Surg.* 1996;183(4):297-306.

The third trial was the mandatory postmarket study ordered by the FDA at the time of approval, Study 601. This was a prospective, randomized controlled clinical trial designed to assess the safety and effectiveness of Seprafilm for preventing bowel obstruction following abdominopelvic surgery in 1,791 subjects, published by Beck et al. (2003; safety data)[19] and Fazio et al. (2006; efficacy data).[20]

These studies all were plagued by a host of serious issues, including major protocol violations at one of the key trial sites in Study 901 and several highly questionable re-analyses of the data from Study 601. Most importantly, none of these three studies submitted in support of the Seprafilm PMA application established the product's efficacy in improving any important clinically meaningful outcomes, and two of the studies raised serious safety concerns that have not been adequately addressed by the product's sponsor.

i. Studies 902 and 901

Studies 902 and 901, the two pivotal clinical trials submitted to support effectiveness in the original Seprafilm PMA application, were not designed to assess Seprafilm's effectiveness at improving important clinically meaningful outcomes such as bowel obstruction, pain, complications during re-operation, or infertility. Instead, the two trials assessed the incidence, extent, and severity of postoperative adhesions, based on the hypothesis that improvements in these surrogate endpoints could, theoretically, have positive clinical implications.

Study 902 was a randomized, controlled trial enrolling 127 subjects undergoing gynecologic surgery.[21] The study showed that rate and severity of adhesion, evaluated during second-look laparoscopy, were lower in the Seprafilm-treated group, with comparable rates of adverse events between groups.[22] However, the study did not assess clinically meaningful outcomes.

Study 901 was a randomized, control trial enrolling 183 subjects undergoing abdominal surgery.[23] In Study 901, while the overall rates of adverse events were similar in Seprafilm- and control-group subjects (90% versus 94%, respectively), subjects assigned to the Seprafilm group experienced a higher rate of serious adverse events than control subjects, a difference which approached statistical significance (42% versus 24%, respectively; $p = 0.074$).[24] Of note, rates of abscesses and pulmonary emboli were higher among Seprafilm-treated subjects compared to control subjects. Seven of 91 subjects (8%) in the Seprafilm group and two of 92 subjects (2%) in the control group developed abscesses ($p = 0.10$), and four subjects (4%) in the Seprafilm

[18] Diamond MP. Reduction of adhesions after uterine myomectomy by Seprafilm membrane (HAL-F): a blinded, prospective, randomized, multicenter study. *Fertil Steril.* 1996;66(6):904-910.
[19] Beck DE, Cohen Z, Fleshman JW, et al. A prospective, randomised, multicenter, controlled study of the safety of Seprafilm adhesion barrier in abdominopelvic surgery of the intestine. *Dis Colon Rectum.* 2003;46(10):1310-1319.
[20] Fazio VW, Cohen Z, Fleshman JW, et al. Reduction in adhesive small-bowel obstruction by Seprafilm adhesion barrier after intestinal resection. *Dis Colon Rectum.* 2006;49(1): 1-11.
[21] Food and Drug Administration. Summary of safety and effectiveness data: Genzyme Corporation Seprafilm Bioresorbable Membrane. 1996.
[22] *Ibid.*
[23] *Ibid.*
[24] Food and Drug Administration. Summary of safety and effectiveness data: Genzyme Corporation Seprafilm Bioresorbable Membrane. 1996.

group and no subjects in the control group developed pulmonary emboli (p = 0.059).[25,26] These findings raised concerns for the FDA. Although the agency did approve the product, it did so while also ordering a mandatory postmarket clinical study to further assess the safety of Seprafilm (Study 601, described below).[27]

In addition, according to a warning letter previously posted on the FDA website, FDA inspectors uncovered significant problems during an inspection of one of the principal investigators who conducted Study 901, throwing the reliability of the trial's data into question. On February 3, 1997, months after the Seprafilm approval, the FDA sent a warning letter to the principal investigator at one of the institutions that enrolled subjects in Study 901, citing him for failing to maintain blinding in accordance with the study protocol.[28] In fact, an FDA inspector visiting the investigator's trial site on August 5-30, 1996, discovered that for 33 of 37 subjects enrolled at the site, adhesion evaluations were not done by a blinded evaluator. The inspector also found numerous other problems, including adverse-event data that had not been reported, lack of informed-consent documentation, and other incomplete and inaccurate paperwork.[29] The subjects at this research site represented approximately 20 percent of the total assessable subjects in Study 901. Public Citizen notes that the problems uncovered during the FDA inspection were not reported in the published medical journal article associated with Study 901.[30]

For reasons that remain unclear, the FDA team that had approved the Seprafilm PMA application in August 12, 1996 apparently was not notified of the serious deficiencies discovered during the trial site inspection of August 5-30, 1996, and the agency has never, to our knowledge, formally reconsidered the results of Study 901 in light of these violations.

ii. Study 601

As noted above, safety concerns identified by the FDA during its review of data from the two pivotal clinical trials submitted with the initial PMA application for Seprafilm led the agency to require an additional large postmarket safety study as a condition of approval. The FDA proposed that Genzyme conduct a seriously flawed, nonrandomized safety study.[31] Yet Genzyme, possibly hoping to add additional efficacy claims to Seprafilm's label, opted instead to conduct a prospective, randomized controlled trial (Study 601) to assess the efficacy of

[25] *Ibid.*
[26] Becker JM, Dayton MT, Fazio VW, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: A prospective, randomized, double-blind multicenter study. *J Am Coll Surg.* 1996;183(4):297-306.
[27] Food and Drug Administration. Letter from Susan Alpert to Alodia M. Ruiz, Genzyme Corporation, regarding P950034, Seprafilm Bioresorbable Membrane. August 12, 1996.
[28] Food and Drug Administration, Center for Devices and Radiological Health. Warning letter to Merril T. Dayton, M.D. February 3, 1997. https://web.archive.org/web/20100311053539/http:/www.fda.gov/downloads/ICECI/EnforcementActions/WarningLetters/1997/UCM065275.pdf. Accessed June 30, 2015.
[29] *Ibid.*
[30] Becker JM, Dayton MT, Fazio VW, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: A prospective, randomized, double-blind multicenter study. *J Am Coll Surg.* 1996;183(4):297-306.
[31] Food and Drug Administration. Letter from Susan Alpert to Alodia Ruiz, Genzyme Corporation, regarding P950034, Seprafilm Bioresorbable Membrane. August 12, 1996.

Seprafilm in reducing the incidence of bowel obstruction following abdominopelvic surgery, a clinical outcome thought to be associated with adhesions.

Study 601, which eventually enrolled 1,791 subjects, represented a failure for Genzyme's Seprafilm in terms of both safety and efficacy. First, the trial failed to demonstrate efficacy in reducing the incidence of bowel obstruction, the trial's primary endpoint.[32] Second, subjects randomized to the Seprafilm group were significantly more likely to experience anastomotic leak, peritonitis, vomiting, and fistula relative to those randomized to the control group (these data are tabulated in Appendix A, Table A).

Rather than accept these results — which were potentially disastrous with respect to the continued marketability of Seprafilm — Genzyme, in coordination with the Study 601 Steering Committee, engaged in several extensive post hoc re-analyses of the data designed to re-characterize the failed trial as a success. These analyses were submitted in August 2003 and December 2004 as Supplement 26 and Supplement 27, respectively, to PMA application P950034.[33,34]

First, to salvage the safety data, Genzyme, in coordination with the Study 601 Postmarket Study Steering Committee, conducted a new unplanned post hoc subgroup analysis that separated out subjects for whom the surgeon had wrapped Seprafilm around the anastomotic site. In order to do this, Genzyme asked the Postmarket Study Steering Committee to invent a new definition of "bowel anastomosis," as the term had not been prospectively defined in the protocol and had been interpreted in different ways by the various trial investigators.[35] After crafting this post hoc definition, the Postmarket Study Steering Committee members went back through the trial records and reclassified an unspecified number of subjects who previously had not been classified as having a bowel anastomosis.[36] Genzyme failed to report what efforts, if any, were used to ensure that evaluators were appropriately blinded to the treatment received by each subject during the reclassification process.

Disappointingly, the FDA apparently accepted this highly questionable re-analysis, as the Seprafilm label now reads: "a higher incidence of anastomotic leak related events was observed in patients who had Seprafilm wrapped around a fresh anastomotic site. These complications were not observed when Seprafilm was used throughout the abdomen, without deliberately covering the Anastomosis."[37] This labeling misleadingly suggests that the adverse events observed in subjects who received Seprafilm during Study 601 may be avoided, provided the device is not used to wrap a fresh anastomotic site, even though the analysis that led to this conclusion is highly questionable.

[32] Email from Roxolana Horbowyj to David Berkowitz regarding PMA Supplement 27 to P950034. June 15, 2005.
[33] Letter from Jerry Warren, Genzyme Corporation, to David Berkowitz, Food and Drug Administration, regarding PMA Supplement to P950034. August 4, 2003.
[34] Letter from Jerry Warren, Genzyme Corporation, to David Berkowitz, Food and Drug Administration, regarding PMA Supplement to P950034. December 10, 2004.
[35] *Ibid.*
[36] *Ibid*.
[37] Genzyme. Product label: Seprafilm Adhesion Barrier. December 2008.

In addition, FDA reviewers assessing the data from Study 601 noted a "disconcerting" difference in device-related serious adverse events between the Seprafilm and control groups at postoperative day 30 (25 for Seprafilm versus 0 for the control), and at six months (37 in the Seprafilm group versus 1 in the control).[38] This difference in device-related serious adverse events also is not adequately represented in the current Seprafilm label's summary of the results of Study 601, which instead reports any serious adverse events at postoperative day 30 (264, 30 percent, in the Seprafilm group versus 237, 26 percent, in the control) and at 6 months (350, 40 percent, in the Seprafilm group versus 324, 36 percent, in the control).[39]

Second, Genzyme re-analyzed the efficacy data from Study 601. For this analysis, Genzyme invented a new outcome measure, dubbed "adhesive small bowel obstruction [SBO] requiring reoperation," and determined that subjects in the Seprafilm group had significantly lower rates of this outcome relative to the control subjects.[40] In Supplement 27, Genzyme requested that the Seprafilm label be updated to indicate that the device was effective at reducing the incidence of SBO requiring re-operation.[41] FDA reviewers criticized Genzyme's analysis, noting that:

> This unplanned subgroup analysis, revealing a marginal difference between Seprafilm and control groups, may well be an artifact of the multiple subgroup analyses conducted.
>
> FDA believes that additional clinical data from a prospective, randomized, and well-controlled study is necessary to support the safety and effectiveness of your device for your proposed indication of reduction in the incidence of adhesive small bowel obstruction requiring reoperation. Of note, we believe that such a study will require careful design consideration including uniform criteria for surgical intervention across clinical investigators.[42]

In addition to the fact that this subgroup analysis was developed post hoc, it also relied on an endpoint that was highly susceptible to bias: Surgeons in the study were not blinded as to which patients received Seprafilm,[43] which easily could have affected the decision whether or not to re-operate in the presence of symptoms indicating potential bowel obstruction.

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[38] Letter to Jerry Warren, Genzyme Corporation, regarding P950034 Seprafilm Adhesion Membrane. Filed: March 23, 2005. Undated.

[39] Genzyme. Product Label: Seprafilm Adhesion Barrier. December 2008.

[40] Memorandum from David Berkowitz to file regarding P950034/S27 labeling changes, Seprafilm Bioresorbable Membrane, Genzyme Corporation. June 20, 2005. The Seprafilm label presents this analysis of adhesive small bowel obstruction requiring reoperation as derived from "protocol defined criteria," and Genzyme offered FDA three protocol-defined criteria used to diagnose bowel obstruction. However, the FDA reviewer who evaluated this claim pointed out that "[b]owel obstruction due to adhesive as well as non-adhesive etiology are expected to be captured by all of these criteria," and determined that the criteria could not serve to classify the type of bowel obstruction or determine its etiology. Email from Roxolana Horbowyj to David Berkowitz RE: Genzyme, P950034s27, Seprafilm Labeling change request, clinical comments, Wednesday, June 15, 2005.

[41] Letter from Jerry Warren, Genzyme Corporation, to David Berkowitz. Food and Drug Administration, regarding PMA Supplement to P950034. December 10, 2004.

[42] Letter to Jerry Warren, Genzyme Corporation, regarding P950034 Seprafilm Adhesion Membrane. Filed: March 23, 2005. Undated.

[43] Fazio VW, Cohen Z, Fleshman JW, et al. Reduction in adhesive small-bowel obstruction by Seprafilm adhesion barrier after intestinal resection. *Dis Colon Rectum.* 2006;49(1):1-11.

Ultimately, the FDA refused to approve the requested addition to the Seprafilm label of the efficacy claim regarding the reduction of the incidence of SBO requiring re-operation. Genzyme subsequently withdrew its request to modify the product's indication.[44] Nevertheless, the FDA did permit Genzyme to publish a label that remains misleading with regard to the efficacy results of Study 601. The Seprafilm label now reads, in relevant part:

> Using protocol defined criteria, 15 of the 840 intestinal resection patients (1.8%) in the Seprafilm group experienced an adhesive SBO that required reoperation compared to 29 of 861 intestinal resection patients (3.4%) in the control group ($p < 0.05$). When all cases of bowel obstruction were considered, including those in which bowel obstruction could not be ruled out, 109 of 888 patients (12%) in the Seprafilm group and 106 of 903 patients (12%) in the control group had bowel obstruction. Of the 90 patients with existing bowel obstructions, no significant difference in incidence of adhesive SBO requiring reoperation was found (3 of the 48 Seprafilm patients versus 1 of 42 control patients).[45]

Use of the term "protocol defined criteria" is inappropriate and misleading in this case, as it describes criteria that were developed only after the investigators had viewed and analyzed the results of the completed trial, well after the protocol had been written. Moreover, the label fails to document whether the inclusion of the 90 subjects with existing bowel obstruction would have rendered the reported results statistically non-significant by pushing the p-value above 0.05.

Even assuming these issues with the labeling were corrected, the existing evidence from studies 902, 901, and 601 does not justify maintaining the product's approval, because these studies failed to demonstrate that Seprafilm is effective at improving any clinically meaningful endpoint, and two of the studies (901 and 601) indicated that the device increases the risk of serious adverse events. Taken as a whole, these trials failed to demonstrate reasonable assurance that the device is safe or effective under the conditions of use prescribed.

Published reports of Study 601 have drawn ample criticism of Seprafilm from experts in surgery. For example, Dr. Neil Hyman, a professor of surgery at the University of Chicago's Pritzker School of Medicine, published the following criticism of Fazio et al. (2006), in a letter to the editor:

> [E]vidence of clinical efficacy [for Seprafilm] has been sorely lacking despite widespread adoption. Despite ample experimental and clinical evidence that Seprafilm is effective in reducing adhesions, it is far easier to find reports of patients who seem to have been injured by Seprafilm (*e.g.*, developed chemical peritonitis or anastomotic disruption) than to identify a single patient in the world's literature who has derived a definable clinical benefit.[46]

In another letter to the editor published at the same time, Dr. Robin McLeod, a surgeon at Mount Sinai Hospital, Toronto, Canada, wrote:

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[44] Genzyme. Letter to Dr. Stephen Rhodes regarding P950034/S027, Seprafilm Adhesion Barrier, August 30, 2005.
[45] Genzyme. Product label: Seprafilm Adhesion Barrier. December 2008.
[46] Hyman NH. Justifiable conclusions? *Dis. Colon Rectum.* 2006;49(8):1236-7; author reply 1237-8.

> [G]iven that the need for further operation for ASBO [adhesive small bowel obstruction] was not the primary outcome measure, that the clinical significance of the difference is questionable and indeed, the risk of abscess formation may be increased with Seprafilm, it would be hard to conclude that Seprafilm is "safe and effective."[47]

We agree with Dr. Hyman's and Dr. McLeod's assessments, and we urge the FDA to conclude that the strongest available clinical evidence does not demonstrate reasonable assurance that the device is safe or effective under the conditions of use prescribed.

d. Additional Data From Prospective Randomized Clinical Trials

Data from additional prospective, randomized, controlled trials evaluating the safety and efficacy of Seprafilm do not change the overall risk-benefit profile of the device or establish reasonable assurance that the device is safe and effective.

We note at the outset that publication bias could have strongly influenced the results of these studies in favor of showing a benefit from Seprafilm. For example, we identified one unpublished prospective study of 1,885 patients indicating that the use of Seprafilm was associated with "a higher incidence of pelvic sepsis and wound infection."[48] This study was presented as an abstract at an annual conference of the American Society of Colon and Rectal Surgeons, but never published in a peer-reviewed journal.

A Cochrane analysis published in 2009 found too few studies of Seprafilm to develop a funnel plot assessing publication bias.[49] Additional unpublished studies showing negative results similar to the study described above may be missing from the literature.

The results of published randomized, controlled clinical trials are summarized in Appendix A, Table B. While the trials tended to show that the device reduces the incidence, severity and/or extent of adhesions at the site of application, only two studies — Park et al. (2009) and van der Wal et al. (2011) — provided evidence of possible clinically meaningful benefit: reduced incidence of "early" postoperative intestinal obstruction[50] and "abdominal complaints,"[51] respectively. However, both of these studies had serious flaws.

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[47] McLeod R. Does Seprafilm really reduce adhesive small bowel obstructions? *Dis Colon Rectum*. 2006;49(8):1234; author reply 1235-6.

[48] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery (Seprafilm/pack) Seprafilm (sodium hyaluronate, carboxymethylcellulose) membrane bioresorbable adhesion barrier. Event date unknown. MDR Report Key Number: 1591645. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=1591645. Accessed December 10, 2014.

[49] Kumar S, Wong PF, Leaper DJ. Intra-peritoneal prophylactic agents for preventing adhesions and adhesive intestinal obstruction after non-gynaecological abdominal surgery. *Cochrane Database of Systematic Reviews.* 2009, (1). Art. No.: CD005080. DOI: 10.1002/14651858.CD005080.pub2.

[50] Park CH, Lee WY, Cho YB, et al. Sodium hyaluronate-based bioresorbable membrane (Seprafilm) reduced early postoperative intestinal obstruction after lower abdominal surgery for colorectal cancer: The preliminary report. *Int J Colorectal Dis*. 2009;24(3):305-310.

In Park et al. (2009), a trial of 427 subjects undergoing radical resection for sigmoid or rectal cancer between November 2002 and December 2003, the difference in the incidence of early postoperative intestinal obstruction between the Seprafilm and control group subjects barely met statistical significance (2.7% versus 7.0%, p = 0.045).[52] Moreover, during the follow-up period (median follow-up was 25 months) the difference in the rates of re-admission for intestinal obstruction were not statistically significant (2.7% in Seprafilm subjects versus 4.6% in control subjects; p = 0.322). There were also several problems with the trial, including:

(1) The randomization procedure was not described by the study authors, nor did the authors explain the significant imbalance in the numbers of subjects randomized to each of the two trial groups.
(2) The two trial groups were not balanced with respect to many clinically important parameters. For example, a higher proportion of control group subjects than Seprafilm-group subjects (a) underwent an anterior resection, (b) had a stoma created, and (c) had advanced stage (stage 3 or 4) colorectal cancer. The control group subjects also had a longer mean operation time compared to Seprafilm group subjects.
(3) The investigators failed to report the steps that were taken, if any, to ensure investigator and subject blinding to study group assignment, the lack of which could have contributed to bias.
(4) Some cases of "early postoperative obstruction" may have been due to paralytic ileus caused by prolonged inhibition of coordinated bowel activity and not by structural abnormalities such as adhesions. The potential for confusion is particularly troubling given that the investigators may not have been appropriately blinded. Unblinded investigators may have been more likely to miscategorize control group subjects, skewing the trial results.

Indeed, the investigators in Park et al. (2009) acknowledged that "the current study design and results do not allow obvious conclusions to be drawn concerning the effect of Seprafilm on intestinal obstruction."[53]

In van der Wal et al. (2011), the investigators reported long-term follow-up data on 35 of 71 subjects who had undergone a Hartmann's procedure (resection of the rectosigmoid colon with creation of a colostomy) for sigmoid diverticulitis or an obstructed rectosigmoid, between April 1996 and September 1998 and had been randomly assigned to a Seprafilm group or to a control group.[54] The investigators found no statistically significant difference in the rate of readmissions for small bowel obstruction [none in the Seprafilm group versus two of 19 (11 percent) in the control group], but did find a significantly lower incidence of "chronic (3 months or longer existing) abdominal complaints" (mainly symptoms of constipation) in Seprafilm group subjects

[51] Van der Wal JB, Iordens GI, Vrijland WW, et al. Adhesion prevention during laparotomy: Long-term follow-up of a randomized clinical trial. *Ann Surg*. 2011;253(6):1118-1121.
[52] Park CH, Lee WY, Cho YB, et al. Sodium hyaluronate-based bioresorbable membrane (Seprafilm) reduced early postoperative intestinal obstruction after lower abdominal surgery for colorectal cancer: The preliminary report. *Int J Colorectal Dis*. 2009;24(3):305-310.
[53] *Ibid*.
[54] Van der Wal JB, Iordens GI, Vrijland WW, et al. Adhesion prevention during laparotomy: Long-term follow-up of a randomized clinical trial. *Ann Surg.* 2011;253(6):1118-1121.

compared to control group subjects. However, like the Park et al. (2009) trial, this study by van der Wal et al. suffered from numerous flaws, including:

(1) The follow-up study was exceedingly small. Moreover, the number of subjects included in the follow-up study represented fewer than half the subjects originally enrolled in the randomized clinical trial: Twenty-nine subjects were excluded for unclear reasons, and seven (five Seprafilm subjects and two control subjects) had been lost to follow-up.[55]
(2) The investigators failed to indicate whether the 2011 follow-up study was planned when the original randomized clinical trial was initiated in 1996.
(3) The investigators failed to report on the steps that were taken, if any, to ensure investigator and subject blinding to study group assignment. The lack of such blinding could have contributed to bias.
(4) The investigators made obvious errors in reporting the rates of abdominal complaints, asserting that six of 16 subjects in the Seprafilm group constituted 35 percent of that group (the rate is actually 37.5 percent), and that 14 of19 subjects in the control group constituted 78 percent of that group (the rate is actually 73.7 percent).

e. Meta-Analyses

We do not separately summarize the results of meta-analyses, including a report by ten Broek et al. published in the *Lancet* in 2014,[56] and a report by Zeng et al., published in the *World Journal of Surgery* in 2007.[57] This is because all of the meta-analyses we identified during our review of the literature included the inappropriate post-hoc subgroup re-analysis of the efficacy results of Study 601 (published in Fazio et al. [2006]).[58] The size of Study 601 relative to other trials involving Seprafilm meant that this study tended to dominate the results of the meta-analyses.[59] The meta analyses conducted by ten Broek et al. and Zeng et al. also incorporated studies assessing bioresorbable membranes other than Seprafilm, making it difficult to draw conclusions from these analyses regarding the safety and effectiveness of Seprafilm.[60,61]

[55] While both the Seprafilm and control groups initially included 21 subjects from the original randomized clinical trial, five subjects died and five were lost to follow-up in the Seprafilm group, whereas three died and two were lost to follow-up in the control group. Notably, data were not obtained from medical records or a physician questionnaire for four out of the five Seprafilm subjects who died, whereas data were collected from these sources for all three of the control subjects who died.
[56] Ten Broek RP, Stommel MW, Strik C, et al. Benefits and harms of adhesion barriers for abdominal surgery: A systematic review and meta-analysis. *Lancet.* 2014;383:48-59.
[57] Zeng Q, Yu Z, You J, Zhang Q. Efficacy and safety of Seprafilm for preventing postoperative abdominal adhesion: Systematic review and meta-analysis. *World J Surg*. 2007;31:2125-2131.
[58] Fazio VW, Cohen Z, Fleshman JW, et al. Reduction in adhesive small-bowel obstruction by Seprafilm adhesion barrier after intestinal resection. *Dis Colon Rectum.* 2006;49(1):1-11.
[59] Ten Broek RP, Stommel MW, Strik C, et al. Benefits and harms of adhesion barriers for abdominal surgery: A systematic review and meta-analysis. *Lancet.* 2014;383:48-59.
[60] Zeng Q, Yu Z, You J, Zhang Q. Efficacy and safety of Seprafilm for preventing postoperative abdominal adhesion: Systematic review and meta-analysis. *World J Surg*. 2007;31:2125-2131.
[61] Ten Broek RP, Stommel MW, Strik C, et al. Benefits and harms of adhesion barriers for abdominal surgery: A systematic review and meta-analysis. *Lancet.* 2014;383:48-59.

f. Additional Data From Nonrandomized Clinical Studies and Case Reports

Data from several nonrandomized studies also have raised serious concerns about the safety of Seprafilm.

Leitao et al. (2009) conducted a retrospective analysis of a consecutive series of 423 laparotomies (219 with Seprafilm and 204 without Seprafilm) in patients undergoing laparotomies for ovarian, fallopian tube, or primary peritoneal malignancies at Memorial Sloan Kettering Cancer Center from March 2005 to December 2007. The investigators found that use of Seprafilm was associated with a higher rate of postoperative loculated fluid collections in the abdomen or pelvis compared with procedures not involving use of Seprafilm (8.2% versus 2.5%; $p = 0.009$).[62] The incidence of infected fluid collections also was higher in the Seprafilm cohort compared to the non-Seprafilm cohort (4.1% versus 0.5%; $p = 0.02$). The collections occurred with greatest frequency in patients who underwent debulking procedures. The increased rate of the postoperative fluid collections resulted in a significantly higher rate of interventions to address the collections in the Seprafilm cohort compared to the non-Seprafilm cohort (6.8% versus 1.5%; $p = 0.006$). The authors of the study indicated that based on these findings, a majority of surgeons at Memorial Sloan Kettering had chosen to no longer place Seprafilm during extensive debulking procedures and suggested that "the impact of [Seprafilm] use on future surgeries, as well as oncologic outcomes, must be better delineated."[63]

Similarly, Krill et al. (2011) performed a retrospective review of a consecutive series of 375 patients undergoing laparotomies for cytoreductive surgery for ovarian, fallopian tube, or peritoneal cancer (168 with Seprafilm and 207 without Seprafilm) between January 1995 and December 2008 at The Johns Hopkins Medical Institutions.[64] The investigators reported a significantly increased risk of pelvic abscess in the Seprafilm cohort compared to the non-Seprafilm cohort (12% versus 5% ; $p = 0.01$).

Most recently, Bashir et al. (2013) conducted another retrospective study involving the analysis of data on a cohort of adult patients who underwent laparotomy and either a hysterectomy (382,355 patients, of whom 5 percent underwent surgery with Seprafilm) or colectomy (267,368 patients, of whom 8 percent underwent surgery with Seprafilm) from January 2000 to March 2010 at 600 acute-care hospitals in the U.S. The investigators found that after matching and risk adjustment, Seprafilm use was associated with a small, but statistically significant increased risk of abscess in patients undergoing colectomy (17.4% in Seprafilm patients versus 15.0% in non-Seprafilm patients; relative risk = 1.13 with 95% confidence interval, 1.08-1.17). Seprafilm use was not associated with increased risk of abscess in patients undergoing hysterectomy.[65]

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[62] Leitao MM, Natenzon A, Abu-Rustum NR, et al. Postoperative intra-abdominal collections using a sodium hyaluronate-carboxymethylcellulose (HA-CMC) barrier at the time of laparotomy for ovarian, fallopian tube, or primary peritoneal cancer. *Gynecol Oncol.* 2009;115(2):204-208.

[63] *Ibid.*

[64] Krill LS, Ueda SM, Gerardi M, Bristow RE. Analysis of postoperative complications associated with the use of anti-adhesion sodium hyaluronate-carboxymethylcellulose (HA-CMC) barrier after cytoreductive surgery for ovarian, fallopian tube, and peritoneal cancers. *Gynecol Oncol.* 2011; 120(2):220-223.

[65] Bashir S, Ananth CV, Lewin SN, et al. Utilization and safety of sodium hyaluronate-carboxymethycellulose adhesion barrier. *Dis Colon Rectum*. 2013;56(10):1174-1184.

While these analyses are all retrospective in nature and suffer from the same methodological flaws as any retrospective, nonrandomized study, such safety signals must be taken seriously in light of the fact that Seprafilm repeatedly has failed to demonstrate clinically meaningful benefits and has presented troubling safety concerns in randomized, controlled trials.

In addition, there are numerous case reports in the scientific medical literature of adverse events associated with the use of Seprafilm during abdominal or pelvic surgery, including eosinophilic enteritis at an ileostomy site,[66] sterile intra-abdominal fluid collection,[67] and pelvic peritonitis and bacterial abscess.[68] Moreover, there have been several case reports of patients undergoing surgery with Seprafilm who, within several days postoperatively, developed signs of severe acute inflammatory reactions, including sterile peritonitis and paralytic ileus.[69,70,71,72] In some cases, symptoms resolved after the abdominal cavity was thoroughly irrigated and the Seprafilm residue completely removed.[73]

In one particularly dramatic case report published by Trickett et al. (2001), a foreign body granulomata developed in a 71-year old women following a laparotomy for recurrent abdominal pain that included placement of one sheet of Seprafilm under the midline incision.[74] Three weeks after surgery, the patient underwent a second laparotomy because of persistent unresolved high intestinal obstruction and was found to have a "dense, thick, glue-like mass involving 95% of the small bowel and part of the transverse colon, anchoring the abdominal contents to the anterior abdominal wall." Attempts to free the small bowel from the mass were abandoned "because of the extent and density of the encasing mass," and most of the small bowel was resected. The patient subsequently died from postoperative complications. Microscopic examination of the mass of dense fibrotic tissue encasing the resected small bowel revealed that "the serosal surface was congested and encased in adherent fat and fibrous tissue containing numerous foreign-body-type giant-cell granulomata. Birefringent foreign material was identified in the giant cells, appearing as small particles and short fibers."

[66] Laxa BU, Bouchard A, DePetris G, et al. Eosinophilic enteritis confined to an ileostomy site. *Case Rep Gastroenterol*. 2011;5(2):422-427.
[67] Tyler J, McDermott D, Levoyer T. Sterile intra-abdominal fluid collection associated with seprafilm use. *The Am Surg*. 2008;74(11):1107-1110.
[68] Ko ML, Huang LW, Chang JZ, et al. An adhesion barrier may induce peritonitis and abscess after laparoscopy-assisted myomectomy with vaginal extraction: Report of a case. *Gynecol Obstet Invest*. 2010;69(2):109-111.
[69] Klingler PJ, Floch NR, Seelig MH, et al. Seprafilm-induced peritoneal inflammation: A previously unknown complication. *Dis Colon Rectum*. 1999;42(12):1639-1642.
[70] Remzi F, Oncel M, Church J, et al. An unusual complication after hyaluronate-based bioresorbable membrane (Seprafilm) application. *Am Surg.* 2003;69(4):356-357.
[71] David M, Sarani B, Moid F, et al. Paradoxical inflammatory reaction to seprafilm: Case report and review of the literature. *South Med J*. 2005;98(10):1039-1041.
[72] Huang JC, Yeh CC, Hsieh CH. Laparoscopic management for seprafilm-induced sterile peritonitis with paralytic ileus: Report of 2 cases. *J Minim Invasive Gynecol*. 2012;19(5):663-666.
[73] *Ibid*.
[74] Trickett J, Rainsbury R, Green R. Paradoxical outcome after use of hyaluronate barrier to prevent intra-abdominal adhesion. *J o Soc Med*. 2001;94(4):183-184.

g. MAUDE Data

The FDA offers an online search portal that provides easy access to the Manufacturer and User Facility Device Experience (MAUDE) database. This database was recently truncated so that now searches performed via the online portal yield results dating back only 10 years prior to the date of the search.[75] The FDA has made available downloadable zip data files that include MAUDE data more than 10 years old.

Through records from online searches of the MAUDE database performed by a consumer prior to FDA's truncation of the database and by Public Citizen after truncation of the database, we are aware of at least 21 reports of deaths in patients who underwent surgery with placement of Seprafilm, as well as two possible duplicate reports. The earliest report was received by the FDA on December 2, 1997. These reports are listed in Appendix B. Of these reports, catastrophic events described included acute respiratory distress syndrome,[76] peritonitis,[77,78] and overwhelming sepsis.[79]

In addition to death reports, Public Citizen performed a limited search of the MAUDE online database and the downloadable zip data files covering the time period from January 1, 1998, through May 27, 2015, identifying a total of 524 reports of adverse events linked to the brand name Seprafilm. Among the adverse events cited in numerous MAUDE reports for Seprafilm were the following:

- Bowel obstruction
- Abscess
- Peritonitis
- Fever
- Fluid collection
- Inflammatory reaction

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[75] Food and Drug Administration. Manufacturer and user facility device experience database – (MAUDE). Updated April 22, 2015. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm127891.htm. Accessed April 23, 2015.

[76] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery/Genzyme Seprafilm 3 Sheets. Event date January 24, 2006. MDR report key number: 726082. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=726082. Accessed December 10, 2014. (Listed in Appendix B as 7. Report Number MW1039481).

[77] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery Seprafilm adhesion barrier resorbable adhesion barrier. Event date December 20, 2004. MDR report key number: 564911. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=564911. Accessed December 10, 2014. (Listed in Appendix B as 9. Report Number 1220423-2005-00002).

[78] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery Seprafilm adhesion barrier resorbable adhesion barrier. Event date April 20, 2004. MDR report key number: 526527. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=526527. Accessed December 10, 2014. (Listed in Appendix B as 11. Report Number 1220423-2004-00009).

[79] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery (Seprafilm/pack) Seprafilm) bioresonable [sic] adhesion barrier. Event date unknown; report date October 29, 2013. MDR report key number: 3465909. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=3465909. Accessed December 10, 2014. (Listed in Appendix B as 1. Report Number 1220423-2013-11751).

- Leak
- Fistula
- Sepsis
- Wound dehiscence

A causal relationship between Seprafilm exposure and the reported adverse events may be difficult to establish in some cases, as many of these adverse events are common following surgery. However, Genzyme's own analysis of Study 601, which the FDA accepted, strongly suggests that use of Seprafilm can interfere with healing. Genzyme's analysis indicated that the practice of wrapping Seprafilm around a fresh bowel anastomosis likely contributes to increased risk of pelvic abscess and bacterial peritonitis. While we do not believe the risks of Seprafilm are limited only to this wrapping procedure, this evidence of elevated risk does suggest that Seprafilm can interfere with wound healing. Adhesions have the potential to wall off anastomoses, sealing tiny leaks to keep them from becoming large and clinically significant. Interference with this process could cause abdominal and pelvic abscesses and bacterial peritonitis due to leakage of bowel contents into the peritoneal space. We note that similar issues with wound healing may have contributed to the association between use of Seprafilm and fluid collection in patients with pelvic malignancies undergoing debulking procedures, where Seprafilm may come into extensive contact with injured tissue.[80]

Moreover, it is striking that a number of MAUDE database reports described the formation of adhesions, fibrous tissue formation, inflammatory reactions, or other problems precisely where the Seprafilm had been placed and, in some cases, with a geometric size and shape corresponding to a sheet of Seprafilm. Such reports demonstrate that in some patients Seprafilm can promote a severe foreign-body-type inflammatory reaction and the formation of dense fibrous tissue that can lead to severe small bowel obstruction and other serious complications. A non-exhaustive list of examples highlighting such potential problems, taken from MAUDE database reports, includes the following statements:

- "The [patient] underwent radiation therapy and colon resection about one year prior to this report (approximately early 2003). Over the course of the year, the [patient] developed a bowel obstruction, for which the [patient] was re-operated in 2003. The surgeon lysed several adhesions and applied seprafilm prior to closing the [patient]. … The [patient] was admitted to the [hospital] in 2004. The radiologist suspected a 'very thin' abscess, however the [patient] was reoperated the following day and no abscess was found. Instead, the surgeon found a dramatic, fibrotic response everywhere the seprafilm sheets had been applied in the previous surgery. The surgeon noted that these adhesions were 'like concrete' and were notably square-shaped where the seprafilm had been."[81]

[80] Leitao MM, Natenzon A, Abu-Rustum NR, et al. Postoperative intra-abdominal collections using a sodium hyaluronate-carboxymethylcellulose (HA-CMC) barrier at the time of laparotomy for ovarian, fallopian tube, or primary peritoneal cancer. *Gynecol Oncol.* 2009;115(2):204-208.

[81] Food and Drug Administration. MAUDE adverse event report: Genzyme birsurgery [sic] Seprafilm bioresorbable membrane resorbable adhesion barrier. Event date December 1, 2003. MDR report key number: 513662. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=513662. Accessed December 10, 2014.

- "[T]he areas of the small bowel where seprafilm had been placed were intimately adhered to the anterior abdominal wall and appeared to be acutely inflamed with a small amount of fibrinous exudate covering its surfaces … the patient ... died the following day. The reporting surgeon commented that 'seprafilm was the cause of aseptic peritonitis as the bowel loops most in contact with the seprafilm and anterior abdominal wall had the fibrinous exudate. He said the septic episode had caused his patient to die."[82]

- "Female, underwent a right salpingo-oophorectomy by the gynecology service for a fibroma. The [patient] was found to have adhesions in the small bowel area and adhesiolysis was performed by a general surgeon. Three sheets of seprafilm were utilized around the small bowel. One sheet of seprafilm was placed between the retroperitoneum and the small bowel. Two sheets were placed between the small bowel and the intra abdominal wall. The [patient] did well with her postoperative recovery and was subsequently discharged four days later. Within 24 [hours] of discharge, the [patient] was experiencing nausea and vomiting. She was unable to tolerate any oral intake. …The next day, the [patient] was taken to the [operating room]. And re-opened. … The [patient] was found to have a very intense inflammatory reaction of her small bowel and small bowel mesentery were clumped together into a few areas of indurated masses. Her entire small bowel was basically one large conglomerate that was matted together. The tissues appeared somewhat melted together, without any identificable [sic] planes. The tissues were friable, and upon opening the abdomen, injuries were sustained. … The [patient] basically had a 'concrete abdomen' and this was inoperable. … The inflammatory process was limited to the distribution of where the seprafilm was placed. … The next day, she was diagnosed with severe sepsis. … Twenty days later, active measures were withdrawn and the [patient] subsequently passed away."[83]

- "Allergic reaction [information] was received in 2005 from a surgeon, concerning a [patient] with [unknown] past medical and surgical history, who in 2005 underwent an adhesiolysis in order to release an ileus. Three sheets of seprafilm were placed, one at the part of the adhesiolysis and two under the mid incision. Few days later, the [patient] developed an 'allergic reaction at small intestine where seprafilm was obviously placed.' [N]o further details were provided. … The reporting surgeon assessed the allergic reaction as serious, severe, and probably related to the use of seprafilm. … Follow-up information was received from the physician on 10-feb-2006, which clarified that at the time of the re-operation seprafilm had completely absorbed. The area where seprafilm had been placed was calcified like glass and had been removed."[84]

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[82] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery Seprafilm adhesion barrier resorbable adhesion barrier. Event date April 20, 2004. MDR report key number: 526527. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=526527. Accessed December 10, 2014. (Listed in Appendix B as 11. Report Number 1220423-2004-00009).

[83] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery/Genzyme Seprafilm 3 sheets. Event date January 24, 2006. MDR report key number: 726082. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=726082. Accessed December 10, 2014. (Listed in Appendix B as 7. Report Number MW1039481)

[84] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery Seprafilm resorbable adhesion barrier. Event date November 14, 2005. MDR report key number: 654835.

- "The [health care provider] reported that 'a few weeks back', he performed an ileostomy revision on the patient and placed one sheet of seprafilm. About a week later, the patient experienced a complete bowel obstruction. When the patient was taken to surgery, he was noted to have a 'horrible inflammatory reaction corresponding to where the sepra[film] was placed.' the area where the film was placed was rock hard. A bowel resection was performed. Pathology revealed a giant cell foreign body reaction. On (b)(6) 2009, the [health care provider] stated 'given what i [sic] observed at the second surgery and the pathology findings, it seems most likely that a foreign body reaction to seprafilm was involved. '"[85]

- "the patient underwent lower anterior resection with primary anastomosis for rectal cancer in 2003. Upon operation, the patient was found to have a few adhesions from previous procedures. The patient received one sheet of seprafilm under … the incision and was closed with #1 pds run, with skin staples. The patient developed nausea, vomiting, and abdominal pain three to four days after surgery. … The patient was re-operated 11 days later and was found to have massive adhesions with three to four loops of small bowel 'tenaciously pulled in,' very tight and concrete, all local to the area where the seprafilm had been placed. A biopsy was performed on the adhesions, which showed foreign body, giant cells. … The surgeon diagnosed this patient's symptoms as an inflammatory foreign body reaction to seprafillm [sic]."[86]

- "Report received from a physician in 2004 regarding a [patient] … who had a colectomy with anastomosis through low resection with seprafilm placed on the top of the omentum. … The [patient] developed severe peritoneal signs and underwent a second laparotomy. The area where the seprafilm was placed was severely inflamed, and murky fluid was present. … The omentum biopsy showed an inflammatory cellular reaction."[87]

In other cases, it appeared that the Seprafilm did not fully dissolve as intended, and instead persisted in gel or film form, potentially contributing to injury:

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http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=654835. Accessed December 10, 2014.

[85] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery (Seprafilm/pack) Seprafilm (sodium hyaluronate, carboxymethylcellulose) membrane bioresorbable adhesion barrier. Event date unknown; report date July 21, 2009. MDR report key number: 1442740. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=1442740. Accessed December 10, 2014.

[86] Food and Drug Administration. MAUDE adverse event report: Genzyme Corporation Seprafilm adhesion barrier resorbable adhesion barrier. Event date November 24, 2003. MDR report key number: 513621. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=513621. Accessed December 10, 2014.

[87] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery Seprafilm adhesion barrier resorbable adhesion barrier. October 1, 2003. Event date October 1, 2003. MDR report key number: 545156. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=545156. Accessed December 10, 2014.

- "Severe adhesions were found under the median incision where the seprafilm had been placed. ... Reporter stated that it was uncertain whether this adhesion was related to seprafilm, however a clear transparent seprafilm-like thing was strongly adhered at the site."[88]

- "Seprafilm had stayed in gel form between the greater omentum and small intestine, and could not be removed as a strong adhesion had formed and an intestinal injury may have developed."[89]

- "The event of ascites retention was probably related to seprafilm as the ascites went into the area between the abdominal cavity and seprafilm which did not allow for the seprafilm to dissolve and induced pooling of fluid."[90]

- "Upon re-exploration, the [patient] had a gelatinous mass with fibrous strands. There were fibrous bands in between the viscera embedded between the gelatinous mass. The mass was without urine, bowel, or fecal matter. The entire mass could not be removed because it was 'glued' to the intestines. … It was the opinion of the surgeon, that the event was induced by seprafilm as he could not find any other explanation for the gelatinous mass."[91]

These serious events, many of which echo the more detailed case reports found in the scientific medical literature, are not adequately represented in the Seprafilm label, which states only that "[f]oreign body reactions may occur with Seprafilm Adhesion Barrier, as with any implanted material" and "[n]o foreign body reaction was detected in the 882 Seprafilm patients [in Study 601]."[92]

Sadly, the list of adverse events reported in the MAUDE database undoubtedly constitutes only a small fraction of the actual number of serious adverse events associated with the use of Seprafilm. Many medical device adverse events are never reported to the FDA, and this industry-

[88] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery Seprafilm adhesion barrier resorbable adhesion barrier. Event date February 17, 2004. MDR report key number: 521284. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=521284. Accessed December 10, 2014.
[89] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery Seprafilm adhesion barrier resorbable adhesion barrier. Event date December 13, 2004. MDR report key number: 568108. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=568108. Accessed December 10, 2014.
[90] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery Seprafilm adhesion barrier resorbable adhesion barrier. Event date October 7, 2004. MDR report key number: 565473. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=565473. Accessed December 10, 2014.
[91] Food and Drug Administration. MAUDE adverse event report: Genzyme biosurgery Seprafilm adhesion barrier resorbable adhesion barrier. Event date unknown; report date January 25, 2005. MDR report key number: 568111. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=568111. Accessed December 10, 2014.
[92] Food and Drug Administration. MAUDE adverse event report: Genzyme. Product Label: Seprafilm Adhesion Barrier. December 2008.

wide problem of under-reporting may be particularly true in the case of Seprafilm: In 1999, the FDA issued an EIR-483 inspection report form to Genzyme citing the company for inadequate complaint handling and medical device reporting procedures for Seprafilm, which led to a failure to report some adverse events associated with Seprafilm use to the FDA.[93]

h. Additional Risks From Off-Label Uses or Uses Lacking Clinical Trial Evidence of Safety and Effectiveness

In addition to the risks seen when Seprafilm is used according to its labeling and the uses studied in the pivotal clinical trials that led to FDA approval, further concerns arise in the context of off-label uses, as well as uses purportedly within the scope of the labeled indication that were not assessed in the pivotal clinical trial used to support the approval of the PMA application for Seprafilm. Such uses have proliferated in recent years. There are reports of Seprafilm being used (without evidence of benefit) in Cesarean sections,[94,95] in pediatric surgery,[96] during laparoscopic surgery to treat chronic abdominal pain,[97] for the prevention of postoperative SBO in transabdominal aortic aneurysm surgery,[98] as a device to reduce postoperative adhesions after cardiac surgery,[99] during decompressive craniectomy as a dural substitute and anti-adhesion barrier,[100] and in the setting of pediatric ventriculoperitoneal shunt malfunction,[101] among others.

In 2013 Genzyme agreed to pay $22.28 million to the U.S. government to resolve allegations that it marketed a "slurry" version of Seprafilm, a use that is clearly not covered by the product label. The government alleged that doctors were taught to cut the Seprafilm sheets into small pieces, add saline, and allow the pieces to dissolve before injecting the resulting slurry into the abdominal cavity through a catheter.[102] This procedure has not been demonstrated effective and raises a number of potential safety concerns, including the risk that the solution may contribute to impairment in the wound healing process.[103]

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[93] Food and Drug Administration. Genzyme Corporation: Summary of Findings. 1/12-14, 26 & 27/99.
[94] Albright CM, Rouse DJ. Adhesion barriers at cesarean delivery: Advertising compared with the evidence. *Obstet Gynecol*. 2011;118(1):157-160.
[95] Edwards RK, Ingersoll M, Gerkin RD, et al. Carboxymethylcellulose adhesion barrier placement at primary cesarean delivery and outcomes at repeat cesarean delivery. *Obstet Gynecol*. 2014;123(5):923-8.
[96] Inoue M, Uchida K, Miki C, Kusunoki M. Efficacy of Seprafilm for reducing reoperative risk in pediatric surgical patients undergoing abdominal surgery. *J Pediatr Surg.* 2005;40(8):1301-1306.
[97] Khaitan L, Scholz S, Richards WO. Laparoscopic adhesiolysis and placement of seprafilm: A new technique and novel approach to patients with intractable abdominal pain. *J Laparoendosc Adv Surg Tech*. 2002;12(4):241-247.
[98] Kudo FA, Nishibe T, Miyazaki K, et al. Use of bioresorbable membrane to prevent postoperative small bowel obstruction in transabdominal aortic aneurysm surgery. *Surg Today*. 2004;34(8):648-651.
[99] Kaneko Y, Hirata Y, Achiwa I, et al. Adhesion barrier reduces postoperative adhesions after cardiac surgery. *Asian Cardiovasc Thorac Ann*. 2012;20(3):257-262.
[100] Mumert ML, Altay T, Couldwell WT. Technique for decompressive craniectomy using Seprafilm as a dural substitute and anti-adhesion barrier. *J Clin Neurosci*. 2012;19(3):455-457.
[101] Otake K, Uchida K, Inoue M, et al. Efficacy of Seprafilm in abdominal surgery for ventriculoperitoneal shunt malfunction: A report of two pediatric cases. *Pediatr Neurosurg*. 2011;47(3):214-216.
[102] Department of Justice. Genzyme Corp. to pay $22.28 million to resolve false claims allegations related to "slurry" used in patients. December 20, 2013. http://www.justice.gov/opa/pr/genzyme-corp-pay-2228-million-resolve-false-claims-allegations-related-slurry-used-patients. Accessed November 12, 2014.
[103] Chu D, Stucchi A, Becker J. A "solution" to the application of an effective physical barrier for the prevention of intra-abdominal adhesions. *J Surg Res*. 2011;167(1):33-36.

i. Conclusion

The clinical trials of Seprafilm failed to demonstrate convincingly the product's efficacy in improving any important clinically meaningful endpoint. Moreover, there is substantial evidence that the product causes serious, sometimes fatal adverse events, as demonstrated by data from randomized clinical trials, other published scientific literature, and the FDA's MAUDE database.

Given the evidence presented above, much of which was either not available or not considered by the FDA at the time of Seprafilm's approval and supplement reviews, we hereby petition the FDA, pursuant to Sections 515 and 518 of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. Parts 810 and 814, to immediately:

(1) Withdraw the premarket approval of Seprafilm because there is not sufficient evidence to provide reasonable assurance that the product is safe and effective under the conditions of use offered in the product's labeling; and

(2) Initiate a mandatory recall of all remaining unused Seprafilm devices because the device causes serious adverse health consequences, including, in some cases, death.

III. Environmental Impact

The requested recall action is excluded under 21 C.F.R. § 25.30(c). The requested PMA withdrawal is excluded under 21 C.F.R. § 25.34(e). In addition, neither action is expected to have any environmental impact.

IV. Certification

We, the undersigned, certify that to the best of our knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to us which are unfavorable to the petition.

Sarah Sorscher, J.D., M.P.H.
Attorney
Public Citizen's Health Research Group

Michael Carome, M.D.
Director
Public Citizen's Health Research Group

cc: Jeffrey E. Shuren, M.D., J.D., Director, Center for Devices and Radiological Health

Appendix A

Table A: 30-Day and 6-Month Serious Adverse Events that Occurred in ≥ 1% of All Randomized Subjects (N=1,791) Who Had Either Intestinal Resections or Adhesiolysis (Postmarket Study)

Event Description	30-Day Seprafilm Subjects (N=882)	30-Day Control Subjects (N=909)	6-Month Seprafilm Subjects (N=882)	6-Month Control Subjects (N=909)
	n (%) Subjects With Event	n (%) Subjects With Event	n (%) Subjects With Event	n (%) Subjects With Event
Any Serious Adverse Event	*264 (30)*	*237 (26)*	*350 (40)*	*324 (36)*
Ileus	*40 (5)*	*40 (4)*	*51 (6)*	*46 (5)*
Intestinal Obstruction	38 (4)	33 (4)	65 (7)	68 (8)
Anastomotic Leak	*33 (4)**	*16 (2)**	*41 (5)*	*28 (3)*
Dehydration	26 (3)	32 (4)	44 (5)	47 (5)
Abdominopelvic Abscess	30 (3)	27 (3)	48 (5)	43 (5)
Peritonitis	*26 (3)**	*12 (1)**	*31 (4)*	*18 (2)*
Postoperative Wound Infection	30 (3)	27 (3)	37 (4)	30 (3)
Abdominal Pain	18 (2)	15 (2)	28 (3)	26 (3)
Fever	15 (2)	24 (3)	22 (3)	32 (4)
Fistula	*16 (2)**	*2 (<1)**	*26 (3)**	*7 (1)**
Vomiting	*13 (2)*	*13 (1)*	*22 (3)*	*20 (2)*
Sepsis	*17 (2)*	*9 (1)*	*21 (2)*	*13 (1)*
Wound Dehiscence	12 (1)	9 (1)	16 (2)	10 (1)
Gastrointestinal Disorder (Not Otherwise Specified)	7 (1)	8 (1)	13 (2)	13 (1)
GI Hemorrhage	*9 (1)*	*3 (<1)*	*13 (2)*	*8 (1)*
Nausea	6 (1)	5 (<1)	12 (1)	11 (1)
Intra-Abdominal Fluid Collection	9 (1)	6 (1)	11 (1)	6 (1)
Urinary Tract Infection	8 (1)	7 (1)	11 (1)	10 (1)
Line Infection	7 (1)*	1 (<1)*	10 (1)	5 (1)
Thrombophlebitis Leg Deep	3 (<1)	4 (<1)	9 (1)	7 (1)

* Statistically significant difference detected between the Seprafilm and control group ($p < 0.05$). Events in *italics* nominally favored the control group at 30 days and 6 months.

Source: Genzyme. Product Label: Seprafilm Adhesion Barrier. December 2008.

Table B: Summary of Results of Efficacy Studies				
Reference	**N**	**Procedure and Subject Population**	**Reported Outcomes (Seprafilm Versus Control)[a]**	**P-value[a]**
Vrijland 2002	71 (42 analyzed)	Hartmann procedure in adults with sigmoid diverticulitis or obstructed rectosigmoid	Severity of adhesions (Lower severity in Seprafilm versus control)	< 0.05
			Incidence of adhesions to the midline incision	
			Superior segment (67% versus 81%)	0.48
			Middle segment (71% versus 95%)	0.09
			Inferior segment (67% versus 86%)	0.28
			Total midline incision (90% versus 100%)	0.48
			Adhesions to the pelvic area (76% versus 90%)	0.41
Tang 2003	175 (108 analyzed)	Rectal resection and creation of a defunctioning ileostomy in patients 16 years or older with rectal or rectosigmoid cancer, radiation stricture/proctitis, rectal prolapse/cap polyposis, diverticular disease, rectal metastasis, endometrosis with rectal stricture, or rectal carcinoid	Mean ± standard error peristomal adhesion severity score	
			Phase I[b] *(7.42 ± 0.5 versus 7.28 ± 0.4)*	*0.84*
			Phase II[b] (5.81 ± 0.5 versus 7.82 ± 0.6)	0.02
Kusunoki 2005	62	Low anterior resection or anoabdominal rectal resection in patients younger than age 80 with advanced rectal cancer	Severity of midline adhesions Grade 0 (87% versus 14%) Grade 1 (13% versus 38%) Grade 2 (0% versus 48%) Grade 3 (0% versus 0%)	< 0.001
			Severity of peristomal adhesions Grade 0 (13% versus 0%) Grade 1 (60% versus 31%) Grade 2 (20% versus 52%) Grade 3 (7% versus 17%)	0.007
			Extent of midline adhesions Grade 0 (87% versus 14%) Grade 1 (13% versus 10%) Grade 2 (0% versus 52%) Grade 3 (0% versus 24%)	< 0.001
			Extent of peristomal adhesions Grade 0 (13% versus 0%) Grade 1 (60% versus 21%) Grade 2 (23% versus 45%) Grade 3 (3% versus 34%)	0.0003

Salum 2006	191	Temporary loop ileostomy creation through midline incision in adults needing restorative protectomy, coloproctostomy, or restorative proctocolectomy for any diagnosis	Incidence of stomal adhesions (82% versus 95%) Mean operative times (27 minutes versus 28 minutes)	0.021 0.38
Park 2009	427	Radical resection for sigmoid colon or rectum in adults with sigmoid or rectal cancer	Early postoperative small bowel obstruction (3% versus 7%) Readmission for intestinal obstruction (3% versus 5%)	0.045 0.322
Hayashi 2008	150 (144 analyzed)	Gastrectomy in patients younger than age 80 with gastric cancer	Overall incidence of small bowel obstruction (6% versus 10%) Cumulative incidence of small bowel obstruction (6% versus 12%) *Incidence of postoperative complications (33% versus 30%)*	0.534 0.379 *0.722*
Van der Wal 2011	42 (35 analyzed)	Hartmann's procedure in adults with sigmoid diverticulitis or obstructed rectosigmoid	Chronic abdominal complaints (35% versus 78%)[c] Small bowel obstruction (0% versus 11%) Quality of life	0.018[c] NS NS
Dupre 2013	54	Two-stage hepatectomy for resection of liver metastases in adults with metastatic colorectal cancer	Time to complete liver mobilization at second hepatectomy (median: 50 versus 75 minutes) *Complications at first hepatectomy (49% versus 31%)* Complications at second hepatectomy (23% versus 55%)	NS *Not Reported* 0.07

NS = not statistically significant

[a] Outcomes in *italics* nominally favored the control group.

[b] The investigators published results from two successive "phases," each conducted using similar protocols. Phase II was "prompted" by the results of Phase I and was "aimed at eliminating possible bias."

[c] Percentages incorrect based on the number of subjects reported: Seprafilm 6/16 (38%) versus control 14/19 (74%).

Sources:

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Appendix B
MAUDE Death Reports Involving Seprafilm

1. Report Number 1220423-2013-11751
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=3465909
Date FDA Received November 5, 2013
Event Type Death
Event Description
This serious unsolicited device case was received from (b)(6) on (b)(6) 2013 from a physician (transplant specialist) via our marketing partner (b)(4). This case concerns a pt (demographics unk) who experienced sepsis after seprafilm placement. No relevant medical history, past drugs, other concomitant medication or concurrent conditions were reported. On an unspecified date, seprafilm was placed during an unspecified procedure (number of sheets, batch/lot number unk and expiration date unk) into an unspecified anatomical location for unk indication. Later, on an unspecified date (after unk latency), the pt experienced sepsis. On an unk date, the pt died due to sepsis. Corrective treatment: not reported. Outcome: fatal. A pharmaceutical technical complaint (ptc) was initiated and conclusion was pending for the same. Sepsis (sepsis). Reporting physician's seriousness assessment: serious (death). Reporting physician's assessment: not related. Pharmacovigilance comment: sanofi comment dated (b)(4) 2013: in this case the causal role of seprafilm cannot be excluded for the occurrence of sepsis, however there is no info regarding the underlying medical history and the concomitant medications used by the pt precludes the complete case assessment, and moreover the lack of info regarding the autopsy findings of the pt precludes the complete case assessment.

(Possible Duplicate) Report Number 1220423-2013-11736
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Detail.cfm?MDRFOI__ID=3465889
Date FDA Received November 5, 2013
Event Type Death
Event Description
This serious unsolicited device case was received from (b)(4) on (b)(6) 2013 from a physician (transplant specialist) via our (b)(4). This case concerns a pt (demographics unk) who experienced sepsis after seprafilm placement. No relevant medical history, past drugs, other concomitant medication or concurrent conditions were reported. On an unspecified date, seprafilm was placed during an unspecified procedure (number of sheets, batch/lot number unk and expiration date unk) into an unspecified anatomical location for unk indication. Later, on an unspecified date (after unk latency), the pt experienced sepsis. On an unk date, the pt died due to sepsis. Corrective treatment: not reported. Outcome: fatal. A pharmaceutical technical complaint (ptc) was initiated with global ptc number: (b)(4) and conclusion was pending for the same. Sepsis (sepsis). Reporting physician's seriousness assessment: serious (death). Reporting physician's assessment: not related. Pharmacovigilance comment: sanofi comment dated (b)(6) 2013: in this case the causal role of seprafilm cannot be excluded for the occurrence of sepsis, however there is no info regarding the underlying medical history and the concomitant medications used by the pt precludes the complete case assessment, and moreover the lack of info regarding the autopsy findings of the pt precludes the complete case assessment.

2. Report Number 1220423-2011-00045
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=2330071
Date FDA Received November 3, 2011
Event Type Death **Patient Outcome** Death, Hospitalization
Event Description
Afferent loop syndrome [afferent loop syndrome]. Strangulation ileus [mechanical ileus]. Abdominal pain [abdominal pain]. Septic shock [septic shock]. Case description: literature-spont report received on (b)(6) 2011 from an hcp regarding an approx (b)(6)-old male pt, initials unk, who experienced abdominal pain, septic shock, strangulation ileus and afferent loop syndrome. The tittle of the literature article from which this report was obtained was not provided. The pt's medical history was not provided. The pt experienced abdominal pain, for which he was hospitalized. The pt experienced septic shock, strangulation ileus and afferent loop syndrome. The outcome of the pt was reported as death (date not provided). The cause of death was not provided. Further info is expected. The product lot number was not reported.
Manufacturer Narrative
Mfr's comment: the benefit-risk relationship of seprafilm is not affected by this report.

3. Report Number 1220423-2011-00037
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=2230410
Date FDA Received August 15, 2011
Event Type Injury **Patient Outcome** Death, Hospitalization
Event Description
Acute coronary occlusion (slurry) [coronary artery occlusion]. Feeling unwell with ileus [slurry] [ileus]. Case description: literature-trial report was received on (b)(6) 2011 from a physician regarding a pt (identifiers not provided). This report is from a literature article entitled "seprafilm slurry does not increase complication rates after laparoscopic colectomy". There were two groups. Group 2 consisted of 50 pts who underwent laparoscopic colectomy followed by the application of the seprafilm slurry. The slurry was created at the end of the operation by dissolving two procedure packs (each containing six 3 x 6 inch sheets) of seprafilm in 120 ml of warm normal saline. The slurry was delivered into the peritoneal cavity using a 16-fr. Robinson catheter. A (b)(6) pt with a history of coronary artery disease (cad), diabetes, current smoker, stroke and myocardial infarction (status postcoronary artery bypass graft) underwent laparoscopic right hemicolectomy for a large cecal polyp. He was readmitted to the hospital feeling unwell with ileus and died three days after readmission. Postmortem examination confirmed acute coronary occlusion with no abnormality in the peritoneal cavity. The author indicated that the death was not related to any intraabdominal complications. The action taken with seprafilm was not provided. The pt's outcome was fatal. Concomitant medications were not provided. The relationship between seprafilm and the events of coronary artery disease and ileus was not provided by the reporting physician.
Manufacturer Narrative
Mfr's comment: the benefit-risk relationship of seprafilm is not affected by this report.

4. Report Number 1220423-2011-00011
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=2040823
Date FDA Received March 29, 2011
Event Type Death **Patient Outcome** Death
Event Description
Complications from the surgery [post procedural complication]. Inflammatory response [inflammation]. Case description: spontaneous report received on (b)(6) 2011 received from a surgeon via a company sales representative regarding a female pt, (age and initials unk). Approximately two years ago, the pt had a colon resection during which two to three sheets of seprafilm was used. The seprafilm lot number was not available. The pt had an inflammatory response after the surgery. Fifteen days later, a second surgery was performed. The pt died of complications from the surgery and inflammation. No further info was provided. Additional info was received on (b)(6) 2011 from the reporting surgeon. The indication for the surgery in which seprafilm was used was diverticulosis. An autopsy was not performed. He considered that the events of complications from the surgery and inflammation were due to multi factors. He was not sure if there was a causal relationship between the events and seprafilm. The physician was not able to provide further info including pt identifiers, seprafilm lot number, surgery, event onset dates, and pt's medical history. No further info was provided. Mfr's comment: the benefit-risk relationship of seprafilm is not affected by this report.

5. Report Number 1213643-2010-00229
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=1700945
Date FDA Received May 19, 2010
Catalog Number 0112970
Event Date October 4, 2008
Event Type Death **Patient Outcome** Death,Hospitalization
Event Description
Information reported via maude event report: pt's daughter reported pt experienced pain, nausea, severe weakness, elevated white blood cell count, infected mesh, severe rectal bleed, fistulas, and bowel surgeries with an ileostomy, sepsis and death following the mesh implant surgery. Medical record info: (b) (6) 2007 - hernia repairs with 2 bard mesh implants. (upper midline) seprafilm was implanted prior to perfix plug. (lower midline) seprafilm was implanted over the small bowel prior to bard composix e/x mesh. On (b) (6) 2008 - exploratory laparotomy, lysis of adhesions, extended right hemicolectomy for a massive lower gi bleed noted to be related to angiodysplasia. Per or notes: mesh present and preserved. Two sheets seprafilm implanted in peritoneal cavity. Pt developed wound infection, abscess, and colocutaneous fistula due to an anastomotic dehiscence. On (b) (6) 2008: wound packing for abdominal wound infection. On (b) (6) 2008: exploratory laparotomy, lysis of adhesions, drainage of intra-abdominal collection, placement of loop ileostomy. Fistula drainage decreased, but, resulted in infection of mesh. On (b) (6) 2008 - drainage of the abscess, closure of the fistula, partial mesh explant (composix ex mesh). Per operating room report, mesh was clearly infected as a result of the anastomotic dehiscence in the past. Pt began having bilious drainage from the midline incision; findings consistent with an enterocutaneous fistula. On (b) (6) 2008: the pt underwent laparotomy, wound exploration, and debridement, closure of the colocutaneous fistula. On (b) (6) 2008 - pt died. Per

death certificate, immediate cause of death was sepsis syndrome, with significant conditions contributing to death listed as liver failure and sacral decubiti. No autopsy was performed.
Manufacturer Narrative
Based on the medical records provided, it is not clear what the pt's clinical course was beyond (b) (6) 2008 when she was discharged from the hospital and apparently transitioned to another facility for continued rehab up through her death. The info from the provided medical records, and further supported by the photographs of abdominal incisions and wounds, indicates the post mesh implant medical and surgical procedures were located at the abdominal midline and below the midline, and were not associated with the upper midline where the bard perfix plug was implanted. The medical records provided did not include a statement or indication that there was a possible or suspected device failure related to the bard perfix plug mesh. Additionally, there is no indication that the bard perfix plug was explanted. No sample has been returned for eval; however, based on the currently available info, there is no indication the bard perfix plug mesh caused or contributed to the pt's infection or death. For add'l clinical detail and info related to the composix e/x mesh, see mdr 1213643-2008-00366. (same as No. 5 above)

(Possible Duplicate) Report Number MW5014904
Reporter Occupation Patient FAMILY MEMBER OR FRIEND
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=1617164
Date FDA Received February 22, 2010
Lot Number 07NP011
Event Date July 17, 2007
Event Type Death **Patient Outcome** Other,Death,Hospitalization
Event Description
My mom had hernia surgery (b) (6) 2007 passed away (b) (6) 2008. I am an rn. I am very aware of what happened. Three months following this surgery symptoms mom developed, nausea, weakness, elevated wbc and was treated at home. She was then hospitalized severe weakness, elevated wbc in (b) (6) 2008 and never came home. My mom, while hospitalized for 9 months developed severe rectal bleed, fistules, had frequent colectomy's ended up with ileostomy elevated wbc up 49,000. Even her surgeon removed the infected hernia mesh. She suffered horribly in pain. The infection attacked her liver and died of sepsis which is documented on her death certificate. I am aware of the recall on bard hernia mesh. I have researched this and found other people on the internet with the same lot number of my moms. I am 100% this killed our mom, but because of her age and no recall of the product i have no case. If i can help someone from this i have done something. I still have the fight in me to prove this if you can help. My mom was a wonderful mom and grandmother. Her memory will last forever. I retrieved these specific numbers myself at the hospital. This is the lot number used. Bard composix e/x mesh ellipse supra public "6x8" ref no. 0123680, lot no. 43jqd311, bard mesh perfix plug mid abd. Size large ref 0112970, lot 43kqd161, seprafilm x2 abd (b) (4), lot 07np011, sterility no. 2010-01. Dates of use: (b) (6) 2007 - (b) (6) 2008. Diagnosis or reason for use: hernia repair.

6. Report Number 1220423-2007-00022
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.cfm?MDRFOI__ID=958436
Date FDA Received December 4, 2007

Event Date September 27, 2007
Event Type Death **Patient Outcome** Death
Event Description
Fungemia; abscess in the lower abdomen; decline in physical strength. Information was received on 13-nov-2007 from a physician regarding a male patient who had a medical history of gastric cancer. The patient underwent billroth i gastroduodenostomy for his gastric cancer in 2007. One sheet of seprafilm was placed at the gastric and duodenal anastamosis site. The physician reported, that there was a leak posterior to the greater curvature of the stomach at the anastomosis site. Drainage was supposed to be collected subhepatically, but the drainage collected in the lower abdomen because seprafilm prevented and adhesion. According to the physician, this delayed the discovery of the formation of an abscess. Fungemia then developed due to a decline in physical strength and the patient died the next month. The physician assessed the adverse events' intensities as severe and probably related to seprafilm. The investigation summary was received on 03-dec-2007. Complaint investigation summary: no sample was returned and no lot number was provided by the user facility, therefore, genzyme quality assurance is unable to perform an evaluation or lot history review. If a lot number is provided in the future, this complaint will be re-opened and the appropriate investigation will be conducted.

7. Report Number MW1039481
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=726082
Date FDA Received June 5, 2006
Voluntary Report by Family
Event Date January 24, 2006
Event Type Death **Patient Outcome** Death, Other, Hospitalization, Life Threatening, Disability
Event Description
Female, underwent a right salpingo-oophorectomy by the gynecology service for a fibroma. The pt was found to have adhesions in the small bowel area and adhesiolysis was performed by a general surgeon. Three sheets of seprafilm were utilized around the small bowel. One sheet of seprafilm was placed between the retroperitoneum and the small bowel. Two sheets were placed between the small bowel and the intra abdominal wall. The pt did well with her postoperative recovery and was subsequently discharged four days later. Within 24 hrs of discharge, the pt was experiencing nausea and vomiting. She was unable to tolerate any oral intake. She was not experiencing abdominal bloating or distension. She presented to the emergency dept on two occasions. First on the evening of the next day and then again at the early evening the following day. She was hydrated with intravenous fluids on both occasions. Her symptoms persisted, however, and she re-presented to the emergency dept 3 days later. She was found to have a benign abdominal examination. Her while blood cell count, however, was elevated at 14. 95. She was clinically dehydrated with hyponatremia, hypokalemia and hypochloremia. She was admitted to the hosp for further evaluation and management. A nasogastric tube was placed. She had greater than two liters of output. A ct scan of abdomen and pelvis was obtained revealing dilatation of the stomach and proximal small bowel. There was a transition point with distal decompression. This was consistent with a mechanical small bowel obstruction. The next day, the pt was taken to the o.R. And re-opened. The pt was found to have a very intense inflammatory reaction of her small bowel and small bowel mesentery were clumped together into a few areas of indurated masses. Her entire small bowel was basically one large conglomerate that was matted together. The tissues appeared somewhat melted together, without

any identificable planes. The tissues were friable, and upon opening the abdomen, injuries were sustained. An area of "deserosalization" was oversewn. Two enterotomies were repaired. A distal ilieal longitudinal tear was not repairable. The pt basically had a "concrete abdomen" and this was inoperable. A resection was impossible, as was exteriorization. The proximal and distal portions of the tear were decompressed with tube ileostomies. The inflammatory process was limited to the distribution of where the seprafilmwas placed. This was around the small bowel and small bowel mesentery. The pelvis was spared from this process, as was the upper abdomen. She was kept on bowel rest/decompression and total parenteral nutrition. Over the next few days, the pt developed progressive confusion and delirium. Her oxygen requirements increased. A chest x-ray revealed patchy infiltrates. The pt was subsequently transferred to icu 2 days later. The next day, she was diagnosed with severe sepsis and began treatment using xigris. The pt's respiratory status worsened and she eventually required intubation and ventilatory support. The pt appeared to develop a systemic inflammatory response and ards. The pt continued on high ventilatory support and intermittent vasopressors. It was felt that she had worsening fibroproliferative ards. Twenty days later, active measures were withdrawn and the pt subsequently passed away.

8. Report Number 1220423-2005-00016
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=606881
Date FDA Received May 24, 2005
Event Type Death **Patient Outcome** Death
Event Description
Spontaneous report received in april 2005 from a surgeon regarding a pt early stage ovarian cancer pt who received seprafilm after an optimal debulking surgery. Subsequent to the surgery the pt's with blood cell count remained elevated and the pt became unresponsive to associated treatments. The pt was re-operated on, and a "fibrotic reaction to seprafilm" was found. The pt subsequently died from the process. It was the opinion of the surgeon that the fibrotic reaction was an allergic reaction to seprafilm. No further information was provided.
Manufacturer Narrative
Anaphylactic reaction, fibrotic reaction, allergic reaction. Follow-up information was received in 2005 from the physician, which provided the primary and secondary causes of death. It was reported that an autopsy was offered, but that the patient's family had refused. The physician felt that the primary cause of death was a severe anaphylactic reaction with symptoms of leukocytosis and eosinophilia on differential. The physician felt that the secondary cause of death was ovarian cancer. The physician declined to provide any additional information. Conclusions: this conclusion code was chosen because no sample was returned and no lot number was provided by the user facility. Co's quality assurance is unable to perform an evaluation or lot history review. If a lot number is provided in the future, this complaint will be re-evaluated at that time.

9. Report Number 1220423-2005-00002
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=564911
Date FDA Received January 10, 2005
Event Date December 20, 2004
Event Type Death **Patient Outcome** Other, Death, Required Intervention
Event Description

Secondary bacterial peritonitis. Spontaneous report was received from a physician via a sales rep in 2004, for 3 days regarding a pt who underwent colorectal surgery 3 days earlier and received two sheets of seprafilm. After the surgery (time interval not provided), the pt developed postoperative pain and consequently underwent an exploratory laparotomy in 2004. The surgeon initially suspected a dead bowel, however he found grayish mucous-like fluid in the abdominal cavity, and irrigated the abdominal cavity. The surgeon described his findings as seprafilm induced peritonitis. The pt's condition deteriorated after this surgery and the pt underwent a second exploratory laparotomy 2 days later, during which the surgeon found secondary bacterial peritonitis. The pt died after surgery. It was the opinion of the surgeon that the event was secondary to the use of seprafilm. No further info was provided.

10. Report Number 1220423-2004-00013
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=531262
Date FDA Received June 23, 2004
Event Date November 15, 2003
Event Type Death **Patient Outcome** Death, Required Intervention
Event Description
Info was received in 05/2004 from a patient's physician via distributor regarding a pt with a medical history of disseminated cancer to the peritoneum. In 11/2003, an intravenous hyperalimentation was placed. The pt underwent surgery "of the pylorus side of gastrectomy" six days later. After resecting the gastric cancer, a drain was placed and the gaster was anastomosed by suturing apparatus. One sheet of seprafilm was placed under the median abdominal incision. There was no seprafilm placed on the anastomosis. The peritoneum was sutured and the skin was sutured by hand. The operation took 4 hours. Drainage was done after the operation. The estimated blood loss was 594 grams without transfusion. After the operation, flomoxef sodium was started for post-operative infection prophylaxis. Two days after, the pt had a wbc of 21,000/mm^3 and the next day, a wbc of 18,100/mm^3 and a crp of 30. 1 mg/l, subileus and pleural effusion. The following day, ct scan of the abdomen revealed a fluid collection in the abdomen and a drain was placed in the median incision. The day after, receliotomy was performed for enterostomy and peritoneal drainage. This revealed an anastomotic leak of the duodenal stamp. The seprafilm had turned to sludge and was removed. After the operation, the pt began to recover. In same day, the pt was started on freeze-dried sulfonated human normal immunoglobulin for sepsis, octreotide acetate for pancreatitis, ulinastatin for cardiovascular failure and imipenem cilastation for infection. Four days later, the splenic artery was found to be bleeding. The pt was treated with hemostasis, irrigation and angiorrhapy. One week later, the splenic artery was again found to be bleeding, which was treated with compression and transcatheter arterial embolization. In 12/2003, the gauze was removed. In 12/2003, the pt experienced a re-occurrence of bleeding from the splenic artery. The pt died in 12/2003. The relationship between the events and seprafilm was considered unlikely, per the reporter.

11. Report Number 1220423-2004-00009
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=526527
Date FDA Received May 21, 2004
Event Date April 20, 2004
Event Type Death **Patient Outcome** Death, Hospitalization, Required Intervention
Event Description

Info was received in april 2004 regarding a pt, who experienced a peritonitis type reaction. The pt has a medical history significant for well-controlled hypertension and non-insulin dependent diabetes. The pt's surgical history includes cholecystectomy (open through a subcostal incision), right lower extremity below-knee amputation due to an accident, and foreign body in skull due to an accident. The patient also has a family history of a sibling diagnosed with colon cancer, who died. In april 2004, the pt experienced abdominal distention, crampy discomfort, and bloating. The pt presented to the e. R. Room the next day and was given dye for a ct scan. The pt had one episode of emesis. Flat and upright films of the abdomen did not reveal an obstructive process, but a ct scan of the abdomen and pelvis revealed evidence of sigmoid diverticulosis with a possible mass in the left lower quadrant possibly from the small intestine, but still no evidence of obstruction. About two weeks later, the patient underwent a laparotomy and segmental small bowel resection, with excision of a very large tumor based in the small bowel. This was very close to the mesentery of both small and large intestine, most likely consistent with a gastrointestinal stromal lesion. Pathology of this lesion diagnosed spindle cell neoplasm compatible with gastrointestinal stromal tumor. Two sheets of seprafilm were placed overlying the small intestines. The omentum, which was firmly adhered to the pt's right upper quadrant, could not be brought up to cover, the remainder of the wound. The fascia was approximated with a running suture of #1 pds looped, alternating with interrupted sutures of #1 prolene, placed at 4 cm intervals. The subcutaneous tissues were throughly irrigated, the skin closed with staples, after assurance of hemostasis within the subcutaneous tissues. The pt was reversed, extubated, and transferred to the recovery room in stable condition, having tolerated the procedure well. Estimated loss was less then 150 cc. The surgeon reported that "8 hours after surgery cpk an mb were elevated, troponin was boderline. Wbc was 18,000." the pt had severe left upper quadrant pain. On the morning of the next day, the patient was found to be tachypneic and their condition worsened throughout the day, eventually requiring admission to the intensive care unit for more aggressive support. The patient developed leukocytosis, fever, and lactic acidosis with changes in mental status, (according to the reporter, all indicative of a "sepsis-like syndrome") and pain localized to the left lower quadrant, at which point the pt underwent re-laparotomy. A moderate amount of slightly turbid, ascitic fluid was found in the abdomen. (cultures of the fluid were taken and came back negative.) the areas of the small bowel where seprafilm had been placed were intimately adhered to the anterior abdominal wall and appeared to be acutely inflamed with a small amount of fibrinous exudate covering its surfaces. There were flimsy adhesions between the small bowels. The anastomosis was intact and no evidence of any intestinal contents to suggest bowel perforation. Scattered areas of fibrinous exudate and/or edema of the bowel wall were found, but no evidence of enterotomy or bowel injury. Most noticeably, on the undersurface of the abdominal wall, the peritoneal surfaces were thickened. Adhesions in the right and left upper quadrant prevented visualization, but no ascites or other abnormalities were noted upon irrigation. After irrigation some additional inspection without notable findings, the pt was closed. Three interrupted sutures of 4-0 pds were placed, followed by additional irrigation and suction. Running sutures of #1 pds, in addition to retention sutures of #5 ethibond which bolsters of a 26 malccot catheter were passed and noted to support the abdominal wall. The subcutaneous tissue was irrigated and staples were placed at 3-4 cm intervals. The subcutaneous tissue was packed with a 1/2 inch packing. The pt was transferred critically ill to the intensive care unit, although appeared to tolerate the procedure well without significant hemodynamic events. The patient's blood pressure started to drop. Pt was given inotropic agents and eventually epinephrine to stabilize the patient, a total of 16 liters of fluid was given including crystalloids

and blood. An echo was done and ventricles were found contracted, however no dyskinesia of the wall was seen. The specialist considered the heart to be strong. The reporting surgeon stated that "through the night the patient developed junctional arrhythmias. Patient was however stabilized after 4 hours. " the patient coded, was resuscitated but coded again and died the following day. The reporting surgeon commented that "seprafilm was the cause of aseptic peritonitis as the bowel loops most in contact with the seprafilm and anterior abdominal wall had the fibrinous exudate. He said the septic episode had caused his patient to die. The relationship between the events and seprafilm was provided as possible, per the reporting surgeon.
Manufacturer Narrative
Conclusions: this conclusion code was chosen because no sample was returned and no lot number was provided by the user facility. Genzyme quality assurance is unable to perform an evaluation or lot history review. If a lot number is provided in the future, this complaint will be re-evaluated at that time.

12. Report Number 1220423-2003-00012
(historical, non-working link)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=461929
Date FDA Received May 22, 2003
Event Date January 1, 2003
Event Type Death **Patient Outcome** Death
Event Description
Information was received in 04/03 from a gynecological oncologist (initial contact via a sales representative) regarding a female patient diagnosed with ovarian cancer who underwent a laparotomy, omentectomy and extensive debulking (date unspecified). Six to seven sheets of seprafilm were placed between the incision line and the abdominal contents, as well as between the mesentery of both the large and the small bowel. Intraperitoneal bacitracin, one ampoule in 120 ml saline, was administered at the conclusion of the surgery. Intraperitoneal administration of chemotherapeutic agents was not performed during surgery. Postoperatively, the patient developed small bowel obstruction. Three weeks after surgery, the patient died (cause unspecified) without re-exploration due to the patient's "precarious conditions". The physician assessed the death as unrelated to the use of seprafilm. The relationship between the event of small bowel obstruction and seprafilm was not assessed by the reporter.

13. Report Number 1220423-2001-00009
(historical, non-working link)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=334775
Date FDA Received May 23, 2001
Catalog Number 4301-02
Device Problem Unknown (for use when the device problem is not known)
Event Date August 24, 2000
Event Type Death **Patient Outcome** Death
Event Description
Adult respiratory distress syndrome, sepsis, multi-organ failure. In aug-2000, a patient underwent a right colectomy and a sigmoid colectomy. Two sheets of seprafilm were placed above and below the greater omentum. On the following day, the patient became hypotensive with a distended abdomen. Pt was returned to or for distended abdomen. Pt was retuned to or for

emergency post operative laparotomy to rule out bleeding which was negative. Two more sheets of seprafilm were placed. The patient was transferred to icu where they developed ards with bilteral infiltrates and worsening pulmonary function. Their status improved for one week. Seven days later, pt became septic and hypotensive requiring vasopressors and increased ventilatory support. Subsequently, the patient developed multi-organ failure and became febrile. In sep-2000, an abdominal ct was negative for abscess, the bowel was intact and there was no evidence of an anastomotic leak. Their white count was normal. Sputum cultures were positive and antibotics were administered. A chest ct was negative for pulmonary embolus. A peritoneal fluid tap produced serous-type fluid that was negative for bacteria. The prognosis for recovery was poor. Further surgery for the source of the sepsis was refused. Patient support was withdrawn and they expired two days later. No autopsy was performed. Because the cause of the patient's events was not established, the investigator assessed the events as possibily related to seprafilm in apr-2001.

14. Report Number 1220423-2001-00007
(historical, non-working link)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=332391
Date FDA Received May 10, 2001
Catalog Number 4301-02
Device Problem Unknown (for use when the device problem is not known)
Event Date August 7, 2000
Event Type Death **Patient Outcome** Death
Event Description
Asystole, adult respiratory distress syndrome: a pt was admitted in 2000 for an elective ventral hernia repair and complex adhesiolysis. Five sheets of seprafilm were placed. The pt initially did well post operatively until 3 days later, when the pt was found to be asystolic on the nursing unit. Cpr and intubation were performed. The initial diagnosis was pulmonary edema and secondary respiratory failure. The pt was gradually diuresed, weaned from the ventilator, and re-extubated but, continued to have labored breathing and pulmonary edema. 14 days after admission, the pt was reintubated after a second episode of asystole just after a large bloodly bowel movement. Upper and lower endoscopy were both negative for a source of patient's gi bleed. Over the next several days, the patient developed acute respiratory distress syndrome which worsened over the next two weeks and required prolonged and excessive pressure control ventilation. The patient was cultured and started on steriods. Pt's sputum culture grew staphylococcus aureus and vancomycin was administered. The pt was also treated for urinary tract infection and gradual weaning from the ventilator was attempted. Relapsing urosepsis developed and additional antibiotics were started. It was noted the pt became diffusely weak and was diagnosed with intensive care polyneuropathy. An mri was recommended of the cspine. During the mdr procedure, the pt went into tachyarrhythmia and was pulseless for approximately 3-5 minutes. The pt did not recover any neurologic function from this episode and the possibility for recovery of function was considered extremely poor. Ventilator support was weaned and the pt expired shortly thereafter. Because no cause of the pt's events could be established, the investigator assessed the relationship of events to seprafilm as possibly related.

15. Report Number 1220423-2000-00032
(historical, non-working link)

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=299641
Date FDA Received October 10, 2000
Catalog Number 4301-02
Event Date August 31, 2000
Event Type Death **Patient Outcome** Death
Event Description
The following is a chronology of events described by the reporting physicians. The pt has a history of ulcerative colitis diagnosed since 1998. The pt had an elective surgery for ulcerative colitis which consisted of; 1) ile0-anal j-pouch anastomosis; 2) total proctocolectomy; 3) proximal diverting loop ileostomy. The surgery was performed in 2000. The operation was successful and the pt woke up from the anesthesia and was alert, and conversing with the physician post-op. Later on that post-op day, approx 24 minutes before midnight, the pt was found unresponsive and pulseless with asystolic rhythm. Cpr protocol was carried out with series of advanced cardiac life support protocol medications with no success. The pt remained asystolic and pulseless without blood pressure. Attempt at resuscitation with defibrillation was performed without any response. At 17 minutes past midnight, the pt was pronounced dead. The reporting site has assessed the event as unrelated to seprafilm. Although this event does not meet the mdr reporting criteria, genzyme is submitting the report due to the fatal outcome of the event.

16. Report Number 1220423-2000-00029
(historical, non-working link)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=289299
Date FDA Received August 10, 2000
Catalog Number 4301-02
Event Date April 1, 2000
Event Type Death **Patient Outcome** Death
Event Description
Pneumococcal pneumonia. The following is a chronology of events described by the reporting physicians. The info includes their experience at the reporting site, from one physician at the admitting site, and from accounts by the pt's spouse: pt underwent total proctocolectomy and end ileostomy in 2000. The pt was discharged on postoperative day 4 in good condition. On postoperative day 8 in 2000, the spouse said the pt was nervous and anxious. Spouse called 911 and took the pt to a community hosp. The pt was found to be hypertensive and tachycardic. Chest x-ray indicated questionable infiltrate, possibly pneumococcal pneumonia, or bacteremia. The pt was on life-support, but then the order was given to "do not resuscitate". The pt died on the same day. No autopsy was performed. The reporting physician suspects that the pt did not die of sepsis as was previously reported, but rather "likely pneumococcal pneumonia". He assessed the relationship as remotely related to the use of seprafilm. The reporting physician has requested a copy of the death certificate from the admitting hosp. However, he is not certain that he will be able to obtain this document or any other documentation concerning this case. Although this event does not meet the mdr reporting criteria, genzyme is submitting the report due to the fatal outcome of the event.

17. Report Number 1220423-2000-00010
(historical, non-working link)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=265252

Date FDA Received February 24, 2000
Catalog Number 4301-02
Event Type Death **Patient Outcome** Death
Event Description
Peritonitis, death. Mfr has been made aware of a report involving a pt who had allegedly rec'd seprafilm, developed peritonitis and subsequently died. Further details at this time are unavailable and the relationship of the events to seprafilm is unknown. Several unsuccessful requests have been made to the attending physician for info regarding this case. A follow-up report will be submitted if these details are obtained.

18. Report Number 1220423-1999-00025
(historical, non-working link)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=246587
Date FDA Received October 25, 1999
Catalog Number 4301-02
Event Date August 13, 1999
Event Type Injury **Patient Outcome** Hospitalization
Event Description
Fibrous rind (dense adhesions). The 75 year old female pt received 1 sheet of seprafilm during surgery for total abdominal colectomy. Ileorectal anastomosis, removal of marlex, and lysis of small intestinal adhesions in 1999. The seprafilm was placed at the anterior abdomen, on top of the small bowel in the pelvis. The pt's history includes multiple remote surgeries for pelvic floor prolapse and ventral hernia with mesh placement. What was described as a thick rind surrounding the small bowel was noted during re-exploration of the abdomen 10 days post surgery. The reporting physician felt that this event was related to the use of seprafilm. The pt developed bowel ischemia and died on 9/3/1999. The reporting physician stated that the death was not related to the event. The autopsy report stated the following diagnoses: ischmeicenteropathy, severely involving the distal duodenum and jejunum due to severely occlusive atherosclerosis of the celiac and superior mesenteric arteries, obstructive enteropathy due to extensive fibrous adhesions of the small intestine, hypertensive cardiovascular disease with left ventricular hypotrophy, probably due to unilateral renal vascular disease with left renal atrophy, atherosclerosis, moderate pulmonary congestion and edema. No further details were made available.

19. Report Number 1220423-1999-00010
(historical, non-working link)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=219259
Date FDA Received April 15, 1999
Catalog Number 4301-02
Event Date January 28, 1999
Event Type Death **Patient Outcome** Death,Hospitalization,Required Intervention
Event Description
Bowel obstruction, abdominal adhesions, outcome: death caused by cachexia due to malabsorption. This 68 yr old male pt had a history of cancer of the right kidney for which he had received radiotherapy treatment in 1997. Following radiotherapy, abdominal surgery had to be performed because of the formation of adhesions. A second adhesiolysis operation was

performed on 1/18/1999. During the latter operation, al aliquot of one bottle of sepracoat and one membrane of separfilm ("placed in pieces behind the bowel") (lot. 306478) were used as adhesion prophylaxis. At the end of the operation, prior to placing the seprafilm, the abdominal cavity was washed with normal saline, removing the supracoat. Ten days after operation, bowel obstruction occurred and re-laparotomy had to be performed on 2/2/1999. A severely adhered bowel mass was observed that required extensive bowel resection and a gastrocecal anastomosis. No tissue material was submitted for pathology. The pt had to be re-operated on feb. 20, because of stenosis of the anastomosis. On 19 mar., the medical dept was informed that the pt had died. The cause of death is unk at the moment. No autospy was performed. The reporting surgeon considered the adverse incident (bowel obstruction, abdominal adhesions) to be probably related to the use of separfilm/sepracoat because of the fact that during previous adhesiolysis (where no separfilm/sepracoat were used) no post-operative complications occurred. Serious: yes. Labeled: yes. Relationship: probably. On 3/31/1999 the following additional info was received: the date of death was 3/10/1999 and the cause of death was reported to have cachexia due to malabsorption. Review of the quality assurance data revealed that seprafilm (lot 306478/n8046) and sepracoat (lot gz6003b) met the release specifications at the time of release.

20. Report Number 1220423-1998-00003
(historical, non-working link)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=157816
Date FDA Received March 18, 1998
Catalog Number 4301-02
Event Date February 12, 1998
Event Type Injury **Patient Outcome** Hospitalization, Life Threatening, Death
Manufacturer Narrative
Box b. 5. : follow-up information obtained on 06/04/1998: the pt died on 03/24/1998. The coroner indicated that the cause of death as adult respiratory distress syndrome and ischemic heart disease, secondarily the re-fashioned ileostomy. The coroner commented, "in my opinion this was a death by natural causes." "adult restiratory distress syndrome occurred as a complication of the ileostomy repair operation. 'sepracoat' was used intra-operatively and the possibility that adult respiratory distress syndrome occurred as a complication of sepracoat cannot be ruled out." the coroner noted no comments regarding seprafilm.
Event Description
Adult respiratory distress syndrome. On 02/11/1998, 45 yr old female pt underwent explorative laparotomy because of a lont-standing history of chronic abdominal pain probably due to slow bowel passage. There were no evident signs of small bowel obstruction. Pt's medical history includes 3-4 abdominal operations (adhesiolysis, colectomy with ileostoma). Pt is a smoker (30 cigarettes/day). Around the operation, pt received antibiotic treatment with cefuroxime & metronidazole. Upon opening the abdomen, multiple peritoneal & small bowel adhesions were noted. Careful adhesiolysis was performed & adhesions were taken down manually & with scissors freeing the entire small bowel. Two peritoneal nodules were resected & sent to pathology for further examination. Results pending. During operation, which proceeded without any complication or major blood loss, aliquots of 100 ml of sepracoat were applied every 30-40 minutes up to a total volume of 300 ml. Prior to closing abdomen, 5 sheets seprafilm were applied; 2 sheets across pelvis, 2 sheets under mid-line incision, & 1 sheet arount the ileostoma. Approximately 12 hours after the operation, pt developed oliguria that responded to intravenous

fluid challenge & diuretics. A transient increase of serum creatinine was noted. One day post-operatively, pt started to show increased respiratory efforts with fever up to 38. 5-39 degrees celcius without any sign of sepsis. Blood tests and bacterial cultures (blood, urine) showed no signs of infection. Therefore, no antibiotic treatment initiated. Blood gas analysis revealed hypoxia, & polyphonic wheezing became apparent. Pt was given oxygen and constant positive airway pressure. At 36 hours after operation, pt's chest xray revealed severe bilateral infiltrates and a diagnosis of adult respiratory distress syndrome was made. Pt was transferred to intensive care unit, intubated, & mechanically ventilated. Besides mild wound pain, no abnormalities were detected concerning the abdominal region in the post-operative period. As concomitant medication, pt received amitriptyline, temazepam, & pethidine. Follow-up information obtained 03/10/1998. Pt had received a tracheostoma & was still mechanically ventilated, without significant improvement of adult respiratory distress syndrome. No other organ failure had developed. Pt had a mild septic episode. Bacterial cultures revealed a methicillin-resistant staphylococcus aureus in the sputum. No abnormalities were observed regarding pt's abdomen, which remained soft, non-tender, & non-distended during the entire hospital admission. Further follow-up information is expected. The reporting surgeon considered the adverse incident to be possibly related to the usage of seprafilm/sepracoat.

21. Report Number 1220423-1997-00015[104]
(historical, non-working link)
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/Detail.CFM?MDRFOI__ID=135324
Date FDA Received December 2, 1997
Catalog Number 4301-02
Event Date November 12, 1997
Event Type Death **Patient Outcome** Death, Hospitalization, Required Intervention
Event Description
Small bowel obstruction, adhesions, foreign body reaction. This 71 year old female pt had a medical history with multiple abdominal operations, i.E. Adhesiolysis because of signs of partial small bowel obstruction in 1974 and 1994 and gynecological operation in 1989 (cystadenoma right ovary). The pt never really recovered after the adhesiolysis operation in 1994. Abdominal pain did not resolve completely and food intake remained insufficient. After the complaints had worsened, a barium enema and ct scan were performed. No signs of bowel obstruction were detected. In 9/97, spasmolytic medication was started without significant improvement. On 10/22/97, the pt was scheduled for laparotomy. Adhesions were observed all over the small bowel and adhesiolysis was performed during this 3. 5-4 hrs lasting operation. A total volume of 600-800 ml of seprafilm was applied under the midline incision. During the operation, no visible enterotomy appeared to have been made accidentally. Following the operation the pt seemed to recover slowly. After 10 days bowel sounds were normal, however, no feces had been produced. Aspiration of gastric contents revealed bowel stained fluid. The pt has slightly elevated body temperature of 37. 5-38. 00c but no signs of sepsis. Total parenteral feeding was started. Contrast examination using gastrografin showed collapsed looking small bowel (not dilated). On 11/12/97, it was decided to re-operate the pt. Upon opening the abdomen which took 0. 5 hrs, it

[104] This case also appears to have been reported in the medical literature as a case report cited in the body of this petition: Trickett J, Rainsbury R, Green R. Paradoxical outcome after use of hyaluronate barrier to prevent intra-abdominal adhesion. *J o Soc Med*. 2001; 94(4):183-184.

appeared that adhesions had formed all over the small bowel. Only one foot of the jejunum was free of adhesions. 9/10 of the small bowel had to be resected and continuity was restored with an end-to-end anastomosis of the jejunum and cecum. During the resection of the small bowel mass with adhesions, a serosal tear in the mid-transverse colon was repaired by suturing it to the serosal surface of the ascending colon. Three days after this second operation the pt developed signs of peritonitis which was caused by a colonic perforation and two days later the pt died. Autopsy was performed on 11/19/97. The pathology report on the resected bowel material described a foreign body reaction (foreign body giant cell granulomata with birefringent foreign material) with fibrosis. The reporting surgeon considered the adverse incidents, i. E. Foreign body reaction and adhesions that were observed during the re-operation mid-november, 1997, to be probably related to seprafilm/sepracoat usage. The death was considered to be due to a surgical complication that resulted in colonic perforation with subsequent peritonitis. Serious; not expected; probably related.

Manufacturer Narrative

This 71 yr old female pt never fully recovered after the adehesiolysis operation in 1994. She experienced intermittent stubbing abdominal pain. Because of increasing abdominal pain, especially after meals, and further impairment of bowel movements she was scheduled for laparotomy which was performed on 22 oct 1997. Multiple adhesions were observed involving the whole of the small bowel from the duodeno-jejunal flexure to the ileocaecal junction. Salbutamol was required on extubation due to wheezing in the recovery room. Following the operation the pt seemed to recover slowly. She had slightly elevated body temperature of 37. 5-38. 0c but no signs of sepsis. Bowel sounds remained sluggish. Following the operation, the abdominal drainage fluid remained non-infectious. On 31 oct 1997 healthy unobstructed bowel sounds were detected and the pt started on naso-gastric feeding. Although the abdomen remained non-tender and non-distended, total parenteral feeding had to be started on 05 nov 1997 because of increased bowel stained nasogastric drainage. On 08 nov 1997, a barium meal follow-through examination using gastrografin showed distended duodenum and proximal jejunum but no evidence of obstruction. Contrast passed through into the colon in 80 mins. Because of complaints of nausea and large quantities of bowel stained naso-gastric drainage, it was decided to perform a second laparotomy on 12 nov 1997. Upon opening the abdomen which took 0. 5 hr, a dense, thick, glue-like adhesive process was observed that involved the small bowel and part of the transverse colon and anchored the entire small bowel to the anterior abdominal wall. During the resetion of the small bowel mass with adhesions, a serosal tear in the mid-transverse colon was repaired by suturing it to the serosal surfae of the ascending colon. The pathology report on the resected bowel material described macroscopically multiple loops of small bowel that were matted together by dense fibrous adhesions. The serosal surface was congested and had adherent fat and fibrous tissue. In these fibrous areas there were foreign body type giant cell granulomata. Birefringent foreign material was identified in the giant cells that appeared as small particles and short fibres. On nov 15, 1997, her condition deteriorated. Signs of peritonitis developed and faeculent bloody discharge was observed from the wound. She became anuric. The pt deceased on nov 17. 1997. Autopsy was performed on nov 19. 1997. On opening the abdomen, there were features of a generalized peritonitis and there was brown, foul smelling fluid in the peritoneal cavity. There was brown fluid leaking from the region of the transverse colon. This region had been damaged at surgery and the repair sutures were identified at the site. The stomach contained bile stained fluid and the duodenum was normal. The colon was empty.