January 29, 2021

Dr. Michael Carome, M.D.
Ms. Sarah Sorscher, J.D., M.P.H.
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Re: Citizen Petition – Docket Number FDA-2015-P-2375

Dear Dr. Carome and Ms. Sorscher:

This letter responds to your Citizen Petition, dated on July 7, 2015, and filed with the Food and Drug Administration (FDA) on July 7, 2015 (Petition). In your Petition, you request that FDA take the following actions "pursuant to Sections 515 and 518 of the Federal Food, Drug, and Cosmetic Act [(FD&C 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."[1]

We have carefully considered your Petition and, for the reasons described below, in accordance with 21 CFR 10.30(e) we are denying your request. We note, however, that in response to the concerns raised in this Petition, additional warnings and labeling changes have been implemented, as discussed in more detail below in various sections of this letter. In addition, we note that Seprafilm remains the only approved product in the US market indicated to reduce adhesion in the abdominal cavity. When used according to the approved Indications for Use, Seprafilm provides surgeons with an important clinical tool for use under the incision in patients who have a high likelihood of requiring reoperation through the same incision.

A. Factual Background

FDA approved the Seprafilm PMA (P950034) on August 12, 1996. Seprafilm is a sterile bioresorbable membrane (adhesion) barrier composed of two chemically modified polymers, *i.e.*, sodium hyaluronate (HA) and carboxymethylcellulose (CMC). Seprafilm 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 such as omentum, small bowel, bladder, and stomach, and between the uterus and surrounding structures such as tubes and ovaries, large bowel, and bladder.

As part of the data supporting Seprafilm's approval, Genzyme conducted two pivotal pre-market clinical studies (HF92-0901/Study 901 and HF92-0902/Study 902), referred to as Study 901 and 902, respectively. These clinical studies were approved on April 22, 1992, and the final reports for these studies were reviewed and acknowledged by CDRH on November 2, 1995 and January 30, 1996, respectively.

Seprafilm was presented to the General and Plastic Surgery Devices Advisory Panel Meeting on March 25, 1996. The panel recommended approval of the Seprafilm PMA based on the safety and effectiveness data presented in studies 901 and 902.

The advisory panel noted the lack of statistical significance and the uncertainty of device relatedness of the adverse

[1] Citizen Petition at 1

events reported in study 901, and recommended that the higher adverse event rates for pulmonary emboli and abscess reported in study 901 be evaluated in a post-approval study. As such, Genzyme conducted a post-approval study (study 601). This study was reviewed under IDE G980066 and approved by FDA on June 26, 1998. The final report was reviewed and acknowledged by CDRH on November 3, 2004.

B. Legal Background

FDA may issue an order withdrawing a PMA if the agency determines that one of the standards under Section 515(e)(1) of the FD&C Act or 21 CFR 814.46(a) is met. In your Petition, you assert the following basis for withdrawal of the Seprafilm PMA:

- On the basis of new information with respect to the device, evaluated together with the evidence available when the application was approved, there is a failure to show reasonable assurance that the device is safe or effective under the conditions of use prescribed, recommended, or suggested in the labeling of the device.

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

As discussed below, the arguments and evidence presented in your Petition do not establish a basis for FDA to withdraw its approval of Seprafilm, nor do they support a mandatory recall.

C. Discussion

Your Petition alleges that withdrawal of Seprafilm's PMA and a mandatory recall of Seprafilm are justified because clinical trials of Seprafilm "failed to demonstrate convincingly the product's efficacy" and that "there is substantial evidence that the product causes serious, sometimes fatal adverse events." Your Petition cites five grounds in support of your position, including clinical trials conducted before and after approval of Seprafilm by the manufacturer, Genzyme, other published scientific literature, and the FDA MAUDE database.

FDA disagrees with your analysis of this information. FDA re-reviewed the clinical evidence that supported its approval of Seprafilm's PMA, in addition to the literature cited in your Petition as well as additional literature and the data in FDA's databases. FDA's analysis, as described in detail below, concludes that Seprafilm has a reasonable assurance of safety and effectiveness when used in accordance with its FDA approved labeling. Your Petition, therefore, has not established a basis on which FDA could withdraw Seprafilm's PMA under section 515(e) of the FD&C Act, nor has it established evidence that justifies issuance of a mandatory recall under section 518(e) of the FD&C Act.

i. <u>Clinical Trials</u>

In your Petition, you cite data from three randomized, controlled clinical trials, including the Seprafilm pivotal trials (901 and 902) that were conducted prior to approval of the original Seprafilm PMA and a post-approval study (601) that was conducted by Genzyme. The premarket pivotal clinical trials 901 and 902 were reviewed by FDA and the General and Plastic Surgery Devices Advisory Panel prior to approval of P950034. You argue that there were several issues associated with these clinical trials including trial design (study 901 and 902), trial conduct (study 901) and adverse events (study 901 and 601), and you argue that those issues mean that that the three clinical trials (901, 902, and 601) conducted using Seprafilm do not support effectiveness in improving any important clinically meaningful outcomes. In addition, you assert that two of the studies (901 and 601) raised serious safety concerns that have not been adequately addressed.

FDA concludes that the information in your Petition about the results of the three clinical trials does not change FDA's interpretation of the effectiveness data provided in the clinical studies, nor does it provide any new

information that changes FDA's understanding of Seprafilm's effectiveness. The interpretation of the results of the original pivotal trials remains unchanged today—Seprafilm significantly reduced the number, severity and extent of adhesions. In addition, new information (post-market clinical experience, Kusunoki et al., Inoue et al., and Park et al.) cited in your Petition confirms the effectiveness results reported in the pivotal studies, and provides additional data supporting a correlation between adhesion reduction and clinical benefits including reduction in the incidence of early postoperative intestinal obstructions; and reductions in operative time, blood loss, and the extent of incisions. Further, there are no new data and no change to the interpretation of the original effectiveness data that alter the conclusion that there is a reasonable assurance Seprafilm is effective in reducing the number and extent of adhesions.

As for the two safety concerns cited in the Petition, FDA believes these concerns have been adequately addressed. The pivotal trial data showed a lack of statistical significance between the Seprafilm- and control-groups sufficient to conclude that either safety concern was related to the device. As a result, the sponsor evaluated these safety issues in the larger post-approval study as recommended by the Advisory Panel. The higher rate of pulmonary embolism observed in the pivotal clinical investigation was not reported in the post-approval study indicating the adverse events reported in the pivotal trial were unlikely to be device related. The second adverse event type (abdominal abscess) was confirmed in the post-approval study with a statistically significantly higher rate of abdominal abscess reported in Seprafilm treated patients.

To address the issue of abdominal abscess, the sponsor conducted a *post-hoc* analysis and stratified the data according to whether Seprafilm was used on suture lines (see table 1). The results of this analysis demonstrated the adverse events were related to use of Seprafilm on suture lines. At that time, FDA concluded the post-approval study results should be communicated in the Seprafilm labeling and that this would mitigate the safety concern. FDA continues to agree with this decision, and additionally requested that the warning against using Seprafilm on anastomotic suture and staple lines be elevated to a contraindication. This labeling change was approved on June 29, 2017 in a Changes Being Effected PMA supplement to the Seprafilm PMA.

In addition, given the Advisory Panel vote and CDRH's decision to approve the Seprafilm PMA based on the adhesion reduction primary endpoint in 1996, and the potential for clinical benefits that were not measured in the Seprafilm pivotal trials, FDA believes that it is now most appropriate to examine the post-market Seprafilm safety and effectiveness outcomes together with the original study results as a whole. The current understanding of Seprafilm's effectiveness should be based on the totality of the evidence derived from the clinical studies and the post-market safety information to determine whether Seprafilm continues to maintain an acceptable benefit-risk profile (as we have done below in the following sections). Ultimately, FDA concludes the information presented in your Petition related to the two original pivotal trials and post-approval study do not change the conclusion that there remains a reasonable assurance that Seprafilm is safe and effective when used according to the labeling. Nor do the data provide evidence there is a reasonable probability that Seprafilm use causes serious adverse health consequences or death.

Below we address the assertions in your Petition specific to each clinical trial.

Study 901

Study 901 was a randomized, controlled trial of 183 abdominal surgery subjects.[2] The trial assessed the safety and effectiveness of Seprafilm for preventing postoperative adhesion formation following abdominal surgery.[3]
You note that in Study 901, the overall rates of adverse events were similar in Seprafilm- and control-group subjects (90% versus 94%, respectively); however, subjects assigned to the Seprafilm group experienced a higher rate of

[2] Food and Drug Administration. Summary of safety and effectiveness data: Genzyme Corporation Seprafilm Bioresorbable Membrane. 1996.
[3] *Id.*

abscesses and pulmonary emboli when compared to control subjects.[4] Seven of 91 subjects (8%) in the Seprafilm group and two of 92 subjects (2%) in the control group developed abscesses (p = 0.10).[5] Four subjects (4%) in the Seprafilm group and no subjects in the control group developed pulmonary emboli (p = 0.059).[6] The General and Plastic Surgery Devices Advisory Panel (Advisory Panel) recommended approval of the PMA based on the overall safety and effectiveness data, but given the lack of statistical significance and the uncertainty of device relatedness of the adverse events, the panel also recommended that the higher adverse events rates for pulmonary emboli and abscess reported in study 901 be evaluated in a post-approval study.

FDA concludes the pulmonary emboli adverse events reported in study 901 are unlikely related to the use of Seprafilm because this adverse event was not reported in the much larger post-approval study (study 601), which evaluated 882 subjects treated with Seprafilm. In addition, the 601 study design is more likely to detect rare adverse events due to the larger number of patients treated with Seprafilm. However, the higher abdominal abscess rate reported in study 901 was confirmed in the post-approval study. The post-approval study also identified additional adverse events including leak, peritonitis, and infection at significantly higher rates than control (see review of post-approval study 601 below).[7] As discussed, both the abdominal abscess and newly identified risks are mitigated by labeling including a contraindication for use of Seprafilm wrapped directly around a fresh anastomotic suture or staple line.

In addition, you cite an FDA warning letter issued in 1997[8], which cited problems with one of the principal investigators who conducted study 901. You allege that this "throw[s] the reliability of the trial's data into question" and assert that FDA did not consider the impact of the issues identified in the warning letter on the results of Study 901. This warning letter was issued to one trial site and cited issues relevant to evaluating the safety and effectiveness results of this study, including lack of blinded adhesion evaluation and failure to report adverse event data. As a result of your Petition, FDA evaluated the impact of these issues on the overall primary effectiveness results and concluded that excluding the effectiveness data from this site due to failure to adequately blind evaluators would not change the effectiveness conclusions of the study. In this study, the proportion of patients with at least one adhesion was 49% (n=42) in the investigational group vs. 94% (n=85) in the non-treatment control group, which represents a p-value from Fisher's Exact test of 0.001. P-values less than 0.05 support the treatment (Seprafilm) affecting the outcome of a study (reduction of adhesions). These are highly significant results for the overall study. FDA verified this result from tabular data in the PMA and found a similarly highly significant result from Fisher's Exact test (p-value of 0.001) when the 37 patients from the questionable site were excluded from the effectiveness analysis. Study 901 also showed significant differences in the extent and severity of adhesions, and FDA verified that these qualitative conclusions would remain the same when the questionable data are excluded. For the extent of adhesions, FDA calculated the minimum variance linear estimator (MVLE) from the site-specific means and standard deviations, and for severity of adhesions FDA used the StatXact method for two ordered multinomials, and determined highly significant p-values in all cases. In addition, although underreporting of adverse events is a serious concern, FDA notes that a much larger post-approval study was conducted as recommended by the Advisory Panel to evaluate the higher adverse event rates for pulmonary emboli and abscess reported in study 901. FDA concluded the abdominal pivotal study as reviewed in the PMA and the post-approval study taken together were adequate to evaluate the safety profile of the Seprafilm product. The adverse events reported in these studies are summarized in the Seprafilm labeling.[9]

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[4] *Id.*
[5] *Id.*
[6] *Id.*
[7] *See* Seprafilm labeling at https://advancedsurgery.baxter.com/sites/g/files/ebysai2106/files/2020-02/Seprafilm.pdf
[8] 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; Citizen Petition at 5.
[9] *See* Seprafilm labeling at https://advancedsurgery.baxter.com/sites/g/files/ebysai2106/files/2020-02/Seprafilm.pdf

Study 902

Study 902 was a controlled trial enrolling 127 subjects to assess the safety and effectiveness of Seprafilm for preventing postoperative adhesion formation following uterine myomectomy in patients undergoing gynecologic surgery.[10] This study showed that the rate and severity of adhesions, evaluated during second-look laparoscopy, were lower in the Seprafilm-treated group, with comparable rates of adverse events between groups. This study evaluated postoperative adhesion formation in patients following myomectomy and did not identify safety concerns with the use of Seprafilm.

Trial design: Studies 901 and 902

At the time of PMA approval, the safety and effectiveness outcomes identified in studies 901 and 902 were deemed to have met the statutory threshold for valid scientific evidence supporting the use of Seprafilm in surgical procedures involving abdominal and pelvic procedures as identified in the approved Indications for Use statement in the labeling. You criticize the primary endpoints used in these trials, claiming that the studies did not assess clinically meaningful outcomes. However, the choice of evaluating adhesion formation was thoroughly considered by FDA. FDA acknowledges that direct clinically relevant endpoints are the best choice for clinical investigations; however, alternative endpoints can be used in clinical studies that pose clinical trial design challenges. For example, endpoints such as infertility can be problematic to study given the multiple potential causes of infertility and the difficulty controlling for confounding variables. Additionally, FDA has consistently used determination of adhesion incidence, extent and severity as primary effectiveness criteria in clinical studies that have been approved for other gynecologic adhesion barriers (for example, Ethicon's Interceed Absorbable Adhesion Barrier, P880047, and Baxter Healthcare's Adept 4% Icodextrin solution, P050011). Finally, FDA notes the Advisory Panel evaluated Seprafilm and discussed the use of this primary endpoint at length. The Advisory Panel concluded the results of the two pivotal studies were adequate to demonstrate the safety and effectiveness of the Seprafilm Adhesion Barrier. The Advisory Panel recommended approval of the Seprafilm PMA for the Indications for Use (IFU) as studied in the pivotal trials (adhesion reduction); however, claims of reducing clinical morbidities such as bowel obstruction and infertility were not approved. FDA agreed with the Advisory Panel's recommendation and approved the Seprafilm PMA based on the favorable safety and effectiveness results supporting the following Indications for Use statement:

> Seprafilm 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 such as omentum, small bowel, bladder, and stomach, and between the uterus and surrounding structures such as tubes and ovaries, large bowel and bladder.

Post-approval of Seprafilm, Genzyme conducted a clinical investigation (study 601) to study the correlation between adhesion reduction (incidence, extent and severity) and clinical benefit (reduction in small bowel obstruction). While the study did not demonstrate this clinical benefit, it should be noted that reducing small bowel obstruction is only one potential clinical benefit that may result from using an adhesion barrier capable of reducing the number, extent and severity of adhesions. Reducing adhesion formation in the abdominal cavity has been reported post-market to provide other clinical benefits. For example, reported clinical benefits with the use of Seprafilm include reducing adhesions at midline and peristomal sites as well as reducing operation time, blood

[10] *Id*; *see also* Citizen Petition at 4.

loss, and the extent of the incision at ileostomy closure.[11] Similarly, Seprafilm use reduced the incidence and severity of adhesions under abdominal incisions and reduced operation times.[12] In addition, reduced incidence of early postoperative intestinal obstruction and abdominal complaints have been reported with the use of Seprafilm.[13] You assert that these published studies have trial design flaws that reduce the confidence in the conclusions, and that publication bias could influence the outcome of the literature review by favoring publication of positive results. These published reports of post-market clinical experience with Seprafilm; however, confirm the adhesion reduction results of the pivotal clinical trials, and provide additional evidence supporting a correlation between adhesion reduction and clinical benefit. Finally, FDA notes that volvulus, a rare, but potentially life-threatening condition, can be caused by a single abdominal adhesion, and Seprafilm remains the only approved product in the US market indicated to reduce adhesion in the abdominal cavity. The potential to prevent this condition, by reducing the incidence of abdominal adhesions, is clinically significant.

Study 601

Study 601 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. The study failed to meet this primary effectiveness endpoint. In addition, subjects randomized to the Seprafilm group were significantly more likely to experience anastomotic leaks, peritonitis, fistula formation, and surgical incision infection when compared to subjects randomized to the control group. The primary objectives of this study, however, were to evaluate both the effectiveness of Seprafilm in reducing the incidence of bowel obstruction, and to evaluate the incidence of all serious adverse events, in particular, pulmonary emboli and abdominal abscess that were reported in the abdominal surgery pivotal trial as requested by the Advisory Panel.[14] You note that this study failed to demonstrate effectiveness in reducing the incidence of bowel obstruction; because of this, FDA did not approve an expansion of the indications for use statement following review of these study results.[15] You also raise the following three issues with the presentation of the post-approval study 601 results in the current Seprafilm labeling[16]:

> 1. "First, to salvage the safety data, Genzyme, in coordination with the Study 601 Post-market 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 Post-market 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.[17] After crafting this *post-hoc* definition, the Post-market Study Steering Committee members went back through the trial records and reclassified an unspecified number of subjects who previously had not

[11] Masato Kusunoki, Hiroki Ikeuchi, Hidenori Yanagi, Masafumi Noda, Hitoshi Tonouchi,Yasuhiko Mohri, Keiichi Uchida, Yasuhiro Inoue, Minako Kobayashi, Chikao Miki, Takehira Yamamura. Bioresorbable Hyaluronate-Carboxymethylcellulose Membrane (Seprafilm) in Surgery for Rectal Carcinoma: A Prospective Randomized Clinical Trial. *Surg Today* (2005) 35:940–945.

[12] 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.

[13] 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; 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.

[14] The pulmonary emboli adverse events reported in study 901 were not reported in the larger post-approval study. The post-approval study did identify other adverse events in Seprafilm treated patients including leak, peritonitis and infection at significantly higher rates than control (*see* table 4 in *supra* note 7).

[15] Citizen Petition at 8

[16] Citizen Petition at 6.

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

been classified as having a bowel anastomosis.[18] 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.'[19] 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."

FDA notes the purpose of including the post-approval data in the Seprafilm labeling (see Table 1, below) was to inform users of the number and percentage of patients with anastomotic leak-related abdominal events based upon a retrospective analysis of the use of Seprafilm at the site of bowel anastomosis thirty days post-surgery. The information was added to the labeling to highlight the risks observed with use of Seprafilm on bowel anastomotic suture lines as compared to use of Seprafilm in other anatomical locations. You have criticized the presentation of these data in the Seprafilm labeling because the analysis of the data was conducted *post-hoc* and therefore, without the use of pre-specified terms and blinding of investigators. FDA acknowledges these limitations of the analysis but considered the importance of developing labeling to warn against such events to outweigh such limitations and to be consistent with FDA's regulations regarding valid scientific evidence.[20] In particular, this study identified the risks associated with the use of Seprafilm on suture lines. FDA determined that such risks should be mitigated by labeling presenting the results as well as including a contraindication for use of Seprafilm wrapped directly around a fresh anastomotic suture or staple line. FDA believes the inclusion of these data in the Seprafilm labeling is not misleading because it accurately reflects the results of the study and it represents a worst case assessment of Seprafilm use and anastomotic leak.

Table 1: From Seprafilm Instruction for Use: Number and percentage of patients with anastomotic leak-related abdominal events. A retrospective analysis of the use of Seprafilm at the site of bowel anastomosis 30 postoperative days.

Serious Adverse Events	Seprafilm On Bowel Anastomotic Suture Line (N=289 Patients)	Seprafilm Not On Bowel Anastomotic Suture Line (N=593 Patients)	Control (N=909 Patients)
	n (%) Patients With Event	n (%) Patients With Event	n (%) Patients With Event
Fistula [1]	11 (3.8)*	5 (0.8)	2 (0.2)
Leak	20 (6.9)*	13 (2.2)	16 (1.8)
Abdominopelvic Abscess [2]	16 (5.5)*	14 (2.4)	27 (3.0)
Peritonitis	14 (4.8)*	12 (2.0)	12 (1.3)
Sepsis	10 (3.5)*	7 (1.2)	9 (1.0)
Patients ≥ 1 event	37 (12.8)*	31 (5.2)	45 (5.0)

*Statistically significant difference from control group detected ($p<0.05$).
[1] Fistula includes fistula and intestinal fistula.
[2] Abdominopelvic Abscess category includes abscesses in the abdominal and pelvic cavities.

[18] *Id.*
[19] Genzyme. Product label: Seprafilm Adhesion Barrier. December 2008.
[20] See 21 CFR 860.7

> 2. "FDA assessed the data from Study 601 noted a 'disconcerting'[21] 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). 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)."

While FDA initially referred to the difference in device-related serious adverse events between the Seprafilm and control groups as "disconcerting,"[22] our concerns were resolved by the time of approval. As noted above, anastomotic leak-related serious adverse events occurred at a statistically significantly higher rate when Seprafilm was used on suture lines, explaining the difference between device-related serious adverse events reported in the Seprafilm group versus the control group. This concern was resolved by labeling that reflects the statistically higher rates of AEs when Seprafilm is used on suture lines, as well as a contraindication against such use. In addition, FDA notes that while the adverse events resulting from the use of Seprafilm on sutures lines were determined from a *post hoc* subgroup analysis of the post market study, it confirmed a trend that was noted in the premarket study. Furthermore, the results are consistent with current clinical understanding that suture lines can lead to subclinical leaks in many patients. These leaks are thought not to progress to clinical leaks because adhesion of the anastomosis to surrounding anatomic structures serve to seal the leak.[23] This perspective offers a mechanism by which the adverse event profile observed in this study can be understood - preventing such adhesions by applying Seprafilm on the suture line would be expected to allow those leaks to continue and become clinically significant. Regardless of the mechanism, though, the presentation of the data and warning included in the labeling are accurate and important to the continued safe use of this device.

FDA believes the serious adverse events are appropriately communicated in the Seprafilm labeling. Table 3 of the labeling presents serious adverse events without device relatedness, because device-relatedness can be difficult to ascertain in certain contexts and thus decision-making for device relatedness can be subjective[24]. The device relatedness criteria were not prospectively defined in the protocol, and related adverse events were not objectively distinguishable from adverse events that were unrelated to device use. FDA notes that during the review of the Investigational Device Exemption, FDA requested that all serious adverse events be collected for the duration of the study, and that the relevant sections of the case report forms be revised to collect this information. The presentation of serious adverse events in Table 3 is not misleading, because Table 4 in the labeling reports the number of patients with anastomotic leak-related abdominal events when Seprafilm was used on suture lines—i.e., the cause of FDA's initial concern about the device-related serious adverse events, as discussed above.

> 3. "FDA permitted Genzyme to publish a label with regard to the effectiveness 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 small bowel obstruction 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

[21] Citizen Petition at 7.

[22] We note that this concern was expressed in a deficiency letter from FDA to Genzyme. Deficiency letters represent an interim part of FDA's review, providing the sponsor an opportunity to address FDA's concerns, and do not reflect the Agency's conclusions.

[23] For Example see Clinical and subclinical leaks after low colorectal anastomosis: a clinical and radiologic study. Lim et al. Dis Colon Rectum 2006 49:1611-9

[24] It is not unusual for serious adverse events to be reported in this manner where device-relatedness may be difficult to determine. See table 2, e.g., https://www.accessdata fda.gov/cdrh_docs/pdf5/P050011B.pdf

the control group had bowel obstruction. Of the 90 patients with existing bowel obstructions, no significant difference in incidence of adhesive small bowel obstruction requiring reoperation was found (3 of the 48 Seprafilm patients versus 1 of 42 control patients)."

Although FDA concluded that the post-approval study failed to demonstrate effectiveness in reducing the incidence of bowel obstruction, which was the primary effectiveness endpoint of this study, Seprafilm is effective for reducing the incidence, extent and severity of postoperative adhesions. As for the use of the term "protocol defined criteria"[25] in the Seprafilm labeling, FDA acknowledges that the labeling is describing criteria that were developed after the investigators had viewed and analyzed the results of the completed trial. Thank you for bringing this labeling issue to our attention. FDA will consider whether this language on the labeling should be changed. Nonetheless, this labeling issue does not warrant the relief requested in your Petition. The Seprafilm label does accurately report that there was no difference in the percentage of patients that experienced a small bowel obstruction when all cases of bowel obstruction were evaluated, which is an important result of the study that is included in the labeling.

In conclusion, the analysis of the post-approval study 601 data and its presentation in the Seprafilm labeling are not issues that rise to the level of supporting withdrawal of Seprafilm. The current labeling for Seprafilm includes adequate contraindications and warnings, and accurately presents the serious adverse events and issues with the study design, which helps to provide reasonable assurance that the device is safe and effectives under the labeled conditions of use.

ii. Additional Data From Prospective Randomized Clinical Trials

Your Petition asserts that data from additional prospective, randomized, controlled trials evaluating the safety and effectiveness of Seprafilm do not change the overall risk-benefit profile of the device or establish reasonable assurance that the device is safe and effective. You further note that publication bias could have strongly influenced the results of the post-market studies showing a benefit for Seprafilm. For example, you identified an unpublished abstract review of 1,885 patients reporting that the use of Seprafilm was associated with "a higher incidence of pelvic sepsis and wound infection."[26] This information was presented as an abstract at an annual conference of the American Society of Colon and Rectal Surgeons but does not appear to have been published in a peer-reviewed journal or be otherwise publicly available. FDA has therefore been unable to evaluate this information and cannot determine how these data might inform an understanding of the device's safety and effectiveness. In addition, you assert that the Cochrane analysis published in 2009 found too few studies of Seprafilm to develop a funnel plot assessing publication bias, and that additional unpublished studies showing negative results similar to the study described above may be missing from the literature. Although a more robust publication landscape could provide additional insight into the questions raised in your Petition, it is not possible for FDA to evaluate information to which it does not have access. The lack of studies showing negative results is not adequate to affirm the Petition's assertions that the Seprafilm device should be removed from the market. You summarize the results of published randomized, controlled clinical trials in Appendix A, Table B of the Petition, and note that the trials tended to show that the device reduces the incidence, severity and/or extent of adhesions at the site of application. However, you assert that only two studies — Park et al. (2009) and Van der Wal et al. (2011)[27] — provided evidence of possible clinically meaningful benefit and that both of these studies had serious flaws.

FDA reviewed the cited randomized clinical trials that have been conducted after the approval of Seprafilm. Six of these published studies replicated the pivotal trial results with results showing that Seprafilm reduced at least one of

[25] Seprafilm product label: https://www.seprafilm.us/Content/pdf/SeprafilmPackageInsert.pdf
[26] 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.
[27] *See* Park and Van der Wal *supra* note 13.

the following: incidence, severity and/or extent of adhesions at the site of application. In addition, two published studies reported evidence of a clinically meaningful benefit: reduced incidence of early postoperative intestinal obstruction and abdominal complaints.[28] You have criticized these studies noting issues with randomization, blinding and follow-up. Regardless of the issues cited with these studies, however, they all reported similar results as the pivotal studies with respect to effectiveness, and none reported serious safety concerns. Even if these studies are considered so methodologically flawed that FDA cannot use any of the data, the pivotal studies that supported approval of the PMA and the original conclusions from those studies demonstrating a reasonable assurance of safety and effectiveness, remain. FDA, therefore, concludes that these studies do not change our understanding of Seprafilm effectiveness, *i.e.*, the ability of Seprafilm to reduce the incidence, severity and extent of adhesions. In addition, FDA notes that in all 8 cited studies, the incidence of complications was similar in both the Seprafilm and control groups.

In addition to the literature you cited, FDA conducted its own literature review. The purpose of this systematic literature review was to qualitatively synthesize the available data on the labeled use of Seprafilm per the abdominal indication since 1996. A total of 11 articles were found that met the criteria for inclusion in this systematic literature review.[29] Based on our review of the literature cited in the Petition and our own literature review, FDA concludes the results of the randomized clinical trials conducted after the approval of Seprafilm replicate the Seprafilm pivotal trial effectiveness results, and do not report higher rates of complications in patients treated with Seprafilm. The only exception is the Seprafilm post-approval study publication that reported an elevated rate of peritonitis, leak, and infection.[30] The results of the post-approval study (study 601) were reviewed by FDA, and these risks were mitigated by presenting the data in the labeling, because they were related to the use of Seprafilm on suture lines. FDA concludes the information in the Petition related to additional published clinical trials studies does not change the conclusion that there remains a reasonable assurance the Seprafilm product is safe and effective when used according to the labeling, and these studies do not provide evidence there is a reasonable probability Seprafilm use causes serious adverse health consequences or death.

iii. Additional Data From Nonrandomized Clinical Studies and Case Reports

With regards to the third ground, you assert the following data from nonrandomized studies raises serious concerns

[28] *See* Park and Van der Wal *supra* note 13.

[29] 1. Oikonomakis, I. et al. Seprafilm: a retrospective preliminary evaluation of the impact on short-term oncologic outcome in colorectal cancer. Dis Colon Rectum 45, 1376-1380 (2002).
2. Beck, D.E. et al. A prospective, randomized, multicenter, controlled study of the safety of Seprafilm adhesion barrier in abdominopelvic surgery of the intestine. Dis Colon Rectum 46, 1310-1319 (2003).
3. Salum, M. et al. Does sodium hyaluronate- and carboxymethylcellulose-based bioresorbable membrane (Seprafilm) decrease operative time for loop ileostomy closure? Tech Coloproctol 10, 187-190; discussion 190-181 (2006).
4. Beck, D.E. The role of Seprafilm bioresorbable membrane in adhesion prevention. Eur J Surg Suppl, 49-55 (1997).
5. Fazio, V.W. et al. Reduction in adhesive small-bowel obstruction by Seprafilm adhesion barrier after intestinal resection. Dis Colon Rectum 49, 1-11 (2006).
6. Fujii, S. et al. Reduction of postoperative abdominal adhesion and ileus by a bioresorbable membrane. Hepatogastroenterology 56, 725-728 (2009).
7. Hashimoto, D., Hirota, M., Yagi, Y. & Baba, H. Hyaluronate carboxymethylcellulose-based bioresorbable membrane (Seprafilm) reduces adhesion under the incision to make unplanned re-laparotomy safer. Surg Today 42, 863-867 (2012).
8. 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 40, 1301-1306 (2005).
9. Inoue, M. et al. Efficacy of Seprafilm for preventing adhesive bowel obstruction and cost-benefit analysis in pediatric patients undergoing laparotomy. J Pediatr Surg 48, 1528-1534 (2013).
10. Kawamura, H. et al. A sodium hyaluronate carboxymethylcellulose bioresorbable membrane prevents postoperative small-bowel adhesive obstruction after distal gastrectomy. Surg Today 40, 223-227 (2010).
11. Kudo, F.A. et al. Use of bioresorbable membrane to prevent postoperative small bowel obstruction in transabdominal aortic aneurysm surgery. Surg Today 34, 648-651 (2004).

[30] 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.

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.[31] The incidence of infected fluid collections was higher in the Seprafilm cohort compared to the non-Seprafilm cohort (4.1% versus 0.5%; p = 0.02).[32]

- 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. The study reported a significant increased risk of pelvic abscess in the Seprafilm cohort compared to the non-Seprafilm cohort (12% versus 5%; p = 0.01).[33]

- 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 US.[34] 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.[35]

- Other Case Reports: 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,[36] sterile intra- abdominal fluid collection,[37] and pelvic peritonitis and bacterial abscess.[38]

- 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.[39] In some cases, symptoms resolved after the abdominal cavity was thoroughly irrigated and the Seprafilm residue was completely removed.[40]

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[31] 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.

[32] *See id.*

[33] 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.

[34] 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.

[35] *Id.*

[36] Laxa BU, Bouchard A, DePetris G, et al. Eosinophilic enteritis confined to an ileostomy site. *Case Rep Gastroenterol*. 2011;5(2):422-427.

[37] Tyler J, McDermott D, Levoyer T. Sterile intra-abdominal fluid collection associated with seprafilm use. The Am. Surg. 2008;74(11):1107-1110.

[38] 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.

[39] Klingler PJ, Floch NR, Seelig MH, et al. *See also* Seprafilm-induced peritoneal inflammation: A previously unknown complication. Dis Colon Rectum. 1999;42(12):1639-1642; 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; 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; and 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.

[40] *See id.*

We agree that the information cited in your Petition, specifically the *Krill* and *Leitao* studies, raise serious concerns about the safety of the use of Seprafilm in cancer patients with reported higher rates of abscess and fluid collection in Seprafilm treated patients. FDA reviewed your claims, as they relate to pelvic indications, and recommended that Genzyme should elevate the current Seprafilm labeling precaution against use in cancer patients to a warning. FDA further recommended that an additional warning be included in the Seprafilm labeling stating that the safety and effectiveness of Seprafilm Adhesion Barrier has not been evaluated in clinical studies in patients with abdominopelvic malignancy. FDA's labeling recommendations were based on the lack of safety and effectiveness data available in the use of Seprafilm in cancer patients and the results of the *Krill* and *Leitao* studies. This labeling change was made in a Changes Being Effected PMA supplement to the Seprafilm PMA submitted on 12/23/2016.

Although the Bashir study reported 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),[41] Seprafilm use was not associated with increased risk of abscess in patients undergoing hysterectomy. FDA concludes abscess is a known risk that is currently adequately communicated in the Seprafilm labeling (see e.g., table 1 of Seprafilm labeling).

Finally, you cite nine case reports describing patients undergoing different surgeries that included Seprafilm use.[42] The case reports identify a number of different types of inflammatory reactions including sterile peritonitis and foreign body reactions.[43] FDA notes it is difficult to determine a causal relationship between Seprafilm use and these adverse events. However, the foreign body reactions reported in the case reports appear to be consistent with at least some of the MDRs, which state the inflammatory reaction was located at the site where Seprafilm was placed by the surgeon. Foreign body reactions were not reported in the pivotal or post-approval studies, and the current labeling includes the following precaution: "Foreign body reactions may occur with Seprafilm Adhesion Barrier, as with any implanted material." FDA does not have sufficient information to estimate the rate at which these inflammatory reactions are occurring, to definitively determine whether these adverse events are device related, or identify factors that may be responsible for eliciting these responses. However, it is apparent that inflammatory responses to Seprafilm may be occurring in the post-market experience. On review of the MDRs and literature on Seprafilm, FDA noted that many of these complications attributed to Seprafilm use occurred when Seprafilm was being used off label. Such off label uses included placement of Seprafilm throughout the peritoneal cavity, use in cancer surgery and use in a grossly contaminated abdominal cavity. In light of this, FDA recommended that Genzyme strengthen the Seprafilm labeling with a warning to inform users of the potential for inflammatory reactions and foreign body reactions to Seprafilm, and with the addition of new warnings against uses of Seprafilm that have not been submitted to FDA for approval. These labeling changes were made in a Changes Being Effected PMA supplement to the Seprafilm PMA submitted on 12/23/2016.

In conclusion, while the information presented in your Petition, as it relates to non-randomized clinical studies and case reports, raised valid concerns, FDA believes that these concerns are mitigated by the current labeling. As such, this information does not change the conclusion that there remains a reasonable assurance that Seprafilm is safe and effective when used according to the labeling. In addition, this information does not provide evidence that there is a reasonable probability Seprafilm use causes serious adverse health consequences or death.

iv. Manufacturer and User Facility Device Experience (MAUDE) Data

With regards to the MAUDE data, you allege that 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

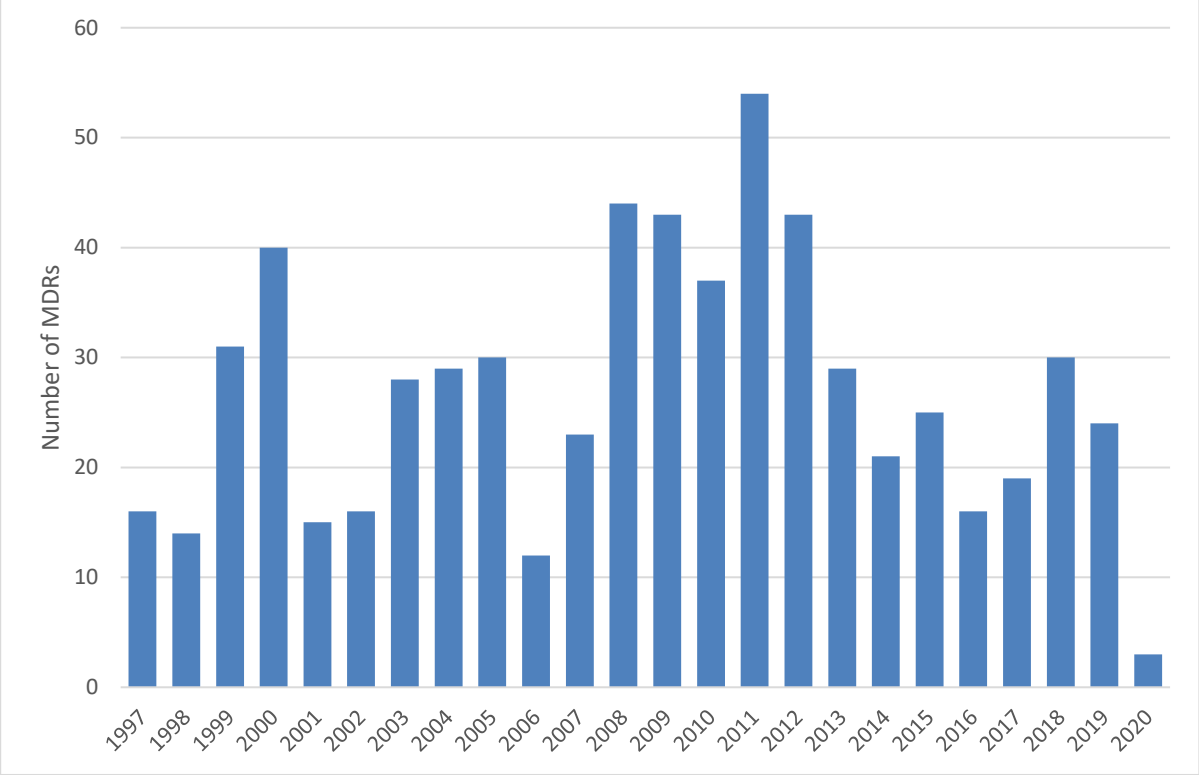
[41] *See* Bashir et al., *supra* note 35.
[42] *See supra* notes 32-40.
[43] *Id.*

of Seprafilm."[44] You note that since FDA truncated the MAUDE database, searches *via* the online portal yield results dating back only 10 years.[45] As such, you allege that there are "at least 21 reports of deaths in patients who underwent surgery with placement of Seprafilm, as well as two possible duplicate reports."[46] In addition to death reports, you identified "524 reports of adverse events linked to the brand name Seprafilm."[47] The adverse events you cited in MAUDE reports for Seprafilm included the following: Bowel obstruction, Abscess, Peritonitis, Fever, Fluid collection, Inflammatory reaction, Leak, Fistula, Sepsis, and Wound dehiscence.

You summarized Medical Device Reports (MDRs) related to Seprafilm use retrieved from the MAUDE database. The list includes 21 MDRs for patient deaths that included placement of Seprafilm during surgery. FDA searched the CDRH *Ad hoc* Reporting System (CARS) using the name brand Seprafilm through February 2, 2020. This search identified three additional patient deaths MDRs (MW5014904, 1220423-2019-00022, 1220423-2019-00016) for a total of 24 patient death MDRs, and a total of 615 MDRs with serious injury. FDA reviewed the MDRs including each patient death MDR to decide whether Seprafilm was used on or off label, and to determine whether the use of Seprafilm was related, possibly-related or undeterminable to the patient's death. The summary of this analysis is provided in the tables below.

Table 2: A-MDR Analysis Total Number of MDRs Submitted by Year, B- MDR Analysis Top 15 Reported Patient Problem Codes, C-MDR Analysis FDA clinical review of 24 MDRs with patient deaths

A-MDR Analysis Total Number of MDRs Submitted by Year



[44] Citizen Petition at18.
[45] Citizen Petition at 14.
[46] *Id.*
[47] *Id.*

B: MDR Analysis: Top 15 Reported Patient Problem Codes

Patient Problem Description	Total Reported MDRs*
Abscess	160
Infection and/or Peritonitis	157
Therapy/non-Surgical Treatment, Additional	115
Hospitalization Required	110
Adhesion(s)	114
Obstruction	97
Treatment with medication(s)	89
Fever	88
Pain, abdominal	75
Inflammation	55
Surgical procedure, additional	46
Surgical procedure	41
Pain	49
Infection, bacterial	33

*A single MDR may be associated with more than one problem code.

C: MDR Analysis: Clinical review of 24 MDRs with patient deaths presented in Citizen Petition (Appendix B) and updated FDA MDR analysis. UD-undeterminable

MDR EVENT #	ON/OFF LABEL	related/possibly device related	relatedness Undeterminable
1213643-2010-00229	OFF	X	
MW1039481	OFF	X	
1220423-2001-00009	OFF	X	
1220423-1998-00003	OFF	X	
1220423-1997-00015	OFF	X	
1220423-2007-00022	OFF (malignancy)	X	
1220423-2005-00016	OFF (malignancy)	X	
1220423-2004-00013	OFF (malignancy)		X
1220423-2004-00009	OFF (malignancy)	X	
1220423-2003-00012	OFF (malignancy)	X	
1220423-1999-00010	OFF (malignancy)	X	
1220423-2011-00037	OFF		X
1220423-2013-11751	UD		X
1220423-2011-00045	UD		X
1220423-2011-00011	UD		X
1220423-2005-00002	UD	X	
1220423-2001-00007	UD		X
1220423-2000-00032	UD		X
1220423-2000-00029	UD		X
1220423-2000-00010	UD		X
1220423-1999-00025	UD	X	

MW5014904	UD		X
1220423-2019-00022	OFF (malignancy)	X	
1220423-2019-00016	OFF		X

Based on this analysis, FDA concluded that 14 of the 24 patient death MDRs were off-label use with 11 of those events being related or possibly-related to the use of Seprafilm. 10 MDRs did not contain sufficient information to determine whether Seprafilm was used on- or off-label with 8 of those events also being undeterminable device relatedness. There were no deaths with on-label use and determined to be related or possibly related to the use of Seprafilm. FDA notes that determining whether a medical device caused a specific event can be difficult based solely on the information provided in a MDR. However, FDA concludes the safety profile defined by pre-market pivotal studies and the post-approval study is consistent with the types of reported adverse events. The exception to this conclusion is the MDRs reporting inflammation reactions. FDA notes that foreign body reaction was an anticipated adverse event in the pivotal trials, and the Seprafilm labeling currently states that foreign body reactions may occur. However, no foreign body reactions were reported in the pivotal trials or in the post-approval study. FDA further notes that foreign body reaction was explicitly identified in the case report forms used during the post-approval study. The MDRs reporting inflammatory reactions are consistent with at least some of the cited case reports, which describe an inflammatory reaction being located at the site where Seprafilm was placed by the surgeon. The current Seprafilm labeling includes the following precaution: "Foreign body reactions may occur with Seprafilm Adhesion Barrier, as with any implanted material." As it does appear that inflammatory responses to Seprafilm may be occurring in the post-market setting, FDA recommended that Genzyme strengthen the precaution to a warning to more effectively inform users of the potential for inflammatory reaction to Seprafilm. This labeling change was made in a Changes Being Effected PMA supplement to the Seprafilm PMA submitted on 12/23/2016.

In conclusion, the information you present, as it relates to MDRs, does not change the reasonable assurance the Seprafilm product is safe and effective when used according to the product label, and the MDRs do not provide evidence that there is a reasonable probability that Seprafilm use causes serious adverse health consequences or death.

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

Lastly, you raise questions about reported off-label uses, as well as uses purportedly within the scope of the labeled indication that were not assessed in the pivotal clinical trials (901 and 902) used to support the approval of the PMA application for Seprafilm.[48] The reports you reference describe use of Seprafilm during Cesarean sections, pediatric surgery, laparoscopic surgery to treat chronic abdominal pain, prevention of postoperative small bowel obstruction in transabdominal aortic aneurysm surgery, to reduce postoperative adhesions after cardiac surgery, use in decompressive craniectomy as a dural substitute and anti-adhesion barrier and in the setting of pediatric ventriculoperitoneal shunt malfunction.[49]

FDA reviewed the cited studies reporting off-label use of Seprafilm[50] and concluded the studies report various

[48] Citizen Petition at 19
[49] *Id.*
[50] *See generally* 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; 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; 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; 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; and Mumert ML, Altay T, Couldwell WT. Technique for decompressive craniectomy using Seprafilm as a dural substitute and anti-adhesion barrier. *J Clin Neurosci*.

degrees of clinical benefit without increased rates of complications with the use of Seprafilm. FDA acknowledges that publication bias may affect this literature search in favor of showing a benefit to Seprafilm use. However, doctors using a medical device for an indication that is not in the FDA-required labeling have a responsibility to use the medical device based on a firm scientific rationale and on sound medical evidence.[51] FDA concludes that the reported uses are not consistent with FDA-required labeling and, therefore, do not change FDA's interpretation of the safety or effectiveness of the device within the context of its labeled use. Nor do the reported uses establish evidence of serious adverse health consequences to support a recall.

With regards to the Albright *et al*. and Edwards *et al*. publications cited in the Petition, FDA agrees the use of Seprafilm at the time of Cesarean delivery lacks sufficient evidence of clinical benefit, as there is limited clinical data evaluating the use of adhesion barriers at the time of cesarean delivery, and the existing studies do not demonstrate an "improvement in meaningful clinical outcomes."[52] [53] Considering these reports, FDA recommended that Genzyme revise the existing precaution as follows: "The safe and effective use of Seprafilm Adhesion Barrier in pregnancy and Cesarean section has not been evaluated." This labeling change was made in a Changes Being Effected PMA supplement to the Seprafilm PMA submitted on 12/23/2016.

FDA agrees with your assertion that the use of Seprafilm as a slurry has not been demonstrated to be safe and effective. A search of the PMA database did not identify a PMA supplement with data supporting the use of Seprafilm in this altered form. Given the noted off-label promotion of Seprafilm, and the absence of safety and effectiveness data, FDA recommended adding the following addition to the directions for use: "The Seprafilm Adhesion Barrier should not be used in altered physical forms, other than cutting to conform to anatomical requirements." This labeling change was made in a Changes Being Effected PMA supplement to the Seprafilm PMA submitted on 12/23/2016.

Taken together, FDA concludes the information presented in your Petition related to Seprafilm use that is not consistent with FDA-required labeling does not change the conclusion that there remains a reasonable assurance the Seprafilm product is safe and effective when used according to the labeling, and this information does not provide evidence there is a reasonable probability that any Seprafilm use causes serious adverse health consequences or death.

vi. Recall Data

We note that there have been 4 recalls for Genzyme's PMA (P950034)-Seprafilm Adhesion Barrier. All 4 recalls were classified as Class II recalls. A Class II recall occurs when use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences, or where the probability of serious adverse health consequences is remote (21 CFR 7.3). A review of these recalls indicates that two recalls occurred in 2008 for compromised sterility, and two recalls occurred in 2012 for compromised sterility. FDA notes that infection is a potential risk posed by all implanted devices and infection is identified as a reported MDR for the Seprafilm product. Additionally, the products subject to these recalls were classified as having only a remote possibility of causing serious adverse health consequences, and these issues were adequately addressed by compliance actions.

The information in your Petition, together with the MAUDE data summarized above and Seprafilm's recall history, failed to establish evidence of a reasonable probability of serious adverse health consequences or death from use of

2012; 19(3):455-457.

[51] *See*"Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices; https://www fda.gov/regulatory-information/search-fda-guidance-documents/label-and-investigational-use-marketed-drugs-biologics-and-medical-devices.

[52] Albright CM, Rouse DJ. Adhesion barriers at cesarean delivery: Advertising compared with the evidence. *Obstet Gynecol*. 2011;118(1):157-160.

[53] 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.

Seprafilm. Therefore, we do not find that there is evidence to support mandating a recall under section 518(e) of the FD&C Act.

C. Conclusion

For the reasons described above, your Petition fails to provide new information which demonstrates lack of reasonable assurance of safety and effectiveness under the conditions of use prescribed, recommended, or suggested in Seprafilm's labeling. While we acknowledge that your Petition identified certain safety concerns with respect to specific uses of Seprafilm, these concerns are mitigated by labeling changes FDA recommended after receiving your Petition and made by Genzyme in 2016. Moreover, your Petition failed to provide evidence of reasonable probability that Seprafilm use causes serious adverse health consequences or death. Therefore, in accordance with 21 CFR 10.30(e), we are denying your requests that FDA withdraw the premarket approval of Seprafilm (P950034) and initiate a mandatory recall of all remaining unused Seprafilm devices. FDA appreciates your Petition and takes all medical device safety concerns very seriously.

If you have any questions about this response, please contact Josh Chetta in the CDRH Office of Policy at (240) 402-4910.

Sincerely yours,

Ellen J. Flannery -S

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