



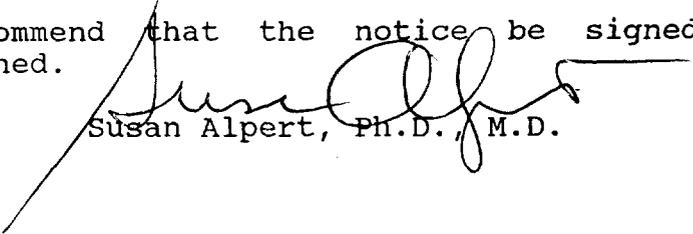
Memorandum

Date • **AUG 12 1996**
From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)
Subject Premarket Approval of Genzyme Corporation's
Septrafilm™ Bioresorbable Membrane - ACTION
To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:
(1) a premarket approval order for the above referenced medical device (Tab B); and
(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.


Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by David Berkowitz, CDRH, HFZ-410, July 19, 1996, 594-3090
Stephen Rhodes, CDRH, HFZ-410, July 23, 1996, 594-3090

|

A

3

DEPARTMENT OF HEALTH AND HUMAN SERVICES

DRAFT

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

Genzyme Corp.; PREMARKET APPROVAL OF Septrafilm™ Bioresorbable Membrane

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Genzyme Corp., Cambridge, MA, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of Septrafilm™ Bioresorbable Membrane. After reviewing the recommendation of the General and Plastic Surgery Devices PANEL, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on August 12, 1996, of the approval of the application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

3

FOR FURTHER INFORMATION CONTACT:

Mr. Stephen P. Rhodes,
Center for Devices and Radiological Health (HFZ-410),
Food and Drug Administration,
9200 Corporate Blvd.,
Rockville, MD 20850,
301-594-3090

SUPPLEMENTARY INFORMATION: On October 27, 1995, Genzyme Corp., Cambridge, MA 02139-1562, submitted to CDRH an application for premarket approval of Seprafilm™ Bioresorbable Membrane. The device is an Absorbable Adhesion Barrier and 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.

On March 25, 1996, the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee, an FDA advisory committee, reviewed and recommended approval of the application.

On August 12, 1996, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Opportunity For Administrative Review

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under §10.33(b) (21 CFR 10.33(b)). A petitioner shall identify



the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.



This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h), (21 U.S.C. 360e(d), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: _____.

7

13

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Alodia M. Ruiz
Director, Regulatory Affairs
Genzyme Corporation
One Kendall Square
Cambridge, Massachusetts 02139-1562

AUG 12 1996

Re: P950034
Septrafilm™ Bioresorbable Membrane
Filed: October 27, 1995
Amended: December 6, 1995; February 1, 1996; February 2,
1996; February 15, 1996; April 17, 1996; April
30, 1996; May 7, 1996; May 13, 1996; June 20,
1996; and June 28, 1996

Dear Ms. Ruiz:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Septrafilm™ Bioresorbable Membrane. This 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 such as omentum, small bowel, bladder, and stomach, and between the uterus and surrounding structures such as tubes and ovaries, large bowel and bladder. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section

9

520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the postapproval requirements in the enclosure, the postapproval reports must include the results of a post-approval study to be performed as outlined in the Amendment of June 25, 1996. Because the frequency of serious adverse events in the abdominal trial approached statistical significance, additional data are required to determine whether these events are associated with the device. A complete description of the postapproval study protocol must be submitted in the form of a PMA Supplement and approved before the study begins. The control group will be the first eligible 500 patients who underwent surgery without the use of Seprafilm™ before the date of this approval order and the treatment group will be the first eligible 500 patients treated with Seprafilm™ who undergo surgery after the date of this approval order. The data from both groups will be collected by a retrospective examination of patient charts.

Expiration dating for this device has been established and approved at 12 months for storage temperatures between 2 and 30 degrees Celsius.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

10

Page 3 - Ms. Alodia M. Ruiz

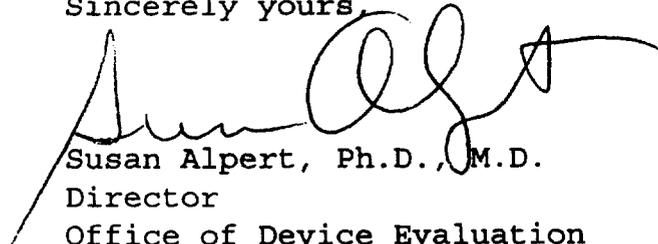
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Mr. Stephen P. Rhodes at (301) 594-3090.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Susan Alpert', with a long horizontal flourish extending to the right.

Susan Alpert, Ph.D., M.D.

Director

Office of Device Evaluation

Center for Devices and

Radiological Health

Enclosure

//

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the **addition** of, but **not the replacement** of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. **This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.**

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

- (1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).
- (2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:
 - (a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

- (b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

- (1) A mixup of the device or its labeling with another article.
- (2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and
 - (a) has not been addressed by the device's labeling or
 - (b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.
- (3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

- (1) may have caused or contributed to a death or serious injury or
- (2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Room 240
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

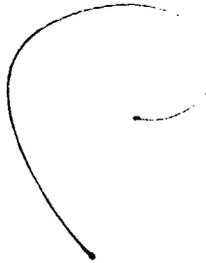
Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

(

(

(



16

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

GENZYME CORPORATION
SEPRAFILM™ BIORESORBABLE MEMBRANE

I. GENERAL INFORMATION

DEVICE GENERIC NAME: Absorbable Adhesion Barrier

DEVICE TRADE NAME: Seprafilm™ Bioresorbable Membrane

APPLICANT: Genzyme Corporation
One Kendall Square
Cambridge, MA 02139

PREMARKET APPROVAL
(PMA) APPLICATION: P950034

DATE OF PANEL
RECOMMENDATION: March 25, 1996

Date of GMP Inspection: May 23, 1996

DATE OF NOTICE OF
APPROVAL OF APPLICATION: August 12, 1996

Expedited Review: Expedited processing was authorized on July 28, 1996 based on the potential public health benefit from the reduction of the incidence and severity of adhesions at sites of surgical trauma in abdominal or pelvic surgery.



II. INDICATIONS FOR USE

Seprafilm™ Bioresorbable Membrane, hereinafter called Seprafilm™ or HAL-F™, 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.

III. DEVICE DESCRIPTION

Seprafilm™ (HAL-F™) Bioresorbable Membrane is a sterile, bioresorbable translucent membrane barrier composed of two chemically modified biocompatible biopolymers, sodium hyaluronate (HA) and carboxymethylcellulose (CMC). Together, these biopolymers are chemically modified by a proprietary method developed by Burns et al. (1991), U.S. Patent No. 5,017,229, with the activating agent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) to form a water insoluble powder, HA-CMC. HA-CMC powder is suspended in water for injection (WFI) and then cast to form a membrane. Seprafilm™ is available as a 12 x 15 cm membrane. It is packed in a sterile Tyvek® holder within an inner polyolefin/polyester sleeve, an outer trilaminate pouch, and a protective envelope carton. This packaging is then sterilized by gamma radiation to a sterility assurance level of 10^{-6} microorganisms. When stored as directed, the product is stable as indicated on the label.

The mechanism by which barriers reduce adhesion formation involves physically separating damaged peritoneal surfaces from apposing surfaces during the early stages of wound repair (Shimanuki et al. 1987). Reperitonealization occurs within approximately three days after tissue damage (Ellis 1983). After reperitonealization is complete, the likelihood of adhesion formation between tissue surfaces is greatly reduced. Within 24 to 48 hours after placement,

18

Seprafilm™ membrane becomes a hydrated gel that is absorbed by seven days and excreted in less than 28 days. In animal studies, Seprafilm™ was not visible at the site of application after 7 days.

In both human and animal studies Seprafilm™ has not been completely effective in preventing postsurgical adhesion development. A number of factors may potentially reduce membrane effectiveness. These include: membrane movement away from the application site; insufficient coverage of potential adhesiogenic sites due to improper membrane application; variability in the physiological environment at the point of application; and differences in the peritoneal inflammatory response due to infection, disease, or other predisposing factors.

IV. CONTRAINDICATIONS

There are no known contraindications associated with the use of Seprafilm™.

The warnings and precautions can be found in the Seprafilm™ labeling.

V. ALTERNATIVE PRACTICES AND PROCEDURES

The mainstay of adhesion reduction remains "good surgical technique."

There is a commercially available device, formulated from oxidized regenerated cellulose, that is indicated as an adjuvant in gynecological microsurgery for reducing the incidence of adhesion formation.

VI. MARKETING HISTORY

Seprafilm™ Bioresorbable Membrane is a new product although one of its components, sodium hyaluronate (HA), has been used successfully for many years as an aid in ophthalmic surgery.

19

Currently, Genzyme has marketing authorization for Seprafilm™ Bioresorbable Membrane in Canada, EEC, Denmark, Hong Kong, Ireland, Israel, Netherlands, and Sweden. Genzyme received the CE mark for Seprafilm™ January 1996, and has begun distribution in the European Economic Community (EEC).

Seprafilm™ Bioresorbable Membrane has not been withdrawn from marketing for any reason related to the safety and effectiveness of the device.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A total of 342 patients were enrolled in the four clinical trials conducted for the evaluation of Seprafilm™. Adverse events were reported in 90% (155 of 172) of the treated patients and in 94% (160 of 170) of the control patients. The adverse events could all be considered related to the complexity of the surgical procedures performed. The relationship to complexity is supported by the roughly ten-fold increase in the incidence of serious adverse events in the abdominal trial relative to the pelvic surgery trial. In the pelvic trial serious adverse events were reported in 3.4% (2 of 59) of the treatment and in 4.4% (3 of 68) of the nontreatment patients, while in the abdominal study serious adverse events were reported in 42% (38 of 91) of the treated patients and in 24% (22 of 92) of the nontreatment patients.

The increase in the number of serious adverse events in the treated patients in the abdominal study (safety and effectiveness) approached but did not reach statistical significance, $p = 0.0744$. Of most concern were abscesses, reported in 8% of the treated population but in only 2% of the control population. This approached significance with $p = 0.0998$ (two-tailed Fisher's Exact Test). Deep vein thrombosis (DVT) was reported in 2 treatment patients and pulmonary embolus (PE) was reported in 4 treatment patients. The control group had only 1 DVT and no PE. Abscess, PE and DVT were not reported in the pelvic trial. Postapproval studies will be conducted to determine if there is a statistical association between the abscess rate or other serious adverse events and the abdominal use of the device.

There was one death in this study. The patient had a mild myocardial infarction during or shortly after the

20

There was one death in this study. The patient had a mild myocardial infarction during or shortly after the surgery, was discharged, and died 13 days after the surgery.

In the clinical trials section, all adverse events occurring at a frequency of 5% or higher are listed, and the frequencies of all serious adverse events in the treatment and control groups are reported.

VIII. SUMMARY OF PRE-CLINICAL STUDIES

Safety and effectiveness testing were performed on the HA component of Seprafilm™ (HAL-F™) and on the device. The objectives of the animal studies were to evaluate the device's potential for toxicity, immunogenicity, biocompatibility, and its effectiveness in reducing the incidence, extent, and severity of postoperative adhesions.

The following section summarizes preclinical study data from *in vitro* and *in vivo* models showing that Seprafilm™ is non-toxic, non-immunogenic, biocompatible and effective in reducing the incidence, extent, and severity of postoperative adhesions.

Safety

The safety of Seprafilm™, including packaging and product contact materials, has been demonstrated in a battery of *in vitro* and *in vivo* studies. These studies and the results are listed in (Table 1).

21

TABLE I
SEPRAFILM™ (HAL-F™) BIORESORBABLE MEMBRANE,
NON-CLINICAL SAFETY STUDIES

Septrafilm™ (HAL-F™) Bioresorbable Membrane	
Safety Studies	Results
Microbiological Studies	
Infectivity Study, HAL-F™ Bioresorbable Membrane	Does not enhance growth of microorganisms
Toxicological Studies	
Mutagenicity	non mutagenic
Chromosomal Aberration	non mutagenic
Sister Chromatid Exchange	non mutagenic
U.S.P. Pyrogen	non pyrogenic
Intracutaneous Toxicity	non irritant/non toxic
Acute Toxicity - Intraperitoneal	non toxic
Systemic Toxicity	non toxic
Immunological Studies	
Maximization/Dermal Sensitization	non sensitizing
Systemic Antigenicity	non antigenic
Biocompatibility Studies	
Muscle Implantation (7 day and 30 day)	slight irritant
Hemolysis	non hemolytic
Complement Activation	non reactive
Cytotoxicity of HAL-F™ Irradiated at Different Doses	non toxic
Cytotoxic Response in Agar Overlay and Muscle Implant Studies	non toxic and non reactive
Cytotoxicity of HAL-F™	non toxic
Production and Packaging Studies	
Qualification of HAL-F™ produced on PMMA* trays	PMMA is a suitable casting material.
Cytotoxicity of HAL-F™ Membrane in Packaging Materials Irradiated at Different Doses	inner packaging in not toxic. No leachables from outer packaging.
Cytotoxicity Testing of Packaging Materials: Polyolefin/Polyester Sleeve	non toxic
Cytotoxicity - HAL-F™ Casting Trays: PMMA	non toxic

* Polymethylmethacrylate-coated trays

27

Seprafilm™ was scored as negative in all the tests shown in Table 1 except in the muscle implant test. Phagocytic cellular infiltration observed at the product implant site resulted in a microscopic histological score as a slight irritant, but these early cellular infiltrates disappear as the device is resorbed. Macroscopically, Seprafilm™ was a nonirritant in both the 7- and 30-day tests.

In a complement activation study, Seprafilm™ did not activate C3a or C4a but slightly stimulated C5a production. The significance of the *in vitro* activation of C5a complement by Seprafilm™ in this study, is unclear. It is known that activation of C3a and C5a complement may be important in the recruitment of phagocytic cells, such as macrophages, to remove foreign material (Anderson 1988).

In vitro studies have shown that Seprafilm™ is almost completely hydrated in less than one minute and can absorb about eight times its own weight of water in less than two minutes. When it is in contact with saline solutions, Seprafilm™ swells and undergoes a phase transition from a solid to a gel which is associated with an increase in volume. As the volume increases, the swelling pressure decreases from 6.4 atmospheres to zero. Furthermore, as Seprafilm™ transforms to a gel, its tensile strength decreases by 90% within 30 minutes (gel transformation is completed in approximately 24 hours). These studies suggest that Seprafilm™ does not impart a swelling pressure that could affect tissue and organ function in the peritoneal cavity.

Disposition and clearance studies have been conducted in animals using radiolabeled HA, CMC and ethyl-(3-dimethylaminopropyl)-urea (EDU) peritoneal implants of Seprafilm™. EDU is a potential by-product of Seprafilm™ degradation. The majority of the implanted materials was cleared from the peritoneal cavity in seven days and was excreted in urine within less than 28 days.

In vitro and *in vivo* infectivity studies were conducted in animals to determine if Seprafilm enhances microbial growth of common large bowel organisms. These studies showed Seprafilm did not promote the growth of test organisms within the abdominal cavity.

Effectiveness

Effectiveness studies conducted in support of Seprafilm™ Bioresorbable Membrane were:

1. Adhesion Reduction in a Rat Cecal Abrasion Model
2. Effects of Irrigation on the Efficacy of Seprafilm™
3. The Effects of Multiple Layering on Seprafilm™ in a Rat Cecal Abrasion Model
4. Effects on Adhesion Reformation of Seprafilm™ in the Rat Cecal Adhesiolysis Model
5. Adhesion Reduction in a Rat Sidewall Defect Model

The results of these studies showed that the use of Seprafilm™ Bioresorbable Membrane resulted in fewer adhesions of all grades, as well as in a greater number of animals with zero adhesions. Saline or lactated Ringer's solution instilled into the abdominal cavity following a standardized cecal abrasion procedure did not reduce effectiveness. The use of multiple layers of Seprafilm™ membrane neither improved nor reduced its adhesion reduction efficacy. Seprafilm™ membrane effectively reduced the mean incidence of both reformed adhesions and *de novo* adhesions, and effectively reduced adhesions to sidewall defects.

The potential migration of Seprafilm™ from the site of application has not been studied in humans. Although the product initially adheres well to tissue, as observed in the animal studies described above, the rat uterine horn study showed that product migration from the application site is possible. Migration may result from bathing the membrane in excess fluid following application or insufficient contact with tissue surface area.

24

In addition, Yarali et al. 1994 evaluated Seprafilm™ in a rat uterine horn injury model, in which the uterine horns were thermally injured using a surgical laser. Adhesions were graded 14 days later at a second laparotomy. The authors found that Seprafilm™ did not prevent adhesions in this model. Genzyme's Biopolymers Research and Development Laboratory and Dr. Yarali's group discovered that Seprafilm™ did not stay on the uterine horn long enough to be effective. It is possible that because the rat uterine horn is only a few millimeters in diameter, there was insufficient tissue area for membrane adherence. This situation was exacerbated by the fact that the rat uterine horns sit in the pelvic cavity where fluid may accumulate. This may have caused Seprafilm™ to hydrate quickly, possibly increasing degradation or movement by flotation. In response to this information, the design of the abdominal and gynecologic clinical trials included using sheets of Seprafilm™ large enough to allow ample coverage of the intended site even if the membrane moved.

IX. SUMMARIES OF THE RESULTS OF THE CLINICAL INVESTIGATIONS

Seprafilm™ Bioresorbable Membrane was clinically evaluated in four human clinical trials under IDE G920007. The objectives of the clinical trials were to evaluate the safety of the Seprafilm™ Bioresorbable Membrane, and to evaluate Seprafilm's™ ability to reduce the incidence, extent and severity of postoperative adhesions in the abdominal and pelvic cavities.

Safety studies were conducted in abdominal surgery under Protocol HF91-1201, "Evaluation of the Safety of Seprafilm™ Bioresorbable Membrane in Abdominal Surgery" and in gynecologic surgery under Protocol HF91-1202, "Evaluation of the Safety of Seprafilm™ Bioresorbable Membrane in Gynecological Surgery".

The effectiveness of Seprafilm™ Bioresorbable Membrane was evaluated, in conjunction with safety, in abdominal surgery under Protocol HF92-0901, "Evaluation of the Safety and Effectiveness of Seprafilm™ Bioresorbable

Membrane in Limiting Postoperative Adhesion Formation to Serosal Tissue (Abdominal Surgery)" and in gynecologic surgery under Protocol HF92-0902, "Evaluation of the Safety and Effectiveness of Seprafilm™ Bioresorbable Membrane in Reducing Postoperative Adhesion Formation to Serosal Tissue (Gynecologic Surgery)".

Each of the four clinical trials is described below.

Protocol HF 91-1201 Evaluation of the Safety of Seprafilm™ Bioresorbable Membrane in Abdominal Surgery:
Patient Enrollment: March 27, 1992-October 30, 1992

Of a total of 15 patients at 3 sites undergoing a variety of open abdominal surgeries, 10 received Seprafilm™ (HAL-F™) treatment (8 male, 2 female) and five were nontreatment controls (2 male, 3 female). All enrolled in this study completed all study requirements. The demographic characteristics of the Seprafilm™ and nontreatment group were comparable, except for the greater frequency of women in the smaller control group. The average age of the Seprafilm™ patients was 48.3 years. The average age of the nontreatment patients was 39.2 years. The most frequent surgical procedures performed were exploratory laparotomy, cholecystectomy, and lysis of adhesions.

Study inclusion criteria were as follows:

1. Patients, male and female, 18 years of age and older who were scheduled for open abdominal surgery (celiotomy);
2. Patients capable of providing written informed consent prior to study initiation.

Patients were excluded for the following reasons: they did not meet the inclusion criteria, were diagnosed with cancer, were treated with irrigants/instillants containing corticosteroids, heparin, non-steroidal anti-inflammatory agents, or dextran was required during surgery, would receive any other anti-adhesion therapy, have any medical condition that might alter metabolism or compromise excretion of Seprafilm™, patients with any

medical condition that would interfere with the safety or effectiveness evaluation of the device or prevent study completion, patients with a history of severe allergies, patients with a purulent intra-abdominal infection, patients who are pregnant.

The safety endpoints for this study were defined as the incidence of all reported adverse events and/or changes in vital signs and laboratory values from baseline.

In the Seprafilm™ group patients, Seprafilm™ was applied on the omentum and viscera directly under the peritoneal cavity incision just before abdominal cavity closure. The mean total quantity of Seprafilm™ membrane applied in the Seprafilm™ patients was 1.9 membranes.

A total of 28 adverse events were reported for 10 of 10 Seprafilm™ patients and 14 adverse events were reported for five of five nontreatment group patients. The most commonly reported adverse event in both groups was fever. Four serious adverse events occurred in the study: One Seprafilm™ patient, who required prolonged hospitalization and two reoperative surgeries to treat injuries from an industrial accident that occurred prior to the surgery, developed sepsis. Two patients, one Seprafilm™ and one nontreatment, were rehospitalized. One Seprafilm™ patient experienced two separate episodes requiring rehospitalization on postoperative day 16 for a facial abscess and again on postoperative day 31 for a deep vein thrombosis. A nontreatment patient was rehospitalized on postoperative day 16 for abdominal pain and removal of a foreign body. Abnormal laboratory values were consistent with the effects of surgery or the patient's medical condition. It could not be determined whether or not there was a causal relationship between any of the adverse events and the treatment.

Safety data were evaluated for all 15 patients enrolled. No patients were discontinued from this study. There were no specific reported patient complaints definitely related to the use of Seprafilm™ in this study. All reported patient complications, discomforts, symptoms, and/or complaints were evaluated as adverse events.



There were no device failures or replacements in this study. Twenty-four membranes were used. No statistical analysis of postoperative adhesion formation was planned or performed in this study.

**Protocol HF91-1202 Evaluation of the Safety of
Seprafilm™ Bioresorbable Membrane in Gynecologic Surgery:
Patient Enrollment: April 27, 1992-July 12, 1993**

A total of 17 female patients, 12 Seprafilm™ (HAL-F™) treatment patients and five nontreatment patients, all undergoing a myomectomy via laparotomy, were enrolled in this study at one of two sites and completed all study requirements. The average age of the Seprafilm™ patients was 33.3 years. The average age of the nontreatment patients was 35.4 years. Overall, the demographic characteristics of both the Seprafilm™ and the nontreatment groups were comparable.

Study inclusion criteria were as follows:

1. Female patients, 18 years of age and older who were scheduled for a uterine myomectomy via laparotomy;
2. Patients capable of providing written informed consent prior to study initiation.

Patients were excluded for the following reasons: did not meet inclusion criteria, had cancer or were pregnant, patient in whom the use of irrigants/instillants containing corticosteroids, heparin, non-steroidal anti-inflammatory agents, or dextran was required during surgery, Who would receive any other anti-adhesion therapy, patients with any medical condition that might alter metabolism or compromise excretion of Seprafilm™, patients with any medical condition that would interfere with the safety or effectiveness evaluation of the device or prevent study completion, patients with a history of severe allergies, patients with active pelvic inflammatory disease.

Clinical endpoints for this study were defined as the incidence of all reported adverse events and/or changes in vital signs and laboratory values from baseline.

In the Seprafilm™ patients, Seprafilm™ was placed directly on the uterine incision area before pelvic cavity closure. The mean total quantity of Seprafilm™ membrane applied in Seprafilm™ patients was 0.4 membranes.

A total of seven adverse events were reported by five of 12 Seprafilm™ patients and a total of seven adverse events were reported by two of five control patients. The most commonly reported adverse event in the treatment group was fever (2) and in the control group, minimal wound separation (3). No serious adverse events were reported in this study. Changes in postoperative vital signs and laboratory values from baseline were reported in both patient groups and no significant differences were observed between the Seprafilm™ and control groups. Most of the abnormal values were consistent with the effects of surgery or hemodilution.

Safety data were evaluated for all 17 patients enrolled. No patients were discontinued from this study. All reported patient complications, discomforts, symptoms, and/or complaints were evaluated as adverse events. There were no device failures or replacements in this study. No statistical analysis of postoperative adhesion formation was planned or performed in this study. No known contraindications or precautions were identified in this study.

It was concluded that the application of Seprafilm™ to the uterus in gynecologic surgery resulted in no clinically significant changes in vital signs or laboratory values that altered any patient's expected course of surgical recovery or resulted in the occurrence of serious adverse events.

Protocol HF92-0901 Evaluation of the Safety and Effectiveness of Seprafilm™ Bioresorbable Membrane in Limiting Postoperative Adhesion Formation to Serosal Tissue (Abdominal Surgery) Patient Enrollment: May 12, 1993-September 8, 1994

The purpose of this study was to determine if Seprafilm™ (HAL-F™) is safe and effective for reducing postoperative adhesion formation in the patients diagnosed with

ulcerative colitis or familial polyposis undergoing major abdominal surgery. The study was a controlled, prospective, randomized, blinded, multicenter study that measured adhesion formation following a major surgical procedure. The study model permitted all investigators to follow a standard surgical protocol, thereby minimizing variables that may influence postoperative adhesion formation and to conduct adhesion evaluation at a follow-up surgery.

Study inclusion criteria were as follows:

1. Patient 18 years of age and older;
2. May be of either sex (all female patients of childbearing potential required to have a negative pregnancy test prior to enrollment and agree to avoid pregnancy during their first complete menstrual cycle following study enrollment);
3. Primary diagnosis of ulcerative colitis or familial polyposis;
4. Patients scheduled to undergo an abdominal endorectal ileal pouch-anal anastomosis with diverting loop ileostomy, to be followed by loop ileostomy closure approximately 8-12 weeks later;
5. Patients willing and able to adhere to protocol requirements, to provide written consent, and who signed the IRB approved written informed consent within 14 days prior to enrollment.

Patients were excluded for the following reasons: did not meet the inclusion criteria, were pregnant or had cancer, patients in whom the use of irrigants/instillants containing corticosteroids, heparin, non-steroidal anti-inflammatory agents, dextran 70, or routine antibiotic irrigants would be required during surgery, who would receive any other anti-adhesion therapy, patients with any medical condition that would interfere with the safety or effectiveness evaluation of the device, patients who received any investigational product during study participation that may have interfered with the evaluation of the safety or effectiveness of the study device, patients who had undergone a previous colectomy or midline abdominal incision, or patients with a history of severe drug allergies.

30

The primary measure for this study was the incidence of adhesions defined as the proportion of patients with one or more adhesions to the initial midline incision at the follow-up surgery (comparison of treatment group vs. control group) and the extent of adhesion involvement as a proportion of the overall initial midline incision length (comparison of treatment group vs. control group). The severity of adhesions was measured as a secondary endpoint using a scale that grades the thickness and vascularity of adhesions. Safety endpoints were assessed through the monitoring of adverse events, the incidence of patients reporting one or more adverse events, serious adverse event reports, abnormal vital signs, and abnormal laboratory values at baseline and at study completion.

A total of 183 patients, 91 Seprafilm™ and 92 nontreatment patients, with either ulcerative colitis or familial polyposis, were enrolled in this study. The population contained 106 males and 77 females and 174 whites and 9 nonwhite patients. There were no statistically significant demographic differences between the treatment and control groups. In the Seprafilm™ group, the membrane was applied on the omentum and viscera directly under the abdominal midline incision just before abdominal cavity closure. The mean total quantity of Seprafilm™ membrane applied in the treatment patients was 2.3 membranes per patient.

Safety

One or more adverse events were reported by 82 of 91 (90%) Seprafilm™ group patients and by 86 of 92 (94%) control patients. The most commonly reported adverse events in both groups were nausea, abdominal pain and fever (Table 2).

31

TABLE 2
SUMMARY OF THE INCIDENCE OF ADVERSE EVENTS (AE's) OCCURRING
IN GREATER THAN OR EQUAL TO 5 PERCENT OF PATIENTS IN
EITHER TREATMENT GROUP

	HAL-F™ (n=91)			Control (n=92)		
	AE's	Patients		AE's	Patients	
	n	n	(%)	n	n	(%)
Nausea	35	31	(34)	46	41	(45)
Abdominal Pain	32	26	(29)	27	23	(25)
Fever	23	22	(24)	22	22	(24)
Rash	18	17	(19)	16	16	(17)
Vomiting	15	14	(15)	13	12	(13)
Nausea Vomiting	19	13	(14)	19	17	(19)
Dehydration	13	11	(12)	13	13	(14)
GI Distress	12	11	(12)	12	12	(13)
Pruritus	12	11	(12)	15	13	(14)
Infection	10	10	(11)	9	9	(10)
Pain	10	10	(11)	16	16	(17)
Dizziness	10	9	(10)	6	6	(7)
Intestinal Obstruction	9	9	(10)	13	11	(12)
Paresthesia	8	8	(9)	11	10	(11)
Abscess	8	7	(8)	2	2	(2)
Anemia	7	6	(7)	7	7	(8)
Asthenia	6	6	(7)	4	4	(4)
Ileus	6	6	(7)	6	6	(7)
Tachycardia	6	6	(7)	7	6	(7)
Hypertension	5	5	(6)	5	5	(5)
Back pain	4	4	(4)	9	9	(10)
Urinary Tract Infection	4	4	(4)	6	6	(7)
Headache	2	2	(2)	6	6	(7)

No statistical difference between treatment groups ($p > 0.05$, Fisher's Exact) in any categories listed above.

A total of sixty serious adverse events were reported, in 35% of the treated patients and in 23% of the control patients. This approached statistical significance, with $p = 0.074$. Comparison of the incidence of specific adverse events between the treatment groups did not

30

identify a significant difference ($p > 0.05$ Fisher's Exact Test), but abscesses were four times more frequent in the treatment group ($p = 0.10$). Deep vein thrombosis and pulmonary embolus were each reported in 2 and 4 treatment patients, respectively, but the control group had only 1 deep vein thrombosis and no pulmonary emboli.

Changes in postoperative vital signs and laboratory values were reported in both the Seprafilm™ treatment and nontreatment groups. Most abnormal values were consistent with the effects of surgery or the patient's medical condition. No adverse events were definitely related to the treatment.

Effectiveness

The incidence of patients with one or more adhesions to the midline incision was significantly reduced from 94% in the nontreatment patients, to 49% in the Seprafilm™ group ($p < 0.0001$, Fisher's Exact Test) (Table 3).

TABLE 3
SUMMARY OF THE INCIDENCE* OF POSTOPERATIVE
ADHESION FORMATION TO THE MIDLINE INCISION BY
TREATMENT GROUP

	HAL-F™		Nontreatment		p Value**
	n	(%)	n	(%)	
Evaluable Patients	85		90		
No Adhesions	43	(51)	5	(6)	<0.0001
Adhesions	42	(49)	85	(94)	
Intent to Treat Patients	91		92		
No Adhesions	43	(47)	5	(5)	<0.0001
Adhesions	48	(53)	87	(95)	

* Any patient presenting with one or more adhesions to the initial surgery midline incision

** Fisher's Exact Test

The overall mean extent of adhesions (percent of the incision length involved) among Seprafilm™ patients was 23%, significantly less than in the nontreatment group, 63% ($p < 0.0001$, Student's t Test) (Table 4).

TABLE 4
 SUMMARY OF THE EXTENT OF POSTOPERATIVE
 ADHESION FORMATION TO THE MIDLINE INCISION BY
 TREATMENT GROUP

	HAL-F™	Nontreatment	p Value**
Evaluable Patients Mean%±SD	n=85 23±34	n=90 63±34	<0.0001
Evaluable Patients with Adhesions Mean%±SD	n=42 47±34	n=85 67±31	=0.0008
Intent to Treat Patients Means%±SD	n=91 28±38	n=92 64±34	<0.0001
Intent to Treat Patients with Adhesions Mean%±SD	n=48 54±36	n=87 67±31	=0.0105

* The proportion, expressed as percent, of the total length of the initial surgery midline incision associated with any adhesion, as determined by dividing the length associated with adhesions (cm) by the overall length of the initial midline incision (cm)

** Student t Test

In addition, the evaluation of severity of adhesions demonstrated that 90% of the nontreatment patients, as compared to only 35% of the Seprafilm™ patients, had one or more adhesions that were assessed as Grade 2 or 3, using a standardized grading scale of 1 (filmy, avascular), 2 (moderate thickness, limited vascularity) or 3 (dense thickness, vascularized). Overall adhesions in the Seprafilm™ group were significantly less severe than in the nontreatment group ($p < 0.0001$, Wilcoxon Rank Sum) (Table 5).

TABLE 5
SUMMARY OF THE SEVERITY * OF POSTOPERATIVE
ADHESION FORMATION TO THE MIDLINE INCISION BY
TREATMENT GROUP

	HAL-F™ n=85		Nontreatment n=90		p Value**
	n	(%)	n	(%)	
Evaluable Patients	85		90		<0.0001
No Adhesions	43	(51)	5	(6)	
Grade 1	12	(14)	4	(4)	
Grade 2	17	(20)	29	(32)	
Grade 3	13	(35)	52	(58)	
Evaluable Patients with Adhesions	42		85		<0.0001
Grade 1	12	(29)	4	(5)	
Grade 2	17	(40)	29	(34)	
Grade 3	13	(31)	52	(61)	
Intent to Treat Patients	91		92		<0.0001
No Adhesions	43	(47)	5	(5)	
Grade 1	12	(13)	4	(4)	
Grade 2	17	(19)	29	(32)	
Grade 3	19	(21)	54	(59)	
Intent to Treat Patients with Adhesions	48		87		=0.0018
Grade 1	12	(25)	4	(5)	
Grade 2	17	(35)	29	(33)	
Grade 3	19	(40)	54	(62)	

* Grade 1, filmy thickness, avascular;
Grade 2, moderate thickness, limited vascularity;
Grade 3, dense thickness, vascularized

** Wilcoxon Rank-sum

A multivariate analysis of possible confounding factors demonstrated that Gender was a significant predictor of the incidence of adhesion formation, but not of extent or severity. Males were more likely to form adhesions (100% Control, 62% HAL-F™) than females (87% Control, 31% HAL-F™). Also, females experienced a larger therapeutic effect, as measured by a relative reduction of incidence (56% for females, 38% for males). The reduction of adhesions remained statistically significant after accounting for the gender of the patients. Also, in subgroup analyses of each sex, the treatment effect remained highly significant. The selection ratio of men

versus women in the initial safety and pivotal abdominal trials was reasonably reflective of general distribution of gender in abdominal surgery.

Other demographic parameters were not significant predictors of adhesion formation, severity, or extent outcomes. A multivariate model was also employed for the intraoperative parameters. No variables were found to be significant predictors of adhesion formation. The duration of surgery, however, was found to be a significant predictor for the severity of adhesion formation. Longer surgeries showed more severe adhesions in both the Seprafilm™ and nontreatment groups. There were no significant intraoperative predictors for the extent outcome. The number of patients treated systemically with corticosteroids was found to be a statistically significant predictor of a reduction in the incidence and overall severity of adhesion formation. However, the number of Seprafilm™ patients not receiving corticosteroids was small (n=11), and of the nontreatment patients, nearly all patients developed adhesions irrespective of corticosteroid administration. The effect of Seprafilm™ remained intact after controlling for these factors.

Safety data were evaluated for all 183 patients enrolled. Effectiveness data were evaluated for 175 patients. Six Seprafilm™ patients and two nontreatment patients were found to be not eligible for the effectiveness evaluation because there was no second surgery (4), a premature second surgery (1), a delayed second surgery (1), and incorrect randomization (1), and a death (1). Inclusion of these patients in the analyses of effectiveness, and assuming worst case outcomes, did not significantly alter the benefit provided by use of the membrane.

Seprafilm™ significantly reduced the incidence, severity, and extent of postoperative adhesion formation between the abdominal wall and the underlying viscera such as omentum, small bowel, bladder, and stomach compared to the current standard of surgical practice.

Protocol HF92-0902 Evaluation of the Safety and Effectiveness of Seprafilm™ Bioresorbable Membrane in Reducing Postoperative Adhesion Formation to Serosal Tissue (Gynecologic Surgery) Patient Enrollment:
December 2, 1993-May 17, 1995



This prospective multicenter clinical trial was conducted in a randomized, controlled manner. Following myomectomy, patients underwent second-look laparoscopy and were subsequently evaluated for efficacy via video tape for postoperative adhesion formation by an expert independent evaluator not having knowledge of treatment status.

Study inclusion criteria were as follows:

1. Female patients, 18 years of age and older;
2. Scheduled for uterine myomectomy via laparotomy and a second-look laparoscopy;
3. Patients with at least one uterine incision or segment of their uterine incision on the posterior uterine surface; the posterior incision or incision segment must be greater than 1 cm;
4. Patients willing and able to adhere to protocol requirements, to provide written consent, and who signed the IRB approved written informed consent within 14 days prior to enrollment.

Patients were excluded for the following reasons: If they were less than 18 years of age, if they were pregnant, if they had cancer, patients in whom the use of irrigants/instillants containing corticosteroids, heparin, non-steroidal anti-inflammatory agents (NSAIDs), or dextran 70 was required during or immediately following surgery, patients who required chronic corticosteroid therapy or who required use of systemic corticosteroids and/or NSAIDs perioperatively, who would receive any other anti-adhesion therapy, patients with any medical condition that would interfere with the safety or effectiveness evaluation of the device, patients who had undergone salpingectomy (partial or total), oophorectomy or salpingo-oophorectomy; patients who had active pelvic inflammatory disease, patients who received any investigational product during study participation that may have interfered with the evaluation of the safety or effectiveness of the study device, patients with a history of severe drug allergies.

The primary analysis included incidence, extent, severity, and area of all adhesions to the uterus as well as to the separate anterior and posterior aspects of the uterus, respectively. Safety endpoints were assessed through the monitoring of adverse events, the incidence

of patients reporting one or more adverse event, serious adverse event reports, abnormal laboratory and abnormal vital sign values at baseline and at study completion.

The total patient population in this study was 127 patients, 59 Seprafilm™ and 68 nontreatment patients. All of the 127 patients enrolled in the study had a history of uterine fibroids.

One or more adverse events were reported in 58 of the 59 (98.3 %) of the Seprafilm™ patients and in 67 of the 68 (98.5 %) of the nontreatment patients (Table 6).

TABLE 6
SUMMARY OF THE INCIDENCE OF ADVERSE EVENTS (AE's) OCCURRING
IN GREATER THAN OR EQUAL TO 5 PERCENT OF PATIENTS IN
EITHER TREATMENT GROUP

	HAL-FTM (n=59)			Nontreatment (n=68)		
	AE's	Patients		AE's	Patients	
	n	n	(%)	n	n	(%)
Pain	63	42	(71)	77	50	(74)
Fever	38	35	(59)	34	33	(49)
Abdominal Pain	35	23	(39)	45	33	(49)
Nausea	26	23	(39)	34	30	(44)
Constipation	9	9	(15)	8	8	(12)
Anemia	8	8	(14)	9	9	(13)
Headache	8	8	(14)	7	7	(10)
Nausea Vomiting	7	7	(12)	4	4	(6)
Pruritus	7	7	(12)	10	10	(15)
Dizziness	6	6	(10)	3	3	(4)
Atelectasis	6	6	(10)	4	4	(6)
Pharyngitis	6	6	(10)	4	4	(6)
Rash	5	5	(8)	2	2	(3)
Diarrhea	4	4	(7)	5	5	(7)
Wound Drainage	4	4	(7)	5	5	(7)
Vomiting	3	3	(5)	7	7	(10)
Urinary Tract Infection	3	3	(5)	2	2	(3)
Insomnia	3	3	(5)	1	1	(1)
Vaginal Hemorrhage	3	3	(5)	0	0	(0)
Urinary Retention	2	1	(2)	4	4	(6)

No statistical difference between treatment groups ($p > 0.05$, Fisher's Exact, 2-Tail) in any categories listed above.

Pain (unspecified), fever, abdominal pain, and nausea were the most frequently reported adverse events in both treatment groups. There were no statistically significant differences in the overall incidence of adverse events between the treatment and control groups when evaluated by specific term. All adverse events listed are recognized complications of the surgical procedure and/or existing comorbid disease. No adverse event was considered to be definitely related to the study device. Five patients, two (3.4 %) Seprafilm™ and three (4.4 %) control patients, had a total of six serious adverse events. One treated patient had ileus and fever and the other had fever and a blood typing error. There were no reports of abscess, pulmonary embolus or thromboembolic events in this study among the treated population.

Vital signs consisting of temperature, heart rate, and blood pressure were measured at baseline and postoperatively at 2-5 days and 2-4 weeks. No trends in these vital signs were observed that might suggest a relationship to the study device.

There were no significant differences between the patients treated with HAL-F™ and those in the control group at baseline in either demographic or intraoperative factors. The mean time to evaluation at second look surgery was identical in both groups (23 postoperative days).

Of 119 women who completed the trial and were eligible for analysis, HAL-F™ patients (n=54) had an overall significant reduction in uterine adhesions versus nontreatment patients (n=65) as determined by incidence (number of adherent sites), extent, severity, and area. The means number of sites adherent to the entire uterine surface in the HAL-F™ group was 4.98 in comparison to 7.88 in the nontreatment group ($p < 0.0001$) (Table 7).

Table 7

**SUMMARY OF NUMBER OF SITES ADHERENT TO THE UTERUS -
INDEPENDENT REVIEWER - INTENT TO TREAT ANALYSIS**

		HAL-F™		Nontreatment		p-Value*
		n	mean	n	mean	
Anterior	Incisional	49	0.74	51	1.76	<0.0001
	Entire Surface	49	1.45	50	2.88	<0.0001
Posterior	Incisional	54	1.74	65	2.02	0.3610
	Entire Surface	54	3.54	63	4.49	0.0536
Entire Uterine Surface		49	4.98	4	7.88	<0.0001

* Student's t-Test (2-Tail)

The mean severity score was reduced to 1.94 in HAL-F™ patients versus 2.43 in the nontreatment group ($p=0.0044$) (Table 8).

Table 8

**SUMMARY OF THE SEVERITY OF ADHESIONS TO THE UTERUS -
INDEPENDENT REVIEWER - INTENT TO TREAT ANALYSIS**

	HAL-F™		Nontreatment		p-Value*
	n	mean	n	mean	
Anterior Surface	54	1.61	64	2.16	0.0308
Posterior Surface	54	2.26	63	2.71	0.0150
Entire Uterine Surface	54	1.94	65	2.43	0.0044

* Student's t-Test (2-Tail)

The mean extent score was 1.23 among the HAL-F™ patients and 1.68 in nontreatment patients ($p=0.0049$) (Table 9).

40

Table 9

SUMMARY OF THE EXTENT OF ADHESIONS TO THE UTERUS -
INDEPENDENT REVIEWER - INTENT TO TREAT ANALYSIS

	HAL-F™		Nontreatment		p-Value*
	n	mean	n	mean	
Intent to Treat					
Anterior Surface	54	0.94	64	1.44	0.0134
Posterior Surface	54	1.52	63	1.95	0.0230
Entire Uterine Surface	54	1.23	65	1.68	0.0050

* Student's t-Test (2-Tail)

The mean area involved with adhesions at second look was more than a third greater in nontreatment patients (18.7 cm²) than in HAL-F™ patients (13.2 cm², p=0.0226) (Table 10).

Table 10

SUMMARY OF THE AREA (CM²) OF THE UTERUS INVOLVED WITH ADHESIONS -
INDEPENDENT REVIEWER - INTENT TO TREAT ANALYSIS

	HAL-F™		Nontreatment		p-Value*
	n	mean	n	mean	
Anterior Surface	54	4.14	63	7.19	0.0158
Posterior Surface	54	9.09	63	12.12	0.0680
Entire Uterine Surface	54	13.23	65	18.72	0.0226

* Student's t-Test (2-Tail)

Significant reductions in adhesions for each of these determinations was present on both the anterior and posterior aspects of the uterus.

A multivariate analysis of possible confounding factors was performed. The number of prior posterior uterine adhesions, incisions, and duration of surgery were associated with an increase in the number of posterior adhesions. Other factors which were associated with posterior uterine adhesion formation included race (African Americans were more likely to form adhesions), percent change in hematocrit, and use of a scalpel rather than lasers or electro-surgical devices to incise the uterus. On the anterior uterine surface, duration of

H11

surgery and length of uterine incisions were predictive of adhesion formation. Controlling appropriately for these factors did not abrogate the treatment effect of HAL-F™. Of note, the use of GnRH agonists which have been reported to reduce adhesions in animal models did not affect adhesion formation in HAL-F™ or nontreatment patients.

A particularly important measure in this study was the frequency with which adhesions formed to the adnexa from the uterus. The proportion of patients with adnexal adhesions adherent to the posterior uterus was significantly reduced in the HAL-F™ group, (p=0.0400).

X. CONCLUSIONS DRAWN FROM THE STUDY

Valid scientific evidence from four well-controlled investigations has been presented in this Premarket Approval (PMA) to support the reasonable safety and effectiveness of Seprafilm™ Bioresorbable Membranes. The scientific evidence used to determine safety demonstrates the absence of unreasonable risk of illness or injury associated with the use of the device. In four well-controlled clinical trials, a total of 172 patients who received Seprafilm™. The number and types of adverse events were similar in the treated and control groups. The possibility that the device may be associated with abscesses or other serious adverse events in abdominal surgery will be addressed by a postapproval study. The benefit of the reduction of incidence, extent, and severity of post surgical adhesion formation was significant in patients who received the device as compared to those who did not.

Therefore it is reasonable to conclude that the benefits of the device for the indications studied in the clinical trials outweigh the risk of illness or injury when used in accordance with the directions for use.

XI. PANEL RECOMMENDATION

At an advisory meeting held on March 25, 1996, the General and Plastic Surgery Panel recommended that Genzyme's PMA for the Seprafilm™ Bioresorbable Membrane



XII. CDRH DECISION:

CDRH concurred with the General and Plastic Surgery Panel's recommendation of March 25, 1996, and issued a letter to Genzyme, on April 24, 1996, advising that its PMA was approvable subject to Genzyme amending the product labeling and submitting a protocol for a postapproval studies.

The approvable letter from the FDA requested the following:

In addition, the applicant was asked to provide:

1. a discussion of the gender differences related to the effectiveness of Seprafilm™
2. a discussion of the likelihood and potential effects of device migration
3. a discussion and explanation of the fact that Seprafilm™ is not completely effective at the location it is placed.

In amendments received by FDA on June 17 and June 25, 1996 Genzyme submitted the requested data.

FDA issued an approval order on 8/12/96. The sponsor's manufacturing facilities were inspected between 1/26/96 and 3/4/96 and was found to be in compliance with the device Good Manufacturing Practice regulations.

XIII. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

43

XIV. Bibliography

Anderson, J.M. *Inflammatory Response to Implants*. Transactions -American Society for Artificial Internal Organs, 1988. 34: 101-107.

Burns, J.W., S. Cox, and A.E. Walts. *Water Insoluble Derivatives of Hyaluronic Acid: United States Patent Number 5,017,229*. 1991.

Ellis, H. *Prevention and Treatment of Adhesions*. Infections in Surgery, 1983. (November): 803-817.

Hakim, R.M. *Clinical Sequelae of Complement Activation in Hemodialysis*. Clinical Nephrology, 1986. 26(1): S9-S12.

Johnson, R.J. *The Design of Cellulosic Based Membranes That Do Not Activate Complement*. Medical Progress Through Technology, 1989. 15: 77-81.

Shimanuki, T., K. Nishimura, F.J. Mantz, R.M. Nakamura, and G.S. diZerega. *Localized Prevention of Postsurgical Adhesion Formation and Reformation with Oxidized Regenerated Cellulose*. Journal of Biomedical Materials Research, 1987. 21: 173-185.

Yarali, H., B.F.H. Zahradka, and V. Gomel. *Hyaluronic Acid Membrane for Reducing Adhesion Formation and Reformation in the Rat Uterine Horn*. Journal of Reproductive Medicine, 1994. 39(9): 667-670.

44

SEPRAFILM™ BIORESORBABLE MEMBRANE
(Chemically Modified Sodium Hyaluronate/Carboxymethylcellulose
Absorbable Adhesion Barrier)

Reorder No. 4301-02

SEPRAFILM™ BIORESORBABLE MEMBRANE

DESCRIPTION:

Seprafilm™ Bioresorbable Membrane is a sterile, bioresorbable translucent adhesion barrier composed of two anionic polysaccharides, sodium hyaluronate (HA) and carboxymethylcellulose (CMC). Together, these biopolymers have been chemically modified with the activating agent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC).¹ Seprafilm™ should be stored between 36 - 86°F (2 - 30°C) until the package expiration date.

INDICATIONS:

Seprafilm™ Bioresorbable Membrane 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.

ACTIONS:

Seprafilm™ Bioresorbable Membrane serves as a temporary bioresorbable barrier separating apposing tissue surfaces. The physical presence of the membrane separates adhesiogenic tissue while the normal tissue repair process takes place. When applied as directed Seprafilm™ membrane can be expected to reduce adhesions within the abdominopelvic cavity. Approximately 24 to 48 hours after placement, the membrane becomes a hydrated gel that is slowly resorbed within one week. Components are excreted in less than 28 days.

YH

CONTRAINDICATIONS:

There are no known contraindications for the use of Seprafilm™ Bioresorbable Membrane.

WARNINGS:

Seprafilm™ Bioresorbable Membrane is supplied sterile and must not be re-sterilized.

PRECAUTIONS:

The safety and effectiveness of Seprafilm™ Bioresorbable Membrane in combination with other adhesion prevention products and/or in other surgical procedures not within the abdominopelvic cavity have not been established in clinical studies.

The safe and effective use of Seprafilm™ in pregnancy has not been evaluated. No clinical studies have been conducted in pregnant women or women who have become pregnant within the first month after exposure to Seprafilm™ Bioresorbable Membrane. Therefore, this product is not recommended for use during pregnancy and avoidance of conception should be considered during the first complete menstrual cycle after use of Seprafilm™ membrane.

Foreign body reactions may occur with Seprafilm™ membrane, as with any implanted material, although none were identified during the Seprafilm™ membrane clinical trials.

The safety and effectiveness of Seprafilm™ Bioresorbable Membrane has not been evaluated in clinical studies in the presence of frank infections in the abdominopelvic cavity. Seprafilm™ did not promote the growth of test microorganisms within the abdominal cavity in animal studies.

The safety and effectiveness of Seprafilm™ Bioresorbable Membrane has not been evaluated in clinical studies in the presence of malignancies in the abdominopelvic cavity.

yle

In clinical studies of Seprafilm™, a maximum of four membranes per patient were used. The safety and effectiveness of implanting more than four membranes has not been evaluated in human subjects. Animal safety studies have been conducted with the human equivalent of ten membranes without evidence of toxicity.

Long-term clinical outcomes such as chronic pain, infertility and small bowel obstruction have not been determined in clinical studies.

ADVERSE EVENTS:

Seprafilm™ Bioreosorbable Membrane has been studied in four clinical trials involving 342 patients. Two safety studies enrolled a total of 32 patients and two pivotal studies enrolled a total of 310 patients. One of the pivotal studies enrolled ulcerative colitis and familial polyposis patients undergoing colectomy followed by ileal pouch anal anastomosis with temporary ileostomy and the other enrolled uterine myomectomy patients. No statistically significant differences were observed in the incidence of adverse events, serious or non-serious, comparing 172 Seprafilm™ treated patients and 170 control patients for a period up to 53 weeks after the initial surgery. A summary of all serious adverse events occurring the pivotal trials are provided in the table below.

47

**SUMMARY OF SERIOUS
ADVERSE EVENTS IN CLINICAL TRIALS
COLECTOMY/ILEAL POUCH ANAL ANASTOMOSIS PATIENTS**

Event Description	Percentage of Seprafilm™ Membrane Patients With Event n=91	Percentage of Control Patients With Event n=92
Small Bowel Obstruction	9%	10%
Abscess	8%	2%
Generalized signs and symptoms - nausea/vomiting/diarrhea	4%	5%
Pulmonary Embolus	4%	0%
Deep Vein Thrombosis	2%	1%
Ileus	2%	1%
Fever	2%	0%
Adrenal Insufficiency	2%	0%
Sepsis	1%	1%
Myocardial Infarction/Death	1%	0%
Pancreatitis	1%	0%
Mesenteric Thrombus	1%	0%
Hepatotoxicity	1%	0%
Ventricular Arrhythmia	1%	0%
Large Blood Clot/Rectum	0%	1%
Urinary Retention	1%	0%
Dehydration	0%	1%
Pouchitis	1%	0%
Rectovaginal Fistula	0%	1%

Statistical difference between Seprafilm™ and the control group (p>0.05)

48

**SUMMARY OF SERIOUS
ADVERSE EVENTS IN CLINICAL TRIALS
MYOMECTOMY PATIENTS**

Event Description	Percentage of Seprafilm™ Membrane Patients With Event n=59	Percentage of Control Patients With Event n=68
Ileus and Fever *	2%	0%
Fever-blood typing error	2%	0%
Laparoscopy converted to Laparotomy	0%	1%
Intraabdominal bleeding	0%	1%
Atelectosis and Ileus	0%	1%
Postoperative Fever	0%	1%

* Due to retained laparotomy pack

Statistical difference between Seprafilm™ and the control group (p>0.05)

There were no unanticipated adverse events reported in either trial.

Almost 90% (n = 39) of all serious adverse events reported in Seprafilm™ treated patients and nearly 81% (n = 22) of those reported in control patients occurred during the trial which required colectomy followed by ileal pouch anal anastomosis (IPAA). The frequency of serious adverse events during the uterine myomectomy study was 3% (n = 2) in the Seprafilm™ group and 4% (n = 4) in the control group.

DIRECTIONS FOR GENERAL USE:

1. Seprafilm™ membrane should be applied immediately prior to abdominopelvic cavity closure following laparotomy.
 2. Membrane must be kept dry prior to application.
 3. The surgical field, especially desired site of application, should be as dry as possible. Thoroughly aspirate excess fluid.
 4. Open the trilaminar pouch immediately prior to application and drop the interior sterile polyolefin sleeve containing Seprafilm™ on the dry sterile field.
-

-
5. Remove the holder containing Seprafilm™ from the polyolefin sleeve.
 6. Where applicable, cut membrane and holder with scissors to desired size and shape.
 7. The membrane should be handled gently with dry instruments and/or gloves.
 8. Expose 1-2 cm of the membrane through the open end of the holder.
 9. When necessary, facilitate entry into abdominopelvic cavity by slightly curving or arching the membrane/holder.
 10. When applying, avoid contact with tissue surfaces until directly at site of application. If contact occurs, moderate application of standard irrigation solution may be used to gently dislodge membrane from unintended tissue surfaces.
 11. Allow exposed membrane to first adhere to desired position on the tissue or organ by gently pressing the membrane down with a dry glove or instrument and then withdraw the holder.
 12. Extend membrane sufficiently beyond the margins of incision and associated surgical trauma to achieve adequate coverage.
 13. When necessary lightly moisten membrane with standard irrigation solution to facilitate its coverage around the contours of tissues or organs.
 14. Allow sufficient overlap of individual membranes to ensure complete, continuous coverage of traumatized tissue surface.

AFTER PLACEMENT:

1. Discard holder(s) following application.
 2. Care should be taken not to disturb the membrane once it is placed on the tissue.
 3. Do not suture the membrane in place.
 4. Abdominopelvic cavity should be closed according to the standard technique of the surgeon.
-

JD

HOW SUPPLIED:

Seprafilm™ Bioresorbable Membrane is available as a 5" x 6" (12.7 x 15.2 cm) single packaged membrane. It is packaged in a holder within an inner sleeve and an outer trilaminate pouch. This packaging is sterilized by gamma radiation. Seprafilm™ membrane is supplied in a envelope carton.

Seprafilm™ Bioresorbable Membrane should be stored between 36 - 86° F (2 - 30° C).

CAUTION:

Federal law restricts this device to sale by or on the order of a physician.

CLINICAL STUDIES:

Multicenter safety studies have been performed in abdominal and gynecological surgical procedures enrolling a total of 32 treatment and control patients. No serious adverse events were definitely attributed to the use of Seprafilm™ Bioresorbable Membrane in these studies. Vital signs and laboratory values showed no clinically relevant differences between treatment and control groups.

A randomized, masked, multicenter clinical study involving 183 patients was conducted to evaluate the safety and effectiveness of Seprafilm™ Bioresorbable Membrane in ulcerative colitis and familial polyposis patients undergoing abdominal surgery. Seprafilm™ membrane was applied directly on the omentum and bowel to separate tissues from the overlying abdominal wall and midline incision. Patients enrolled were undergoing major abdominal surgery involving colectomy followed by ileal pouch anal anastomosis and formation of a temporary loop ileostomy. During the ileostomy closure several weeks later, the incidence, extent, and severity of adhesions to the midline incision were evaluated.

In the abdominal study, the incidence of adhesions to the area of membrane use, the midline incision, was 94% (n = 85) in control patients and 49% (n = 42) in patients treated with Seprafilm™ (p<0.0001). An absence of adhesions was observed in 51% (n = 43) of patients treated with Seprafilm™ and 6% (n = 5) of control patients. The mean extent of adhesions (percentage of the incision length involved) among Seprafilm™ patients was 23% (n = 85) compared to 63% (n = 90) in the control group (p<0.0001). A comparative analysis of the severity* of adhesions demonstrated the presence of dense adhesions occurring in 58% (n = 52) of the control group and in 15% (n = 13) of the Seprafilm™ group. Overall, the adhesions in the Seprafilm™ group were significantly less severe than in the control group (p<0.0001).

A second randomized, masked, multicenter clinical study involving 127 women was conducted to evaluate the safety and effectiveness of Seprafilm™ Bioresorbable Membrane on serosal tissue and pelvic organ structures deep in the pelvis in patients undergoing gynecologic surgery. Seprafilm™ was applied to the anterior and posterior surfaces of the uterus following a myomectomy via laparotomy. Postoperative adhesion formation was evaluated during a second-look laparoscopy performed an average of 23 days later. The incidence of adhesions to the uterus (number of abdominopelvic locations adherent to the uterus) in patients treated with Seprafilm™ was 4.98 (n = 49) compared to control values of 7.88 (n = 48) (p<0.0001). The severity** of adhesions was reduced from 2.43 (n = 65) in the control group to 1.94 (n = 54) in the Seprafilm™ group (p<0.01). Reduction in extent scores from 1.68 (n = 65) to 1.23 (n = 54) (p<0.01) were also demonstrated in the control and Seprafilm™ groups, respectively. The area of uterus associated with adhesions was reduced from 18.72 (n = 54) to 13.23 (n = 65) in the patients treated with Seprafilm™ versus control patients (p<0.02). The portion of patients with adnexal adhesions to the posterior uterus was reduced from 69% (n = 45) to 52% (n = 28) in patients with Seprafilm™ compared to control patients (p<0.05).

* Severity is defined as: (1) Filmy thickness, avascular; (2) moderate thickness, limited vascularity; or (3) dense thickness, vascularized

** Severity is defined as: (0) No adhesions present; (1) filmy avascular; (2) some vascularity; (3a) cohesive, falls apart upon touch; (3b) cohesive, visible dissectable planes and can be separated with minimal dissection; or (3c) cohesive, no visible dissectable planes and requires extensive dissection for separation

52