



**Final Review Memorandum:
Evarrest™ Fibrin Sealant Patch
OBE/DE Review for Pharmacovigilance Planning**

BLA STN 125392
Evarrest Fibrin Sealant Patch
Omrix

Date: August 27, 2012

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1. Introduction

Submission type: Class 2 Resubmission of Original BLA
Complete Response letter sent September 11, 2011
Action Due Date: 30 Sept 2012

OBE/DE has completed a review of the pharmacovigilance plan for Biological Licensing Application STN 125392, **EVARREST™** Fibrin Sealant Patch. The purpose of this review is to identify potential safety issues that may need to be addressed through post-market safety monitoring, studies, or other pharmacovigilance activities, should the product be approved.

2. Product Background

EVARREST™ Fibrin Sealant Patch is a yellow white bioabsorbable product made from a combination of a flexible matrix, coated with two human plasma derived proteins. The matrix component consists of an oxidized, regenerated cellulose backing, under a layer of polyglactin 910 non-woven fibers. This provides physical support for the biological

components, imparts mechanical integrity and supports clot formation. The Matrix components are well-known biomaterials found in medical devices ---b(4)----- and have a long history of safe clinical use.

The biological components contain the biologically active ingredients Human Fibrinogen and Human Thrombin. On contact with a bleeding wound surface, the biological components hydrate and the fibrinogen-thrombin reactions initiate the clot formation in the usual cascade. The manufacturing procedures include processing steps designed to reduce the risk of viral transmission.

1. Human Fibrinogen undergoes solvent-detergent (SD) treatment ----b(4)----- and pasteurization (----(b)(4)----).
2. Human Thrombin undergoes SD treatment ----b(4)----- followed by nanofiltration.

Additional inactive ingredients are: arginine hydrochloride, calcium chloride, glycine, human albumin, mannitol, sodium acetate, sodium chloride and, sodium citrate.

The non-active side of the matrix has an embossed wave pattern, to distinguish it from the active side.

EVARREST™ Fibrin Sealant Patch is indicated as an adjunct to hemostasis for soft tissue bleeding for **Mild to Moderate bleeding** during retroperitoneal, intra-abdominal, pelvic and non-cardiac thoracic surgery when control of bleeding by standard surgical techniques proves ineffective or impractical.

Contraindications include use in cases of severe bleeding from defects in large arteries or veins, where injury to vascular wall requires repair and maintenance of vessel patency. Persistent exposure of Fibrin Patch to blood flow and pressure during healing and absorption of the product is not advised. Intravascular application of Fibrin Patch may result in life-threatening thromboembolic events.

It is not advised to use in individuals who have had anaphylactic reactions to human blood products or other components of the Fibrin Patch. It is not advised for use in infected tissue.

The quantity to be applied is dependent on the size and location of the site to be treated. The patch should cover the entire target bleeding site, with overlap of 1 to 2 cm as necessary. Manual pressure should be applied for 3 minutes. The use of more than four 4 x 4 units, or the use in patients who have been previously exposed, has not been studied.

The pharmacology of Fibrin Patch has been studied in a number of animal models. Fibrin Patch was evaluated in vascular repair models to evaluate usefulness in primary and permanent repair or large defects in large vessels. In this scenario, Fibrin Patch is exposed to persistent blood flow and high pulse pressure. In these models, early and late

failures, pseudo-aneurysm and emboli were observed. The conditions under which these were observed were beyond the intended indication.
(BLA module 2.2)

3. Clinical Safety Data

A total of 229 subjects have been treated with Fibrin Patch during three completed clinical studies. Each subject was treated during a single surgical procedure. This population is referred to as the **Integrated Safety Set**.

Study # 400-07-002

A Prospective, Randomized, Controlled Superiority Evaluation of Fibrin Patch as an adjunct to Control Soft Tissue Bleeding during Abdominal, Retroperitoneal, Pelvic, and Thoracic Surgery

This was a randomized, controlled, clinical study to evaluate the superiority of Fibrin Patch compared to SURGICEL® as an adjunct to hemostasis when conventional methods were ineffective or impractical.

Subjects were randomized in a 2:1 fashion, 2 Fibrin Patch:1 SURGICEL®. Surgery was performed using standard of care, except that use of other fibrin sealants or topical thrombin was not permitted.

A total of 90 subjects were enrolled into the randomization phase of the study, 60 treated with Fibrin Patch and 30 treated with SURGICEL®. SURGICEL® is an absorbable hemostatic adjunct to surgery made of oxidized regenerated cellulose. An additional 51 subjects were enrolled in the non-randomized phase and treated with Fibrin Patch.

The safety analysis set is comprised of 141 subjects, of whom 111 were treated with Fibrin Patch and 30 with SURGICEL®. The incidence of subjects who experienced at least one adverse event was comparable between groups: 94.6% (105/111) in the FP group and 90% (27/30) in the SURGICEL group. The incidence of serious adverse events was lower in the Fibrin Patch group than in the SURGICEL® group, 36% (40/111) versus 83.3% (25/30) for the SURGICEL® group.

Serious adverse events that were related or possibly related to the study product were experienced by 3/111 (2.7%) in the Fibrin Patch group and 2/30 (6.7%) in the SURGICEL® group. One subject randomized to FP experienced a serious adverse event of intraluminal GI hemorrhage and one non-randomized Fibrin Patch subject experienced operative hemorrhage. Both events were assessed as possibly related to treatment. One additional non-randomized fibrin patch subject experienced 4 events assessed as possibly related to treatment (ascites, infected pancreatic fluid, suspected pulmonary embolism and deep vein thrombosis). Imaging studies failed to confirm DVT or PE.

The most frequently reported AE was metabolism and nutritional disorders.

Hypomagnesemia was the most frequently reported event in this study, occurring in 41.8% of subjects overall. This can be easily corrected with repletion of magnesium, and did not lead to other adverse events.

Seven deaths occurred during the study. 6 were in the Fibrin Patch group (6/111 or 5.4%) and 1 was in the SURGICEL group (1/30 or 3.3%). One case was assessed as possibly being related to study treatment. This event was massive intraluminal GI bleed

in a subject who had undergone Whipple pancreaticoduodenectomy. In 5 cases, the event was assessed to be possibly related to the surgical procedure.

All AEs were evaluated for possible relationship to thrombosis. The overall incidence of potential thrombotic events in the Fibrin Patch group was 7.2% compared to 6.7% in the SURGICEL® group.

6/111 of these events were venous thromboemboli and 2 were arterial events. Both cases in the SURGICEL group were venous thromboemboli.

This study was conducted in 11 US institutions.

(Module 5.3.5.1)

Study # 400-08-002

Phase III Randomized, Controlled Superiority Study Evaluating the Fibrin Patch versus Standard of Care treatment in controlling severe, soft tissue bleeding during abdominal, retroperitoneal, pelvic and thoracic surgery

This was a randomized, controlled superiority study to evaluate the effectiveness of Fibrin Patch compared to Standard of Care techniques to control severe soft tissue bleeding during abdominal, retroperitoneal, pelvic and thoracic surgery.

Subjects who met eligibility criteria were randomized in a 2:1 fashion Fibrin Patch vs. Standard of Care Control. A total of 91 subjects were randomized into the study. 59 were treated with Fibrin Patch, 32 were treated with Standard of Care.

The control group was to be treated with the surgeons' standard of care methods.

Standard of care was initiated with continuous manual pressure with or without gauze or sponge, and with or without topical absorbable hemostat.

The primary efficacy endpoint was the proportion of subjects achieving hemostasis at the bleeding site at 4 minutes after randomization with no re-bleeding requiring treatment at any time prior to wound closure.

Safety variables included incidence of adverse events potentially related to bleeding at the bleeding site, incidence of adverse events potentially related to thrombotic events and incidence of adverse events.

The percentage of subjects who experienced at least one adverse event was comparable between treatment groups. 98.3% (58/59 subjects) in the Fibrin Patch group experienced an adverse event as compared to 100% (32/32) in the standard of care group.

The percentage of subjects who experienced at least one serious adverse event was lower in the fibrin patch group than in the standard of care group. 25.4% (15/59 subjects) in the fibrin patch group and 31.3% (10/32 subjects) experienced a severe adverse event. The proportion of subjects experiencing severe adverse events was also lower in the fibrin patch group; 22.0% (13/59) versus 28.1% (9/32).

Adverse events that were considered to be related or possibly related to the study product were experienced by 5/59 subjects in the fibrin patch group (8.5%) and 1/32 subjects in the control group (3.1%).

The most frequently occurring type of adverse event was gastrointestinal disorder.

Within this class, nausea and constipation were the most frequently reported, occurring in 53.8%. Vomiting, pain, pyrexia and hypotension were also commonly reported, occurring in more than 20% of subjects.

Adverse events were assessed for the potential relationship to re-bleeding and to determine if they were potential thrombotic events. Two thrombotic events occurred in the fibrin patch treated group (3.4%) and one in the standard of care group (3.1%). Seven deaths occurred during the study. Four were in subjects treated with fibrin patch (6.8%) and three in the standard of care group (9.4%). One subject from the fibrin patch group died from gastric aspiration due to ileus. This was assessed by the investigator as possibly related to study treatment. In all other cases, the terminal event was not assessed as having a causal relationship to the study product. No safety concerns were identified by the study. The AE and SAE and mortality profiles in this study were considered by the investigators to be what would be expected following long surgical procedures in the treated population.

This study subjects from 15 centers in the UK, Germany, Australia and New Zealand. (Module 5.3.5.1)

Study 400-10-001

A Phase III Randomized, Controlled, Superiority Study Evaluating the Fibrin Patch Versus Standard of Care Treatment in Controlling Parenchymal Bleeding During Elective Hepatic Surgery

This was a randomized, controlled, superiority, study evaluating the effectiveness of the Fibrin Patch (FP) compared with Standard of Care (SoC) methods utilized to control bleeding in hepatic parenchyma for which standard methods of achieving hemostasis were ineffective, impractical or inappropriate.

One hundred and four (104) subjects were included in the study. Twenty (20) non-randomized subjects were treated with FP during the run-in phase of the study. The Safety Set therefore consists of 59 subjects treated with FP and 45 subjects treated with Standard of Care. The Intent To Treat Set, defined as all randomized subjects (with treatment defined by planned treatment), consisted of 40 FP subjects and 44 Standard of Care subjects.

The percentage of subjects who experienced at least one Adverse Event was comparable between the treatment groups. 94.9% (56/59) subjects in the FP group and 95.6% (43/45) subjects in the SoC group experienced an adverse event.

The percentage of subjects experiencing at least one serious adverse event was slightly higher in the Fibrin Patch group. The incidence rates were 27.1% (16/59) in the Fibrin Patch group and 22.2% (10/45) in the Standard of Care group.

Adverse events considered to be related to the study product were experienced by 3/59 subjects (5.1%).

The most frequent adverse event by SOC was gastrointestinal disorders, with nausea, constipation and vomiting the most frequently occurring.

A statistically significant increase bleeding parameters of PT and INR was observed between Screening and Discharge in the Fibrin Patch group. These changes were not considered to be clinically relevant. The most common adverse event in clinical trials was an increased fibrinogen level, which occurred in 1.2% of subjects.

Fibrinogen was elevated at discharge in both treatment groups. One thrombotic event occurred in the FP group, and two occurred in the SoC group.

The event in the Fibrin Patch group was a pulmonary embolism, and the events in the Standard of Care group were vena cava thrombosis and portal vein thrombosis. The study was conducted at 10 institutions in the UK, Germany, The Netherlands, Australia, and New Zealand. No deaths occurred in the study.
(BLA 5.3.5.1.3)

Study # FL-PN-001-IS

Study FL-PN-001-IS was a phase I study during which Fibrin Patch was used as an adjunct to hemostasis in addition to conventional surgical methods in partial nephrectomy. 10 subjects were included.
(5.3.5.2)

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-----b(4)-----

Both Studies FL-PN-001-IS and -b(4)----- were conducted in Israel. These studies were not included in the analysis for safety.

Data from studies **400-07-002**, **400-08-002**, and **400-10-001** have been integrated into the **Integrated Safety Set**.

The combined population from these three studies is referred to as the **Integrated Safety Set** and does not include the 10 subjects included in non-randomized Phase I study FL-PN-001 IS, in which Fibrin Patch was used as an adjunct to hemostasis in partial nephrectomy, nor the data from ---b(4)-----

All subjects included in the five studies of Fibrin Patch were adults. The majority of subjects were in the age range of 50 to 64 years. The overall population in the Integrated Safety Set was predominantly male and of white/Caucasian race and approximately 70% in each treatment group had a body mass index (BMI) defined as overweight, obese, or morbidly obese.

A total of 1,771 AEs were reported in 229 subjects receiving treatment with Fibrin Patch and 1,038 AEs in 107 subjects receiving control treatment in the Integrated Safety Set. Of the 229 subjects in the Integrated Safety Set who were treated with Fibrin Patch, 219 (95.6%) experienced at least one serious or severe AE. A total of 212/229 (92.6%) subjects treated with Fibrin Patch experienced at least one AE that required medical, surgical, or other action, and 11/229 (4.8%) experienced an AE that was judged to be possibly related or related to study treatment. The most frequently occurring type of AE by SOC was Gastrointestinal Disorders and within this class, nausea was the most frequently reported event, occurring in 47.0% of subjects overall. Other commonly reported events (in decreasing order of frequency) were pyrexia, hypotension, constipation, pain, hypomagnesemia, hypokalemia,

and anemia which all occurred in more than 20% of all subjects. Clinically significant increases in fibrinogen levels were reported as possibly related to treatment in 3/59 subjects (5.1%) treated with Fibrin Patch and 1/32 subjects (3.1%) treated with Standard of Care; all 4 subjects were treated in the same center. In the Integrated Safety Set, potential venous thromboembolic events (VTE) were reported in 8/229 subjects (1.7%) treated with Fibrin Patch, as compared to 4/107 subjects (3.7%) treated with control methods. (BLA 2.7.4)

4. Post-market Experience

There is no post-market experience with this product, as it has not been marketed in any country. The projected forecast for product usage in the first year after licensure is up to –b(4)--- 4 x 4 in. (10.2 cm x 10.2 cm) Fibrin Pad units.

5. Pharmacovigilance Planning

When a new product is marketed, the exposed population may differ from the population studied in pre-approval trials.

For most products, routine pharmacovigilance (i.e., compliance with applicable postmarket reporting requirements under FDA regulations) is sufficient for post-marketing risk assessment. As outlined in Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (<http://fda.gov/CDER/guidance/63590CC.htm>), FDA believes pharmacovigilance plans may be appropriate when: 1) Serious safety risks have been identified pre- or post-approval, or 2) at risk populations have not been adequately studied. The pharmacovigilance plan is developed by a product's sponsor and is specifically focused on detecting new safety risks and/or evaluating already identified safety risks.

Clinical Trial Safety Assessment

Theoretical potential risks identified prior to the clinical development program were:

- Re-bleeding at the site of application
- Thrombotic Events
- Immunogenicity of the biological components
- Rare occurrence of severe anaphylaxis, especially if the preparation is applied repeatedly, or administered to patients with known hypersensitivity to the constituents of the product
- Antibodies to any components of the product may form. Adverse events that could be attributed to immunogenicity include allergic reactions or anaphylactic reactions.
- Medicinal products prepared from human blood or plasma may carry a risk of transmitting infectious agents such as viruses, and could theoretically transmit Creutzfeldt-Jakob disease. This risk has been minimized by screening plasma donors for prior exposure and by inactivating and removing infectious agents during the manufacturing process.

- Some viruses, such as Parvovirus B19 are particularly difficult to remove or inactivate. Parvovirus B19 seriously affects pregnant women, immunocompromised individuals, or individuals with hemolytic anemia.
- The Matrix may swell during use. If used in, around, or in proximity to foramina in bone or areas of bony confine, this presents a potential risk of nerve compression.
- The matrix components should be used with caution in contaminated areas of the body, and in common with other topical hemostatic devices, should not be used in the presence of active infection.

These potential risks were specifically evaluated during **Study 400-07-002, Study 400-08-002 and Study 400-10-002.**

Immunogenicity

Immunogenicity of the biological components was assessed by assaying plasma samples collected at baseline and 4 to 6 weeks and 8 to 10 weeks after treatment.

The antibody response to Human Thrombin and Fibrinogen was evaluated in patients treated with Fibrin Patch or Surgicel during study 400-07-002. Samples from 99 subjects treated with Fibrin Patch and 22 subjects treated with Surgicel were analyzed. 2% of the Fibrin Patch treated group had a slight increase in antibody response to Human Thrombin. The 2% rate of change in the detection signal of antithrombin antibodies was well within the expected rate reported in the literature after treatment with Human Thrombin. At the four week post-treatment mark, neither group had abnormal coagulation parameters. No response to Human Fibrinogen was detectable. There is no data available about re-exposure. Experience with the biological and matrix components of Fibrin Patch does not suggest any potential for overdose. However, this has been included as a potential risk.

Adverse Events Identified as Potentially Related to Fibrin Patch during Clinical Studies

During Study 400-07-002, six AE's in 3/111 subjects were identified as being possibly related to study treatment. One subject developed GI hemorrhage, thought to be possibly related. The subject had undergone a Whipple pancreatico-duodenectomy and subsequently developed massive GI bleeding. This was determined to not have been from the target bleeding site, but causal relationship could not be ruled out. One subject developed ascites, infected pancreatic fluid, deep vein thrombosis and suspected pulmonary embolism, thought to be possibly related. DVT and PE were based on clinical assessment at the bedside, but Duplex scanning of the lower extremities and CT scan were negative for DVT and PE. One subject developed operative hemorrhage, thought to be possibly related. The principal investigator confirmed that the event was related to the surgical procedure and occurred at a site other than the TBS. However, it was reported as a potential bleeding site re-bleed.

Thrombotic and thromboembolic Adverse Events

Fibrin Patch was evaluated in vascular repair models for usefulness in --b(4)-----
----- In this scenario, Fibrin Patch is exposed to ---b(4)-----
----- In these models, early and late failures, --b(4)-----
----- The conditions under which these were observed were beyond the intended indication. The results of this study were not included in the final analysis. (Study # --b(4)-----

Evaluation of the safety data showed a random distribution of AE's and SAE's, with the exception of a temporal cluster of thrombotic/thromboembolic events observed during the non-randomized phase of Study 400-07-002 in subjects treated with a single lot of Fibrin Patch.

In the randomized Study 400-08-002, potential thrombosis related serious adverse events were seen in 2/69 subjects (2.9%).

**Other
Potential for Off-Label Use**

Off-Label Use could potentially include:

- -----(b)(4)-----
- -----(b)(4)-----
- -----(b)(4)-----
- -----(b)(4)-----
- -----(b)(4)-----

Pharmacovigilance Planning

Important Identified Risks

Non-clinical data indicate that Fibrin Patch should **not** be used to treat severe bleeding from large defects in large arteries or veins where injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of **EVARREST™** to blood flow and pressure during healing and absorption of the product.

Important Potential Risks

The following important potential risks have been identified for Fibrin Patch:

- Potential risk of thrombotic events
- **Do not apply EVARREST™ intravascularly.** Intravascular applications of EVARREST may result in life-threatening thromboembolic events.
- EVARREST should not be used to treat severe bleeding from large arteries or veins.
- Development of pseudoaneurysm has occurred in these situations.
- Rare occurrence of hypersensitivity/allergic reactions
- Isolated occurrence of severe anaphylaxis, especially if preparation is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product

- Incorrect application could represent a potential risk of lack of efficacy (includes application of the inactive side to bleeding surfaces, application of insufficient patches to adequately cover the bleeding site, or incomplete contact of the product to tissue, wrinkles or folds or displacement of the Fibrin Patch during the surgical procedure.)
- As with all therapeutic proteins, there is the potential for immunogenicity
- There is the possibility of transmitting infectious agents
- Overdose is a possible, but unlikely, risk
- Risk of non-absorption. In animal models, re-absorption occurred after up to 8 weeks

Important Missing Information

- Uncommon or rare events may be missed due to the small size of the population in the clinical trials.
- There is no data available about re-exposure to the product.
- There is no data on pediatric use.

6. Pharmacovigilance Plan

Routine Pharmacovigilance Practices

Omrix Biopharmaceuticals Ltd. operates a routine pharmacovigilance system in accordance with current international regulations and guidelines.

Summary of Planned Actions for Each Safety Concern

1. To supplement the complete instructions for storage, handling, assembly, and use, the following resources will be provided to ensure the proper use of Fibrin Patch:
 - Certified sales specialists will provide an in-service demonstration of the storage, handling and use to the hospital staff and surgeons in accordance with the approved product labeling. Particular attention will be called to the following points:
 - Fibrin Patch is contraindicated for use in the treatment of severe bleeding from large defects in large arteries or veins where the injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of the Fibrin Patch to blood flow and pressure during healing and absorption of the product.
 - Fibrin Patch should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.
 - Physicians will be made aware that allergic reactions, including anaphylactic reaction and/or lack of efficacy events may be related to immunogenicity, and will be instructed to take appropriate medical action and to report such events. Contact numbers for reporting of these events will be provided.

- Physicians will be instructed to follow up on any use in children and to report such use immediately to the distributor/sponsor, including related medical information.
 - Printed and digital training materials for product usage will be made available to physicians. These resources will also emphasize the product contraindications and potential immunogenic risk and the requirement for follow-up of pediatric use.
 - If a physician requests hands-on training on the use of the product in an animal model, he or she may participate in scheduled ETHICON Professional Education programs on the use of adjunctive hemostats and sealants that are held several times per year at training facilities.
 - If physicians become aware of any long-term untoward effects following use of Fibrin Patch, they will be instructed to report them to ETHICON. Contact numbers for reporting of these events will be provided.
2. Proactive literature searches will be conducted at routine intervals to identify any reports of adverse events and/or off-label usage, including pediatric cases.

Omrix Biopharmaceuticals will ensure that all aspects of the pharmacovigilance system are maintained and executed in accordance with the international regulations and local market commitments. This will be accomplished via direct execution of activities and contracting of service providers. Where services are outsourced, there will be agreements in place to outline roles and responsibilities.

- -b(4)----. Will provide case processing/submission of ICSR (Individual case safety reports) and PSUR (Periodic safety update reports) compilation, literature reviews and drug safety database management.
- Ethicon, Inc. (a Johnson & Johnson Company), will provide clinical affairs, medical affairs, pharmacovigilance, sales and marketing distribution, and customer interface support.
- An initial safety report may be sent to OMRIX or directly to -b(4)- pharmacovigilance service provider from any source, such as physicians, pharmacists, literature or non-medical sources. If the report is sent directly to OMRIX, it will be immediately forwarded to -b(4)----- acknowledges receipt, assesses and classifies the report, checks for validity, accuracy, completeness and seriousness. The report is then assigned a number and entered into the global safety database. If expedited reporting is required, a MedWatch report is prepared and sent to the appropriate regulatory authorities within statutory timelines.
- Cases may be closed after the appropriate number of follow-up attempts have been made (at least two at two week intervals for serious cases), and re-opened if additional information is received.
- All relevant case reports and information concerning the safety of the product is described in the PSUR and Annual safety reports.
- Quality Assurance at OMRIX is responsible for the overall management of the -----b(4)--Quality Assurance program. b(4) has a dedicated quality and process training function at the global and regional levels, which

control operating guidelines and ensure the pharmacovigilance functions and procedures are harmonized.
(BLA 1.16)

Non-Routine Plans

Pediatric patients have not been included in studies with Fibrin Patch. A post-marketing pediatric study is planned.

The proposed study design for evaluation of pediatric subjects is of an Open-label randomized, multicenter, active controlled trial to evaluate the safety and efficacy of EVARREST as an adjunct to control mild to moderate bleeding in children from 1 month to less than 16 years of age requiring surgery. A 1:1 randomization is proposed. At least 50 evaluable patients will be included, with at least 25 enrolled subjects less than 9 years of age.

The main inclusion criteria is presence of mild or moderate bleeding in a soft tissue “Target Bleeding Site” identified intra-operatively by the surgeon. The primary endpoint is the absolute time to hemostasis defined as no detectable bleeding at the target bleeding site. The relevant secondary safety endpoints are the hemoglobin, hematocrit, platelet levels, volume of blood loss and use of blood product transfusions, compared to Surgicel (active comparator). The study is to be initiated no later than December, 2013 and completed no later than December, 2016.

Omrix has an ongoing US program to obtain a general adjunct to hemostasis indication, in which immunogenicity information can be obtained. Safety and Efficacy data will also be obtained from the ongoing study under ----b(4)-----

An advice letter sent to Omrix on June 29, 2012 asked for Omrix to submit repeat exposure data in a pre-clinical study.

7. Conclusions and Recommendations

- The Sponsor has submitted a Pharmacovigilance Plan according to ICH E2E guidance. A high number of adverse events were noted in both the Fibrin Patch group and the control group, likely due to the population enrolled. The enrollees had a high rate of obesity, malignancy, and other co-morbidities.

- Available data indicate the potential for a serious risk of thrombotic events and bleeding events. The studies performed had a small number of subjects, most of whom had multiple co-morbidities to place them at increased risk for thromboembolic and bleeding events. For this reason, an additional safety and efficacy study is to be completed, in -b(4)-----

- The sponsor should submit of all reports of thrombotic events and adverse events related to post-surgical adhesion formation, regardless of investigator determination of relatedness, labeling or seriousness. There is no data on pediatric use, and a pediatric study is planned, and outlined above.

- As part of the PVP, the sponsor should submit all reports of thrombotic events and events related to post-surgical adhesion formation, regardless of labeling or seriousness as 15-day reports. 15-Day ‘‘Alert Report’’ for Drugs and Biological Products : A reporter must submit to FDA a report of an adverse experience associated with the use of a drug or biological product that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 days of initial receipt of the information as set forth in §§ 314.80(c)(1) and (e), and 600.80(c)(1) and (e).

- A post-marketing pediatric study is planned and outlined above. The proposed study design is of an Open-label randomized, multicenter, active controlled trial to evaluate the safety and efficacy of EVARREST compared to Surgicel.

- Additional Safety and Efficacy data will be obtained from an ongoing study under ---b(4)--- -----

- At this time, OBE/DE does not recommend additional PMR/PMC studies for immunogenicity or repeat exposure.