

MEMORANDUM



Department of Health and Human Services
Public Health Service
United States Food and Drug Administration
Center for Biologics Evaluation and Research



To: File for BLA (STN 125392/0) and Sondag Kelly, CSO, CBER/OBRR/DBA

From: Natalya Ananyeva, Ph.D., Laboratory of Hemostasis (LH), Division of Hematology (DH)/OBRR

Through: Timothy Lee, Ph.D., Acting Chief, LH/DH/OBRR

Subject: Summary Review of the original BLA for Fibrin Pad (Applicant - Omrix Biopharmaceuticals Ltd., Israel)

This memorandum includes executive summaries and recommendations of the Review Committee members for the original Biologics License Application (BLA), STN 125392/0, for Fibrin Pad, a Biologics-Device combination product, with the proposed proprietary name EVARREST. The application was submitted by Omrix Biopharmaceuticals Ltd. on 19 November 2010. PDUFA Action Due date is 19 September 2011.

Description:

Fibrin Pad is a sterile bio-absorbable hemostatic agent. It is a combination product made from a flexible composite Matrix (Device component) coated with Human plasma-derived Fibrinogen and Thrombin (biological Drug Substances). Fibrin Pad is supplied in units measuring 4 x 4 in. (10.2 x 10.2 cm). The composition is described in terms of Human Fibrinogen, Human Thrombin, and Matrix, as assessed on the Fibrin Pad, per unit area. For Human Fibrinogen, the concentration is 50.3 mg/in² (7.8 mg/cm² measured as -----(b)(4)-----); for Human Thrombin - 203.2 IU/in² (31.5 IU/cm² measured as "Thrombin Activity"); and for Matrix, the content is -----(b)(4)------. The proposed proprietary name is EVARREST. The intended route is direct application onto bleeding tissue during surgery.

In this class of combination Fibrin Sealants, EVARREST is the second product for which Omrix is seeking the US licensure; a similar product, TachoSil from Nycomed (Austria) was approved by FDA under STN 125351/0 in April 2010.

Manufacturers:

Drug Substances – plasma-derived Human Fibrinogen and plasma-derived Human Thrombin are manufactured at -----
------(b)(4)-----

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

The device component of the Fibrin Pad consists of a Matrix made of two absorbable polymers: polyglactin 910 (PG910, a carrier of the biologic components) and oxidized regenerated cellulose (ORC, a backing layer). The Composite Matrix is manufactured by -----
----- (b)(4) -----
----- . Both components are used in other products currently marketed by ETHICON.

The Fibrin Pad is manufactured, tested, and packaged at Omrix Biopharmaceuticals Ltd., Fibrin Pad Production Facility (FPPF; FEI number 3008640339) located at Weizmann Science Park, Nes-Ziona, Israel. Fibrin Pad is the first product manufactured at FPPF for which Omrix is seeking US licensure.

Proposed indication: Fibrin Pad is intended for use as an adjunct to hemostasis for soft tissue bleeding during retroperitoneal, intra-abdominal, pelvic, and (non-cardiac) thoracic surgery when control of bleeding by standard surgical methods of hemostasis is ineffective or impractical.

RECOMMENDATION OF REVIEW COMMITTEE

Complete Response Letter

REVIEW COMMITTEE MEMBERS

RPM:	Sonday L. Kelly	OBRR/DBA/RPMB
RPM:	Mark Shields	OBRR/DBA/RPMB
CMC/Chairperson:	Natalya Ananyeva	OBRR/DH/LH
Consult CMC:	Nancy Kirschbaum	OBRR/DH/LH
DMPQ:	Randa Melhem	OCBQ/DMPQ/BII
DMPQ:	Nancy Waites	OCBQ/DMPQ/BI
Pre-Clinical:	La’Nissa Brown-Baker	OBRR/DH
Clinical:	Kimberly Lindsey	OBRR/DH/CRB
CDRH Consult Clinical:	Roxolana Horbowj	ODE/DSORD/GSDB
Statistics:	John Scott	OBE/DB/TEB
BiMO:	Dennis Cato	OCBQ/DIS/BMB
APLB:	Loan Nguyen	OCBQ/DCM/APLB
OBE:	Faith Barash	OBE/DE/TBSB
DBSQC:	Karen M. Campbell	OCBQ/DBSQC

HISTORY OF REVIEW PROCESS

December 07, 2010	First Committee Meeting
January 03, 2011	Filing Meeting
January 18, 2011	Filing Notification Letter

January 25-27, 2011	BIMO Inspection (Site 022)
January 31, 2011	Deficiencies Identified (DI) Letter
February 23, 2011	Proprietary Name Acceptable Letter (First review)
March 02-15, 2011	BIMO Inspection (Site 011)
March 15, 2011	Amendment 125392/0.3 (Responses to DI Letter)
April 05, 2011	Amendment 125392/0.4 (Reclassification of the air quality Laminar Flow zones in the Fibrin Pad clean room production facility)
April 11-14, 2011	BIMO Inspection (Site 014)
April 20, 2011	Mid-Cycle Meeting
May 05, 2011	Information request (DMPQ)
May 12, 2011	Mid-Cycle Meeting (Clinical)
May 10 – 19, 2011	Pre-License Inspection
May 31, 2011	Information Request (CMC, Pre-Clinical, Clinical)
June 02, 2011	Post-PLI Committee Meeting
June 07, 2011	Amendment 125392/0.5 (Clinical Study Report for completed OUS soft tissue study #400-08-002)
June 24, 2011	Amendment 125392/0.6 (Responses to 05 May 2011 IR)
June 30, 2011	Amendment 125392/0.7 (Responses to 31 May 2011 IR)
July 11, 2011	Clinical Committee Meeting

EXECUTIVE SUMMARY

CMC/PRODUCT

Formulation development studies for optimizing doses of the biological Drug Substances and composition of the Matrix for the Fibrin Pad commercial product are extensive and scientifically valid. The selected dose ranges for Fibrinogen ---(b)(4)--- input dose resulting in the -----(b)(4)----- range of -----(b)(4)----- in the Drug Product) and Thrombin (---(b)(4)--- input dose resulting in the Thrombin Activity range of ----(b)(4)----) are supported by the monitoring of physicochemical parameters and hemostatic performance of the Fibrin Pad in animal models. The selected input doses take into account the losses during the manufacturing process (specifically, for Thrombin) to ensure potency at release to be within the set Specification range. The Specification dose ranges for both Fibrinogen and Thrombin are consistent with dose ranges tested in non-clinical and clinical studies.

The manufacturing changes implemented in the course of Fibrin Pad product development are described in the BLA and are supported by Comparability Reports. All changes were reported to FDA under IND 13563 and have been reviewed and considered acceptable. Specifically, the

input doses for the biological substances were changed from non-clinical to clinical and to commercial material; however, they all remain within the set Specification ranges. Thus, the Specification ranges for Fibrinogen and Thrombin have not been changed throughout product development.

The validation of the Fibrin Pad manufacturing process was conducted by manufacturing (b)(4) consecutive maximal-scale Fibrin Pad batches - -----(b)(4)----- using the -----(b)(4)----- application of Drug Substances to the Matrix and final sterilization by e-beam irradiation within the validated dosage range of -----(b)(4)----- . The in-process testing results and release data were compliant with pre-determined acceptance criteria, for all parameters, reflecting consistency of the manufacturing process. The established -----(b)(4)-----, are appropriately validated.

The manufacturing process is adequately controlled. The implemented controls over the input doses (----- (b)(4) -----) and potencies in the Drug Product (----- (b)(4) ----- Thrombin Activity) minimize the risk of dosing outside of the Specification limits. Analytical procedures are validated for determination of Potency (----(b)(4)---- Thrombin Activity -----(b)(4)-----), Matrix performance (----(b)(4)-----) and Purity (----- (b)(4) -----, Endotoxin, Sterility, and Package Integrity) of the Fibrin Pad Drug Product. The implemented sampling procedure allows for reliable control of coating uniformity of Drug Substances across a Fibrin Pad and across production days.

Available 18-month stability data for Validation batches thus far support the proposed shelf-life of 24 months when stored at 2 to 25°C.

Omrix performed risk assessment of potential immunogenicity of the Fibrin Pad due to exposure of its components to --- (b)(4) --- solvent (--- (b)(4) ---) and e-beam irradiation during the manufacturing process. The 90-day sub-chronic toxicity study in the rat demonstrated toxicological and immunological comparability between Fibrin Pad and the predecessor fibrin sealant, EVICEL. Review of the data collected in the Phase 2 Clinical Study 400-07-002 (with observation period of up to 10 weeks) indicated that the risk of development of a clinically relevant immune response in patients treated with Fibrin Pad is low.

Comparability Reports FLC-001 and QA-R-FP-0015-00 indicated comparability of Fibrin Pad product used in non-clinical and in Phase 1 clinical studies, and of Fibrin Pad product used in the Phase 2 clinical study and in process validation studies. Comparability was demonstrated by analytical parameters and by comparable abilities to achieve hemostasis in animal models. Animal safety data were not completely informative because the observation period was shorter than the time of Fibrin Pad resorption (56 days).

Omrix performed expanded investigation of the manufacturing, analytical and clinical data for the lots L11F284 and M06F164 that were associated with thromboembolic events reported during the Phase 2 Clinical Study 400-07-002 (soft tissue surgery study). No plausible mechanisms were identified that could reasonably account for the reported adverse events.

Recommendation:

From a Product reviewer standpoint, the manufacturing process for the Fibrin Pad is validated and is sufficiently controlled to assure consistent production of the product that meets the set Specifications. The Applicant addressed recommendations made by FDA at the pre-BLA meeting of 1 October 2009, regarding CMC/Product quality. Thus, from a CMC/product quality perspective, ***this BLA can be approved at this time.*** However, there are outstanding issues related to product safety in light of adverse events observed in the Phase 2 Clinical Study 400-07-002.

CMC/FACILITY/PROCESS (DMPQ)

Fibrin Pad is the first product manufactured at FPPF for which Omrix is seeking US licensure. As part of the review process of this BLA, CBER conducted Pre-License Inspection (PLI) of the -----(b)(4)----- Fibrin Pad Production Facility (FPPF; FEI number 3008640339) from May 10 -19, 2011. (b)(4) has been previously inspected by FDA in 2002 and 2009, and this is the first FDA inspection for FPPF. The findings of the PLI are documented in the Establishment Inspectional Report (EIR). Nine objectionable observations were noted on the Form FDA 483 Inspectional Observations for (b)(4), and eight objectionable observations were noted for FPPF.

The firm submitted their initial responses to the 483 Observations on June 9, 2011 (by email), and a subsequent submission (paper copy) received August 19, 2011 which provided a detailed description of the corrective actions taken thus far, and the progress towards completion of the remaining corrective actions to the 483 observations. The responses to the 483 observations were reviewed and not all responses were deemed acceptable as the corrections of several deficiencies identified in the 483 observations have not yet been completed.

Recommendation:

DMPQ ***recommends a Complete Response*** letter since outstanding issues from the Pre-License Inspection have yet to be resolved.

NON-CLINICAL

Non-clinical studies were completed with various lots of Fibrin Pad. A large portion of studies was for biocomparability due to multiple manufacturing changes implemented since the submission of the initial IND 13563 (changes in the manufacturing site for Matrix, method of biologics application, and dose optimization). Absorption pre-clinical studies were completed using earlier versions of the Fibrin Pad product, whereas Phase 1 and Phase 2 clinical studies were performed with the later versions of the investigational product. The CMC reviewer determined, based on review of the Comparability Reports, that the pre-clinical and clinical Fibrin Pad products are comparable. To date, acute dose toxicity (10X pads use simultaneously), local tolerance, degradation (requires additional clinical monitoring), mutagenicity, immunogenicity and efficacy (proof-of-concept) studies in the pre-clinical program have been

submitted for Omrix's Fibrin Pad, EVARREST. In pre-clinical studies that tested the proposed indication for the Fibrin Pad as an adjunct to hemostasis, a number of adverse events were noted including pulmonary embolism formation (uncertain causes), re-bleeding at treatment bleeding site, inflammation (persistent), hemorrhage at wound site, and adhesion formation at treatment bleeding site. It appears that the immune mediated responses following treatment with Fibrin Pad are higher in normal animals versus immunocompromised animals and likely reflect xenogenic reactions. While the hemostatic efficacy of the Fibrin Pad was convincingly demonstrated, the safety profile can not be adequately assessed based on accumulated pre-clinical data. Noteworthy, the same safety concerns (adhesion formation, re-bleeding, thrombotic events, and inflammation) were noted in clinical trials.

There is additional safety concern with subsequent and/or sequential operations resulting in multiple use/chronic use of product that needs to be addressed in a repeat dose toxicity animal study. The study should entail a recovery period, histopathology, hematology and serum chemistry panel, etc. in parallel with ADME (specifically complete absorption) determination in a pre-clinical model as related to *in situ* administration of the fibrin pad in repeat use setting (worst case clinical scenario).

There appears to be another safety concern related to potential carcinogenicity of the Fibrin Pad due to its slow degradation and the long-term presence of the product in situ ($\geq 60+$ days). Therefore, we recommend Omrix assesses the carcinogenic potential of the Fibrin Pad. This can be addressed by completing a longer-term ($> 60+$ days) monitoring and follow-up in clinical trials, ex vivo cell studies and/or a well-powered and controlled study in an animal model. Although Omrix performed a literature search on the carcinogenic potential of PG910 to obviate the need for carcinogenicity studies in animals, Omrix's responses are not concurred by FDA as there is precedence with similar CDRH products.

Recommendation:

Omrix should address outstanding safety concerns related to repeated use of Fibrin Pad and to its potential carcinogenicity. Clinical experience that has been compiled with the use of Fibrin Pad negates the necessity for additional toxicity studies in higher order animals as component of the pre-clinical program. ***The clinical data may be used in lieu of additional pre-clinical data to substantiate the safety profile of the Fibrin Pad*** in the proposed indication to support its US licensure.

CLINICAL

The phase 2 study (400-07-002), evaluating the hemostatic efficacy of the Fibrin Pad (FP) when used as an adjunct to hemostasis in mild or moderate soft tissue bleeding during abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery was a randomized, controlled, study evaluating the superiority of FP compared to Surgicel as an adjunct to hemostasis when conventional methods of control are ineffective or impractical. Main entry criteria included: age greater than or equal to 18 requiring non-emergent abdominal, retroperitoneal, pelvic, or thoracic (non- cardiac) surgical procedures and the presence of an appropriate soft tissue target bleeding site (TBS) as identified intraoperatively by the surgeon.

The primary endpoint of the study was the “proportion of subjects achieving hemostatic success at 4 minutes after randomization with no re-bleeding requiring treatment during a subsequent 6 minute observation period.” Hemostasis was defined as no detectable bleeding at the TBS. The primary efficacy endpoint was met.

FDA had advised the sponsor that study 400-07-002 was not designed to support licensure. In addition, review of the submitted data raised safety concerns with regard to thromboembolic events, adhesions and infections. However, the sponsor concluded that “No safety concerns were identified by the study. The incidence of clinically meaningful AEs (adverse events) was similar in the two treatment groups and the events were of the types that were expected following these major surgical procedures.” There were more fatal events (6) in the FP arm compared to the Surgicel arm (1) and the adverse events in several AE categories (infections (25 vs 10), obstructions (5 vs 0) demonstrated an unfavorable imbalance towards the FP arms. Since the baseline demographics were matched in the two arms, one cannot exclude that the imbalance in AEs was not product-related. The majority of the adverse events can be traced to common product lots and a specific time frame (last quarter of 2008 to January 2009). The sponsor claims to have thoroughly investigated the manufacturing and use of these lots. They were not able to find a manufacturing or investigator use of the products as explanations for the adverse events. FDA facilities and manufacturing inspections did not reveal any differences in production of FP lots that could reasonably account for the specific lot related thromboembolic events.

From review of the operative reports and case report forms one cannot be certain where the FP or Surgicel was applied (other than in general terms such as thoracic muscle). Since the protocol allowed the use of additional FP or Surgicel (according to assigned treatment) if additional bleeding sites were identified, it is important to know the primary site of application to understand if the product might have been placed in a location that predisposed to thrombotic or other adverse events.

Overall this phase 2 study design comports with a preliminary safety and effectiveness assessment for two categories of bleeding (mild and moderate). It is important to note that a lack of validated bleeding severity scale limits assessment of product performance, outcome reproducibility and repeatability.

Additional issues identified from the review of the data submitted from study 400-07-002 include the following:

- Sample size per anatomic site was too small for independent assessment per anatomic site;
- Outcomes of device use (hemostasis) and adverse events may not be poolable across anatomic sites, e.g.: pneumothorax;
- Currently marketed products, vicryl and oxidized regenerated cellulose (ORC) devices, are not explicitly indicated for use at anatomic sites of cancer resection. The use of these materials in patients with active oncologic disease should be studied independently to assess influence of local recurrence and progression of oncologic disease, as well as survival.
- The follow up period of the subjects should have been 60 days as the product is expected to fully resorb in 60 days.

Study 400-07-002 was not designed as a pivotal study. It was permitted to proceed as a Phase 2 exploratory study given the limited (10 patient) prior human experience and preclinical data. The venous thromboembolism (VTE) risk factors, short length of follow up (30 days) and potential thrombotic risk factors suggest that a confirmatory study should be conducted. Based on my review of the clinical data, in order to support an indication for soft tissue surgery for initial US licensure of the Fibrin Pad [EVARREST], an additional study with or without different surgical settings, to include additional safety monitoring, should be requested.

Additionally, in terms of risk-benefit assessment, there is a variety of approved adjuncts to hemostasis currently available, including fibrin sealants such as Tisseel and Evicel, topical thrombins, and devices such as gelfoam. These products effectively address “mild and moderate” types of surgical bleeding and they have proved over time to be generally safe when used within their intended indications. The Fibrin Pad’s potential risks of thrombosis, infection, and adhesions must be weighed against benefits of currently approved or cleared adjunctive hemostats.

Recommendation:

The regulatory option is to send a Complete Response and request data from an additional adequate and well controlled study designed primarily to assess safety in the proposed population. The study should be designed to include a prospective monitoring plan for thrombotic events. Alternatively, the sponsor may submit safety data from an adequate and well controlled study with the Fibrin Pad in a different surgical population.

BIMO

Bioresearch monitoring inspections of three clinical sites for study 400-07-002 have been performed. The three sites enrolled 78 subjects, representing 55 percent of the total enrolled subjects for the study.

Site 011 (R. Adams Cowley Shock Trauma Center, Baltimore, MD) was issued a three-part Form FDA 483 classified as Voluntary Action Indicated. Review of the Establishment Inspection Report and the accompanying exhibits revealed issues with maintaining operation reports, performing procedures not under the investigator’s personal supervision, and deviations from the investigational plan. In particular, for more than a third of subjects, operation reports did not mention the use of the study article. For seven of eight of the subjects involved, the attending surgeon was neither the Clinical Investigator nor a sub-investigator listed on the signed FDA Form 1572 nor the Staff Delegation of Authority and Signature Logs.

There were no inspectional observations issued for Site 014, Medical College of Georgia in Augusta, Georgia. Site 022, University of Alabama, Division of Cardiothoracic Surgery, was issued an inspectional observation that 16 of 32 subjects had dual enrollment.

STATISTICAL

Although the sponsor's study 400-07-002 met its primary efficacy objective, it is not clear that sufficient information has been presented in this submission to support licensure. In favor of the Fibrin Pad, the treatment effect on rate of 4-minute hemostatic success relative to Surgicel in study 400-07-002 was quite large. In the FP group, 59/60 subjects met the primary endpoint, while 16/30 control subjects met the primary endpoint. The study 400-08-002 (in a different but related indication) was performed outside of the U.S. and was not conducted under IND. However, there are serious and inevitable questions of generalizability and reproducibility raised by relying primarily on evidence of effectiveness from a single small Phase 2 study to support product licensure. Furthermore, it is not clear that an adequate safety database has been established to date for FP in the indicated population, particularly given the concerns related to thrombotic events raised in study 400-07-002.

PHARMACOVIGILANCE

The Sponsor submitted a Pharmacovigilance Plan according to ICH E2E guidance. An extremely high number of adverse events were noted in both the Fibrin Pad group and the control group in the study 400-07-002, likely due to the population enrolled. The enrollees had a high rate of malignancy and multiple co-morbidities. The study 400-08-002 fails to add further safety information to the existing data from study 400-07-002 due to a high level of adverse events in both groups. Available data indicate the potential for a serious risk of thrombotic events. The studies performed had a small number of subjects most of whom were at increased risk for thromboembolic events, due to the increased risk from both malignancy and lengthy surgery. There is additional risk of infection, abscess formation and other adverse events. There is no information available regarding re-exposure or the possibility of coagulopathy or thrombosis in light of increased fibrinogen levels detected. Because of the high level of background "noise" in the patient population, it is not possible to confidently identify a true safety signal.

Recommendation:

Should re-application be considered, a well-designed Phase 3 study should be conducted, with a larger study population that is more representative of a general population (with and without co-morbidities and undergoing a variety of surgical procedures) and with prospective monitoring for adverse events.

FINAL RECOMMENDATION

The manufacturing process for the Fibrin Pad at Omrix is adequately validated and is sufficiently controlled. However, a number of outstanding issues identified during the Pre-License Inspection of the Omrix's manufacturing facilities remains to be resolved. The hemostatic efficacy of Fibrin Pad has been convincingly demonstrated in both non-clinical and clinical studies. However, there are outstanding issues related to product safety in light of adverse events (thromboembolic events, inflammation, adhesions, obstructions) observed in the Phase 2 Clinical Study 400-07-002. Study 400-07-002 was not designed as a pivotal study. The information captured on case

report forms and limited operative reports did not permit reviewers to exclude potential association of adverse events with the product use. The available clinical data appear statistically insufficient for generalizing the conclusions. The clinical reviewer's assessment of the BIMO inspections raised concerns regarding conduct of the trial. Together, these factors suggest that the additional safety data from a well controlled study with the use of the Fibrin Pad in the proposed population (or from an adequate ongoing study in a different surgical population) is required in order to meet the criteria for the US licensure of the Fibrin Pad with an indication for soft tissue surgery. In conclusion, the Review Committee recommends a ***Complete Response*** to this BLA.

COMPLETE RESPONSE TO OMRIX:

CMC

1. Outstanding issues from the Pre-License Inspection (PLI) performed on May 10 through May 19, 2011 at -----(b)(4)----- Fibrin Pad Production Facility and detailed in form FDA 483 are not resolved. Please submit documentation that demonstrates that all outstanding inspectional issues identified during the PLI have been corrected.

CLINICAL

2. The review of the submitted data shows an unfavorable trend towards the investigational product (FP) with regard to thrombotic events (TEs). Specifically, our review identifies the following:
 - a. In the non-randomized part of the study 400-07-002, a total of nine TEs were reported in seven subjects of 51 subjects enrolled in the study. As the cluster of TEs was seen in the non-randomized, uncontrolled part of the study, it is not possible to draw a conclusion regarding the association of the investigational product with these AEs.
 - b. Given the lack of sufficient detail regarding operative placement of all investigational products used per patient, it is difficult to conclude with any degree of certainty that the FP did not contribute to the thrombotic events.
 - c. The safety data captured under Protocol 400-08-002 (non-IND study) do not adequately address FDA's concern with regards to the AEs seen in the 400-07-002 because it is unclear if the patients were adequately monitored to capture the TEs.

Therefore, in order to support licensure of Fibrin Pad for use as an adjunct to hemostasis in soft tissue surgery, please submit data from an additional adequate and well controlled study designed primarily to assess safety in the proposed population. The study should be designed to include a prospective monitoring plan for thrombotic events.

Alternatively, you may submit safety data from an adequate and well controlled study with the Fibrin Pad in an ongoing study in a different surgical population.

BIMO INSPECTIONS

3. FDA inspections and monitoring reports reveal issues with regard to conduct of the trial.

a. Please submit detailed information on how all the investigators and sub-investigators were trained to comply with the study requirements.

b. Failure to prepare or maintain case histories with respect to observations and data pertinent to the investigation:

The protocol required that certain Inclusion and Exclusion criteria be determined by the Clinical Investigator during surgery, where study specific procedures, such as randomization and the application of the study drug, are to be performed. Operation Reports for subjects 11104, 11106, 11108, 11109, 11113, 11114, 11115, and 11203, which constitute more than a third of the study subjects at this site, do not mention the use of the study drug during surgery, yet this data was submitted to the Sponsor, as stated in the Soft Tissue Study Worksheets (found in the subject's records) and in the data listings provided by the Sponsor. Please identify and submit the source of the missing information in the Operative Reports that were submitted to the FDA.

c. Failure to comply with 21 CFR 312.61:

Study drug was administered to subjects not under the investigator's supervision or under the supervision of a sub-investigator responsible to the investigator.

Specifically, the Operative Report for subject 11112, dictated by ----(b)(6)---- (not listed in the Statement of Investigator, Form FDA 1572), described the use of the study drug during the surgery but did not mention the Clinical Investigator or Sub-Investigator as being present at any point during the procedure. The Nurse Intraoperative Report also did not list the Clinical Investigator or Sub-Investigator as being present during the surgery. Please explain.

d. An investigation was not conducted in accordance with the investigational plan. Specifically:

i. The protocol states that: "Prior to participation, the study procedures and any known or likely risks will be explained to the subjects by the investigator or other medically qualified co-investigator." In 4 of 18 instances, the study procedures and any known or likely risks were explained to potential subjects (who were eventually enrolled into the study) by Study Coordinators who also signed the Informed Consent Form, when the Clinical Investigator or Sub-Investigator were not available to do so. Except for a letter from the Sponsor dated March 10, 2011, provided to FDA during the inspection by Dr. Bochicchio, a Co-Investigator was not identified anywhere in the protocol as a Study Coordinator or any other study staff member. This letter stated that the term "medically qualified co-investigator" should have been edited as "or designee", yet this was not edited or reviewed and approved by the IRB. Study Coordinators listed in the "Delegation of Authority" for protocol 400-07-002, which was signed by Dr. Bochicchio, are not qualified to practice medicine. Please explain.

- ii. There is no evidence that five members from the research study staff, listed in the “Delegation of Authority” as being Study Coordinators, authorized to obtain Informed Consent, complete Case Report Forms, obtain Medical History and conduct subject follow-up, were qualified and trained on the specifics of the protocol to do so. Please explain.
- e. The “Site Initiation Training” attendance log, dated April 10, 2008, provided by -----(b)(4)-----, at the University of Maryland Medical Center, does not list the following individuals as being present during the site initiation training, yet they are listed in the “Delegation of Authority” (Exhibit 3) for this study: -----(b)(6)-----, Sub-Investigator (attended protocol-specific training on 06/24/2008, but was not present at the site initiation); -----(b)(6)-----, Study Coordinator; -----(b)(6)-----, Study Coordinator; -----(b)(6)-----, Study Coordinator; -----(b)(6)-----, Study Coordinator; and -----(b)(6)-----, Study Coordinator. Please submit all training documentations at this site. Also, please submit documentation to confirm that the above mentioned investigators underwent training.
- f. Sixteen of thirty two subjects were enrolled in another investigational study while participating in Protocol 400-07-002 at University of Alabama, Birmingham, Alabama site and there was no documented evidence of sponsor and/or IRB notification and/or approval to enroll the subjects in concurrent studies. Please submit detailed information on the sponsor/IRB notification and subject consents to participate in another investigational study.

COMPARABILITY PROTOCOL (CP)

- 4. Regarding the validation of the revised manufacturing process for the Fibrin Pad with introduction of an -----(b)(4)-----, please provide the following specific details:

- a. -----
----- (b)(4) -----
-----.
- b. -----
-----(b)(4)-----.
- c. -----
----- (b)(4) -----
-----.
- d. -----
----- (b)(4) -----
-----.

- e. -----

----- (b)(4) -----
-----.
- f. -----
----- (b)(4) -----
-----.
- g. ----- (b)(4) -----
-----:
 i. ----- (b)(4) -----
 ii. ----- (b)(4) -----

5. Regarding Comparability Program for the Fibrin Pad Drug Product:

- a. Please include testing at refrigerated storage conditions (---(b)(4)---) in your stability program for the revised process and continue to use the ----- (b)(4) ----- test and the ----- (b)(4) ----- test until the shelf life is established. Please note that at least ---(b)(4)--- stability data should be submitted in a Prior Approval Supplement for these changes
- b. Please specify statistical methods you plan to use to compare the in-process, release, characterization, and stability data for Fibrin Pad batches manufactured with the revised and current processes. Please provide a definition for “similar” trends in stability indicating parameters.
- c. ----- (b)(4) -----.
- d. Please specify the length of the observation period, parameters to be monitored and pre-determined acceptance criteria in your studies of the functional performance of the Fibrin Pad (revised process) in the non-clinical model. Please note that the observation period should correlate with the period of Fibrin Pad resorption.

Please note that a list of all protocols, validation studies and documents that you intend to provide data for in the executed CP report, have to be included in the CP. In addition, all deviations and investigational reports generated during the execution of the CP should be submitted to FDA in the executed CP report.

As previously discussed with FDA, the data from the executed CP QA-P-FP-0017-00 for introduction of an ----- (b)(4) ----- should be submitted to the FDA for review as a prior approval supplement following approval of the original BLA.