

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 Sonday 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: Final Review of CMC information in the original BLA for Fibrin Pad (Applicant - Omrix Biopharmaceuticals Ltd., Israel)

This memorandum summarizes the Final Review of the CMC information in the original Biologics License Application (BLA), STN 125392/0, for Fibrin Pad, a Biologics-Device combination product, with the proposed proprietary name EVARREST, 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).

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.

This memorandum summarizes the review of the CMC information in the original submission, Omrix's responses to the Information Requests (Amendment 125392/03 dated 15 March 2011 and Amendment 125392/07 dated 30 June 2011) and includes discussions during the Pre-License Inspection of Omrix Biopharmaceuticals, Ltd. (May 10 - 19th, 2011). The memo was drafted on 30 August 2011, revised on 05 September 2011, and the current document is a concurred version.

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 (Omrix) 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.

EXECUTIVE SUMMARY

1. 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 and functional parameters of the Fibrin Pad (analytical data, ---(b)(4)---, coating uniformity, adhesiveness, and hemostatic performance in animal models). The selected input doses take into account the losses during the manufacturing process (specifically, for Thrombin) and ensure Thrombin Activity 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, factoring in the validated manufacturing and analytical capabilities.
2. 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.
3. The validation of the Fibrin Pad manufacturing process was conducted by manufacturing three 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 intermediate hold times, in particular the ----(b)(4)-----, are appropriately validated.
4. The manufacturing process is adequately controlled. The implemented controls over the input doses (----(b)(4)-----) and potencies in the Drug Product (----(b)(4)----- and Thrombin Activity) minimize the risk of dosing outside of the Specification limits. Analytical procedures are validated for determination of Potency (---(b)(4)-----, Thrombin Activity and ---(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 (homogeneity) of Drug Substances across a Fibrin Pad and across production days.

5. The stability studies with Clinical batches are completed. The stability studies with Validation batches are ongoing; available 18-month data for all parameters remain within the Specification, consistent with the proposed shelf-life of 24 months when stored at 2 to 25°C.
6. 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.
7. Comparability Report FLC-001 comparing Fibrin Pad used in non-clinical studies to Fibrin Pad used in Phase I clinical studies indicated their analytical comparability, which was further supported by comparable abilities to achieve hemostasis in a swine acute aortotomy model. Animal safety data were not completely informative because the observation period was shorter than the time of Fibrin Pad resorption (56 days).
8. Comparability Report No. QA-R-FP-0015-00 for Fibrin Pads produced during Process Validation (---(b)(4)---) versus Pivotal* (M06F164) batches demonstrated similar release results (except for higher ----(b)(4)----- in the Validation batch) and improved matrix- and protein-characterizing parameters (----- (b)(4) -----) for the Validation batch. The hemostatic efficacy of Pivotal (Phase 2 Clinical) and Validation batches in a porcine partial nephrectomy model was comparable and without recorded thromboembolic adverse events within a 48-h observation period. The observation period, however, was shorter than the time of Fibrin Pad resorption. Comparability of the Pivotal and Validation batches was also supported by stability data.
9. 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. Therefore, additional clinical safety data will likely be required as determined by the Clinical reviewer.

* Omrix defines Clinical Study 400-07-002 as Pivotal; FDA classifies this Study as a Phase 2 study. The definition “pivotal” is used in this review for consistency with the information in the BLA.

REVIEW SUMMARY

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” on the Fibrin Pad) and for Matrix, the content is ----(b)(4)----- The proposed proprietary name is EVARREST. The intended route of administration is direct application onto bleeding tissue during surgery.

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

3.2.S. HUMAN FIBRINOGEN (BIOLOGICAL DRUG SUBSTANCE)

The design and manufacture of the Fibrinogen and Thrombin biological components complies with the CGMP regulations as specified in 21 CFR 210, 211, and 600 through 680.

Human Fibrinogen Drug Substance is a ----(b)(4)-----
----- Human Fibrinogen is manufactured by Omrix Biopharmaceuticals Ltd., ----(b)(4)-----; FDA Registration Number: ----(b)(4)-----
-----, Israel. ----(b)(4)----- for Human Fibrinogen Drug Substance is manufactured at Omrix Biopharmaceuticals Ltd. from human Source Plasma collected from qualified donors in FDA-licensed facilities or alternatively purchased from ----(b)(4)-----
-----, an FDA-approved supplier (FDA Establishment License Number: (b)(4)). Source Plasma complies with the requirements of 21 CFR Part 640 and applicable FDA memoranda.

The manufacturing process is essentially the same as for ----(b)(4)-----

The manufacturing process includes Solvent/Detergent (S/D) treatment (---(b)(4)-----
-----) and pasteurization step (----- (b)(4)---
-----) for virus inactivation.

3.2.S. HUMAN THROMBIN (BIOLOGICAL DRUG SUBSTANCE)

Human Thrombin Drug Substance is ----(b)(4)-----
----- Human Thrombin is also manufactured by Omrix Biopharmaceuticals Ltd., ----(b)(4)-----, Israel (FDA Registration Number: ----(b)(4)---). The starting material is ----(b)(4)-----
----- is derived from human Source ----(b)(4)----- plasma collected from qualified donors in FDA-licensed facilities. Source Plasma complies with the requirements of 21 CFR Part 640 and applicable FDA memoranda. ----(b)(4)-----

Human Thrombin Drug Substance is ----(b)(4)----- The manufacturing process for Thrombin includes S/D treatment (----- (b)(4)-----
-----) and ---(b)(4)--- filtration for virus reduction.

The device component of the Fibrin Pad consists of a Matrix made of two absorbable polymers: oxidized regenerated cellulose (ORC) and polyglactin 910 (PG910). The polyglactin 910 (PG910) component was chosen as the main carrier of the biologic components. The physical configuration of the nonwoven fibers provides a surface for retaining the dry powders during storage, flexibility and good adhesion to tissue. Knitted oxidized regenerated cellulose (ORC) was chosen as a backing layer for the PG910 nonwoven felt to provide mechanical strength to the product and due to its fast absorption. In Matrix composition, nominal amounts for PG910 are ----(b)(4)-----and for ORC----(b)(4)-----that yields total matrix content of ----(b)(4)-----

(b)(4)

The Composite Matrix is currently manufactured by----- (b)(4)-----, at the facility in ----- (b)(4)----- (FDA registration number: --- (b)(4)-----). The Matrix is ----- (b)(4)----- (FDA registration number: --- (b)(4)-). The design and manufacture of the Matrix component complies with the QS regulations as specified in 21 CFR Part 820.

(b)(4)

The Fibrin Pad is manufactured, tested, and packaged at Omrix Biopharmaceuticals Ltd., Fibrin Pad Production Facility (FPPF), located at 14 Einstein Str., Weizmann Science Park, Nes-Ziona, Israel.

<u>Components</u>	<u>Average Value</u>			<u>Function</u>
	<u>Quality Designation</u>	<u>Per cm²</u>	<u>Per in²</u>	
Matrix	In-house Standard	(b)(4)	(b)(4)	Backing and Carrier
Human Fibrinogen	In-house Standard	7.8 mg	50.3 mg	Active Ingredient

Human Thrombin	In-house Standard	31.5 IU	203.2 IU	Active Ingredient
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----- (b)(4) -----

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

3.2.P.2.2.1 FORMULATION DEVELOPMENT

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

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

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

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

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

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

3.2.P.2.2.3 PHYSICOCHEMICAL AND BIOLOGICAL PROPERTIES OF FIBRIN PAD

The Fibrin Pad was characterized by physical/biochemical properties and by functional performance.

Mechanism of Action

The primary mechanism of action of Fibrin Pad follows the principles of physiological fibrin clot formation. Upon contact with a bleeding wound surface, the biological components (Human Fibrinogen and Human Thrombin) hydrate, and the subsequent fibrinogen-thrombin reactions initiate the last step of blood clot formation. The resultant fibrin clot adheres to the tissue and becomes integrated with the fibers of the Matrix component, thereby forming a barrier to blood flow and providing a surface for initiation of the normal endogenous hemostatic cascade.

Physical Characterization

The physical characteristics that define the Fibrin Pad can be summarized as follows:

- Appearance
- ---(b)(4)---
- Coating uniformity
- Mechanical strength
- ----(b)(4)----

Methods are described in Module 3.2.P.5.2, Analytical Procedures.

Appearance

The Fibrin Pad has a characteristic white to yellowish appearance, uniformly coated on one surface with a white to yellowish powder. An embossed wave pattern is present on the oxidized regenerated cellulose (ORC) surface of the Fibrin Pad to distinguish between the active (coated with biological components) and the non-active (ORC) surfaces.

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

Coating Uniformity

(b)(4)

Mechanical Strength

In bleeding wound sites, the Fibrin Pad is exposed to blood pressure forces and must be capable of withstanding such forces until hemostasis is complete and physiologic hemostatic mechanisms become operative. The mechanical integrity of the Fibrin Pad is characterized by its --(b)(4)-----, i.e., the force required to tear the pad, and is primarily a function of the Matrix component.

Studies were conducted to evaluate the impact of the mechanical properties of the Matrix on those of the Fibrin Pad. Matrix samples prepared by the routine manufacturing process were compared with Matrix samples which were purposely weakened by partially degrading the Matrix (treated Matrix):

- _____
 _____ (b)(4) _____

- _____
 _____ (b)(4) _____

Fibrin Pad manufactured with treated Matrix exhibited lower ----(b)(4)----- when compared to Fibrin Pad manufactured with untreated Matrix thus suggesting that the Matrix is the main contributor to the ----(b)(4)----- of the product.

(b)(4)

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

(b)(4)

Chemical/Biochemical Characterization

The chemical and biochemical properties of the product are characterized by:

- Content and activity of the primary components (Drug Substances and Matrix)
- ----(b)(4)----- of the biological material
- Product and process-related impurities

Content and Activity of Matrix and Drug Substances

-(b)(4)-

-(b)(4)-

-(b)(4).

-(b)(4)-

-(b)(4)-

-(b)(4)-

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In Vivo Functionality

Three well-established animal models of hemostasis were used in development and characterization of the Fibrin Pad: the rat kidney hemorrhage model, the swine aortotomy model, and the swine partial nephrectomy model. These models simulate clinical severe wound settings and therefore were used to assess the hemostatic efficacy of Fibrin Pad.

Detailed analysis of this information is performed by the Pharmacology/Toxicology reviewer.

Physicochemical and Biological Properties Conclusion

The physical properties of the product are characterized by the --(b)(4)--, coating uniformity, and ---(b)(4)---- of the product. The chemical identity of the Matrix components is shown by the --- (b)(4)----- test methods. The identity and purity of the biologic components is verified by the -- --(b)(4)---; the potency of Drug Substances within the Fibrin Pad product is measured by the ---- -(b)(4)----- assay and the Thrombin Activity assay. The functional properties of the Fibrin Pad are characterized by the -----(b)(4)----- methods, which demonstrate the ability of the product to adhere to tissue and withstand pressure. The hemostatic performance of the product has been demonstrated in live animal models, including the rat kidney hemorrhage model, the swine acute aortotomy model, and the swine partial nephrectomy model. Overall, the methods used indicate that the Fibrinogen and Thrombin active components remain essentially intact and functional within the Fibrin Pad Drug Product.

3.2.P.2.3 MANUFACTURING PROCESS DEVELOPMENT

Reviewer's comment:

Most steps of the current manufacturing process for the Fibrin Pad were observed by the FDA inspectors (Randa Melhem and Destry Sullivan from OCBQ/DMPQ and Natalya Ananyeva from OBRR/DH) during the Pre-License Inspection of the Fibrin Pad Production Facility (FPPF) in May 2011. The details are described in the Establishment Inspection Report (EIR). Results of the PLI were discussed at the Post-PLI Committee Meeting on 2 June 2011 and at the LH Meeting on 6 June 2011. The flow chart of the manufacturing steps within the FPPF production area is attached to this memo.

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[(b)(4)]

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

[(b)(4)]

[(b)(4)]

HISTORY OF TEST METHODS AND SPECIFICATIONS

Release and Stability

Descriptions of the release and stability analytical procedures for Fibrin Pad are presented in Module 3.2.P.5.2, Analytical Procedures. The analytical procedures and specifications have not changed during Fibrin Pad development for the following tests: Appearance, ---(b)(4)-----, ----

----- (b)(4) -----, Endotoxin, Sterility, Irradiation Dose, Package Integrity ((b)(4))
test, ----(b)(4)-----, Visual Inspection of foil pouch seal integrity, and ----(b)(4)----- . The
following analytical procedures and/or specifications were changed during Fibrin Pad
development and were validated:

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

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

Thrombin Activity

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

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

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

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

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(b)(4)

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3.2.P.3.5 PROCESS VALIDATION

The validation of the Fibrin Pad manufacturing process was conducted by manufacturing three consecutive production-scale Fibrin Pad batches at maximum batch size using nominal process parameters and validated equipment in the Omrix FPPF production facility. These process validation batches - -----(b)(4)----- – were manufactured using the (b)(4) application of Drug Substances to the Matrix and were final sterilized by e-beam irradiation within the validated dosage range of -----(b)(4)----- . Intermediate materials with hold times were challenged to the maximum hold times. In-process control and characterization of intermediates as well as release testing of the Final Drug product were conducted, and these batches were included in stability studies. In-process acceptance criteria and limits were met for all steps of the manufacturing process. The results were comparable among the batches supporting consistency of the process. -----(b)(4)----- . The full Fibrin Pad Process Validation Report QA-R-FP-0014-00 is provided in Module 3.2.R.4, Regional Information.

Release and Stability Testing

All characteristics of the Final Drug Product that was produced from the intermediates prepared within the process validation met the Fibrin Pad Release Specifications (Module 3.2.P.5.4, Batch Analyses) and the acceptance criteria on stability testing (Module 3.2.P.8.1, Stability Summary and Conclusion).

Release results for -----(b)(4)-----, Thrombin Activity, and ---(b)(4)--- are summarized in the Table below and are compared to the results for non-sterile Fibrin Pad. All samples met the release acceptance criteria. -----

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

3.2.P.5.1 SPECIFICATIONS

Table 1 Fibrin Pad release specifications ^a		
Test	Acceptance Criteria	
	Metric Units	US Units
Identity		
Appearance	Complies ^b	Complies
Potency		
---(b)(4)---	----(b)(4)----	----(b)(4)----
---(b)(4)---	----(b)(4)----	----(b)(4)----
Thrombin Activity	----(b)(4)----	----(b)(4)----
---(b)(4)---	----(b)(4)----	----(b)(4)----
Purity/Impurity		
---(b)(4)---	----(b)(4)----	----(b)(4)----
---(b)(4)---	----(b)(4)----	----(b)(4)----
Endotoxin	----(b)(4)----	----(b)(4)----
Sterility ^c	Sterile	Sterile
Irradiation Dose ^d	----(b)(4)----	----(b)(4)----
Package Integrity ((b)(4)) Test	----(b)(4)----	----(b)(4)----
Visual Inspection of Foil Pouch Seal Integrity	Complies ^e	Complies ^e
^a There is no General Safety Test. Omrix has submitted a waiver pursuant to 21 CFR 610.11(c)(3) for “non liquid products other than freeze dried products,” which is provided in Module 1. ^b The active side is powdery and white to yellowish in color. The non-active side is white to yellowish in color with an embossed wave pattern. ^c ----- ----- ----- (b)(4) ----- ----- ----- ^d The result is obtained from the irradiation certification as determined by ---(b)(4)---. ^e Pouch seal is clear of non-conformances in visual inspection.		

Stability testing includes the same tests and acceptance criteria as for release except for --(b)(4)-----, irradiation dose, and visual inspection of foil pouch seal integrity. ----(b)(4)----- analysis is performed during stability testing.

Reviewer’s comment: ----- (b)(4) ----- test will be also included in release and stability testing per FDA recommendation. Please refer to Omrix’s response to IR question #4.

3.2.P.8.1 STABILITY SUMMARY AND CONCLUSIONS

Omrix requests a shelf life for Fibrin Pad of 24 months when stored at 2 to 25°C.

Three batches of Fibrin Pad used in the Pivotal (Phase 2) Clinical Study and three consecutive Process Validation Batches, which were manufactured according to the current Fibrin Pad manufacturing process, were put on long-term and accelerated stability studies:

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

Table 1 Fibrin Pad, status of stability studies for production-scale batches						
<u>Fibrin Pad Pivotal Batches</u>				<u>Fibrin Pad Process Validation Batches</u>		
<u>Batch</u>	<u>L11F284^a</u>	<u>M05F094</u>	<u>M06F164</u>	<u>--(b)(4)---</u>	<u>--(b)(4)----</u> <u>---</u>	<u>--(b)(4)---</u>
Date of Manufacture	Nov 2007	May 2008	June to July 2008	July 2009	July to August 2009	August 2009
Status of Study at ----- ----- (b)(4) ----- -----	Completed	Completed	Completed	Ongoing 18 months	Ongoing 18 months	Ongoing 18 months
Status of Study at ----- ----- (b)(4) -----	Completed	Completed	Completed	Ongoing 18 months	Ongoing 18 months	Ongoing 18 months
Status of Study at ----- ----- (b)(4) ----- -----	Completed	Completed	Completed	Completed	Completed	Completed
^a Stability was performed on Batch L11F284. Batches L11F284 and L11F294 started as the same batch with the same starting materials and intermediates, but were arbitrarily split at the (b)(4) application step to supply separate clinical (L11F294) and stability (L11F284) needs.						

Stability Program for Pivotal (Phase 2) Clinical Batches

The parameters which were tested for the Pivotal Clinical Batches included release test methods and additional characterization methods:

In vitro activity

- ----- (b)(4) --, Thrombin Activity and ----- (b)(4) ----- test methods provide a measure of potency of active biological components in Fibrin Pad and are stability-indicating.
 --- (b)(4) -----
- ----- (b)(4) -----

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

Matrix components

- -----(b)(4)----- are identity tests used at the beginning and at the end of the stability study.
- -----(b)(4)----- values are required to ensure mechanical strength of the Fibrin Pad.

Physical tests

- Appearance test is used to assess powder coating uniformity on the PG910 side and the presence of an embossed wave pattern on the ORC side.
- -----(b)(4)-----
- Package integrity ((b)(4)) test is used to characterize the integrity of the foil pouch seals.
- -----(b)(4)-----

Excipients/impurities

- --(b)(4)-- test is used to verify its concentration in the Fibrin Pad at the beginning and end of the stability study.
- --(b)(4)-- test is used to monitor this process-related impurity during the pivotal clinical stability study.

Microbiological tests

- Endotoxin is tested at the beginning, middle and at the termination of the stability study.
- Sterility is verified at the beginning and at the termination of the stability study.

Ex vivo tests

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

In vivo tests

- Rat kidney hemorrhage model is used to characterize the hemostatic performance of the Fibrin Pad throughout the study.
- Porcine aortotomy is tested at baseline for all three pivotal clinical stability study batches.

Stability Program for Process Validation Batches

The parameters which were tested for the Process Validation Batches included those used for the Pivotal Clinical Batches, with the following changes:

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

standard governing the ethical use of animals. *In vitro* and *ex vivo* methods were found sufficient for assessing stability of the Fibrin Pad.

Stability Program for Commercial Batches

The parameters to be tested in the post-approval commercial stability program include those used in stability studies of the Process Validation Batches, with the following changes:

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

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

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

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

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

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

Stability Data for Pivotal Batches

For clinical batches, 24 months of stability data for Thrombin Activity, ---(b)(4)-----
----- were subjected to statistical analysis using ---(b)(4)-----
----- . The projected shelf-life for all parameters extends beyond
the requested dating period if based on the long-term storage conditions. For Lot L11F284, a ---
----(b)(4)----- over time was observed, as opposed to the other two batches,
although the values remained within Specification. This trend was observed for both long-term
storage conditions at -----(b)(4)----- . Based on projections from the
accelerated stability study, the shelf-life is ---(b)(4)---

Batch M06F164 showed a trend for -----(b)(4)----- under both long-term storage conditions at -----(b)(4)-----

(b)(4)

(b)(4)

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

[(b)(4)]

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

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

Reviewer's comment:

Lots L11F284 and M06F164 were used in the Pivotal (Phase 2) Clinical Study 400-07-002 in which thromboembolic adverse events had been recorded. Please refer to Omrix's response to IR question #8 for explanation of the aberrant trends observed for Lots L11F284 and M06F164 on stability testing and the potential correlation of this observation with the adverse events in the Clinical Study. For review of stability data for the Validation batches, please refer to Omrix's response to IR question #7.

Control of Premature Fibrin Formation on the Fibrin Pad at Release and During its Shelf Life

Control of premature fibrin formation i.e., potential interaction between biological substances on the Fibrin Pad before application to the wound site, is critical to final product quality. In Amendment STN 125392/0.3, Omrix clarified their approach to monitor potential premature conversion of fibrinogen to fibrin on the Fibrin Pad.

Several approaches were considered for such monitoring, including -----
----- (b)(4) -----

(b)(4)

(b)(4)

- Reviewer's comment:**

3.2.R REGIONAL INFORMATION

This study compared Fibrin Pad material used in **Non-clinical studies** ((b)(4) application method) and material intended for **Phase I** clinical studies ((b)(4) application method)

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

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

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

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

Reviewer's comment:

Data presented in the Comparability report were adequate to conclude that Fibrin Pads manufactured using a (b)(4) method were comparable to those manufactured with (b)(4) in analytic parameters and hemostatic performance. Animal safety data were not informative because the observation period was shorter than the time of Fibrin Pad resorption (56 days).

Study Report No. QA-R-FP-0015-00: Comparability Report – Fibrin Pads Produced During Process Validation Versus Pivotal Batches

Main changes to the manufacturing process since the conduct of the pivotal clinical study:

- (b)(4)

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[(b)(4)]

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

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

[(b)(4)]

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

Reviewer's comment:

This study demonstrated comparability of Pivotal and Validation batches in analytical parameters and in hemostatic performance. Safety data were not completely informative because the observation period was shorter than the time of Fibrin Pad resorption (56 days).

RESPONSES TO INFORMATION REQUEST

FDA Question #1:

Contents of Fibrinogen and Thrombin as presented in Table 1 Composition of Fibrin Pad (Module 3.2.P.1 Description and Composition of the Drug Product) are incongruent with those Table 1 Fibrin Pad Release Specifications (Module 3.2.P.5.1 Specifications). For example, the target Fibrinogen content of “7.8 mg/cm² measured as -----(b)(4)-----” may be confused with “the range -----(b)(4)-----”. Therefore, please specify in a footnote

comment to Table 1 Composition of Fibrin Pad that target values for Fibrinogen and Thrombin are the average values based on analysis of N lots of Fibrin Pad in respective assays.

Response to Question #1:

Footnotes “c” and “e” of Module 3.2.P.1, Description and Composition of the Drug Product, Table 1 have been modified to indicate that the target values for Fibrinogen and Thrombin are average values based on analysis of ---(b)(4)--- Fibrin Pad batches in ----(b)(4)----- and Thrombin Activity assays, respectively.

Reviewer's comment:

This response is satisfactory.

FDA Question #2:

Please explain how your dose optimizing studies address and exclude the overdosing of the biological drug substances that may lead to potential thrombogenicity of the Fibrin Pad. Also, please comment on how the established input dose ranges for Thrombin and Fibrinogen affect the performance of the Fibrin Pad.

Response to Question #2:

Omrix stated that dose optimization studies for Biologic Drug Substances showed that Fibrin Pad was safe and effective across a wide dose range extending beyond the target input doses of-----
------(b)(4)-----Fibrinogen and -(b)(4)- for Thrombin (summary of dose optimization studies is presented in Module 3.2.P.2.2.1, Formulation Development and summary of pre-clinical studies in animal models is presented in Module 2.6.2, Pharmacology Written Summary of the original BLA).

(b)(4)

(b)(4)

Omrix claimed four Fibrin Pads (each 4 x 4 in.) as the maximal recommended dose (Table 2). This dose was verified in a subchronic toxicity study in rats using 2.5 times this maximum dose (10 times the anticipated clinical dose) of Fibrin Pad (one 4 x 4 in. Fibrin Pad). No safety issues, including evidence of thrombogenicity, were identified (Module 2.6.6, Toxicology Written Summary and Module 2.6.7.5, Single Dose Toxicity GLP Study 05-0474).

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

2 Pages Determined to be Not Releasable: (b)(4)

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Reviewer's comment:

The response is satisfactory. This issue was also discussed during the Pre-License Inspection of May 10-19th, 2011. Dose optimization studies for Fibrinogen and Thrombin supported the established ranges for the input doses and for their potencies in the final product. These specification dose ranges are within the dose ranges tested and established as safe and effective in animal studies. The implemented controls over the input doses (-----
----- and potencies in the Drug Product (----- and Thrombin Activity) minimize the risk of dosing outside of the specification limits.

FDA Question #3:

*Please describe in detail how you establish the in-process acceptance criteria for the -----

-----*

Response to Question #3:

Analytical Procedures. Justification for the specification is provided in Module 3.2.P.5.6, Justification of Specifications of the original BLA.

Reviewer's comment:

This recommendation was addressed.

FDA Question #5:

*Please submit to the BLA Report Number FLC-013: Verification of the Holding Time -----
----- (b)(4) -----*

Response to Question #5:

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

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

Reviewer's comment:

This response is satisfactory. The hold time of ----- (b)(4) -----
----- appears validated.

FDA Question #6:

Please provide a risk assessment on the potential immunogenicity of the Fibrin Pad due to exposure of its components to --(b)(4)--solvent and e-beam irradiation, with reference to specific sections of the BLA containing the relevant Study Reports.

Response to Question #6:

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 was developed based on the method of -----

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

The biological active components in Fibrin Pad are conserved proteins of human origin and therefore the risk level posed by the source of raw material in terms of immunogenicity is relatively low. The overall effect of the manufacturing process on the antigenic potential of Fibrin Pad was assessed *in vitro*, *in vivo*, and in a human clinical trial.

The effect of exposure of individual biologic components (Human Fibrinogen and Human Thrombin) to --- (b)(4) --- was evaluated in a study -----

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

The effect of e-beam irradiation on the Final Pad characteristics was evaluated by -----

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

Immunogenicity and antigenicity of Fibrin Pad and Matrix were evaluated using standard and nontraditional animal models (Module 2.6.6, Toxicology Written Summary and Module 2.6.7, Toxicology Tabulated Summary in the original BLA). The humoral immunogenicity of Fibrin Pad was evaluated in a 90-day sub-chronic toxicity study in the rat (single implant/dose, subcutaneous tissue implantation), with immunogenicity as a secondary endpoint (Table 2.6.7.5, GLP Study 05-0474). Fibrin Pad was administered at a dose approximately 10 times greater (based on mass/body weight) than a typical surgical dose (one 4 x 4 in. unit) and 2.5 times greater than a worst-case surgical exposure (four 4 x 4 in. units). Fibrin Pad was compared to EVICEL sprayed over Matrix, Matrix alone, and EVICEL alone at similar doses. Omrix states that no adverse effects of Fibrin Pad treatment were identified in mortality, morbidity, clinical observations, food consumption, body weight, clinical pathology, macroscopic evaluation, or microscopic evaluation of sections of selected organs and tissues. An increased incidence of inflammation (minimal to mild) was observed at the implantation sites of animals that received Matrix alone compared to the group that did not receive Matrix. Immunogenicity was investigated by ----- (b)(4) -----

----- indicated there were no relevant differences in antigenicity of the biological components of Fibrin Pad when compared to EVICEL Fibrin Sealant components. Immunohistochemical evaluation of lymphoid tissues indicated no treatment-related effects on the relative numbers and distribution of B-cells and T-cells. The presence of inflammation at the implant site was expected due to the xenogenic reaction in the rat to the Fibrin Pad components.

These studies demonstrated toxicological and immunological comparability between Fibrin Pad and the predecessor fibrin sealant, EVICEL.

The antigenicity of Fibrin Pad was further evaluated in a liver defect model by directly comparing the early tissue (cellular immune-mediated) response to Fibrin Pad-treated sites between immunocompetent and immunocompromised athymic rats (Table 2.6.7.16, non-GLP Study 09-0077). This study confirmed that the tissue reaction was a xenogenic response, which is not expected to occur in humans.

The immunogenicity of Fibrin Pad was further assessed in humans in the Phase 2 Clinical Study 400-07-002. Blood samples were tested for antibodies to Human Fibrinogen and Human Thrombin by validated ELISA at baseline, 4 to 6 weeks, and 8 to 10 weeks post-surgery. The background level of antibodies to Thrombin and Fibrinogen in the untreated population was used to set a cut-off value. The antibody levels were evaluated by two parameters: a categorical parameter (below or above the cut-off value) and a relative quantitative parameter (antibody titer). Only 2% (2/99) of the Fibrin Pad-treated patients showed a seroconversion in response to Human Thrombin at 2 weeks post surgery. Neither of these patients had abnormal coagulation parameters such as prothrombin time, activated partial thromboplastin time, or international normalized ratio at 4 weeks after surgery that indicates the transient nature of the antibodies. The 2% of seroconversion is close to the expected rate in the normal population based on historical data. There was no increase in anti-Thrombin antibody titer and no response was detected at 8 weeks. There was no detectable response to Human Fibrinogen at all time points tested (for details, please refer to Module 5.3.5.1, Reports of Efficacy and Safety Studies, Immunogenicity Report).

Reviewer's comment:

The immunogenicity aspect was also discussed during the Pre-License Inspection of May 10-19th, 2011. Review of the collected data indicated that the risk of developing a clinically relevant immune response in patients treated with Fibrin Pad is low. The data related to potential association of long-term presence of the Matrix with inflammatory reactions are not completely informative.

FDA Question #7:

*Please submit to the BLA up-to-date stability data for the Fibrin Pad Validation Batches -----
----- (b)(4) -----*

Response to Question #7:

Omrix submitted 18 months of stability data for Validation Batches ----- (b)(4) -----
----- for long-term conditions ----- (b)(4) -----
----- storage conditions (Tables 10-18) to support the shelf-life for Fibrin Pad of 24 months when stored at 2 to 25°C.

Reviewer's comment:

Results for all parameters remained well within Specification ranges for all conditions. There was a trend for ----(b)(4)----- and a trend for -----(b)(4)----- under accelerated and room temperature conditions. This trend was not observed under refrigerated conditions. These tests are For Information Only. Thus, the Fibrin Pad shelf-life of 24 months when stored at 2 to 25°C can be granted.

FDA Question #8:

In your stability studies, we note the trends for the -----(b)(4)----- for Pivotal Lot L11F294 and in --(b)(4)-- for Pivotal Lot M06F164 when compared to other lots. We also note that these 2 lots were used in Clinical Study 400-07-002 in which several adverse events had occurred. Please explain the aberrant stability trends, and comment on the potential correlation between these two observations.

Response to Question #8:

Omxrix explained that the -----(b)(4)----- for batch L11F284 (clinical batch L11F294) was attributed to random sample selection at various time points and expected sample-to-sample variation. This can have an impact on the calculation of the (b)(4). Nevertheless, this batch remained within the proven safe and effective range throughout the 2-year study period, with values for ----(b)(4)---- ranging from -----(b)(4)----- over all time points and temperatures. In the clinical study 400-07-002, the rate of thrombotic events seen in association with batch L11F294 (2/55; 3.6%) was no different than the Standard of Care (2/30; 6.7%). No plausible mechanism could be envisioned whereby a -----(b)(4)----- would render the material more thrombogenic.

Regarding batch M06F164, the ---(b)(4)--- is a stability indicating parameter for the Matrix component of the Fibrin Pad. The -----

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

----- No plausible
mechanism could be envisioned whereby the ---- (b)(4) ----- would render the material
more thrombogenic.

The adverse events observed during clinical study 400-07-002 prompted a clinical investigation and analysis of the CMC data (physical, chemical, and biochemical properties) related to batch M06F164. A detailed summary of the investigation is presented in report QA-R-FP-0016-00 “Expanded Investigation of Clinical, Manufacturing and Analytical Data of Fibrin Pad Pivotal Batch M06F164” in Module 3.2.R, Regional Information. In particular, a controlled *in vitro* kinetic study did not reveal any significant difference in the PG910 degradation profiles for three batches. The clinical investigation concluded that the events observed were consistent with the patient population and were not related to treatment with the Fibrin Pad.

Reviewer's comment:

The trend observed in ----(b)(4)----- for batch L11F284 (clinical batch L11F294) and the trend in -----(b)(4)----- for batch M06F164 appear related to analytical issues. No plausible mechanisms were identified that could reasonably account for the adverse events observed in the clinical study 400-07-002.

CONCLUSION FROM BLA REVIEW

No product related issues have been identified that may prevent approval of this BLA.

COMPARABILITY PROTOCOL QA-P-FP-0017-00 FIBRIN PAD MANUFACTURING CHANGES

Objective:

(b)(4)

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

3 Pages Determined to be Not Releasable: (b)(4)