



DEPARTMENT OF HEALTH & HUMAN SERVICES

U.S. Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
Division of Manufacturing and Product Quality

**To:** Administrative File, STN 125392/0 for Fibrin Pad

**From:** Randa Melhem, Ph.D., OCBQ, DMPQ, MRBII, HFM-676

**Cc:** Nancy Waites, OCBQ, DMPQ, MRBI, HFM-675

**Through:** Chiang Syin, Ph.D., Branch Chief, OCBQ, DMPQ, MRB II, HFM-676

**Subject:** **Review Memo (BLA):** [Omrix Biopharmaceuticals Ltd. License No. 1603]: Review of a Comparability Protocol (CP) which was submitted as part of the Original BLA in support of approval for planned changes to the manufacturing process (----- (b)(4) -----) of the Fibrin Pad. The final Fibrin Pad product is manufactured at Omrix Fibrin Pad Production Facility (FPPF) in Rehovot, Nes-Ziona, Israel and sterilized at ----- (b)(4) -----.

**Action Due:** September 19, 2011

**Action Recommended:**

A Complete Response (CR) Letter should be sent to Omrix,

**CR Letter Ready Comment:**

The submitted Comparability Protocol provides an overview of the revised manufacturing process, and the acceptance criteria for the in-process and final release testing of the three validation lots. However it lacks specific details, protocols and acceptance criteria as listed below:

- a. -----  
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----- (b)(4) -----  
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- b. ----- (b)(4) -----  
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- c. -----  
----- (b)(4) -----  
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- d. ----- (b)(4) -----  
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1 page redacted (b)(4)

## **SUMMARY / BACKGROUND**

CBER received this electronic submission on November 19, 2010. Omrix Biopharmaceuticals Ltd. (Omrix) submitted a BLA in support of approval of the Fibrin Pad, a sterile bio-absorbable combination product made from a flexible composite Matrix (device component) coated with Human Fibrinogen and Human Thrombin plasma-derived proteins (biological drug substances). 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.

In addition, Omrix submitted a CP to report planned changes to the manufacturing process of the Fibrin Pad to -----  
----- (b)(4) -----  
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Following approval of this CP, the results for this protocol will be submitted as a post-approval supplement.

## **INTRODUCTION**

Omrix Biopharmaceuticals Ltd. (Omrix) submitted an Original BLA to get approval for Fibrin Pad, a sterile bio-absorbable combination product intended for use as an adjunct to hemostasis for soft tissue bleeding. As part of the BLA they submitted a CP to describe proposed changes to the manufacturing process in order to -----  
----- (b)(4) -----:

- ----- (b)(4) -----  
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- ----- (b)(4) -----  
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- ----- (b)(4) -----  
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- ----- (b)(4) -----  
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The CP is aimed to verify comparability of the Fibrin Pad proposed manufacturing process with the current manufacturing process, and to demonstrate that the changes made to the Fibrin Pad manufacturing process will have no adverse impact on the identity, strength, quality, purity and potency of the final Fibrin Pad drug product.

## **PROPOSED FIBRIN PAD MANUFACTURING CHANGES**

----- (b)(4) -----  
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----- (b)(4) -----  
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2 pages redacted (b)(4)

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

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

- \_\_\_\_\_ (b)(4) \_\_\_\_\_

## **STUDY DESIGN**

Omrix stated that all equipment associated with the proposed manufacturing process including -----(b)(4)-----, will be qualified prior to use. In addition the e-beam sterilization process will be validated prior to the execution of the process validation batches to ensure the product meets the current specified limits, including the required sterility assurance level.

They stated that three consecutive Fibrin Pad batches will be manufactured using the revised/proposed process. The added that increased sampling may be used during process validation to increase confidence in that the changes have minimal impact. Omrix stated that in-process and final product release testing and product characterization will be performed for the three batches.

They added that they will compare the data collected from the three batches (modified process) to similar data obtained from three Fibrin Pad batches manufactured concurrently with the current manufacturing process.

The batches manufactured using the current (three batches) and revised (three validation batches) process will be entered in long term (----- (b)(4) -----) and accelerated (-- (b)(4) -----) stability programs to support the proposed shelf-life of Fibrin Pad, under both long-term and accelerated storage conditions.

Omrrix stated that QA will evaluate any deviation that occurs during the manufacturing process, any out of specification in-process or final product release testing, and any deviation in the stability studies. QA will also evaluate the seriousness of the deviation and determine whether the batch is acceptable as process validation batch.

**Reviewer's comment:**

- Please specify the increased testing that will be performed during process validation

## Acceptance Criteria

Omrix stated that the following acceptance criteria should be met to demonstrate successful comparability of the revised manufacturing process:

- Fibrin Pad validation batches, produced with the revised manufacturing process, meet the established in-process and release specifications. Using appropriate statistical methods, results will be compared with data collected from concurrently produced Fibrin Pad batches manufactured using the current manufacturing process.

- Characterization (including functional performance) tests results of Fibrin Pad validation batches will be compared with data collected from the Fibrin Pad batches manufactured concurrently with the current process using appropriate statistical methods
- The functional performance of Fibrin Pad manufactured with the revised process should comply with the pre-determined acceptance criteria of the non-clinical model as for Fibrin Pad manufactured with the current process.
- Stability results for the final Fibrin Pad drug product must meet stability specifications. The slopes observed for stability indicating parameters should be similar to the ones observed for Fibrin Pad stability batches manufactured with the current process.

**Reviewer's comments:**

- Please specify the statistical methods used to compare the results of the validation batches with the concurrently manufactured Fibrin Pad batches using the current process.
  - For the stability (accelerated and long term) studies, please specify at what interval you deem the stability of the validation batches (revised process) and the current process batches comparable.
  - Please specify the protocol for testing the functional performance of the Fibrin Pad (revised process) and acceptance criteria of the non-clinical model.
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