

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)

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: Filing memorandum for original BLA for Fibrin Pad (Applicant - Omrix Biopharmaceuticals Ltd., Israel)

On 19 November 2010, Omrix Biopharmaceuticals Ltd. submitted electronically an original Biologics License Application (BLA), STN 125392/0, for Fibrin Pad, a Biologics-Device combination product, with proposed proprietary name EVARREST.

Description: Fibrin Pad is a sterile bio-absorbable hemostatic agent made from a flexible composite Matrix (device component) coated with Human Fibrinogen and Human Thrombin plasma-derived proteins (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); for Human Thrombin - 203.2 IU/in² (31.5 IU/cm²); and for Matrix, the content is -----(b)(4)-----.

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. The intended route is direct application onto bleeding tissue during surgery. OMRIX proposes a new SPL acceptable term for dosage form as -----(b)(4)-----.

Recommendation:

The electronic BLA submission, STN 125392/0 contains general categories of information required by 21 CFR 601.2(a), such as description of the manufacturing process, manufacturing sites, characterization, and stability of Biological Drug Substances and Final Drug Product, Fibrin Pad. The information is organized in the Common Technical Document (CTD) format according to current ICH Guidelines. The submission appears complete to permit a substantive and meaningful review and *can be filed*.

Structure of the Submission

The information in the submission is organized in the CTD format according to the *ICH Harmonised Tripartite Guideline: The Common Technical Document for the Registration of Pharmaceuticals for Human Use*, 12 September 2002.

Module 1 contains:

- Forms 356h and 3397 (Section 1.1)
- Cover Letter (Section 1.2)
- Debarment Certification and Financial Disclosure (Section 1.3)
- Letters of Authorization (Section 1.4)
- Previous Meetings with FDA (Section 1.6)
- Pediatric administrative information (Section 1.9)
- Other correspondence (Section 1.12)
- Labeling (Section 1.14)
- Risk Management Plans (Section 1.16)

Module 2 contains CTD Summaries:

- Introduction (Section 2.2)
- Quality Overall Summary (Section 2.3)
- Nonclinical Overview (Section 2.4)
- Clinical Overview (Section 2.5)
- Nonclinical Written and Tabulated Summaries (Section 2.6)
- Clinical Summary (Section 2.7)

Module 3

The quality section is organized according to the *ICH Guidance M4Q(R1)* and contains the following folders:

3.2.S Drug Substance

Contains pertinent information on Human Fibrinogen, Human Thrombin, and Matrix

3.2.P. Drug Product

3.2.P.1 Description and Composition of the Drug Product

3.2.P.2 Pharmaceutical Development

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

3.2.P.3.2 Batch Formula

3.2.P.3.3 Description of Manufacturing Process and Process Controls

3.2.P.3.4 Controls of Critical Steps and Intermediates

3.2.P.3.5 Process Validation and/or Evaluation

3.2.P.4. Control of Excipients

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification(s)

3.2.P.5.2 Analytical Procedures

3.2.P.5.3 Validation of Analytical Procedures

- 3.2.P.5.4 Batch Analyses
- 3.2.P.5.5 Characterization of Impurities
- 3.2.P.5.6 Justification of Specifications
- 3.2.P.6 Reference Standards and Materials
- 3.2.P.7 Container Closure System
- 3.2.P.8 Stability
 - 3.2.P.8.1 Stability Summary and Conclusion
 - 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment
 - 3.2.P.8.3 Stability Data

3.2.A Appendices

- 3.2.A.1 Facilities and Equipment (to be evaluated by DMPQ reviewers)
- 3.2.A.2 Adventitious Agents Safety Evaluation
- 3.2.A.3 Excipients

3.2.R Regional Information

Includes Fibrin Pad Batch Records; Comparability Reports for Fibrin Pad and Matrix; Validation Reports

3.3 Literature References

Human Fibrinogen (Biological Drug Substance)

Human Fibrinogen drug substance is a -----(b)(4)-----
 -----. Human Fibrinogen is manufactured by Omrix Biopharmaceuticals Ltd.,
 (b)(4)-----Israel (FDA Registration Number ----(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.

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

-----. These changes are described in Section 3.2.S.2.6, Manufacturing Process Development,
 Human Fibrinogen. The manufacturing process includes Solvent/Detergent (S/D) treatment (-----
 -----(b)(4)-----) and pasteurization step (-----
 --- (b)(4)-----) for virus inactivation.

Human Thrombin (Biological Drug Substance)

Human Thrombin drug substance is a -----(b)(4)-----
 -----. Human Thrombin is manufactured by -----
 -----(b)(4)----- . The starting
 material is ---(b)(4)--- plasma -----(b)(4)-----

----- (b)(4) ----- plasma is derived from human source ----- (b)(4) -----
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) -----

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

----- . These
changes are described in Section 3.2.S.2.6, Manufacturing Process Development, Human
Thrombin. The manufacturing process for Thrombin includes S/D treatment (-----
---- (b)(4) -----) and ---- (b)(4) ---- filtration for virus
elimination.

Composite Matrix (Device component)

The device component of the Fibrin Pad consists of a Matrix made of two absorbable polymers:
oxidized regenerated cellulose (ORC) and polyglactin 910 (PG910). -----

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

Matrix is currently manufactured by ----- (b)(4) -----
----- (FDA registration number: #---- (b)(4) -----). The Matrix is ----
----- (b)(4) -----

The initial manufacturing process was developed at -----
----- (b)(4) -----

----- . A comparability study report is included in Module 3.2.R, Regional Information, and is
summarized in Module 3.2.S.2.6, Manufacturing Process Development, Matrix.

Reviewer's comment: The composition of the Matrix, the changes in the manufacturing process
for Matrix and their validation throughout development, as well as the FDA compliance status of
the current manufacturing site require a CDRH consult review. The Inter-center request was
initiated on 21 December 2010.

Fibrin Pad Drug Product

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

For application to the surface of a carrier Matrix, Biological Drug Substances -----
----- (b)(4) -----

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

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

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

The Fibrin Pad is sterilized by e-beam irradiation at a -----
--(b)(4)----- . Validation of the sterilization
process is described in Module 3.2.P.3.5, Process Validation and/or Evaluation, Validation of
Sterilization Process.

Reviewer's comment: Changes in the manufacturing process for Matrix and Fibrin Pad were
implemented during production of the clinical material and also after manufacture of the clinical
material and prior to manufacture of process validation batches. Therefore, comparability of the
material used in pre-clinical and clinical studies as well as comparability of the clinical material
and process validation material should be rigorously evaluated. Comparability studies are
presented in Module 3.2.R. Regional Information. Additionally, attention should be given to the
effects of e-beam irradiation on the Fibrin Pad characteristics.

Inspection of Omrix Biopharmaceuticals Ltd., Fibrin Pad Production Facility, appears to be
necessary.