

MEMORANDUM

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

Date: 30 August 2011

To: STN 125392 File and Natalya Ananyeva, Committee Chair

From: Nancy Kirschbaum, PhD, Chemist, HFM-392

Subject: Review memorandum for Original BLA from Omrix Biopharmaceuticals for Fibrin Pad
– Module 3.2.A.2 Adventitious Agents Safety Evaluation

Through: Timothy Lee, HFM-392
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Background

Fibrin Pad is manufactured from three components: (1) composite matrix of non-woven polyglactin 910 –b(4)----- onto an oxidized regenerated cellulose backing, (2) –b(4)----- human fibrinogen concentrate and (3) ---b(4)----- human thrombin concentrate. Safety from adventitious agents was evaluated for the manufacture and control of each component as well as for the manufacture and control of the Fibrin Pad final product.

References

- Guidance for Industry M4Q: The CTD – Quality [August 2001]
- Guidance for Industry Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products [January 2002]
- CHMP Position Statement on Creutzfeldt-Jakob Disease and Plasma-derived and Urine-derived Medicinal Products. EMEA/CPMP/BWP/2879/02/rev 1 [23 June 2004]
- Potential Risk of Variant Creutzfeldt-Jakob Disease (vCJD) From Plasma-Derived Products found on CBER website at:
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>

3.2.A.2. Adventitious Agents Safety Evaluation

Non-viral adventitious agents

A. Bioburden

Fibrin Pad is a sterile product. The final product, Fibrin Pad, is terminally sterilized with electron (e-) beam irradiation in the final package at dose range, ---b(4)----- . Control of bioburden during manufacture of components and final product prior to e-beam sterilization is critical to consistent manufacture and release of a sterile product.

Omrix presented its integrated approach to bioburden control that included: (1) operational controls during manufacture (including environmental monitoring and manufacture in controlled areas) to minimize introduction of exogenous microbial contamination, (2) inclusion of targeted

steps to remove bioburden (3) validated cleaning and sanitization procedures and (4) in-process and release bioburden b(4)- and endotoxin testing for components and Fibrin Pad prior to e-beam sterilization.

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

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

Fibrin Pad e- beam sterilization process was validated to provide a sterility assurance level (SAL) of b(4). Validation was performed in compliance with ISO 11137 standard. Final product is subjected to sterility and endotoxin testing (endotoxin limit –b(4)----- in accordance with ---- b(4)).

Package integrity was addressed. Visual inspection and b(4) test of the foil pouch are both performed to provide assurance of an adequate barrier to moisture and microbial contamination.

Detailed information regarding Omrix’s integrative approach to bioburden control may be found in modules 3.2.S.2, 3.2.P.3 and 3.2.A.1.

Assessment of Adequacy: The information on bioburden control contained in other CTD module 3 sections and summarized in 3.2.A.2 appears adequate to support safety from bioburden related adventitious agents. A more complete summary, however, would have included information regarding bioburden control of source materials e.g. plasma ----(b)(4)------. Since the information has been included in other parts of the BLA, its omission in 3.2.A.2 would not rise to mention in an information request letter. Not addressed in 3.2.A.2 and an issue that may be considered for information request relates to inspection of and detection in the final package of pinhole breaches in package integrity.

B. TSE agent/Prion protein

Omrix presented a summary of relevant aspects from its “Risk Assessment for Transmission of Animal Transmissible Spongiform Encephalopathy (TSE) or Variant Creutzfeldt Jakob Disease (vCJD).”

Control of Starting Material and Biological Excipients

Human plasma is the starting material with theoretical potential for transmission of vCJD (but not CJD). –b(4)----- (in Human Thrombin component) also being assessed.

Human plasma is supplied exclusively from US-licensed blood banks. Omrix cites the FDA guidance recommendations for geographic donor deferral for collection of plasma, implemented in all US-licensed blood banks. Omrix has established a system for traceability of each plasma donation for look-back notification and procedures for subsequent product recall, if necessary.

Omrix sources its --b(4)----- as the licensed product from ---b(4)-----
-----, Omrix and --b(4)----- have a quality agreement that includes a mechanism for
look-back notification.

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Sanitization of Equipment and Cleaning Procedures

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Assessment of Adequacy. A PHS assessment of the potential for US licensed or investigational
plasma derivatives to transmit vCJD may be accessed from the CBER website (see reference
above for link). In brief, the assessed risk has been determined by FDA/PHS to be small. In
addition to sourcing plasma from US-licensed blood banks and using US-licensed ---b(4)--

Viral adventitious agents

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Virus reduction validation studies performed by Omrix

Human Fibrinogen – targeted manufacturing steps: 1) solvent detergent treatment and 2) pasteurization.

Human Thrombin – targeted manufacturing steps: 1) solvent detergent treatment and 2) –b(4)----- nanofiltration.

Viral validation studies supporting viral inactivation or clearance (as applicable) during human fibrinogen or human thrombin manufacture were submitted to and approved with original BLA 125010 or supplement 125010/102. Since no changes to targeted virus reduction manufacturing steps have been implemented for Fibrin Pad component manufacture, the original studies are applicable. Omrix has re-submitted in an electronic format to BLA 125392, all completed study reports, for ease of reference (BLA 125010 was a paper submission).

Since the submitted studies have already been determined by FDA to be adequate, no further review is required.

Review Summary and Conclusion with regard to adequacy of information and data

Adequate

Information Request items

Consideration may be given to requesting information regarding inspection and detection of pinhole leaks in the final package. This may be included in an information request letter in the section pertaining to container closure issues.