



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 Sealant Patch

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

Cc: Nancy Waites, M.S., OCBQ/DMPQ/MRBI, HFM-675
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Through: Marion Michaelis, Acting Chief, OCBQ/DMPQ/MRB II, HFM-676

Subject: **Review Memo (CR letter):** [Ethicon, Inc. License # 1879] Review of Responses to CR letter submitted by Ethicon, for the production of the Fibrin Sealant Patch at Omrix Biopharmaceuticals Ltd. facilities PFI and FPPF in Israel.

Action Due: September 29, 2012

Action Recommended

I have reviewed Ethicon/Omrix responses to the CR letter items applicable to DMPQ (Outstanding inspectional issues from the Pre-License Inspection performed May10-19, 2012) and found them to be acceptable. I recommend approval of this submission with the following PMC received September 18, 2012 (amendment 125392/0/27);

ETHICON, Inc. commits to modify the acceptance limits for -----(b)(4)----- for -----(b)(4)----- of equipments, and to complete the cleaning validation (CV) studies based on a (b)(4) CV strategy for major equipment groupings, as specified in the proposal submitted with this amendment, at Omrix Biopharmaceuticals Ltd., Fibrin Pad Production Facility, Nes-Ziona, Israel and Omrix Biopharmaceuticals Ltd. --(b)(4)-----Israel. The report for this commitment and updated relevant SOPs will be submitted to the FDA by February 2013 as a PMC Submission/Final Study Report.

Review of the Complete Response

On September 19, 2011, a CR letter was sent to Omrix Biopharmaceuticals Ltd., License No. 1603 for the production of the Fibrin Pad (renamed Fibrin Sealant Patch in August 2012). The BLA changed ownership to Ethicon, Inc. (License # 1879) in January 2012 (amendment STN 125392/1). DMPQ items included in the CR letter were outstanding

inspectional issues from the Pre-License Inspection performed on May 10 through May 19, 2011, at Omrix Biopharmaceuticals Ltd. -----(b)(4)-----
----- Israel Fibrin Pad Production Facility (FPPF), Nes-Ziona, Israel and detailed in form FDA 483, that were not resolved.

The observations for PFI included inadequate cleaning validations and programs for facility and equipment; inadequate environmental monitoring program and monitoring of compressed air system; wall surfaces at PFI were rough, pitted scratched, and thus unsuitable for cGMP manufacturing.

The observations for FPPF included a Special Processing Request procedure that allows for the implementation of deviations to the established manufacturing process without performing adequate documentation of the deviation and formal tracking of the occurrence; inadequate cleaning validations and programs for facility and equipment; inadequate qualification of the ---(b)(4)---; inadequate environmental monitoring program and handling of EM deviation # 56-09; inadequate smoke studies to establish that classified, critical manufacturing areas provide and maintain laminar air flow; and inadequate shipping validation and procedures.

Ethicon/Omrix provided additional studies and information to address the outstanding inspectional issues in the following amendments and in the August 2, 2012 Telecon:

- Amendment 125392/0/11 received March 30, 2012 – Complete Response
- Amendment 125392/0/12 received April 30, 2012 – Cleaning validation reports
- Amendment 125392/0/17 received July 16, 2012 in response to June 13, 2012 Information Request
- Amendment 125392/0/26 received September 10, 2012 – Equipment Clean and Sanitize hold time reports for FPPF
- Amendment 125392/0/27 received September 18, 2012 to confirm the PMC

My review of the amendments which is documented in the 483-response review memo found the responses to be acceptable with Ethicon/Omrix committing to modify the acceptance limits for -----(b)(4)----- of equipment, and to complete the cleaning validation (CV) studies based on a (b)(4) CV strategy for major equipment groupings, at Omrix Biopharmaceuticals Ltd., Fibrin Pad Production Facility, Nes-Ziona, Israel and Omrix Biopharmaceuticals Ltd.,----- (b)(4)-----
-----Israel as specified in the proposals submitted with the PMC in amendment 125392/0/27. The report for this commitment and updated relevant SOPs will be submitted to the FDA by February 2013 as a PMC Submission/Final Study Report.