

MEMORANDUM



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



To: Administrative file BLA STN 125392/0

Meeting Date: 19 April 2012; 10:00 A.M.

From: TRACY TILGHMAN, Regulatory Project Manager
CBER/ OBRR/ DBA/ RPMB

Subject: First Committee Meeting for Amendment to original BLA,
STN 125392/0.11 (responses to the CR letter)

Applicant: ETHICON Inc.

Product: Fibrin Pad [EVARREST]

Call-in Telephone Number: --b(4)-----

Meeting Attendees:

RPM: Tracy Tilghman, Consumer Safety Officer, OBRR/DBA
CMC/Chairperson: Natalya Ananyeva, Senior Staff Fellow, OBRR/DH/LH
CMC: Nancy Kirschbaum, Chemist, OBRR/DH/LH
Clinical: Kimberly Lindsey, Medical Officer, OBRR/DH/CRB
Pharm-Tox: La’Nissa Brown-Baker, Pharmacologist, OBRR/DH
Statistics: John Scott, Acting Deputy Director, OBE/DB/TEB
OBE: Faith Barash, Medical Officer, OBE/DE
DBSQC: Karen Campbell, Biologist, DBSQC,
APLB: Loan Nguyen, Consumer Safety Officer,
OCBQ/DCM/APLB
Kristine Khuc, Consumer Safety Officer,
OCBQ/DCM/APLB
DH Supervisory: Howard Chazin, Deputy Director of Medical Affairs,
OBRR/DH

Meeting Objective

To announce submission of an Amendment to the original BLA from Ethicon for the Fibrin Pad [EVARREST] with responses to the CR letter, and to discuss the proposed review timelines

Meeting Minutes

The Chairperson (Natalya Ananyeva) provided an overview of the original BLA and the current status of the submission. The original application for the Fibrin Pad [EVARREST], a biologics/device combination fibrin sealant product, was submitted by Omrix (currently Ethicon) in November 2010. The first review cycle resulted in issuance of a Complete Response (CR) letter to Omrix (dated September 19, 2011) due to deficiencies in clinical safety data and outstanding issues from the Pre-License Inspection of the manufacturing facilities and BIMO inspections.

Ethicon responded to the CR in the Amendment STN 125392/0.11, which was received by FDA on March 30, 2012. The review team was given 14 days to determine whether the response was sufficient to start the review clock. Summarizing opinion of the review committee members, the Chairperson determined that the Amendment STN 125392/0.11 can be considered as a Complete Response to the CR letter as Omrix/Ethicon formally addressed all CR items. The Amendment is classified as a Class 2 re-submission as it contains a large amount of new clinical data and the Applicant's corrective actions to address the issues from the Pre-License Inspection. The Acknowledgement letter to Ethicon was issued on April 12, 2012, stating the new Action Due Date of September 29, 2012. The purpose of the First Committee Meeting for this Amendment is to set preliminary review timelines for the review team to adhere in order to complete the review within the 6-month period.

The RPM (Tracy Tilghman) went through the timelines associated with this submission. The important dates include: the follow-up meeting to update on any identified deficiencies (to be scheduled for early May 2012), the Mid-Cycle date, and the Promotional Labeling Review.

Aspects discussed at the Meeting

1. *To assess whether the application is subjected to BPAC (Blood Products Advisory Committee) review*

The Clinical Reviewer informed that this submission will not trigger an Advisory Committee review because the Fibrin Pad does not represent a historically novel product class, as fibrin sealants have been on the market for extended time. A similar approved product, TachoSil, did not go to an Advisory Committee. The justification will be provided.

2. *To assess whether the application triggers PREA (Pediatric Review Equity Act)*

The Clinical Reviewer confirmed that this application triggers PREA. This application will be submitted to the PERC Committee Meeting, which is usually 2-3 months before Action Due Date. Kimberly will discuss with the PREA point of contact (Nisha Jain) the relevant dates to present this BLA at the PERC Committee Meeting. The RPM will follow-up with the Clinical Reviewer on this information at the next Committee Meeting.

3. To identify if facility and BIMO inspections are needed

The Chairperson stated that the Pre-License Inspection of the --b(4)-----
----- and Fibrin Pad Production Facility (--b(4)-----, Israel) was performed in May 2011. Considering that the review of the responses to the CR letter occurs within the two-year period from May 2011, the results of the first inspection remain valid and do not warrant another inspection. For the final decision, the Chairperson needs to hear the recommendation of the DMPQ reviewer at the next Committee Meeting.

The Clinical reviewer informed that the Amendment includes the Final Report of the new Phase 3 Clinical Study. As this data is in response to the CR letter, a BIMO inspection of the international clinical site(s) involved in this Study would be informative. Kimberly will perform a cursory review of the clinical data quality and will work with the BIMO reviewer to plan an inspection. As BIMO inspections are performed by the Field Office and require advanced scheduling, the short review timeframe presents a serious challenge.

4. The labeling aspect of the submission

Generally, the APLB reviews the Prescribing Information text and other labeling components after obtaining confirmation from the Clinical Reviewer that the clinical information is sufficient to warrant an approval. Therefore, Kimberly plans to complete her review tentatively by the Mid-Cycle in order to have sufficient time to work with the APLB on the Labeling.

5. To determined if Press Release is needed

The Clinical Reviewer stated that a Press Release does not appear to be needed for this submission as EVARREST will be the second combination fibrin sealant product after TachoSil. The Press Release was prepared for TachoSil. The Chairperson and Clinical reviewer will clarify the need for the Press Release with their supervisors by the next meeting.

6. Lot Release

The CMC reviewer/Chairperson will cooperate with the DBSQC reviewer (Karen Campbell) to develop Lot Release Testing Plan and Lot Release Protocol. The DBSQC reviewer inquired whether the Lot Release process will include sample testing. The Chairperson stated that the Lot Release process for EVARREST will likely follow ---b(4)-----
----- . The critical tests are potency tests developed by Omrix/Ethicon for biological substances applied on the medical device. These tests are not established at CBER. Justification will be provided in the Lot Release Plan.

7. Summary Basis for Regulatory Action (SBRA)

The Chairperson will verify the timelines associated with the preparation of the SBRA and will obtain the current SBRA template at a later stage of review, when the recommendation for this submission is developed.

8. To assess whether PMC/PMR will be needed

The Clinical Reviewer indicated that there might be a PMR/PMC associated with this submission, including post-marketing monitoring for product's immunogenicity. However, it is premature to provide a definite recommendation and to define whether the submission needs to go before the Safety Working Group (SWG).

Action Items

1. To schedule the next Committee Meeting for early May 2012 in lieu of the Filing meeting, as this submission has previously been filed. The purpose of the Meeting:
 - a. To obtain an update from the reviewers on any identified deficiencies in order to meet the Day 74 milestone.
 - b. To make a decision whether the facilities and BIMO inspections are warranted, based on the recommendation from the DMPQ and Clinical/BIMO reviewers, respectively.
2. The RPM will prepare the detailed Review Schedule to assist the reviewers.
3. To schedule the Mid-Cycle Meeting on June 22, 2012. The Chairperson requested that the reviewers complete their general review and general recommendation for this submission by Mid-Cycle. The RPM will confirm whether the Mid-Cycle review memo should be signed off by the immediate supervisor as recommended by the Chairperson.
4. To follow-up regarding scheduling presentation of the submission at the PERC Committee Meeting.