

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 of BLA STN 125392/0

Meeting Date: 17 May 2012; 10:00 A.M.

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

Subject: Second Committee Meeting for Amendment to original
BLA, STN 125392/0.11 (in lieu of the Filing Meeting)

Applicant: ETHICON Inc.

Product: Fibrin Pad [EVARREST]

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

Review Committee Members (listed according to attendance):

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|------------------|----------------------------------------------------------|
| RPM: | Tracy Tilghman, Consumer Safety Officer, OBRR/DBA |
| RPM: | Mark Shields, OBRR/DBA/RPMB |
| CMC/Chairperson: | Natalya Ananyeva, Senior Staff Fellow, OBRR/DH/LH |
| CMC/Facility: | Randa Melham, OCBQ/DMPQ |
| Clinical: | Kimberly Lindsey, Medical Officer, OBRR/DH/CRB |
| Pharm-Tox: | La’Nissa Brown-Baker, Pharmacologist, OBRR/DH |
| BIMO: | Dennis Cato, OCBQ/DIS/BMB |
| OBE: | Faith Barash, Medical Officer, OBE/DE |
| CDRH: | Roxolana Horbowyj, OMPT/CDRH/ODE/DSORD/GSDB |
| DBSQC: | Karen Campbell, Biologist, DBSQC, |
| APLB: | Loan Nguyen, Consumer Safety Officer, OCBQ/DCM/APLB |
| APLB | Kristine Khuc, Consumer Safety Officer, OCBQ/DCM/APLB |
| DH: | Nisha Jain, Supervisory Medical Officer, OBRR/DH/CRB |

First Committee Meeting Summary (19 April 2012):

On 30 March 2012, FDA received from ETHICON Amendment to their original BLA for Fibrin Pad [EVARREST], STN 125392/0.11, which contains the Applicant's responses to the Complete Response letter issued on 19 September 2011. FDA issued an Acknowledgement Letter on 12 April 2012, and classified STN 125392/0.11 as a Class 2 re-submission (6-months review clock), with a new Action Due Date of 29 September 2012.

Meeting Objective for the Second Committee Meeting:

- To obtain an update on items discussed during the First Committee meeting
- To obtain an update from all the reviewers on any identified deficiencies in order to meet the Day 74 milestone (Deficiencies Identified date: **12 June 2012**)

MEETING MINUTES

1. *Inspections: To make a decision regarding the need for any facilities and/or BIMO inspections based on the recommendations from the DMPQ, Clinical, BIMO reviewers, and the Chairperson.*

The DMPQ reviewer (Randa Melhem) did not identify the need for a new facility inspection: FDA inspection of Omrix's manufacturing facilities – --b(4)-----
-----, and Fibrin Pad Production Facility in
----b(4)-, Israel, was conducted in May 2011. The results of facility inspections are valid for 2 years; therefore, a new inspection is not required. Additionally, Ethicon/Omrix recently completed the cleaning validation of equipment and submitted validation reports as part of their response to the FDA Form 483 comments. Upon reviewing these reports, DMPQ considers that several inspectional issues were not adequately resolved so that the DMPQ reviewer is preparing an Information Request for additional clarifications.

The Committee Chair (Natalya Ananyeva) concurred with Randa that the results of the 2011 inspection remain valid and another facility inspection is not warranted.

The Clinical and BIMO reviewers (Kimberly Lindsey and Dennis Cato) commented on inspections of the clinical sites. The Clinical reviewer summarized that the clinical data for Fibrin Pad in the original submission was collected in a Phase 2 soft tissue study 400-07-002 and Phase 3 soft tissue study 400-08-002 performed outside the US (submitted in June 2011). While the primary efficacy endpoint was met, the submitted data was found insufficient to support the safety profile of the Fibrin Pad during the first round of review. With the current Amendment, additional safety data from the liver study conducted outside the US have been submitted in support of the indication proposed under original BLA 125392, i.e. as an adjunct to hemostasis in soft tissue bleeding. The total safety data set includes about 230 patients. ---b(4)-----
-----). The initial review of the liver surgery study did not identify any obvious safety signals that

would warrant another BIMO inspection. However, the review of the case reports is on-going, and final conclusions cannot be made at this time. The Clinical reviewer is planning to complete the primary review and to provide recommendation at the Mid-Cycle Meeting. At this time, the Clinical reviewer does not request another BIMO inspection for this submission.

BIMO reviewer (Dennis Cato) stated that BIMO inspections in such cases are initiated only when the need for such inspection is identified. The Clinical reviewer does not request another BIMO inspection for the current submission. Additionally, considering that the liver surgery study was conducted at foreign clinical sites, there is not enough lead time to conduct a foreign inspection and to obtain the results to meet the 29 September 2012 Action Due Date (ADD). The earliest time to perform such an inspection would be October 2012 and that would be past the ADD.

The Committee Chair concurred that additional BIMO inspection is not indicated. This decision of the committee will be documented as a memo from BIMO.

2. *PREA: To schedule presentation of the submission at the PeRC Committee Meeting.*

This submission does trigger PREA, and Ethicon/Omrix is requesting a deferral. The scheduling of the presentation at the PeRC Committee Meeting will be coordinated by the Clinical reviewer following the Mid-Cycle meeting.

3. *BPAC (Blood Products Advisory Committee) review*

It was determined that this submission does not trigger a BPAC review because the Fibrin Pad does not represent a historically novel product class. The Chair will include "Justification" in the SBRA.

4. *Safety Working Group (SWG)*

It is premature to conclude that this submission does not need to go before Safety Working Group. The Clinical reviewer may have to revisit this at the Mid-Cycle meeting. Two issues - involving immunogenicity and repeat exposure to Fibrin Pad - may cause this submission to have to be presented at the SWG. The Clinical reviewer would like to use TachoSil as a precedent for this submission, but the details will be further discussed at the Mid-Cycle meeting.

5. *The labeling aspect of the submission*

- a. *Re-evaluation of Proprietary Name Request (PNR), i.e. [EVARREST] – is a new request from Ethicon needed?*

The Consultant APLB reviewer (Loan Nguyen) made the following clarification: Ethicon does not need to submit a new request for the PNR since it was submitted with the original BLA and the initial PNR review

was performed earlier (please refer to the ABLB's memo dated 7 February 2011). The next evaluation for current market trends will be conducted by APLB 90 days prior to Action Due Date.

*b. How to address ETHICON's proposal for a new term, --b(4)-----
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APLB does not review proper name and defers its determination to the Product Office. APLB has a concern about the --b(4)--- part of --b(4)----- as it may imply some live interaction.

The committee members' general opinion was that the term --b(4)----- Matrix is promotional and misleading.

The Chairperson expressed opinion of the Product Office: Fibrin Pad from Ethicon/Omrix will be the second (after TachoSil) combination fibrin sealant product. The proper name for this class of products was established with TachoSil as Fibrin Sealant Patch and is sufficient. Therefore, the proper name for EVARREST should be Fibrin Sealant Patch.

The RPM will relay to Ethicon the request not to use the term "---b(4)-----
----- in the labeling components.

6. To determine if Press Release will be needed

As discussed at the First Committee Meeting, Press Release for EVARREST does not appear to be needed as Press Release was prepared for TachoSil, the first combination fibrin sealant product.

The Chairperson may have to revisit this decision, as historically Press Release used to be created with each new BLA. Press Release may be needed for EVARREST as the indication for EVARREST (adjunct to hemostasis for soft tissue bleeding) differs from the indication for TachoSil (adjunct to hemostasis in cardiovascular surgery).

Nisha Jain explained that if the review committee moves forward with a press release, it should be drafted 40 days prior to ADD provided that the product will be approved. This aspect will be followed up at the Mid-Cycle Meeting.

7. Lot Release Testing Plan and Lot Release Protocol

The DBSQC reviewer (Karen Campbell) commented on procedures, documentation and timelines for the Lot Release process. The SOPP 8408.1 provides the general guidance for this process which includes (i) development of the Lot Release Protocol by the Applicant and its review by FDA; and (ii) development of the Lot Release Testing Plan by the Product Office in cooperation

with PRB and DBSQC. Due to the confidential nature of the Testing plan, the DBSQC reviewer would like to prevent these memos from being posted on the web.

The RPM will inquire about redacting the memos to be posted and will provide the DBSQC reviewer with an update.

The draft of Lot Release Protocol should be submitted to the BLA for review and the final agreed-upon version should be submitted again to the BLA file. The interim versions during the negotiations can be corresponded by email. The emails should be recorded as telecons to the BLA in order to monitor changes to the Lot Release Protocol.

Around the time the Lot Release Protocol is finalized, the Lot Release Testing Plan needs to be developed, which should include assignment of reviewers for each test. These documents need to be finalized at least a month prior (30 days) to the ADD. The Testing Plan can be developed in parallel with Lot Release Protocol but can be signed off only based on the finalized Protocol.

RPM will reflect these timelines in the Review Schedule.

8. *PMC/PMR*

The Clinical reviewer considers surveillance for immunogenicity and effects of repeat exposure as potential items of PMC/PMR. However, as these are general questions, their regulatory surveillance post-approval will require a broader input from the management and OBE and definite recommendation can not be provided at this stage of review.

Action Items:

1. Information Requests (IR) related to any identified deficiencies should be sent to the Applicant by 12 June 2012. Requests for additional information can be sent as a regular IR afterwards. Any Information Requests should be concurred by immediate supervisors before they are sent to the Applicant.
2. The Mid-Cycle meeting will be scheduled for June 22, 2012. The purpose is to make a preliminary conclusion on the adequacy of Ethicon's responses to the CR letter and to identify any significant issues that may prevent approval of this submission.
3. Preparation of the Mid-Cycle memo should follow reviewer's office requirements as they are different.