

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: 22 June 2012; 10:30 A.M.

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

Subject: Mid-Cycle Meeting for Submission of Amendment to
original BLA, STN 125392/0.11

Applicant: ETHICON Inc.

Product: Fibrin Pad [EVARREST]

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

Meeting Attendees:

RPM: Tracy Tilghman, Consumer Safety Officer,
OBRR/DBA/RPMB

RPM: Mark Shields, Consumer Safety Officer
OBRR/DBA/RPMB

RPM: Iliana Valencia, Consumer Safety Officer,
OBRR/DBA/RPMB

CMC/Chairperson: Natalya Ananyeva, Senior Staff Fellow, OBRR/DH/LH
CMC/Facility: Randa Melham, OCBQ/DMPQ
CMC: Timothy Lee, Branch Chief, OBRR/DH/LH
Clinical: Kimberly Lindsey, Medical Officer, OBRR/DH/CRB
Pharm-Tox: La’Nissa Brown-Baker, Pharmacologist, OBRR/DH ,
CDRH: Roxolana Horbowyj, OMPT/CDRH/ODE/DSORD/GSDB
DBSQC: Karen Campbell, Biologist, DBSQC
APLB: Loan Nguyen, Consumer Safety Officer,
OCBQ/DCM/APLB
Kristine Khuc, Consumer Safety Officer,
OCBQ/DCM/APLB

DH: Basil Golding, Director, OBRR/DH
DH: Mahmood Farshid, Deputy Director, OBRR/DH
DH: Paul Mintz, Deputy Director, OBRR/DH

Meeting Objective for Mid-Cycle Meeting:

- To obtain a comprehensive update on the state of review from each reviewer in order to assess the adequacy of Ethicon's responses to the CR letter.

MEETING MINUTES

The Chairperson briefed the committee on the regulatory history of the BLA and deficiency items cited in the CR letter of 19 September 2011, and requested that the reviewers provide their assessment of Ethicon's responses to the CR letter (please refer to the Power Point presentation).

1. Form 483 Inspection Issues:

The DMPQ reviewer briefed the committee on the results of Pre-License Inspection of May 10th-19th, 2011. A nine item FDA Form 483 was issued for objectionable conditions related to cGMP Compliance observed during the inspection at b(4), and an eight item FDA Form 483 was issued for the FPPF. The observations included inadequate cleaning validations and programs for facility and equipment, inadequate environmental monitoring program, and inadequate qualification of equipment ---b(4)-----

DMPQ reviewed the information in Ethicon's responses to the CR letter and determined that the responses to a number of the 483 observations are not adequate at this time, and several inspectional issues remain unresolved. The DMPQ reviewer sent information request (IR) containing 37 questions to Ethicon on 13 June 2012 to address these issues. The remaining non-compliance issues include the cleaning validation and the environmental monitoring of the facility where the Fibrin Pad is manufactured. DMPQ also requested that Ethicon revises SOPs to state that the validated shippers must be used for shipping the product. The responses are due by 13 July 2012. DMPQ informed Ethicon that all inspectional issues must be resolved and the relevant data submitted prior to the commercial launch of the product. Depending on Ethicon's response to the IR, Postmarketing Commitments (PMCs) may be requested.

2. Clinical Report on Safety Data and Monitoring Immunogenicity:

The Clinical reviewer stated that the major problem with the original submission was insufficient clinical information to assure safety of EVARREST in the intended surgical population: there was an unfavorable trend for Fibrin Pad for Thromboembolic Events (TEEs) observed in the Phase 2 Clinical Study 400-07-002.

In their complete response, Ethicon submitted additional data from a study in liver resection surgery in which EVARREST was evaluated for safety and efficacy as an adjunct to hemostasis (Study 400-10-001). Upon review of the data, the Clinical reviewer did not find any significant imbalance of TEs with the use of

Fibrin Pad in this additional study. Based on the totality of the clinical data, the potential safety issues appear to be resolved. Other categories that were reviewed include cardiac events and coagulation disorders, and no significant imbalances were found.

Other issues of potential concern can be addressed in the labeling.

One of such concerns is potential formation of lesions, which could form due to Fibrin Pad dislodgement. In addition to providing warning information in the labeling, these potential post-surgery events can be indexed and captured utilizing telephone calls. Additionally, information is lacking regarding the long term effects of the implanted device component on patients with cancer or local recurrence of cancer. Other potential issues include inaccurate use of Fibrin Pad by providers which can be addressed by preparing clear instructions for use.

Natalya provided a summary of Immunogenicity Reports from two Clinical Studies – 400-07-002 and 400-08-002 – intended to assess the immunogenic potential of Fibrin Pad. Testing for antibodies to Human Fibrinogen and Human Thrombin was performed by ELISA for up to 10 weeks post-surgery. The rate of seroconversion in response to Human Thrombin in the Fibrin Pad group (~ 2%) was close to the expected rate in the normal population. There was a transient or no response to Human Fibrinogen. There were no clinical signs of systemic effects of antibodies (normal prothrombin time, activated partial thromboplastin time). The overall conclusion is that the immunological risk associated with the use of Fibrin Pad appears to be low (please refer to the Power Point Presentation).

Kimberly proposed two options for continuing monitoring for immunogenicity post-approval: either in a separate PMR clinical study or ----b(4)-----

----- The review committee seeks the advice from the Division of Hematology Director on this issue.

Another potential concern relates to repeat exposure to the Fibrin Pad. Although Fibrin Pad is to be marketed as a one-time use product, there is a potential for repeat exposure in staged operations or subsequent operation in the distant future. In the case of re-exposure, the possibility of incomplete pad absorption should be taken into consideration. A recent case example involves the product TachoSil, where the patient was treated with the patch and the patch remnants were found six years post-study by another surgeon. It appears infeasible to explore repeat exposure in clinical studies due to several reasons including ethical and practical. It appears more feasible to collect this information in pre-clinical studies. Potential follow-up timeframe may last past 30 days in order to capture the required information. Such request for a pre-clinical study for repeat exposure was sent to Ethicon under -b(4)----- . The

Clinical reviewer seeks advice from the management if this regulatory pathway is applicable for the BLA.

BIMO inspections: of the two inspections classified as VAI, a response was requested from one site (Site 011, R. Adams Cowley Shock Trauma Center in Baltimore, MD). OCBQ determined that all issues identified during the BIMO inspection were adequately addressed in the response letter from Site 011. Additional BIMO inspections are not indicated.

3. PMRs/PMCs:

PMRs/PMCs have not yet been identified at this time. The need for cGMP-related PMCs will be identified based on Ethicon's responses to the IR (due on 13 July 2012).

The need for clinical PMRs (for immunogenicity and repeat exposure) is pending the DH Director's advice.

4. Labeling:

The Labeling review will start shortly after mid-cycle. The Clinical reviewer will work directly with the APLB on the labeling for this submission. The comments from the review team should be provided directly to the Clinical Reviewer tentatively by July 16th.

The new term proposed by Ethicon - --b(4)----- - was found to be misleading and promotional. The Chairperson stated that utilizing the proper name (Fibrin Sealant Patch) and the proprietary name (EVARREST) should be sufficient for this product. No additional terms are necessary for the product's description. The proper name "Fibrin Sealant Patch" is recommended by the Product Office because this term accurately describes the primary mode of action (fibrin sealant) and the mode of biologics delivery to the wound site (patch). This term for fibrin sealant combination products was previously established for the first product in this class – TachoSil (approved under STN 125351/0).

5. Lot Release Testing Plan and Protocol:

Lot Release Protocol was developed by Ethicon and initially reviewed by FDA in July 2011 during the first round of review. Revised version was submitted on 23 May 2012.

Teleconference with Ethicon to discuss the Technology Transfer and Lot Release process was held on 13 June 2012. A follow-up teleconference is scheduled for 27 June 2012. Lot Release Testing Plan is in preparation by Product Office, DBSQC and DMPQ/PRB.

Action Items:

1. Follow-up teleconference with Ethicon on Technology Transfer/Lot Release: 27 June 2012 (reviewers from Product Office, DBSQC/PRB, and CRB are required).
2. Scheduling presentation of the BLA at the PeRC meeting (Clinical reviewer).
3. Preparation of draft BPAC Waiver Memo and draft Press Release (Chairperson).
4. As the submission is a response to the CR letter, the involved reviewers will determine the need for a mid-cycle memo or Information Request according to office specific requirements.
5. Labeling review: preliminary comments from reviewers to Kimberly by July 16th.
6. Due to the short review timeframe, no additional joint committee meetings are planned. The reviewers will work in sub-groups according to review disciplines. The Chairperson requested that Final Review Memos and Executive Summaries are prepared in parallel, and Executive Summaries be sent to Chairperson by August 30th.