

MEMORANDUM



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



To: File for BLA (STN 125392/0) and Tracy Tilghman, CSO, CBER/OBRR/DBA

From: Natalya Ananyeva, Ph.D., Laboratory of Hemostasis (LH), Division of Hematology (DH)/OBRR

Through: Timothy Lee, Ph.D., Acting Chief, LH/DH/OBRR

Subject: Final Review of CMC information in the original BLA for Fibrin Sealant Patch [EVARREST] (Applicant – Ethicon, Inc.)

This memorandum summarizes the Final Review of the CMC information in the original Biologics License Application (BLA), STN 125392/0, for Fibrin Sealant Patch, with the proposed proprietary name EVARREST. The original application was submitted by Omrix Biopharmaceuticals Ltd. on 19 November 2010. The ownership of the BLA was transferred to Ethicon, Inc. on 9 January 2011, and accepted by Ethicon, Inc. on 10 January 2011.

Description: Fibrin Sealant Patch* is a ready-to-use, sterile, bio-resorbable hemostatic agent. EVARREST is a biologics/device, single-entity combination product consisting of plasma-derived Human Fibrinogen and plasma-derived Human Thrombin (biologics components) coated onto a backing layer** (device component). The backing layer consists of an oxidized regenerated cellulose (ORC) layer under a layer of polyglactin 910 (PG910) non-woven fibers. The PG910 side contains the embedded biologics components.

Proposed indication: EVARREST Fibrin Sealant Patch is indicated for use with manual compression as an adjunct to hemostasis for soft tissue bleeding during open retroperitoneal, intra-abdominal, pelvic, and (non-cardiac) thoracic surgery when control of bleeding by standard surgical methods of hemostasis (e.g., suture, ligature, cautery) is ineffective or impractical.

Regulatory History

The pre-BLA meeting with Omrix Biopharmaceuticals, Ltd. (Omrix) was held on 1 October 2009, and the original BLA for EVARREST was submitted to the Agency on 19 November 2010. Upon a complete review of the submission, no CMC issues were identified that might prevent approval of the BLA; however, there were outstanding issues identified by the Clinical and Facility reviewers that led to issuance of a Complete Response (CR) letter by FDA on 19 September 2011. The main deficiencies cited in the CR letter included (i) insufficient clinical information to assure safety of EVARREST in the intended surgical population in light of the adverse events observed in the Phase 2 Clinical Study 400-07-002, and (ii) outstanding cGMP

issues identified during the Pre-License Inspection (PLI) performed from May 10th to May 19th, 2011 at Omrix's -----(b)(4)----- and Fibrin Pad Production Facility (FPPF). Procedural non-compliance observations were also made during the bioresearch monitoring inspections and were stated in the CR letter.

Ethicon's complete response to the CR letter was received on 30 March 2012. Ethicon submitted a report of an additional clinical study in which EVARREST was prospectively evaluated for safety and efficacy as an adjunct to hemostasis in liver resection surgery. The outstanding observations in the FDA Form 483 issued at the Pre-License Inspection were also addressed.

During the second round of review, the CMC information in the original BLA and subsequent amendments was re-evaluated based on a better perception of the manufacturing process and product characteristics gained during the PLI. This analysis has further confirmed my recommendation of BLA approval from a product-reviewer perspective. This memorandum summarizes the review of the CMC information in the original submission, Omrix/Ethicon's responses to the Information Requests (Amendments #03 dated 15 March 2011, #07 dated 30 June 2011, and #19 dated 13 August 2012), and includes discussions during the Pre-License Inspection of Omrix Biopharmaceuticals, Ltd. (May 10 - 19th, 2011). The memo was drafted on 14 September 2012, and the current document is a concurred version.

RECOMMENDATION

The Applicant has provided sufficient data and comprehensive information on Chemistry, Manufacturing and Controls, and I recommend APPROVAL of the BLA for EVARREST Fibrin Sealant Patch. Two remaining items (related to the ----(b)(4)---- Drug Substances and Final Product Specifications) will be addressed in Post Marketing Commitments listed at the end of this memorandum. The Applicant confirmed their commitment in Amendment #27 dated 17 September 2012.

The Facility reviewer concludes that the corrective actions described in Ethicon's responses to the CR letter have adequately addressed the outstanding FDA Form 483 observations. One remaining item is addressed in a Post Marketing Commitment. It is related to the completion of -
------(b)(4)-----.

The Clinical reviewer concludes, based on review of the results from the overall clinical program, that both efficacy and safety of EVARREST have been adequately demonstrated for the proposed indication in adult surgical population.

** Throughout the memorandum, Fibrin Sealant Patch (the proper name), Fibrin Pad (the term used during product development and in pre-clinical and clinical studies) and EVARREST (the proprietary name) are used interchangeably.*

***FDA uses the term "backing layer" to define the device component of EVARREST. The term "matrix" is used in the memorandum for consistency with the information in the BLA only, and does not confer any clinical meaning.*

EXECUTIVE SUMMARY

1. Formulation development studies for optimizing doses of the biological Drug Substances and composition of the backing layer for the Fibrin Sealant (FS) Patch commercial product are extensive and scientifically valid. The selected dose ranges for Fibrinogen (measured as ----(b)(4)----- in the Drug Product: -----(b)(4)-----]) and Thrombin (measured as Thrombin Activity in the Drug Product: -----(b)(4)----- are supported by the monitoring of physicochemical and functional parameters of the FS Patch (analytical data, ---(b)(4)--, coating uniformity, adhesiveness, and hemostatic performance in animal models). The input doses take into account the losses of Thrombin during the e-beam irradiation and ensure Thrombin Activity at release to be within the set Specification range. The Specification dose ranges for both Fibrinogen and Thrombin are consistent with dose ranges tested in non-clinical and clinical studies, factoring in the validated manufacturing and analytical capabilities.
2. The manufacturing changes implemented in the course of FS Patch product development are described in the BLA and are adequately supported by Comparability Reports. These changes were reported to FDA under IND 13563, and were reviewed and considered acceptable. Specifically, the input doses for the biological substances were changed from non-clinical to clinical and to commercial material; however, they all remain within the set Specification ranges. The Specification ranges for Fibrinogen and Thrombin have not been changed throughout product development. Study Report FLC-001 supports the comparability of FS Patches used in non-clinical and Phase 1 clinical studies in analytical characteristics and ability to achieve hemostasis in a swine acute aortotomy model. Study Report QA-R-FP-0015-00 further supports the comparability of Clinical and Validation batches of EVARREST by *in vitro* potency and hemostatic efficacy in a porcine partial nephrectomy model.
3. The validation of the manufacturing process was conducted by manufacturing three consecutive maximal-scale FS Patch batches - -----(b)(4)----- -- using the -----(b)(4)----- for the application of Drug Substances to the backing layer and final sterilization by e-beam irradiation within the validated dose range of ----(b)(4)----- The in-process testing results and release data were compliant with pre-determined acceptance criteria, for all parameters, reflecting consistency of the manufacturing process. The established intermediate hold times, in particular the -----(b)(4)-----are appropriately validated in stability studies and by ----(b)(4)--- testing.
4. The manufacturing process is adequately controlled. The implemented controls over the input doses (----- (b)(4)-----) and potencies in the Drug Product (----(b)(4)----- and Thrombin Activity) minimize the risk of dosing out of the Specification limits. Analytical procedures are validated for determination of Potency (---(b)(4)-----, Thrombin Activity and ----(b)(4)-----) and Purity (----- (b)(4)-----, Endotoxin, Sterility, and Package Integrity) of the FS Patch Drug Product. The implemented sampling procedures allow for reliable control of the coating uniformity of Drug Substances across a FS Patch and consistency of the coating process across production days.

5. The stability studies with Clinical and Process Validation batches are completed. The available 24-month data for recommended storage conditions and ---(b)(4)--- data for the accelerated condition remain within the Specification for all parameters and all batches, thus supporting the proposed shelf-life of 24 months when stored at 2 to 25°C.
6. Ethicon/Omrix performed risk assessment of potential immunogenicity of the FS Patch due to exposure of its components to --(b)(4)-- solvent --(b)(4)- and e-beam irradiation during the manufacturing process. The 90-day sub-chronic toxicity study in the rat demonstrated toxicological and immunological comparability between FS Patch and the predecessor fibrin sealant, EVICEL. Review of the data collected in the Clinical Studies 400-07-002 and 400-08-002 (with the observation period of up to 10 weeks) indicated that the rate of change in the detection signal of anti-thrombin antibodies was within the expected rate, with no increase in the antibody titer and no evidence of systemic effects (thrombotic complications of coagulopathy). There was no detectable response to Fibrinogen. Thus, the risk of development of a clinically relevant immune response in patients treated with EVARREST can be considered low.
7. Omrix performed expanded investigation of the manufacturing and analytical data for Lots L11F284 and M06F164 that were associated with thromboembolic events in the Phase 2 Clinical Study 400-07-002. No plausible association of the adverse events with the product quality was identified. Based on the totality of the clinical data (in the original submission and responses to the CR letter), the Clinical reviewer concludes that the safety of EVARREST has been demonstrated for the proposed indication in adult surgical population.

REVIEW SUMMARY

Fibrin sealants mimic the final stage of the blood coagulation cascade via the combination of concentrated solutions of thrombin and fibrinogen. The two-component fibrin sealants, in frozen liquid or lyophilized forms, have a long history of clinical use, including FDA-licensed products – TISSEEL and ARTISS (Baxter Healthcare Corp.), and EVICEL (Omrix Biopharmaceuticals Ltd.).

The underlying concept for EVARREST is to combine the hemostatic properties of fibrin sealants with the mechanical integrity and adhesive strength of the backing layer to promote rapid and targeted hemostasis at the wound site. The flexibility of the backing layer accommodates the physiological movements of tissues and organs. In this class of fibrin sealant combination products, EVARREST is the second product seeking U.S. licensure; a similar product, TachoSil from Nycomed, Austria (currently Takeda Pharmaceuticals Intl.) was approved by FDA under STN 125351/0 in April 2010 (U.S. license 1825).

Both biologics components, Human Fibrinogen and Thrombin, are-----
 -----(b)(4)-----

Both components of the backing layer - oxidized regenerated cellulose and PG910 polymer fiber

-(b)(4).

EVARREST is supplied in 4 x 4 in. (10.2 x 10.2 cm) patches, with the active side being white-to-yellowish in color and powdery in appearance, and the non-active side having an embossed wave pattern. Each patch of EVARREST contains nominally 50.3 mg/in² (7.8 mg/cm²) of Fibrinogen and 203.2 IU/in² (31.5 IU/cm²) of Thrombin.

3.2.S. HUMAN FIBRINOGEN (BIOLOGICAL DRUG SUBSTANCE)

The design and manufacture of the Fibrinogen and Thrombin biological components complies with the CGMP regulations as specified in 21 CFR 210, 211, and 600 through 680.

Human Fibrinogen Drug Substance is (b)(4). Human Fibrinogen is manufactured by Omrix Biopharmaceuticals Ltd., (b)(4); FDA Establishment Identifier [FEI] Number: (b)(4) (b)(4), Israel. (b)(4) for Human Fibrinogen Drug Substance is manufactured at Omrix Biopharmaceuticals Ltd. from human Source Plasma collected from qualified donors in FDA-licensed facilities in the United States or alternatively purchased from (b)(4), an FDA-approved supplier (U.S. License Number: (b)(4)). Source Plasma complies with the requirements of 21 CFR Part 640, applicable FDA memoranda, and additional requirements of the International Quality Plasma Program (IQPP) of the Plasma Protein Therapeutics Association.

The manufacturing process is essentially the same as for -----(b)(4)-----
-----). The manufacturing process includes Solvent/Detergent (----(b)(4)-----
-----) and pasteurization step (----(b)(4)-----) for
virus inactivation.

3.2.S. HUMAN THROMBIN (BIOLOGICAL DRUG SUBSTANCE)

Human Thrombin Drug Substance is a (b)(4)-----
----- Human Thrombin is also manufactured by Omrix's
----- (b)(4)----- The starting material is (b)(4)-----
----- is
derived from human Source Plasma --(b)(4)----- plasma collected from qualified donors in
FDA-licensed facilities in the United States. Source Plasma complies with the requirements of 21
CFR Part 640, applicable FDA memoranda, and additional requirements of the International
Quality Plasma Program (IQPP) of the Plasma Protein Therapeutics Association. --(b)(4)-----

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

Human Thrombin Drug Substance is ----- (b)(4) ----- . The manufacturing process for Thrombin includes S/D treatment (----- (b)(4) -----) and --- (b)(4) --- filtration for virus reduction.

3.2.S. COMPOSITE BACKING LAYER (DEVICE COMPONENT)

The device component of the FS Patch consists of two absorbable polymers: oxidized regenerated cellulose (ORC) and polyglactin 910 (PG910). The PG910 component was chosen as the main carrier of the biologics components. The physical configuration of the nonwoven fibers provides a surface for retaining the dry powders during storage, flexibility and good adhesion to tissue. Knitted ORC was chosen as a backing layer for the PG910 nonwoven felt to provide mechanical strength to the product and due to its re-absorption. The nominal amounts for PG910 are ----- (b)(4) ----- and for ORC – ----- (b)(4) ----- that yields a total backing layer content of ----- (b)(4) -----

Both components of the backing layer - oxidized regenerated cellulose and PG910 polymer fiber

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

-----.

The backing layer is currently manufactured by ----- (b)(4) -----, at the facility in ----- (b)(4) ----- . The backing layer is -- (b)(4) ----- . The design and manufacture of the device component complies with the QS regulations as specified in 21 CFR Part 820.

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

-----.

3.2.P. FIBRIN SEALANT PATCH (DRUG PRODUCT)

The Fibrin Pad is manufactured, tested, and packaged at Omrix Biopharmaceuticals Ltd., Fibrin Pad Production Facility (FPPF), located at 14 Einstein Str., Weizmann Science Park, Nes-Ziona, Israel (FEI Number: 3008640339).

Table 1. Composition of EVARREST Fibrin Sealant Patch

<u>Components</u>	<u>Average Value</u>			<u>Function</u>
	<u>Per in²</u>	<u>Per cm²</u>	% of patch mass	
Backing Layer	---(b)(4)---	---(b)(4)---	---(b)(4)--- ---(b)(4)--- ---(b)(4)---	Backing and Carrier
Human Fibrinogen	50.3 mg	7.8 mg	---(b)(4)---	Active Ingredient
Human Thrombin	203.2 IU	31.5 IU		Active Ingredient

-(b)(4)-

-(b)(4)-

3.2.P.2.2.1 FORMULATION DEVELOPMENT

-(b)(4).

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3.2.P.2.2.3 PHYSICOCHEMICAL AND BIOLOGICAL PROPERTIES OF FIBRIN PAD

The FS Patch was characterized by physical & biochemical properties, and by functional performance.

Mechanism of Action

Fibrin Sealant Patch is made of two biological components (human plasma-derived fibrinogen and human plasma-derived thrombin) embedded into a flexible composite backing layer.

The primary mechanism of action of FS Patch to achieve and maintain hemostasis is provided by the fibrin sealant component of the product and follows the principles of physiological fibrin clot formation. Upon contact with a bleeding wound surface, the biological components (Human Fibrinogen and Human Thrombin) within the backing layer are hydrated, and their subsequent interaction initiates the last step in the cascade of biochemical reactions - conversion of fibrinogen into fibrin monomers that further polymerize to form the fibrin clot.

The backing layer provides a large surface area for the delivery of the biological components to the wound site and imparts mechanical integrity to the product. The flexibility of the backing layer accommodates the physiological movements of tissues and organs. Hemostasis is achieved when the formed fibrin clot integrates with the backing layer to adhere to the wound surface and provide a physical barrier to bleeding.

Physical Characterization

The physical characteristics that define the FS Patch are:

- Appearance
- ---(b)(4)---
- Coating uniformity
- Mechanical strength
- ---(b)(4)---

Appearance

The FS Patch has the active PG910 side (coated with the biological components) and non-active ORC side. The two sides are distinguished in that the active side is white-to-yellowish in color and powdery in appearance, and the non-active side has an embossed wave pattern.

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

(b)(4)

Coating Uniformity

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

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

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

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

Mechanical Strength

In bleeding wound sites, the FS Patch is exposed to blood pressure forces and must withstand such forces until hemostasis is complete. The mechanical integrity of the FS Patch is characterized by its ----- (b)(4) -----, i.e., the force required to tear the patch, and is primarily a function of the backing layer (Matrix) component.

The critical role of the Matrix in the mechanical properties of the product was established by comparing the ----- (b)(4) ----- of the FS Patches with the backing layer produced by the routine manufacturing process (untreated Matrix) or after treatment that partially degrades the Matrix (treated Matrix):

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

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

FS Patch manufactured with treated Matrix exhibited lower --- (b)(4) ----- compared to FS Patch manufactured with untreated Matrix. In contrast, the adhesive strength of the FS Patch was not impacted by the treatment of the backing layer as evaluated by the ----- (b)(4) -----

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

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

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

Chemical/Biochemical Characterization

The chemical and biochemical properties of the product were characterized by:

- Content and activity of the primary components (Drug Substances and Matrix)
- --- (b)(4) ----- of the biological material
- Product and process-related impurities

Content and Activity of Drug Substances

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

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

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

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(b)(4)

(b)(4)

Three well-established animal models were used to assess the hemostatic efficacy of the Fibrin Pad in dose optimization and characterization studies. *This information was evaluated by the Pharmacology/Toxicology reviewer, and brief description of the models is provided below.*

This model was used for evaluation of Fibrin Pad hemostatic performance during formulation development. In this test, a sagittal hemi-nephrectomy of the left kidney is performed after occluding the renal vessels. Fibrin Pad is applied onto the cut surface of the kidney, the renal vessel clamp is released after 1 minute, and the kidney is observed for bleeding. The results are reported as blood loss within 60 min.

The swine aortotomy model is an acute model of more severe bleeding and was used in dose optimization studies for Fibrinogen. Following laparotomy and aortic dissection, a reproducible 4.4 mm diameter infrarenal aortotomy is created, and free bleeding is allowed for 5 seconds. Bleeding is stopped by applying the Fibrin Pad over the aortotomy site with manual compression applied for 3 minutes. Following treatment, hemostasis is observed, and the result is reported as

“pass” or “fail”. With the current formulation (i.e. with input doses of ---(b)(4)--- for Fibrinogen and ---(b)(4)--- for Thrombin), the success rate in this model is 87.5 to 100% (Table 27).

Swine Partial Nephrectomy Model

The swine partial nephrectomy model is a model of severe hemorrhage used to determine the safety and efficacy of a hemostatic product, and survival. The partial nephrectomy of the right kidney is performed, with manual compression applied to occlude the right renal artery. A FS Patch sample is next applied to the cut surface, and manual compression is held for 3 minutes. This model was used to verify performance of the Fibrin Pad at the target Fibrinogen input dose of ---(b)(4)--- and at the low end of the -----(b)(4)----- specification range (---(b)(4)---). All 11 animals in the low dose study achieved hemostasis and survived the 48-hour post-operative period with no evidence of post-operative bleeding.

Reviewer’s comments:

The Applicant presented an integral approach to characterize the Fibrin Sealant Patch that included characterization of both physical & biochemical properties and functional performance. The physical properties of the product were evaluated by the ---(b)(4)---, coating uniformity, and ---(b)(4)----- . All FS Patch components were characterized by their identity and purity (----- (b)(4)-----) as well as potency of Drug Substances within the FS Patch (----(b)(4)----- and Thrombin Activity assays). The - --- (b)(4)--- test and - (b)(4)- demonstrate the adequate adhesive strength (ability to adhere to tissue) and cohesive strength (ability to withstand pressure) of the product. The hemostatic performance of EVARREST was assessed in a variety of animal bleeding models, including the rat kidney hemorrhage model, swine acute aortotomy model, and swine partial nephrectomy model. The results demonstrate that optimization studies for the biologics dosing and matrix composition, and the developed manufacturing process yield a product with the satisfactory functional performance as a hemostatic agent. ----- (b)(4)-----

3.2.P.2.3 MANUFACTURING PROCESS DEVELOPMENT

Reviewer’s comment:

The Fibrin Sealant Patch manufacturing is a bioburden controlled process performed with aseptic techniques. The Pre-License Inspection of Omrix’s ----- (b)(4)----- and Fibrin Pad Production Facility (FPPF) was performed on May 10th-19th, 2011. The FDA inspectors (Randa Melhem and Destry Sullivan from OCBQ/DMPQ and Natalya Ananyeva from OBRR/DH) observed and evaluated the manufacture of Human Thrombin and Human Fibrinogen Drug Substances at the (b)(4) and the manufacture of the Fibrin Sealant Patch final product at the FPPF.

In their Complete Response to the CR letter dated 30 March 2012, Ethicon provided description of the corrective actions to the observations listed on the FDA Form 483 for each facility, and most of the responses were found to be adequate. One remaining item is addressed in a Post Marketing Commitment. It is related to -----(b)(4)-----

Please refer to the Review memorandum for Ethicon/Omrix responses to the 483 Observations from the DMPQ reviewer (Randa Melhem).

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

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

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

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

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

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(b)(4)

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

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

3.2.P.5.2 ANALYTICAL PROCEDURES

The history of test methods is described in Module 3.2.P.2.3 Manufacturing Process Development. Due to the composite nature of EVARREST and co-localization of Fibrinogen and Thrombin on the patch, most analytical methods were custom-developed and validated as adaptation of their respective methods described in the -----(b)(4)-----

The Quality Control Laboratory testing (in-process, release, and stability) for FS Patch was also evaluated during the PLI of Omrix's Fibrin Pad Production Facility when I observed performance of potency and purity tests. There were no objectionable observations made. Overall, all procedures associated with receiving, sampling, and testing of in-process and final product samples in each of the assays are adequately described in respective SOPs. Acceptance criteria for each assay appear stringent to assure reliability of the results. The analytical procedures and acceptance criteria for each test are described in detail in the EIR and are summarized below.

Release Testing

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

(b)(4)

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3.2.P.3.5 PROCESS VALIDATION

Release Testing

-(b)(4)-

3.2.P.5.1 RELEASE SPECIFICATIONS OF FIBRIN SEALANT PATCH

^a The active side is powdery and white to yellowish in color. The non-active side is white to yellowish in color with an embossed waved pattern.

[ETHICON] Fibrin Sealant Patch, BLA STN 125392/0

^c The result is obtained from irradiation certification as determined by ---(b)(4)---.

^d Pouch seal is clear of non-conformances in visual inspection.

There is no General Safety Test. Omrix has submitted a waiver pursuant to 21 CFR 610.11(c)(3) for “non liquid products other than freeze dried products,” which is provided in Module 1.

Stability testing includes the same tests and acceptance criteria as for release except for ---(b)(4)-----, irradiation dose, and visual inspection of foil pouch seal integrity. ----(b)(4)----- is performed during stability testing.

Reviewer’s comment:

As discussed above, -----(b)(4)----- will be added in Specification after the technical transfer of the analytical method to Omrix Biopharmaceuticals Ltd. The Applicant confirmed this Post Marketing Commitment in Amendment #27 dated 17 September 2012.

3.2.P.7 CONTAINER CLOSURE SYSTEM

The primary container closure for EVARREST is a polyester tray-and-lid assembly (the same one used for the backing layer) that is sealed within an outer pouch composed of polyester-laminated aluminum foil with an inner heat seal coating (manufactured by -----(b)(4)-----). The tray-and-lid assembly maintains product integrity during storage and transport. The aluminum pouch serves as a barrier to moisture and microbial contamination to maintain product sterility. The integrity of the container closure system was validated by testing the primary packaging upon return of the product from----(b)(4)----. The testing included seal strength measurements (Package Integrity ((b)(4)) Test) and visual inspection of the pouch and seal areas, and all results met the acceptance limits. Results of stability studies indicated that the package integrity and barrier properties were acceptable during the dating period. The secondary packaging consists of a paperboard boxelope (with a foam pad). Once the foil pouch has been placed in the boxelope, it is no longer subjected to direct human handling. The boxelope serves as the market package for the product.

3.2.P.8 STABILITY SUMMARY AND CONCLUSIONS

Ethicon requests a shelf life for EVARREST FS Patch of 24 months when stored at 2 to 25°C.

Three batches of FS Patch used in the Pivotal (Phase 2) Clinical Study and three consecutive Process Validation Batches, which were manufactured according to the current FS Patch manufacturing process, were put on long-term and accelerated stability studies:

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

Table 1. Fibrin Sealant Patch: Status of Stability Studies for Production-Scale Batches						
<u>Fibrin Pad Pivotal Batches</u>				<u>Fibrin Pad Process Validation Batches</u>		
<u>Batch</u>	<u>L11F284^a</u>	<u>M05F094</u>	<u>M06F164</u>	<u>---(b)(4)---</u>	<u>---(b)(4)---</u>	<u>---(b)(4)---</u>
Date of Manufacture	Nov 2007	May 2008	June - July 2008	July 2009	Jul - Aug 2009	August 2009
Status of Study at - ----- (b)(4) ----- -----	Completed	Completed	Completed	Completed	Completed	Completed
Status of Study at - ----- (b)(4) ----- -----	Completed	Completed	Completed	Completed	Completed	Completed
Status of Study at - ----- (b)(4) ----- -----	Completed	Completed	Completed	Completed	Completed	Completed
^a Stability was performed on Batch L11F284. Batches L11F284 and L11F294 started as the same batch with the same starting materials and intermediates, but were arbitrarily split at the (b)(4) application step to supply separate clinical (L11F294) and stability (L11F284) needs.						

Stability Program for Clinical and Process Validation Batches

The following parameters were tested for the Clinical and Validation Batches:

In vitro Activity

- ----- (b)(4) ----- Thrombin Activity (---- (b)(4) -----) and --- (b)(4) ---
----- test methods provide a measure of potency of active biological components in the Fibrin Pad product and are considered the primary stability-indicating parameters.

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

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

Matrix Components

- ----- (b)(4) ----- are identity tests used at the beginning and at the end of the stability study.
- ----- (b)(4) ----- which controls the mechanical strength of the Fibrin Pad.
- For commercial batches, ----- (b)(4) ----- test will substitute the ----- (b)(4) ----- tests as a more direct measure of the mechanical strength of the Matrix.

Physical Tests

- Appearance test is used to assess powder coating uniformity on the PG910 side and the presence of an embossed wave pattern on the ORC side.

Stability Data for Pivotal Clinical Batches

For the clinical batches, 24 months of stability data for Thrombin Activity, -----(b)(4)----- were subjected to statistical analysis using -----(b)(4)----- . The projected shelf-life for all parameters extends beyond the requested dating period if based on the long-term storage conditions. For Lot L11F284, a -----(b)(4)----- over time was observed, as opposed to the other two batches, although the values remained within Specification. This trend was observed for both long-term storage conditions at -----(b)(4)----- . Based on projections from the accelerated stability study, the shelf-life is -----(b)(4)----- . Batch M06F164 showed a trend for - -----(b)(4)----- under both long-term storage conditions at -----(b)(4)-----

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

[(b)(4)]

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

[(b)(4)]

1 Page Determined to be Not Releasable: (b)(4)

Reviewer's comment:

The results for all parameters remained within Specifications for all three clinical batches and all storage conditions. While meeting the Specification, Lots L11F284 and M06F164 showed the aberrant stability trends for -----(b)(4)-----. As Lots L11F284 and M06F164 were used in the Pivotal (Phase 2) Clinical Study 400-07-002 in which thromboembolic adverse events had been recorded, the potential correlation of the aberrant stability trends with the adverse events in the Clinical Study was discussed during the PLI and through an Information Request, and the Applicant provided their explanation in Amendment 7 dated 30 June 2011.

Omrix explained that the -----(b)(4)----- for batch L11F284 (clinical batch L11F294) was attributed to random sample selection at various time points and expected sample-to-sample variation. This could have had an impact on the calculation --- (b)(4) ---. Nevertheless, this batch remained within the proven safe and effective range throughout the 2-year study period, with values for -----(b)(4)----- ranging from ----(b)(4)----- over all time points and temperatures. Omrix also stated that in the clinical study 400-07-002, the rate of thrombotic events seen in association with batch L11F294 (2/55; 3.6%) was no different than with the Standard of Care (2/30; 6.7%). No plausible mechanism could be envisioned whereby a -----(b)(4)----- would render the material more thrombogenic.

Regarding batch M06F164, the ---(b)(4)--- is a stability indicating parameter for the Matrix component of the Fibrin Pad. The -----(b)(4)-----

-----No plausible mechanism could be envisioned whereby the -----(b)(4)----- would render the material more thrombogenic.

The adverse events observed during clinical study 400-07-002 prompted a clinical investigation and analysis of the CMC data (physical, chemical, and biochemical properties) related to batch M06F164. A detailed summary of the investigation is presented in report QA-R-FP-0016-00 “Expanded Investigation of Clinical, Manufacturing and Analytical Data of Fibrin Pad Pivotal Batch M06F164” in Module 3.2.R, Regional Information. In particular, a controlled *in vitro* kinetic study did not reveal any significant difference in the PG910 degradation profiles for three batches. The clinical investigation concluded that the events observed were consistent with the patient population and were not related to treatment with the Fibrin Pad.

Based on the above investigations, the aberrant stability trends observed in ----(b)(4)---- for batch L11F284 (clinical batch L11F294) and -----(b)(4)----- for batch M06F164 appear related to analytical issues. No plausible mechanisms were identified that could reasonably link the adverse events observed in the clinical study 400-07-002 to the product quality. Upon review of the totality of the clinical data from four studies, the Clinical reviewer

has concluded that the provided information demonstrates efficacy and safety of FS Patch, and is adequate to make a favorable decision concerning potential risk/benefit balance for EVARREST.

Stability Data for Process Validation Batches

At the time of the original submission, 12-month stability data for long-term storage conditions and --(b)(4)-- data for the accelerated storage condition was available for the Conformance / Validation batches (----- (b)(4) -----). The stability data covering the 18-month period were provided in Amendment 7 dated 30 June 2011, and the results of the completed study (24 months of data) were later submitted in Amendment #19 dated 13 August 2012. The results for all parameters remained within Specifications for all three batches and all storage conditions. No aberrant trends for increase or decrease over time for Fibrinogen, Thrombin or ----(b)(4)---- were observed. There was a trend for decrease in --- (b)(4) --- and a trend for increase in ----- (b)(4) ----- under accelerated and room temperature conditions. This trend was not observed under refrigerated conditions. These tests are For Information Only and will not be used in the future due to method limitations.

Thus, the proposed dating period (shelf-life) for EVARREST is supported by real-time stability data, covering the whole period, for the clinical and validation batches. ***The requested shelf-life for EVARREST FS Patch of 24 months when stored at 2 to 25°C can be granted.***

Control of Fibrinogen-Thrombin Reaction on FS Patch at Release and throughout its Shelf Life

The control of the potential reaction between the biological substances on the FS Patch before its application to the wound site is critical for the safety and effectiveness of the Final Product. In Amendment STN 125392/0.3, Omrix clarified their approach to monitor potential premature conversion of fibrinogen to fibrin on the FS Patch.

Several approaches were considered for such monitoring, including -----
----- (b)(4) -----

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

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[(b)(4)]

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

Reviewer's comment:

The above described integral approach to control the undesirable activation of fibrinogen on the patch appears adequate to prevent its conversion to fibrin before application to the wound site.

3.2.A.2 ADVENTITIOUS AGENTS SAFETY EVALUATION

Detailed review of the information related to Adventitious Agents Safety Evaluation is presented in the memorandum of Dr. Nancy Kirschbaum and is summarized below.

Control of Starting Material

Human plasma ---(b)(4)-- are tested by FDA-licensed Nucleic Acid Tests (NAT) for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus-1 (HIV-1). NAT testing for hepatitis A virus (HAV) and parvovirus B19 is also performed. (b)(4) testing for HCV RNA and parvovirus B19 DNA is also performed on the -----(b)(4)----- . The limit of parvovirus B19 DNA is not to exceed ---(b)(4)---. Human plasma is also tested for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (anti-HCV) and human immunodeficiency viruses types 1 and 2 (anti-HIV1/2), and only units tested negative are allowed into the manufacturing process.

Viral Clearance

Viral safety of EVARREST is based on the control of the starting material (human plasma) and the virus clearance capacity of the manufacturing processes for Human Fibrinogen and Human Thrombin. The virus clearance steps in the manufacture of Human Fibrinogen include Solvent/Detergent (S/D) treatment -----(b)(4)----- and pasteurization (----- (b)(4)-----). The virus clearance steps in the manufacture of Human Thrombin include S/D treatment (----- (b)(4)-----) and nanofiltration using a -----(b)(4)-----

The virus clearance capacity of these procedures was validated in down-scale spiking studies using viruses with a range of physico-chemical characteristics. The viral validation studies were reviewed and approved by the FDA with the BLA under STN 125010/0, and supplement STN 125010/102 for EVICEL.

Table 2 Virus Reduction Factors for Human Fibrinogen

	Reduction Factor (Log ₁₀) of virus tested					
	Enveloped Viruses*			Non-enveloped Viruses**		
Manufacturing Step	HIV-1	BVDV	PRV	EMCV	HAV	CPV
S/D Treatment	> 4.42	> 4.39	> 3.96	Not Tested	Not Tested	0.0
Pasteurization	> 4.39	> 5.46	6.0	3.69	> 5.78	1.33
Cumulative virus Reduction Factor	> 8.81	> 9.85	> 9.96	3.69	> 5.78	1.33

*HIV-1: Human Immunodeficiency Virus Type 1

BVDV: Bovine Viral Diarrhea Virus

PRV: Pseudorabies Virus

**EMCV: Encephalomyocarditis Virus

HAV: Hepatitis A Virus

CPV: Canine Parvovirus

Table 3 Virus Reduction Factors for Human Thrombin

	Reduction Factor (log ₁₀) of virus tested						
	Enveloped Viruses*				Non Enveloped Viruses**		
Manufacturing Step	HIV-1	SBV	BVDV	PRV	EMCV	HAV	CPV
S/D Treatment	> 5.82	> 5.31	> 4.74	> 4.25	Not Tested	Not Tested	0.0
Nanofiltration	> 4.36	> 5.32	Not Tested	> 5.47	6.37	6.95	5.85
Cumulative virus Reduction Factor	> 10.18	>10.63	> 4.74	> 9.72	6.37	6.95	5.85

*HIV-1: Human Immunodeficiency Virus Type 1

SBV: Sindbis Virus

BVDV: Bovine Viral Diarrhea Virus

PRV: Pseudorabies Virus

**EMCV: Encephalomyocarditis Virus

HAV: Hepatitis A Virus

CPV: Canine Parvovirus

Transmissible Spongiform Encephalopathy

The safety of EVARREST with regard to prions is based on strict plasma donor selection criteria employed in FDA-licensed donation centers in the United States. The assessed risk to transmit vCJD has been determined by FDA/PHS (the CBER website) to be small. In addition to sourcing plasma from US-licensed blood banks and using US-licensed human albumin, the -----

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

3.2.R REGIONAL INFORMATION

Study Report FLC-001: Comparability Report for Introduction of -----

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

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

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

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

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

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

Reviewer’s comment:

The presented data appear adequate to conclude that Fibrin Pads manufactured using a (b)(4) (b)(4)--(non-clinical material) were comparable to those manufactured with (b)(4) (Phase 1 clinical material) in analytic parameters and hemostatic performance. The safety information could not be derived from this animal study due to a very short observation period compared to the Fibrin Pad resorption period (56 days).

Study Report No. QA-R-FP-0015-00: Comparability Report – Fibrin Pads Produced During Process Validation versus Pivotal Batches

Main changes to the manufacturing process since the conduct of the pivotal clinical study:

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

1 Page Determined to be Not Releasable: (b)(4)

Comparability Study of Pilot and PG Batches in a Porcine Partial Nephrectomy Model

[(b)(4)]

Reviewer's comment:

Comparability Report QA-R-FP-0015-00 for Fibrin Pads produced during Process Validation (---(b)(4)-----) versus Clinical (M06F164) batches demonstrated similar results of in-process and release testing (except for -----(b)(4)----- in the Validation batch, consistent with the --(b)(4)-----) and improved matrix- and protein-characterizing parameters (----(b)(4)-----) for the Validation batch. The hemostatic efficacy of Clinical and Validation batches in a porcine partial nephrectomy model was comparable and without recorded thromboembolic adverse events within a 48-h observation period. The safety information was not complete because the observation period was significantly shorter than the time of Fibrin Pad resorption (56 days).

IMMUNOGENICITY

Exposure of the biologics components of EVARREST (Fibrinogen and Thrombin) to --(b)(4)-- solvent --- (b)(4)--- and e-beam irradiation during the manufacture can potential result in the formation of neo-epitopes and lead to the formation of antibodies to these components in clinical use. The potential immunogenicity of EVARREST was discussed during the PLI and through Information Request. In Amendment #7 dated 30 June 2011, Ethicon/Omrix submitted the summary of their risk assessment.

The risk assessment program was developed based on the method of -----
----- (b)(4) -----
----- The biologics components of EVARREST are conserved proteins of human origin and therefore the risk level posed by the source of raw material in terms of immunogenicity is relatively low. The overall effect of the manufacturing process on the antigenic potential of Fibrin Pad was assessed *in vitro*, *in vivo*, and in a human clinical trial.

The effect of exposure of individual biologic components (Human Fibrinogen and Human Thrombin) to --- (b)(4)--- was evaluated in a study ----- (b)(4) -----

surgery. Neither of these patients had abnormal coagulation parameters such as prothrombin time or activated partial thromboplastin time at 4 weeks after surgery that indicates the transient nature of the antibodies. The 2% of seroconversion is close to the expected rate in the normal population based on historical data. There was no increase in anti-Thrombin antibody titer and no response was detected at 8 weeks. There was no detectable response to Human Fibrinogen at all time points tested (for details, please refer to Module 5.3.5.1, Reports of Efficacy and Safety Studies, Immunogenicity Report).

Immunogenicity of EVARREST was further assessed in Clinical Study 400-08-002 using the same approach but with a more stringent cut-off control set to capture ~25% of the normal population above the cut-off. Blood samples were tested for antibodies to Human Fibrinogen and Human Thrombin by ELISA at baseline, at Day 30 and Day 60 post-surgery. Only 2.1% (1/46) of the Fibrin Pad-treated patients showed seroconversion in response to Human Thrombin (compare to SoC: 2/19, or 10.5%). Two of the FP-treated subjects developed transient antibodies against Fibrinogen. None of the FP-treated subjects had met the quasi-quantitative criterion of significant increase in antibody titer. Antibodies were clinically silent (normal prothrombin time, activated partial thromboplastin time).

Reviewer's comment:

The results of assessment of FS Patch immunogenicity in animal and clinical studies indicate that the risk of developing a clinically relevant immune response in patients treated with EVARREST is low.

COMPARABILITY PROTOCOL QA-P-FP-0017-00

The Comparability Protocol QA-P-FP-0017-00 to support the post-approval introduction of an -----(b)(4)----- of application to replace the ----(b)(4)----- was part of the original BLA. The CR letter contained comments regarding the validation of the revised manufacturing process with (b)(4), and the comparability program for the FS Patch Drug Product. The Protocol was withdrawn for the BLA due to a change in the company's regulatory strategy, as stated in the Cover Letter in Amendment #10 dated 18 January 2012.

CONCLUSION

The manufacturing process for EVARREST Fibrin Sealant Patch is validated at the commercial scale and is sufficiently controlled to assure consistent manufacture of the product that meets release Specifications. The manufacturing processes for Biological Substances and Final Product provide acceptable safety margins regarding adventitious agents. The Applicant has provided sufficient data and comprehensive information on Chemistry, Manufacturing and Controls, and has adequately addressed all product-related questions during the review process. I recommend **APPROVAL** of Ethicon's BLA for EVARREST Fibrin Sealant Patch.

Other discipline reviewers find the Applicant's responses to the Complete Response letter to be adequate to support the licensure of EVARREST Fibrin Sealant Patch.

Ethicon committed to the following Post Marketing Studies on 17 September 2012 (Amendment #27) which will be included in the Approval Letter:

1. -----
----- (b)(4) -----

2. -----
----- (b)(4) -----

3. -----
----- (b)(4) -----

In Amendment #25 dated 6 September 2012, Ethicon, Inc. commits to the following:

4. -----
----- (b)(4) -----
5. -----
----- (b)(4) -----

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

SELECTED GUIDANCES

1. FDA Guidance for Industry: Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use (May 1999)
2. FDA Guidance for Industry and FDA Staff: Early Development Considerations for Innovative Combination Products FDA (September 2006)
3. Guidance for Industry and FDA Staff: Classification of Products as Drugs and Devices & Additional Product Classification Issues (draft, June 2011) OCP/CBER/CDER/CDRH
4. FDA Proposed Rule (21 CFR Part 4A): Current Good Manufacturing Practice Requirements for Combination Products [Docket No. FDA–2008–D–0409] (September 2009)
5. FDA Proposed Rule (21 CFR Part 4B): Postmarketing Safety Reporting for Combination Products [Docket No. FDA–2008–N–0424] (October 2009)
6. FDA Guidance Q2B: Validation of Analytical Procedures: Methodology (November 1996)
7. FDA Guidance for Industry Q1A (R2): Stability Testing of New Drug Substances and Products (November 2003)
8. FDA Guidance for Industry Q1E: Evaluation of Stability Data (June 2004)