



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 Pad

From: Randa Melhem, Ph.D., OCBQ, DMPQ, MRBII, HFM-676
Nancy Waites, OCBQ, DMPQ, MRBI, HFM-675

Through: Chiang Syin, Ph.D., Branch Chief, OCBQ, DMPQ, MRB II, HFM-676

Subject: **Review Memo (BLA):** [Omrix Biopharmaceuticals Ltd. License No. 1603]: Original BLA to get approval for Fibrin Pad, a sterile bio-absorbable combination product intended for use as an adjunct to hemostasis for soft tissue bleeding. The final Fibrin Pad product is manufactured at Omrix Fibrin Pad Production Facility (FPPF) in Rehovot, Nes-Ziona, Israel.

Action Due: September 19, 2011

Action Recommended:

A Complete Response (CR) Letter should be sent to Omrix,

CR Letter Ready Comment:

- Outstanding issues from the Pre-License Inspection performed on May 10 through May 19, 2011 at b(4) and FPPF and detailed in form FDA 483 have yet to be resolved. Please submit documentation that demonstrates that all outstanding inspectional issues identified during the PLI have been corrected.

SUMMARY / BACKGROUND

CBER received this electronic submission on November 19, 2010. Omrix Biopharmaceuticals Ltd. (Omrix) submitted a BLA to get approval for Fibrin Pad, a sterile bio-absorbable combination product made from a flexible composite Matrix (device component) coated with Human Fibrinogen and Human Thrombin plasma-derived proteins (biological drug substances). Fibrin Pad is intended for use as an adjunct to hemostasis for soft tissue bleeding during retroperitoneal, intra-abdominal, pelvic, and (non-cardiac) thoracic surgery when control of bleeding by standard surgical methods of hemostasis is ineffective or impractical.

Human Fibrinogen and Human Thrombin are manufactured at Omrix ---b(4)-----
-----Isreal-----

-----b(4)---. The Matrix is manufactured at ---b(4)--- -----

---b(4)---

Additional information was also provided in amendment 125392/0/6 and reviewed in the Information Request section at the end of this memo.

As part of the review process of this BLA, CBER conducted Pre-License Inspection (PLI) of the b(4) and FPPF from May 10 -19, 2011, and the findings are documented in the Establishment Inspectional Report (EIR). Nine objectionable observations were noted on the Form FDA 483 Inspectional Observations for b(4), and eight objectionable observations were noted for FPPF. The firm submitted their responses to the 483 Observations on June 9, 2011 (by email) which were reviewed and deemed inadequate as the corrections of several deficiencies identified in the 483 observations have not yet been completed.

PRODUCT DEVELOPMENT

Throughout Fibrin Pad product development, ----b(4)----

---b(4)---

---b(4)---

---b(4)---

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

QUALITY SYSTEM FOR FIBRIN PAD

Fibrin Pad is a combination product, as set forth in 21 CFR 3.2(e). More specifically, Fibrin Pad is considered a product consisting of two or more regulated components (biologic/device) produced as a single-entity combination product. As such, Fibrin Pad is subject to the relevant current Good Manufacturing Practice (CGMP) regulations for pharmaceuticals and biologics (specifically, design and manufacture of the Human Fibrinogen and Human Thrombin biological drug substances) (21 CFR Parts 210, 211 and 600 through 680), as well as the Quality System Regulations (QSRs) for devices (specifically, manufacture of the Matrix component) (21 CFR Part 820) during and after joining together the device and biological constituent parts.

The manufacture of the combination product (Fibrin Pad) complies with both CGMP regulations and QSRs by following CGMP as the primary quality system, and implementing procedures that comply with the specific provisions of the QSRs (based on 21 CFR Part 4; Current Good Manufacturing Practice Requirements for Combination Products-Proposed Rule).

The partitioning of the quality systems by regulation and by responsible party is as follows:

1. The design and manufacture of the Matrix at –b(4)---- complies with the QSRs 21 CFR Part 820.
2. The design and manufacture of the Human Fibrinogen and Human Thrombin drug substances at OMRIX comply with the CGMP regulations as specified in 21 CFR Parts 210, 211, and 600 through 680.
3. The manufacture of the biologic/device final product at OMRIX complies with both CGMP regulations and QSRs by following cGMP as the primary quality system and implementing procedures that comply with specific provisions of the QSRs (based on 21 CFR Part 4; Current Good Manufacturing Practice Requirements for Combination Products—Proposed Rule)

A review of Ethicon’s Quality Systems per QSR and a review of OMRIX’s compliance of applicable QSRs are provided in a later section of this review memo. Both Ethicon’s and OMRIX’s systems appear to meet the required QS regulations that DMPQ is responsible for reviewing.

COMPARABILITY PROTOCOL

*An additional change planned for implementation following submission of a post-approval supplement consists mainly of a change from a –b(4)-----
----- step for –b(4)-- -----
----- A comparability protocol is included in Module 3.2.R Regional Information for review by the Agency. However, this is not submitted with the intent of downgrading the post-approval supplement to a CBE-30.*

DMPQ did not review this protocol.

1 page determined to be not releasable: b(4)

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

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

DEVICE

The Matrix device component of the Fibrin Pad is a flexible composite Matrix composed of polyglactin 910 (PG910) and oxidized regenerated cellulose (ORC). The Matrix size is 4 x 4 in. (10.2 x 10.2 cm), with a thickness of approximately 2 mm; it has an off-white to yellowish appearance, with an embossed wave pattern present on the knitted ORC) surface. The Matrix is considered an implant with “permanent” tissue contact for greater than 30 days, up to the point when the implant is supposed to be absorbed at about 56 days post-implantation.

The primary packaging materials for the Matrix and Fibrin Pad consist of a white,

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

----- for sterilization by e-beam irradiation.

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

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

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

--b(4)-----

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

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

2 pages determined to be not releasable: b(4)

---b(4)---

---b(4)---

Drug Product Stability

Fibrin Pad is intended to be stored at 2 to 25°C for up to 24 months. Stability studies have been conducted to support the intended storage conditions.

Three batches of Fibrin Pad (used in the pivotal clinical study), which were manufactured according to the current manufacturing process, have been entered into long-term and accelerated stability studies, as specified below.

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

Three additional Fibrin Pad batches have been entered into ICH stability studies with samples stored at the conditions above. ---b(4)-----

-----These three batches are also considered process validation batches. Twelve months of long-term storage ---b(4)-----of accelerated storage stability data for these batches have been collected to date; these data supplement the comparability of these batches to the Fibrin Pad batches used in the pivotal clinical trial.

Fibrin Pad, status of stability studies for production-scale batches

Fibrin Pad Pivotal Batches					Fibrin Pad Process Validation Batches	
Batch	L11F284a	M05F094	M06F164	---b(4)---	---b(4)---	---b(4)---
Date of Manufacture	Nov 2007	May 2008	June to July 2008	July 2009	July to August 2009	August 2009
Status of Study at ---b(4)-----	Completed	Completed	Completed	Ongoing	Ongoing	Ongoing
Status of Study at ---b(4)-----	Completed	Completed	Completed	Ongoing	Ongoing	Ongoing
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)- step to supply separate clinical (L11F294) and stability (L11F284) needs.

The predefined stability protocol for the pivotal clinical batches is outlined in Module 3.2.P.8.1, Stability Summary and Conclusions, Table 2 (---b(4)----- storage condition), Table 3 (---b(4)-----), and Table 4 (---b(4)-----). Rationale for selection of parameters for stability analysis is given in Module 3.2.P.8.1, Stability Summary and Conclusions, Selection of Parameters for Stability Analysis.

DMPQ is responsible for reviewing testing for –b(4)----- Endotoxin, Package integrity (-b(4)-) test, and Sterility.

Tests and Time Points

b(4)

---b(4)---

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

---b(4)---

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

b(4)

The data from the stability studies for pivotal clinical batches and process validation batches support storage of the Fibrin Pad product at 2 to 25°C up through a 24-month shelf life.

Testing

The testing for endotoxin, package integrity (b(4)) test, and --b(4)----- are the same tests that are described under the section discussion drug substance stability. Sterility testing is discussed under the section of this memorandum for the release specifications of the Fibrin Pad.

Post-approval Stability Protocol and Stability Commitment

The company commits to completing the stability evaluation of the Fibrin Pad process validation batches through 24 months under the long-term storage conditions. Additional stability data and analysis from these batches will be provided to the Agency via the Annual Report or in relevant supplements to extend the recommended Fibrin Pad shelf life.

The company commits to enter one Fibrin Pad batch annually into a commercial stability program. The stability of Fibrin Pad will be tested for future commercial batches at --b(4)----- for up to and including the expiration date (long-term storage condition). If a confirmed out-of-specification (OOS) is obtained for a sample stored at the recommended condition, FDA will be notified. A change or deterioration of the distributed drug product will be reported as required under 21 CFR 601.14.

FACILITIES AND EQUIPMENT

The manufacture of Fibrin Pad takes place in--b(4)-- major facilities as described below:

Name (location)	Approval Status	Role in Fibrin Pad Manufacture Process
---b(4)-- ----- ----- ----- -----	--b(4)----- ----- ----- -----	--b(4)----- ----- ----- -----
---b(4)----- ----- -----	--b(4)----- ----- --b(4)----- -----	--b(4)----- ----- ----- -----
Omrix Biopharmaceuticals Ltd., FPPF (Fibrin Pad Production Facility) Rehovot, Nes-Ziona, Israel	FDA Registration Number: 3008640339 Not licensed yet	Manufacture of Fibrin Pad final product
--b(4)----- -----	--b(4)----- ----- -----	--b(4)----- ----- -----

1 page determined to be not releasable: b(4)

---b(4)---

----b(4)---

--b(4)--

--b(4)--

---b(4)---

--b(4)--

----b(4)--

-b(4)-

Fibrin Pad Production Facility (FPPF)

FPPF is located at Weizmann Science Park Nes-Ziona, Israel. The Omrix FPPF facility includes production areas –b(4)– quality control testing areas, technical areas, areas in which raw materials, intermediates, and the finished product are stored, and offices. The production area includes

17 pages determined to be not releasable: b(4)

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

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

Final Release Specification – Fibrin Pad

The Fibrin Pad release specifications to ensure the identity, potency, and purity of Fibrin Pad are provided in Table 1 within the submission. The release specifications that DMPQ is responsible for are listed below.

Test	Specification	Result
---b(4)-----	--b(4)----	-b(4)---
Endotoxin	--b(4)-----	--b(4)-----
Sterility ¹	Sterile	Sterile
Package Integrity (b(4)) Test	--b(4)-----	--b(4)-----
Visual Inspection of Foil Pouch Seal Integrity	Complies ²	Complies ²

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

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

Testing

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

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

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

Endotoxin

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

3 pages determined to be not releasable: b(4)

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

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

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

--b(4)-----QUALITY SYSTEM INFORMATION

Quality System—Matrix --b(4)-----

The design and manufacture of the Matrix at --b(4)----- complies with the QSRs 21 CFR Part 820. The Matrix, a device component for the Fibrin Pad, follows the --b(4)----- Quality System to ensure the Matrix consistently meets applicable requirements and specifications. A summary of the --b(4)----- Quality System is provided for the Matrix in accordance with FDA’s guidance document, “Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff” (2003). The italicized text represents information that has been excerpted from that Guidance document.

DMPQ has reviewed the --b(4)----information per SOPP 8790 *Review Responsibilities for the Quality System Regulation (QSR) Section of Premarket Submission Reviews* since --b(4)----- primary quality system is governed by the device regulations. DMPQ reviewed the sections listed below. Any sections not listed, fall under the responsibility of the Product Office to review.

Quality System Procedures 820.20(e) Production Flow
Quality System Procedures 820.20(e) Use of Standards
Purchasing Controls 820.50
Production and Process Controls 820.70
Inspection Measuring and Test Equipment 820.72
Process Validation 820.75
Process Validation 820.75(a)
Final Acceptance Activities 820.80(d)
Corrective and Preventive Action (CAPA) 820.100
Complaint Files 820.198
Servicing 820.200

Quality System Procedures 820.20

You should provide a copy of your basic quality system procedure(s).

Your basic quality system procedure(s) should include:

- *Quality audit or internal audit procedure(s)*
- *Management review procedure(s)*
- *Outline of the structure of the quality system documentation*

The development of a quality manual that includes the referenced elements below would satisfy the requirement in 820.20(e) for an outline of the documentation used in the quality system:

- *Title and scope of application*
- *Table of contents*
- *Definitions (if needed)*
- *Outline of the structure of the quality manual or quality system documentation*
- *Quality policy and objectives*
- *Organizational structure and responsibilities or authority*
- *References to basic quality system procedures*
- *Guide or appendix for supportive data (if needed)*

DMPQ is responsible for the review of all of the QSR documents. I reviewed the documents listed below and found them to be acceptable. The documents included all of the Quality System Procedures per 21 CFR 820.20: Quality Policy, Organizational Structure, Responsibility and Authority, Resources, Management Review, Quality Planning, Quality/internal audits, and an outline of the quality system documents.

- PL-0000001, “Policy for –b(4)----- Franchise Quality Manual”
- EPG054, “Addendum: Quality Manual”
- PL-0000013, “–b(4)----- Franchise Quality Policy”
- EPG002, “Documents Management”
- EPG010, “Records Management Policy”
- PR-0000070, “Franchise Procedure for the Internal Audit Process”
- EPG016, “Internal Audits”
- PR575-001, “Franchise Procedure for Corrective and Preventive Action (CAPA)”
- EPG053 –b(4)----- Management Review Procedure
- PR550-006, “Franchise Procedure for Management Review of the Quality System”
- –b(4)----- Management Structure

Production Flow 820.20(e)

You should provide a production flow diagram that identifies the steps involved in the manufacture of the device under review. This information helps to show the important aspects of your production process.

DMPQ is responsible for reviewing all of the production flow documentation except for the Manufacturing Process which is the responsibility of the Product Office. I

reviewed the following flow diagrams and found them to be acceptable. I do not have any comments.

- ---b(4)----- Matrix Production Areas
- Materials Movement in the Matrix Production Areas
- Sample and Product Movement in the Matrix Production Areas
- Personnel Movement in the Matrix Production Areas
- Waste Movement from the Matrix Production Areas

Use of Standards 820.20(e)

You should provide a list of any standard(s) used in the manufacturing process or for the device itself.

Both DMPQ and the Product Office are responsible for reviewing the use of standards “as appropriate”. Per ---b(4)----- the following standards listed below apply to the manufacturing operations used for the Matrix. ---b(4)----- has provided appropriate documentation for standards.

List of Standards

- AAMI/ANSI/ISO 11137: Sterilization of Healthcare Products – Radiation – Part 2: Establishing the Sterilization Dose
- ISO 11737-2, Sterilization of medical devices – Microbiological methods – Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process
- ISO 13485, Medical devices – Quality management systems – Requirements for regulatory purposes
- ISO 14644, Clean Rooms and Associated Controlled Environments
- ISO 14698, Clean Rooms and Associated Controlled Environments
- QSR 21 CFR 820 Medical Device – Quality System Regulation

Purchasing Controls, 820.50

You should provide a copy of the procedure(s) for purchasing controls. This is especially important if you use a contract design service or contract manufacturer(s) for the device under review. The controls applicable to these suppliers should be specified.

- *Your procedure(s) should describe the supplier evaluation process and describe how you will determine type of and extent of control you will exercise over suppliers.*
- *Your procedure(s) should define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.*
- *Your procedure(s) should explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.*

DMPQ is responsible for the review of purchasing controls as they relate to vendor qualification. The Product Office is responsible for the review of the remaining purchasing controls. I reviewed the documents listed below and found them to be acceptable. A summary of ---b(4)-----vendor qualification process is provided below.

- PR-0000286, “Franchise Procedure for Purchasing Controls”
- PR-0000345, “Franchise Procedure for the Supplier Quality Audit Program”
- PR575-001, “Franchise Procedure for Corrective and Preventive Action”
- PR507-007 “Franchise Procedure for Supplier Selection and Approval”
- EPG03 “Procurement General Procedure”

Summary

Purchasing controls apply to any supplier who can impact the quality of –b(4)----- products or services. The purchasing controls process includes five phases: planning, selection of potential suppliers, supplier evaluation and acceptance, finalization of controls, and delivery measurement and monitoring. The level of controls exercised over suppliers is commensurate to the risk. Risk level is a classification assigned to finished goods, components, or services per the effect on product and the intended use. Risk levels are used to assist in the determination of supplier audit frequency. The selection and approval procedure and requirements depend on the type of supplier. Suppliers are characterized in the following groups: external manufacturers, raw material suppliers, and sterilization suppliers; design and development service suppliers; and non-design service suppliers.

The Supply Chain and Procurement Departments at –b(4)----- is responsible for the purchase of materials and supplies with the objective that they be available at the proper time and place, in the correct quantities and price, and meet or exceed –b(4)----- quality requirements. The quality requirements are determined in conjunction with the QA Department. The Supply Chain and Procurement Departments also are responsible for all purchasing policies and procedures.

Production and Process Controls, 820.70

You should provide a copy of the procedure(s) for environmental and contamination controls, if such conditions could adversely affect your device. (Note: if this involves a large number of procedures, a sample of the most relevant procedures would be sufficient.)

DMPQ is responsible for reviewing all of the production and process controls except for Manufacturing; which the Product Office is responsible for. I reviewed EMSP005, “Environmental Monitoring Program” and found it to be acceptable. A summary of ----(b)(4)---- Production and Process controls is included below.

Production and Process Control Overview

With respect to the operations conducted at the –b(4)----- facility for the Matrix, all such operations are conducted in a controlled and orderly manner to ensure that they are consistent in quality and are in full compliance with approved, documented specifications.

Production-related activities are conducted under environmentally controlled conditions, described in –b(4)----- local procedure EMSP005, “Environmental Monitoring Program”.

Product and process information and appropriate work instructions are established and are communicated to relevant personnel. Production processes are monitored and controlled, and are validated where appropriate. Machines and equipment used in production and for monitoring and measurement activities are maintained. Methods for product release and delivery are defined. –b(4)----- requires controlled conditions to include (as applicable) the following:

- Documented procedures, work instructions, and reference standards, as necessary;
- The use of suitable equipment;
- The use of monitoring and measuring devices;
- The implementation of release activities; and
- The implementation of defined labeling and packaging operations to prevent labeling mix-ups.

The manufacturing environment at –b(4)----- is controlled to ensure an appropriate bioburden level of the Matrix. –b(4)----- has implemented appropriate procedures concerning environmental control, bioburden, and corresponding monitoring. The particle monitoring and cleaning methods in the Matrix manufacturing facility are described later within this review memorandum.

Record-keeping

–b(4)----- maintains records for each production batch of Matrix that provide traceability information, date of manufacturing, individuals performing the manufacturing steps, the quantity manufactured, and quantity approved for final disposition. The records must be verified and approved by QA prior to product release.

Cleanliness of Product and Contamination Control

The manufacturing environment at –b(4)----- is controlled to ensure an appropriate bioburden level of the Matrix. –b(4)----- has implemented appropriate procedures concerning environmental control, bioburden, and corresponding monitoring. The particle monitoring and cleaning methods in the Matrix manufacturing facility are described later in this review memorandum.

Inspection, Measuring, and Test Equipment, 820.72

You should provide a copy of the procedure(s) that explain how inspection, measuring, and test equipment is routinely calibrated, inspected, checked, and maintained. (Note: if this involves a large number of procedures, a sample of the most relevant procedures would be sufficient.)

DMPQ is responsible for reviewing all of the inspection, measuring, and testing equipment except for the manufacturing process, which is the responsibility of the Product Office. I reviewed EPG017, “Metrology” and found it to be acceptable. A summary of –b(4)----- Inspection, Measuring, and Test Equipment Procedure is included below.

Summary of Procedure

–b(4)----- ensures that measuring equipment is calibrated or verified prior to use or at predetermined intervals according to the calibration schedule. All calibration is

conducted utilizing standards traceable to international or national standards when possible. If traceable standards do not exist, rationale is documented for the standard being used. Equipment requiring adjustment is documented. Precautions are taken at all times to protect the equipment from adjustments, damage, or deterioration that would invalidate the calibration.

If equipment is found to be out of calibration, it is removed from the manufacturing / quality control area, or labeled “not for use”, and the impact to product will be assessed as per local nonconformance procedures for all previous measurements from the last known acceptable calibration.

Process Validation, 820.75

You should provide a copy of your process validation master plan, or a description of which manufacturing processes you will validate, for the device under review. Provide a list of processes for the device under review that you do not plan to validate but will verify by inspection and test.

- *Your process validation master plan or your description should also include any validations of software used as part of the production or quality system. (See 820.70(i).)*
- *It would also be very helpful to identify in your process validation master plan or description which type of processes you have never validated before. (For example, a different type of sterilization process.) This would allow us to work with you on validation issues as early as possible before the preapproval inspection.*

DMPQ is responsible for the review of documents related to the facility and equipment only. I reviewed the Master Validation Plan, MVP-587-VS, and found it to be acceptable. I do not have any questions or comments.

The QSR requires the validation of processes whenever the results of a process cannot be fully verified by subsequent inspection and test methods. –b(4)----- --has identified those processes involved in the production of Matrix requiring validation. A table was provided within the submission that listed the equipment used at –b(4)----- for the manufacture of the Matrix, type of documentation required (i.E. URS, FDS, Design Review, FAT, EDQ, Pre-IQ Process Review, IQ Protocol / Report, OQ Protocol/ Report, PQ Protocol / Report, Cleaning Validation Protocol / Report), and Document Reference Number. The PQ Reports for the following pieces of equipment were included in the submission:

[b(4)]

I reviewed the PQ reports and found them to be acceptable.

Process Validation, 820.75(a)

You should provide a copy of the validation procedure(s) or individual validation plan(s) for each process that will be validated for the device under review. When available, you should provide a copy of any completed validation reports.

- *Your validation procedure(s) or plan(s) should contain or refer to objective and measurable acceptance criteria.*
- *Your validation procedure(s) or plan(s) should describe how appropriate statistical methods for data collection and analysis are used.*
- *Your validation procedure(s) or plan(s) should define the criteria for re-validation.*

DMPQ is responsible for the review of documents related to the facility and equipment only. I reviewed the documents listed below and found them to be acceptable. I do not have any questions or comments.

- EPG024 “Validation Management”
- 3.2.S.2.5 Process Validation and/or Evaluation

All new process or test equipment, facilities and utilities, cleaning methods, test methods, and computer systems processes must be prospectively validated in line with –b(4)----- local procedure EPG024 “Validation Management”. In the case of changes to validated systems, the scope of activities may be limited and will only address the area that is impacted by the change. All validation protocols contain measurable acceptance criteria detailed in the applicable document sections. Appropriate statistical techniques are used for process validation. The process validation for the Matrix is described later within this review memorandum. The PQ reports “bolded” within the table above were included in the submission.

Final Acceptance Activities, 820.80(d)

You should provide a copy of the procedure(s) for final acceptance activities. (Note: if this involves a large number of procedures, a sample of the most relevant procedures would be sufficient.)

- *Your procedure(s) should identify the specific release criteria. For example, sterilization release criteria could be based on biological indicator results, validated parametric release protocols, or other valid scientific methods.*
- *Your procedure(s) should describe the quarantine or other controls used for finished devices until it is determined that all acceptance criteria are met and recorded properly.*
- *Your procedure(s) should ensure that finished devices are not released for distribution until:*
 - *Device Master Record requirements for release are met*
 - *Review of associated release data and documentation*
 - *Authorized for release by the signature of a designated person(s)*
 - *The date final release is authorized is recorded*

DMPQ is responsible for the review of documentation related to quarantine controls only. The Product Office is responsible for the remaining documents. I reviewed

EPG057, “MATRIX Batch Review and Release” and found it to be acceptable. The procedure provides a process for quarantine to prevent the inadvertent use of a product, process, or system and for the removal of products, processes, or systems from quarantine.

–b(4)----- has developed a procedure for final acceptance activities for Matrix prior to final disposition. The devices are evaluated and tested prior to sign-off and release as per the –b(4)----- ----local procedure EPG057, “MATRIX Batch Review and Release”. Before devices are released, the completed devices are stored in a quarantine location.

Corrective and Preventive Action (CAPA), 820.100

You should provide a copy of the procedure(s) for your corrective and preventive action (CAPA) system.

- *Your procedure(s) should explain how your CAPA system is tied to your risk management program.*
- *Your procedure(s) should define how your CAPA system will address nonconforming practices as well as nonconforming product.*
- *Your procedure(s) should address the analysis of the multiple data inputs from your quality system. Your procedure(s) should make it clear what will be included in this analysis as well as the mechanism for justification when something is not included.*
- *Your procedure(s) should define the following to ensure that the corrective and/or preventive action is effective and does not have an adverse effect on the device:*
 - *Method for determining verification or validation*
 - *Implementation planning to include recording changes in methods and procedures*
 - *Method for disseminating information on the quality problem or nonconforming product to those responsible*
- *Your procedure(s) should define how and what type of CAPA information will be submitted to management for review.*
- *Your procedure(s) should explain how design changes made under your CAPA program interact with your design change control system and risk management program.*
- *Your procedure(s) should incorporate the need for reviews within your CAPA system to determine whether a record or report should be established, as required by the Corrections and Removal regulation (21 CFR Part 806) or Medical Device Reporting regulation. (21 CFR Part 803).*

DMPQ is responsible for the review of all CAPA system documents. I reviewed PR575-001, “Franchise Procedure for Corrective and Preventive Action (CAPA)” and found it to be acceptable. A summary overview of –b(4)----- CAPA system is below.

1 page determined to be not releasable: b(4)

Per –b(4)----- this is Not Applicable to Matrix device as it is a component of the final single-use disposable combination product.

OMRIX Quality System

The manufacture of the biologic/device final product at OMRIX complies with both CGMP regulations and QSRs by following CGMP as the primary quality system and implementing procedures that comply with the following specific provisions of the QSRs (based on 21 CFR Part 4; Current Good Manufacturing Practice Requirements for Combination Products—Proposed Rule):

- Management Responsibility (820.20)
- Design Controls (820.30)
- Purchasing Controls (820.50)
- Corrective and Preventive Action (820.100)

The following provisions of the QSRs are not applicable to Fibrin Pad:

- Installation (820.170)
- Servicing (820.200)

Procedures for the applicable QSRs have been developed, integrated into existing CGMP procedures, implemented, and followed in the development and manufacture of Fibrin Pad.

DMPQ has reviewed the OMRIX information per SOPP 8790 *Review Responsibilities for the Quality System Regulation (QSR) Section of Premarket Submission Reviews* since OMRIX has the responsibility of meeting both CGMP and QSR at their facility where the Fibrin Pad is manufactured. DMPQ reviewed the sections listed below. Any sections not listed, fall under the responsibility of the Product Office to review.

Quality System Procedures 820.20
Purchasing Controls 820.50
Corrective and Preventive Action (CAPA) 820.100

Quality System 820.20

DMPQ is responsible for the review of all of the QSR documents. I reviewed the documents listed below and found them to be acceptable. The documents included all of the Quality System Procedures per 21 CFR 820.20: Quality Policy, Organizational Structure, Responsibility and Authority, Resources, Management Review, Quality Planning, Quality/internal audits, and an outline of the quality system documents.

- 180-04, “Quality Policy”
- 10-21, “Quality Assurance Policy”
- 10-178, “Management Review Board”
- 180-57, “Quality Management System”

- 10-157, “Document Control Procedures”
- 10-101, “Document Change Form—Revision of Documents”
- 180-13, “Record Types and Retention”
- 201-03, “System Backup and Restore Policy”

Purchasing Controls (820.50)

DMPQ is responsible for the review of purchasing controls as they relate to vendor qualification. The Product Office is responsible for the review of the remaining purchasing controls. I reviewed the documents listed below and found them to be acceptable. A summary of OMRIX's vendor qualification process is provided below.

- 10-177, “Vendor Qualification”
- 10-105, “Material Qualification”
- 10-129, “External Quality Audits”

Vendor Qualification Summary

OMRIX evaluates its suppliers and purchases materials and services only from those that can satisfy the company's quality requirements at the required volumes. Purchasing that relates to calibration, servicing, and service contracts for the facility and equipment are managed by the OMRIX Engineering Department.

Suppliers are not permitted to modify product or service specifications without notification to OMRIX prior to implementation. Suppliers and sites are required to implement specification changes approved by OMRIX in a timely manner. A list of approved suppliers/contractors/consultants for products and services is established and maintained through the existing document control process.

The Quality Assurance Department is responsible to develop an annual audit schedule based on vendor criticality. This applies to vendors of raw materials, components, and indirect supplies and tools; contractors; and subcontractors. Assessments are performed by personnel who have been appropriately trained. Auditors identify and document nonconformities during the audit, then assess and record the significance of the nonconformity. A full report is issued upon completion of the audit. The QA Compliance Department monitors the performance and adequacy of corrective actions. If necessary, a reassessment may be performed to ensure that all necessary actions have been implemented. The audit is closed out only after all required actions are implemented.

Corrective and Preventive Action (820.100)

DMPQ is responsible for the review of all CAPA system documents. I reviewed PR575-001, “Franchise Procedure for Corrective and Preventive Action (CAPA)” and found it to be acceptable. A summary overview of Ethicon’s CAPA system is below.

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

1 page determined to be not releasable: b(4)

INFORMATION REQUEST

Omrix provided additional information in amendment 125392/0/6 in response to CBER information request dated May 5, 2011. CBER comments are in ***bold italics*** followed by Omrix comments in plain lettering. Reviewer's comments are underlined.

SHIPPING VALIDATION

1. *Please explain how the simulated conditions for shipping validation of the Matrix -b(4)-- reflect the actual shipping conditions such as duration/time, temperature, pressure, and handling.*

--b(4)--

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

---b(4)---

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

Response is acceptable.

2. *Please provide the shipping validation of the final product and explain how it represents worst case conditions: temperature, pressure, handling time of the actual shipping of the product.*

--b(4)--

--b(4)--

1 page determined to be not releasable: b(4)

---b(4)---

It was noted during the PLI (483 observation) that Omrix has not specified in their shipping procedures the use of validated ground and air carriers. Omrix has promised to rectify this oversight and to update SOP 10-179 and SOP 23-00 and to train staff on the new process by July 31, 2011.

CONTAINER CLOSURE

4. *You state that the* ---b(4)---

----- *Please provide validation data to support the integrity of these* ---b(4)----- *against bioburden and moisture.*

---b(4)---

---b(4)---

Response is acceptable.

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

---b(4)---

---b(4)---

Response is acceptable.

-----*. Please report how many trays/lids were used during the validation of the entire manufacturing process (from –b(4)----- to final release and simulated shipping to consumers). Please report the in-process and final testing for the integrity of the primary container closure.*

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

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

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

~~$-b(4)$~~ -----PROCESS

Response is acceptable.

1 page determined to be not releasable: b(4)

The qualification of the—b(4)----- is not complete; however, the qualification will be submitted as response to the 483 observations (target date for completion, February 28, 2012), and will be evaluated as an inspectional issue.

9. Please provide the room classification, as well as yemperature/pressure/ humidity and laminar flow, for the loading and unloading of the –b(4)-----, the schedule for environmental monitoring and the acceptance criteria. Please provide room and EM qualification studies to support these results.

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

The qualification of the laminar flow and the EM qualification studies are inadequate as noted during the inspection. Omrix set a target date for completing the laminar flow study by August 10, 2011; and to address the EM sampling by July 31, 2011. This information will be submitted as response to the 483 observations, and will be evaluated as an inspectional issue.

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

10. Please provide the qualification of the equipment and the validation of the processes to assure consistency for the Fibrin Pad manufacturing process.

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

Response is acceptable.

--B(4)----- / STERILIZATION

11. ---b(4)--- -----

• --b(4)----- -----

• --b(4)--- -----

• --b(4)--- -----

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

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

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

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

Response is acceptable.
