

MEMORANDUM

To: STN 125392/0 File

Meeting Date: July 11, 2011

From: Sonday L. Kelly, Regulatory Project Manager

Subject: Committee Meeting minutes

Applicant: OMRIX Biopharmaceuticals, Ltd.

Product: Fibrin Pad

Meeting Attendees:

RPMB	Sonday L. Kelly Mark Shields
CMC:	Natalya Ananyeva (Scientific Lead) Timothy Lee
Clinical:	Kimberly Lindsey Roxolana Horbowyj Nisha Jain
Pre-clinical:	La’Nissa Brown-Baker
DMPQ:	Nancy Waites Marion Michaelis
Statistics:	John Scott
BiMO:	Dennis Cato
APLB:	Loan Nguyen
OBE:	Faith Barash
DH:	Mahmood Farshid Howard Chazin

Purpose of Meeting:

- Provide management with an update/assessment of the status of this original BLA, highlighting problem areas and deficiencies
 - All disciplines with major issues are expected to give a brief update

Meeting minutes:

General comment:

The Final Report for the Clinical Study Protocol 400-08-002 was received by CBER on June 13, 2011. Although the Amendment could be classified as major, it was submitted before the 90-day cut off date so that the extension of the review clock could not be considered.

Clinical

Kimberly:

This meeting was called to update the entire committee on the regulatory status of the submission; Action Due Date (ADD) is September 19, 2011. We have been operating under the principle that this applicant will receive a Complete Response (CR) letter because we have safety concerns. The study that Omrix submitted for licensure is technically a Phase II study; we have told Omrix this several times.

There was a pre-BLA meeting where we told Omrix that we were concerned with their safety analysis. We said that they would be submitting the BLA at their own risk. We tried to discourage Omrix from submitting the BLA with this Phase II study. Omrix still filed the BLA based on the FDA statement that we would look at the totality of the data.

Nisha:

During the pre-BLA meeting, we did everything we could to discourage the submission of the BLA.

Kimberly:

Omrix performed this most recently submitted ex-US Study 400-08-002, and called it a pivotal study, to address the issues with safety. The study was completed on June 1st, 2011 and came in to CBER on June 13th, 2011, but was delayed in being distributed to the review team. This study is the ex-US soft tissue surgery study; however, with a different bleeding classification and with a different standard of care. In the Study 400-07-002, the Fibrin Pad had a comparator Surgicel, both are indicated as an adjunct to hemostasis. The study 400-08-002 uses manual compression as a standard of care, with or without traditional adjuncts to hemostasis. There were 59 patients on the safety side in addition to the US study. Noteworthy, the trial design of this ex-US study came in previously under Special Protocol Assessment (SPA) in IND phase, which we rejected, and Omrix subsequently withdrew the study.

Nisha:

We are looking at the safety perspective. Did they capture the safety database properly?

Kimberly:

It was a controlled study. The adverse event (AE) data for thrombotic events looks clean, but we also have to look at adhesions, infections, and obstructions. These AEs need to be accurately monitored for. It still remains unclear based on the indication of that study (more challenging bleeding) and selected controls, i.e. standard /primary methods of hemostasis with or without adjuncts to hemostasis, that the results of the study can fully support the US soft tissue Phase II trial. Additionally, I would not use this study for licensure because we did not have a passing inspection- there were significant issues with the BIMO inspection of the sites for the Study 400-07-002. The placement of investigational product information was not optimally described on the case report forms (CRFs). There was only general information of where the pad was placed. Omrix said it was not a requirement to capture this information on the CRF. The Study Protocol needs to be changed going forward to capture this information, i.e. the pad application site. This product is still something I would not recommend approval for. There remain many safety issues. AEs, including 7 patients in the non-randomized part of the study 400-07-002, demonstrated an unfavorable imbalance towards the FP arms. An additional study appears to be needed. The safety monitoring (i.e work-up for potential new safety signals –adhesions, infection, and for thrombotic and bleeding events) should be prospectively described. Omrix should start with a patient population without co-morbidities (such as malignancy) and more representative of general population.

Nisha:

The findings in the BIMO inspection are concerning. When you are analyzing safety, it does not matter if the data comes from ex-US or not, we have to look at the robustness. A stronger argument for not approving is the BIMO inspection in addition to the safety concerns. That is what should be put forward to upper management.

Dennis:

For the Study 400-07-002, we inspected three (3) sites. There were no discrepancies between the data submitted in the BLA versus the data from the inspections. However, the nurse's notes from the operating room are not detailed enough. In several instances, the doctors do not mention that the investigational product was used in the surgery; we inferred that it was used because the investigator was listed in the notes or in an addendum added a week later. The inspection results have been submitted. There are a number of questions that make the data incomplete.

Kimberly:

When you break the clinical data down by the Fibrin Pad application site, you will have a situation of 4 small pilot studies, and there is uncertainty to whether the data are poolable.

The latest Study Report for the Protocol 400-08-002 has been submitted at our request for additional safety data to address those thrombotic events. The study was performed in Germany, Australia, EU.

Nisha:

Should we contact our European counterparts to alert them?

Kimberly:

I have not changed my mind that we should issue a CR for this BLA. We have just sent Omrix a Clinical Hold letter for their liver surgery IND. Their whole US program is basically on hold now until we work out this issue.

Dennis:

Please note that a 2-month lead time is needed to set up a BIMO inspection if we consider inspecting the sites related to Study 400-08-002. When the BLA was originally submitted, we were considering an RTF option and encouraging a withdrawal.

Nisha:

At the pre-BLA meeting, we told Omrix that the clinical data was inadequate to support licensure. However, the option of RTF was dismissed, so as not to set precedence of pre-judgment, and with the expectation that the full review of the totality of the data would be beneficial for both Omrix and FDA.

Natalya:

The Pre-License Inspection of Omrix's manufacturing sites was performed on May 10th, through May 19th, 2011 and was led by the DMPQ (Randa Melhem and Destry Sullivan) with participation of the OBRR Product Office (Natalya). Omrix's -----b(4)-----

-----b(4)-----, The latest FDA inspection of b(4) was a Team Bio inspection in October 2009. Regarding the second Omrix's facility, Fibrin Pad Production Facility (FPPF), Fibrin Pad is the first product from this facility for which Omrix is seeking US licensure. It was the first FDA inspection of this establishment. Forms FDA 483 were issued for both facilities. Nine objectionable observations were noted on the Form FDA 483 Inspectional Observations for b(4) and eight objectionable observations were noted for FPPF. Randa and I updated the Review Committee of the results of the inspection at the 2 June 2011 Post-PLI Committee Meeting. I also presented the results of the inspection at our internal LH meeting on 6 June 2011.

Briefly, no objectionable observations were made regarding the product itself; the developed process for the Fibrin Pad appears to be validated and sufficiently controlled to assure consistent production of the product that meets the Specifications. At the Post-PLI and LH meetings, I presented the organizational chart of the Fibrin Pad production area at FPPF, Omrix's strategy for controlling the manufacturing process steps, and Product Specialist discussion items which will be included in the Establishment Inspectional Report. However, a number of outstanding GMP deficiencies were identified, specifically, inadequate cleaning validation for equipment, inadequate facility cleaning program, inadequate procedures describing environmental monitoring and shipping at both facilities, and inadequate qualification of the --b(4)----- at FPPF.

Tim:

As follows from the results of the Pre-License Inspection reflected in the FDA Form 483, there appears to be inadequacy of the validation of the processes in both facilities. If we are moving towards approval of the BLA, we could request resolution of the identified GMP deficiencies as PMCs. Alternatively, if we are moving towards the CR, these deficiencies (the 483 items) should be listed in the CR if they have not been corrected before the ADD. There is a CR letter being circulated right now --b(4)-----, and the inspection issues are listed as deficiencies in the CR letter.

Kimberly:

Do you feel comfortable regarding the way active biologic substances are spread on the Pad? Has it been validated that areas across the Pad will contain the right amounts of active ingredients in case the pad is cut to the smaller wound size?

Natalya:

This question relates to the homogeneity of active ingredients distribution, or coating uniformity. This issue was discussed during the PLI. Coating uniformity across a Fibrin Pad and across multiple production days is characterized by -----

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

----- Thus, it appears that their sampling procedure allows for reliable control of coating uniformity (homogeneity) of Drug Substances across a Fibrin Pad and across production days.

Nisha:

Did this same problem arise with TachoSil from Nycomed?

Tim:

--b(4)-----

Natalya:

---b(4)---

John:

I had objections to this study at the IND stage. Overall, Omrix met efficacy study requirements in their Phase II Study 400-07-002. However, as they rely primarily on evidence of effectiveness from a single small Phase II study, there are serious questions of generalizability and reproducibility. The generated safety database does not appear sufficient for product licensure.

La’Nissa:

I still have questions about the regulatory pathway to request a study on sequential use of the product: will that be a PMR or PMC? With PMR, we will have a better control of this study. In the latest Study Report 400-08-002, Omrix has not submitted anything new for the preclinical review. The study design was very similar to the protocol that we rejected. They performed an ex-US soft tissue study but with different bleeding intensity - “severe or more challenging bleeding.” If we accept these data, are we accepting “severe bleeding” indication? The definitions of “severe bleeding” and “challenging bleeding” are not well defined and thus are subjective. Consequently, adverse events in the severe bleeding and in the challenging bleeding may be different.

Faith:

The OBE considers that PMC’s are not enforceable. If you need to request a study, it has to be a PMR. The safety analysis of the Fibrin Pad is also complicated due to the high risk patient population enrolled in the study. This makes the background noise too high to discriminate whether the observed adverse events were product-related. If the final decision is a CR, an additional study should be conducted, with a larger study population that is more representative of a general population.

Kimberly:

I want to see some comfort level of product safety database in the adult population before we consider pediatric patients. According to BIMO inspection reports, there were multiple instances when the use of the investigation drug was not recorded in the operation notes.

Nisha:

Thus, we have no doubts about efficacy of the Fibrin Pad. It is the safety of the product that represents the current concern, and the BIMO data make the argument for thorough safety analysis even stronger. The final decision must come from the review team.