

MEMORANDUM

To: STN 125392/0 File

Meeting Date: April 20, 2011
May 12, 2011 (Clinical)

From: Sonday L. Kelly, M.S.
Regulatory Project Manager

Subject: Mid-Cycle Meeting minutes

Applicant: OMRIX Biopharmaceuticals, Ltd.

Product: Fibrin Pad

Meeting Attendees	April 20, 2011	May 12, 2011
RPM:	Sonday L. Kelly	RPM: Sonday L. Kelly
RPM:	Mark Shields	CMC: Timothy Lee
CMC/Chairperson:	Natalya Ananyeva	Clinical: Kimberly Lindsey
CMC:	Timothy Lee	Clinical: Nisha Jain
Clinical:	Kimberly Lindsey	Clinical: Basil Golding
Pre-clinical:	La’Nissa Brown-Baker	Clinical: Roxolana Horbowyj
DMPQ:	Nancy Waites	DMPQ: Nancy Waites
DMPQ:	Randa Melhem	DMPQ: Marion Michaelis
Statistics:	John Scott	Statistics: John Scott
BiMO:	Dennis Cato	BiMO: Dennis Cato
APLB:	Loan Nguyen	Pre-clinical: La’Nissa Brown-Baker
OBE:	Faith Barash	
DPQ:	Karen M. Campbell	

Purpose of Meeting:

The goal of the Mid-cycle meeting is to have a comprehensive reading on the state of the review. This would include:

- Identifying any informational requests.
- Identifying issues that could prevent approval.
- Identifying any problems and develop a clear plan for addressing them.
- Discussion and making decisions regarding lot release.
- Ensuring PeRC presentation date is set, the PeRC forms have been submitted (2 weeks before PeRC meeting).
- Determining whether PMCs, PMRs or a REMS is needed.
- Discuss NDC assignments to product/packaging.
- Discuss proper naming convention.

Meeting minutes:

CMC (Natalya)

The Fibrin Pad is a combination product with plasma-derived Human Fibrinogen (Fg) and Human Thrombin adhered to a composite matrix (polyglactin 910 serving as a carrier of the biologic components and knitted oxidized regenerated cellulose as a backing layer). Both biological substances have a manufacturing process and characteristics -----
-----b(4)----- . The major manufacturing changes during the product development are the following:

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

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

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

The Regional Information section of the eCTD contains comparability reports of preclinical to clinical, and pivotal clinical to commercial Fibrin Pad material. The data support comparability of the preclinical and Phase 1 material and suggest that the efficacy information collected in animal studies is applicable for the clinical material. The applicability of the safety data is questionable considering insufficient observation period in comparison with the time of Fibrin Pad resorption (56 days).

There are several aspects that need clarification through an Information Request and during the Pre License Inspection in May 2011. The final product is sterilized by e-beam irradiation. The BLA includes the studies on the effect of irradiation on the components of the Fibrin Pad. Thrombin is the most susceptible to irradiation: the irradiation results in a ---b(4)----- Thrombin activity. We plan to request that the Sponsor provides a risk assessment for potential immunogenicity of the Fibrin Pad due to e-beam irradiation and exposure to the -b(4)-- solvent.

Fibrin Pad characteristics were found to be dependent on the --b(4)-----
-----Thrombin activity -----b(4)----- The
final specification for the --b(4)---- is less than --b(4)-. Omrix should also propose the release
specification for the matrix component (such as-----b(4)-----).
Omrix claims that the Fibrin Pad product is stable for 24 months when kept at room temperature.
They provided 24-months stability data for 3 clinical batches and 12-months stability data for 3
validation batches. As each component appears to behave differently on stability, the data for a
longer period is needed to establish the shelf-life. We need clarification on whether the
calculations in their dose optimizing studies take into account losses of biologic components due
to irradiation and due to storage. We also need clarification how their dose optimizing studies
exclude overdosing that may lead to potential thrombogenicity of the Fibrin Pad. These questions
will be included in the Information Request.

Another important issue is a question of how the shelf life would be determined and how the
dating period for the Fibrin Pad drug product will correlate with the dating periods of the
components. Similar question was raised during review of the TachoSil BLA from Nycomed.

Facilities (Nancy & Randa)

The manufacture of the Fibrin Pad takes place in b(4) facilities: ---b(4)-----
----- FPPF (Fibrin Pad Production Facility, -b(4)----, Israel), --b(4)-----
----- A Pre License Inspection (PLI) is scheduled
for May 10-19, 2011 at b(4) and FPPF used for manufacturing the ----b(4)-----
Fibrin Pad Drug Product respectively.

Our concerns are the ---b(4)-- ----- facility for
preclinical and Phase 1. ---b(4)-- -----
----- We are not sure how they
sampled the product. We have concerns about the quality of the product throughout.

Omrix provided simulated shipping validation studies which did not cover the duration of the
actual shipping of the matrix and Fibrin Pad product. They did not fully describe how the
simulated shipping validation represents the actual shipping (ground and air). Thus we are not
sure how the shipping affects the container closure (tray lid assembly) as it is transported from
--b(4)----- to Omrix FPPF (Israel), --b(4)----- It is very important to
maintain the low moisture content of the product, and thus container closure integrity is critical.

The manufacturing process is not very well defined. We are not sure how they validated the
process. How did they ---b(4)-- ----- What is
the mode of transfer and conditions? Also we are not clear about their sampling and testing of
the product. They stated that they tested b(4) samples, but I am not sure whether they tested --
b(4)---- samples from one Fibrin Pad or --b(4)----- sample from each of --b(4)- different Fibrin
Pads.

Omrix described deviations where the product was not evenly distributed on the Fibrin Pad. This
is an issue considering that the Fibrin Pad is cut to size to fit the wound site, and thus uneven

distribution of the product can result in a too low or too high dose of the drug.

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

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

----- We will ask these questions on inspection. Perhaps they have done the studies, but did not provide the data in the submission.

Omrix stated that the acceptance criteria for ---b(4)----- and for thrombin -b(4)----- Have they manufactured and tested a Fibrin Pad with components at the lower and higher ends of the range to determine if the product works at those extremes?

Natalya: They showed that if -b(4)----- level falls below -b(4)-----, the efficiency is lost. For Thrombin, they do not go -b(4)----- because it does not add to the hemostatic efficacy of the Fibrin Pad while adhesion to tissue is compromised.

Tim: They -----b(4)-----
----- How will they make the product consistent from pad to pad?

Randa: None of the processes are described in enough detail to assure us the process is controlled from lot to lot.

Tim: This is why the inspection is very important.

Natalya: Omrix checks for uniformity of biologic substances distribution across the pad and across production days by ---b(4)--- -----

----- According to the collected data, the % RSD is in the range -b(4)---- The sensitivity of the method probably adds to this the variation. The inspection needs to confirm if this is consistent.

Nancy: Randa and I have worked on an inspection waiver memo for the -b(4)----- facility that makes the matrix. This was sent to Natalya yesterday. We have put in a request to the field office to inspect the -b(4)----- because it is a device inspection under 21CFR800's. It was last inspected in 2002.

Omrix stated that they have a comparability protocol (to go from the ---b(4)----- method to -b(4)----- method) in the Regional Module; they plan to follow up with a Prior Approval Supplement (PAS).

La’Nissa: I believe this was discussed in the pre-BLA meeting minutes, you could reference those.

Tim: This type of change would likely be considered as a critical change of the manufacturing process and can be submitted as a Prior Approval Supplement if the application is approved. We can get a better idea of the status of the –b(4)----- during the inspection. It is reasonable to put a protocol in the Regional Section when using the CTD format. The change from –b(4)----- was mentioned in one of the DMPQ meetings. I guess they will do it post-marketing if the BLA is approved.

Natalya: Regarding the matrix component of the Fibrin Pad, Peter Hudson is reviewing this information.

Preclinical (La’Nissa)

Omrix has submitted numerous studies, but they were not conducted with the current product to be used for commercial marketing. If the CMC reviewers determine that the product used in the pre-clinical studies and the product intended for commercial distribution are comparable after the manufacturing changes, we will rely on that.

In many studies, there were not enough animals used. We are trying to correlate the pre-clinical data to clinical data. I have an additional item for an information request since the Fibrin Pad will be left *in situ*: we are getting inconsistent data on the absorption rate. Omrix has tested up to 56 days, but the Pad could remain for up to 90 or even 190 days as reported in their other studies. We will request that the Sponsor monitors until Day 60 and ask for carcinogenicity studies. This may have to be a PMR or PMC.

I am deferring the final decision to clinical and CMC reviewers because there have been too many changes in the development of the Fibrin Pad and in its testing from the pre-clinical stage until the validation stage such as dosing variations, ---b(4)-----, different animals, and different surgical sites. In lieu of further animal studies, it would be better to use the clinical information to evaluate safety and efficacy. This is an on-going discussion with the firm related to implanted devices. A topical agent and implanted device are very different. The Fibrin Pad hasn’t been studied in animals with active malignancy, but in the clinical trial serving as the basis for proposed initial US licensure many patients have an active malignancy.

Kimberly: The 1st layer of contact in the Fibrin Pad is the Fibrin Sealant, which is used in a lot of patients with malignancies. This combination product (fibrin sealant/device of polyglactin 910/oxidized regenerated oxycellulose) is fairly new to us. The 1st one was approved last year, so we want some preclinical data. We are not sure if we will be able to get the data clinically in patients with malignancy. They usually have a life expectancy of less than 5 years.

Clinical (Kimberly)

Omrix started their clinical program in 2007. They wanted to study severe bleeding; they backed down to mild and moderate- which we still don’t have a definition for. Adjuncts to hemostasis are used for “ mop up” bleeding after other primary methods to achieve bleeding (i.e. suture,

different application sites, the numbers get smaller and smaller. I want to be able to analyze the difference between the application sites in regard to Fibrin Pad hemostatic efficacy.

Faith: In the field, the type of bleeding that would lead you to use either one of the products, of them, Fibrin Pad has more substance. Intuitively, you would expect the pad to do better. Why aren't they using thrombin and Gel Foam or Tachosil as the comparator?

Kimberly: We are in a new territory with the Fibrin Pad so that the things accepted in the past may need to be revisited. They met the efficacy parameters, but safety is an issue. There were some thromboembolic events: 7/111 (Fibrin Pad) vs. 2/30 (Surgicel), about half occurred within 14 days of the index operation. Were these patients on adequate prophylaxis? These are high-risk patients that need to be on strong VTE (venous thromboembolism) prophylaxis. There are lots of papers to go through for each patient and finding the relevant information related to these VTE events can be difficult. It is not sufficient for the applicant to say these patients were at high risk anyway and the VTE events were under the background event rate that they report -6% of surgical patients. We need additional safety data. A Phase 3 study is needed to minimize the background noise.

Not all surgeries need to be done on patients who have malignances. Tachosil is an analogous product, but we didn't see the same AE profile and it was approved for cardiac surgery. In the summary safety report for the ex US soft tissue surgery study I am not seeing a lot of DVTs being reported, but the protocol does not have sufficient monitoring in my opinion. It has to be an active surveillance – this is not ok for a clinical study. It is not spelled out in sufficient detail in the protocol and is a potential protocol design issue. For the US phase 2 soft tissues surgery study, even if the Sponsor won on efficacy – my recommendation is that this BLA is not approvable. There is nothing the Sponsor can say to any of the clinical information requests that would change this, but we have to give them a chance to answer the questions. In some of the reports, the site treated is not described nor is it in the operating notes; we don't know where the Fibrin Pad was placed. My review is concentrated on the VTEs and on the fact that it is an implanted device and that we are seeing infections.

Roxolana: I looked at 9 patients with DVTs. For some, it seems remote that the device was related. It is very difficult to make a good assessment because we don't know where the pad was placed and if pressure was applied. In the safety protocol, it seems the bleeding severity categories are not subjectively assigned and without validation. We don't know how distinct the bleeding severity categories were and there is no a sharp division between the categories – more like a continuum. They performed procedures on four anatomic spaces; some groups have a really small number of patients. They did not stratify data based on the application sites. Reporting everything together prevents us from looking at the percentages. This is problematic. I don't see any significant clinical benefit compared to risks. Small bowel obstruction is a concern. These devices are visceral, cause inflammation, can cause collagen formation and adhesion formation. There were none such observations in Surgicel group and 3% in the investigational group- this is concerning. When all FP patients (111) are divided to 4 application areas and rates of bleeding are compared to 30 patients in the Surgicel group, there is not enough data to consider this study as a confirmatory study. There is concern about patients with malignancy and without. The choice of patients and duration of the follow-up are not ideal. At CDRH we've been

asking sponsors for 5 year follow up.

Natalya: Regarding the two lots that were associated with AE in the Phase 2 study:

Lot L11F294: the release data are within specification for all parameters; stability data are submitted for 24 months and remain within specification. However, the trend analysis revealed a decrease in –b(4)----- compared to other lots and this trend was observed for both RT and refrigerated storage conditions. This was consistent with the results of ---b(4)----- when Fg degradation products accumulated starting at 12 month. This trend might indicate loss of product efficacy.

Lot M06F164: the release data are satisfactory. The trend analysis of the stability data revealed a significant decrease in the –b(4)----- component of the matrix reflecting its structural degradation. This trend was observed at both RT and refrigerated storage conditions. This brings up a question of consistency of the manufacturing process. As this type of matrix is known to have a tendency for acidic pH (discussed at the Severe Bleeding workshop in December 2010), matrix degradation might be related to inflammation. We plan to request that the Sponsor explains the aberrant stability trends, and comments on the potential correlation with AE observations in the Phase 2 study with these two lots.

Kimberly:

This is not a systemic treatment. These patients have some hyper-clottable proteins. At the local level site, we don't know what is going on locally. Small changes can affect the efficacy.

BiMO (Dennis)

Three of the clinical sites were inspected: Baltimore (18 subjects out of 60), Georgia (28 subjects), and Alabama (32 subjects). The Georgia site had no issues. The other 2 sites had a Form FDA 483 issued. For the Alabama site, the 483 is not significant – 16 of 32 patients enrolled were also enrolled in another study for different test articles. Enrolled subjects should not be enrolled simultaneously in another study to avoid interaction between the test articles.

In Baltimore, 1/3 of the subjects do not mention the use of the study drug during surgery. There is nothing in the notes to confirm that the study drug was used. For 7/8 of the subjects, the attending surgeon was not the clinical investigator – the person who performed the surgery was not related to the clinical trial. No evidence that the surgeon was trained according to the protocol or that the surgeon substitution was approved by the IRB. There may have been some issues with the randomization. I am not sure this data can be used in the evaluation.

John: The Sponsor reported one randomization deviation, but I am not sure what site that was

Dennis: I don't have the EIR from Baltimore, yet. This was the Adams Crowley Shock Trauma Center. Baltimore has two sites with two different investigators, we inspected one of those.

Pharmacovigilance (Faith)

There are safety issues. They submitted a pharmacovigilance plan, but it is weak. There is an on-

going study, but it is not complete. We would request they complete their studies, conduct a Phase 3, and Phase 4 to look at re-exposure. There is no data on pediatric use. If this product is going to be approved – it would be for general surgery, not just malignancy. Omrix needs to look at a larger group both with and without co-morbidities. Healthy people do not generally have surgical complications. There is a high rate of AE: 92% AE is very high.

Lot Release (Karen)

When the BLA is close to the approval stage, the DPQ will cooperate with the Product Office to develop a Lot Release Testing Plan. The Sponsor should submit the Lot Release Protocol for the Fibrin Pad.

Labeling (Loan)

We are not ready to talk about labeling. The proper name of the product is a concern. Omrix proposes to introduce a new term, “—b(4)-----” with Human Fibrinogen and Human Thrombin in parenthesis. We have been calling it Fibrin Pad, but the PI states “—b(4)-----
----- This has some hidden promotional meanings and is not consistent with what we have improved for other products. We will have to decide on the proper name.

Action Items:

- All finalized, supervisor-concurred mid-cycle memos should be in the database by Wednesday, April 27, 2011.
- Randa, Destry, and Natalya will be on inspection of the Omrix facilities May 10-May 20, 2011.
- A follow up meeting will be held to discuss clinical issues on May 12, 2011.