

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 Sonday Kelly, 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: Mid-Cycle review of CMC information in the original BLA for Fibrin Pad (Applicant - Omrix Biopharmaceuticals Ltd., Israel)

On 19 November 2010, Omrix Biopharmaceuticals Ltd. submitted electronically an original Biologics License Application (BLA), STN 125392/0, for Fibrin Pad, a Biologics-Device combination product, with the proposed proprietary name EVARREST.

Description: Fibrin Pad is a sterile bio-absorbable hemostatic agent. It is a combination product made from a flexible composite Matrix (device component) coated with Human plasma-derived Fibrinogen and Thrombin (biological drug substances). Fibrin Pad is supplied in units measuring 4 x 4 in. (10.2 x 10.2 cm). The composition is described in terms of Human Fibrinogen, Human Thrombin, and Matrix, as assessed on the Fibrin Pad, per unit area. For Human Fibrinogen, the concentration is 50.3 mg/in² (7.8 mg/cm² measured as “------(b)(4)-----”); for Human Thrombin - 203.2 IU/in² (31.5 IU/cm² measured as “thrombin activity” on the Fibrin Pad); and for Matrix, the content is -----(b)(4)-----.

Proposed indication: 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. The intended route is direct application onto bleeding tissue during surgery. Omrix proposes a new “SPL acceptable” term for dosage form as -----(b)(4)-----.

The memo was drafted in the end of April 2011 and was reviewed by Dr. Nancy Kirshbaum on 04 May 2011 and by Dr. Timothy Lee on 06 May 2011. The memo was revised on 31 May 2011 (due to Pre-License Inspection of Omrix held May 10th – May 20th, 2011) and 08 June 2011. The current document is the concurred version.

Mid-Cycle Review Conclusions:

1. Formulation development studies for optimizing doses of the biological Drug Substances and composition of the Matrix for the Fibrin Pad commercial product are extensive and

scientifically valid. The selected dose ranges for Fibrinogen (----(b)(4)---- input dose resulting in the ----- (b)(4)----- and the ----(b)(4)---- range of ----(b)(4)----) and Thrombin (---(b)(4)--- input dose resulting in the final thrombin activity range of ----(b)(4)----) are supported by the monitoring of physicochemical and functional parameters of the Fibrin Pad (analytical data, ---(b)(4)---, coating uniformity, adhesiveness, and hemostatic performance in animal models). It is noted that the composition of the Fibrin Pad and of TachoSil that may serve as a comparator (Fibrin Patch from Nycomed, Denmark, approved under BLA STN 125351/0) is similar in the content of Fibrinogen but has a ~ 10-fold higher content of Thrombin. While the specification range is defined by the different matrix composition of Omrix's Fibrin Pad and intrinsic variability of the analytical methods, the Sponsor should explain how their dose optimization studies exclude the overdosing of the biological Drug Substances that may lead to potential thrombogenicity of the Fibrin Pad. It also underscores the importance of collecting sufficient safety data in pre-clinical and clinical studies to verify the optimal Fibrinogen/Thrombin ratio.

2. The Sponsor identified the factors that influence Thrombin activity in the Fibrin Pad: (i) amount of Human Thrombin applied to the Matrix during the manufacturing process (input dose), (ii) loss of Thrombin activity during final sterilization by e-beam irradiation; and (iii) loss of Thrombin activity during storage. The losses during the manufacture were accounted for by establishing a correlation between the Input Dose and Thrombin Activity in the Fibrin Pad at release (Figure 13 in Module 3.2.P.2.2.1). The selected Input Dose ensures Thrombin activity at release within the set Specification range. The Sponsor should provide a risk assessment on the potential immunogenicity of the Fibrin Pad due to exposure of its components to --(b)(4)-- solvent during production and to e-beam irradiation during terminal sterilization.
3. The stability studies are ongoing, and available results for all parameters remain within the Specification. Additional, up-to-date stability data for the Fibrin Pad Validation Batches will be necessary to support the proposed shelf-life of 24 months when stored at 2 to 25°C.
4. The validation of the Fibrin Pad manufacturing process was conducted by manufacturing three consecutive production-scale Fibrin Pad batches - -----(b)(4)----- using the -----(b)(4)----- application of Drug Substances to the Matrix and final sterilization by e-beam irradiation within the allowable dosage range of ----(b)(4)----. The release data are satisfactory for all parameters. The Firm's approach to establish in-process acceptance criteria for the -----(b)(4)----- steps needs to be clarified as it appears inconsistent for -----(b)(4)----- Thrombin activity.
5. The Sponsor should develop Specification for the Matrix component of the Fibrin Pad. Specifically, the ----(b)(4)---- reflects the adhesiveness of the Fibrin Pad to the wound area and the ----(b)(4)---- test appears to reflect matrix structural integrity. The proposed Specification for the Matrix component may be set either as an acceptance range or as a lower limit threshold.

6. Comparability studies for Fibrin Pad used in pre-clinical studies (----(b)(4)---- fibrinogen; ----(b)(4)---- thrombin; -----(b)(4)-----) and Fibrin Pad used in Phase I clinical studies (----(b)(4)---- fibrinogen; ----(b)(4)---- thrombin; -----(b)(4)-----) demonstrate their comparable performance (hemostatic efficiency) in a swine acute aortotomy model. Pre-existing animal efficacy data generated with Fibrin Pad material manufactured by the (b)(4) method appears applicable to the product manufactured by the (b)(4) method for Phase I clinical studies. The applicability of the safety data is ambiguous considering (i) further dose adjustments for the pivotal clinical material and (ii) insufficient observation period in comparison with the time of Fibrin Pad resorption (56 days).
7. Comparability Report No. QA-R-FP-0015-00 for Fibrin Pads produced during Process Validation (----(b)(4)----) versus Pivotal (M06F164) batches demonstrates similar release results, except for -----(b)(4)-----, which is higher in the Validation batch due to an increase in Fibrinogen Input Dose. The Validation batch shows improved matrix- and protein-characterizing parameters (----- (b)(4) -----). The hemostatic efficacy of Pivotal and Validation batches in a porcine partial nephrectomy model was comparable and without recorded thromboembolic adverse events within a 48-h observation period. Considering optimized Fibrinogen/Thrombin ratio, optimized Matrix composition and container closure system, the commercial Fibrin Pad product is expected to have an improved safety and efficacy profile in comparison with the Pivotal Batches. However, this hypothesis can only be verified in clinical studies with the use of the Fibrin Pad material manufactured with the optimized and validated process.
8. For information of the Clinical reviewer: All three Batches of the Fibrin Pad used in the Pivotal Clinical Study 400-07-002 had the release data within the set Specification acceptance ranges. The trend analysis of the stability data indicates that the Clinical Batch L11F284 showed a decrease in the -----(b)(4)----- level (an indicator of potential loss of potency). The Clinical Batch M06F164 showed a decrease in --- (b)(4) --- (an indicator of impairment of the Matrix structural integrity). The Sponsor should provide explanation for the aberrant stability trends and for their potential correlation with the adverse events recorded in the Pivotal Clinical Study with these Batches.

Letter-ready comments to the Sponsor are listed at the end of this memo.

REVIEW SUMMARY

3.2.S. HUMAN FIBRINOGEN (BIOLOGICAL DRUG SUBSTANCE)

Human Fibrinogen drug substance ----- (b)(4) -----
 -----, Human Fibrinogen is manufactured by Omrix Biopharmaceuticals Ltd., ----- (b)(4) ----- in Israel (FDA Registration Number ----- (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 or alternatively purchased from ----- (b)(4) -----, an FDA-approved supplier (FDA Establishment License Number: -(b)(4)-). Source plasma complies with the requirements of 21 CFR Part 640 and applicable FDA memoranda.

The manufacturing process is essentially the same as for -----(b)(4)-----
----- The major changes include -----(b)(4)-----
----- (b)(4)-----

----- These changes are described in Section 3.2.S.2.6, Manufacturing Process Development, Human Fibrinogen. The manufacturing process includes Solvent/Detergent (S/D) treatment (-----
----- (b)(4)-----) and pasteurization step (-----
----- (b)(4)-----) for virus inactivation.

3.2.S. HUMAN THROMBIN (BIOLOGICAL DRUG SUBSTANCE)

Human Thrombin drug substance -----(b)(4)-----
----- Human Thrombin is manufactured by Omrix Biopharmaceuticals Ltd., -----(b)(4)-----in Israel (FDA Registration Number: ---(b)(4)---). The starting material is -----(b)(4)-----
----- is derived from human source -----(b)(4)-----plasma collected from qualified donors in FDA-licensed facilities. Source plasma complies with the requirements of 21 CFR Part 640 and applicable FDA memoranda. -----(b)(4)-----

Human Thrombin drug substance is -----(b)(4)-----
----- The manufacturing process is essentially the same, with a few modifications such as: -----(b)(4)-----

----- These changes are described in Section 3.2.S.2.6, Manufacturing Process Development, Human Thrombin. The manufacturing process for Thrombin includes S/D treatment (----(b)(4)-----
-----) and ---(b)(4)--- filtration for virus elimination.

3.2.S. COMPOSITE MATRIX (DEVICE COMPONENT)

The device component of the Fibrin Pad consists of a Matrix made of two absorbable polymers: oxidized regenerated cellulose (ORC) and polyglactin 910 (PG910). The polyglactin 910 (PG910) component was chosen as the main carrier of the biologic 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 oxidized regenerated cellulose (ORC) was chosen as a backing layer for the PG910 nonwoven felt to provide mechanical strength to the product and due to its fast absorption.

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

The Composite Matrix is currently manufactured by -----(b)(4)-----
-----, at the facility in ----(b)(4)----- (FDA registration number: ---(b)(4)-----).
The Matrix -----(b)(4)----- (FDA
registration number: ----(b)(4)-----).

[(b)(4)]

3.2.P. FIBRIN PAD DRUG PRODUCT

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

Table 1 Composition of Fibrin Pad				
<u>Components</u>	<u>Average Value</u>			<u>Function</u>
	<u>Quality Designation</u>	<u>Per cm²</u>	<u>Per in²</u>	
Matrix	In-house Standard	-(b)(4)-	-(b)(4)-	Backing and Carrier
Human Fibrinogen	In-house Standard	7.8 mg	50.3 mg	Active Ingredient
Human Thrombin	In-house Standard	31.5 IU	203.2 IU	Active Ingredient

(b)(4)

3.2.P.2.2.1 FORMULATION DEVELOPMENT

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

(b)(4)

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

(b)(1)

(b)(4)

(b)(4)

(b)(4)

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

(b)(4)

4 Pages Determined to be Not Releasable: (b)(4)

[illegible]

Physicochemical and Biological Properties

The Fibrin Pad was characterized by physical/biochemical properties and by functional performance.

Mechanism of Action

The primary mechanism of action of Fibrin Pad follows the principles of physiological fibrin clot formation. Upon contact with a bleeding wound surface, the biological components (Human Fibrinogen and Human Thrombin) hydrate, and the subsequent fibrinogen-thrombin reactions initiate the last step of blood clot formation in a normal and well-understood biochemical reaction. The resultant fibrin clot adheres to the tissue and becomes integrated with the fibers of the Matrix component, thereby forming a barrier to blood flow and providing a surface for initiation of the normal endogenous hemostatic cascade.

Physical Characterization

The physical characteristics that define the Fibrin Pad can be summarized as follows:

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

Methods are described in Module 3.2.P.5.2, Analytical Procedures.

Appearance

The Fibrin Pad has a characteristic white to yellowish appearance, uniformly coated on one surface with a white to yellowish powder. An embossed wave pattern is present on the oxidized regenerated cellulose (ORC) surface of the Fibrin Pad to distinguish between the active (coated with biological components) and the non-active (ORC) surfaces.

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

Coating Uniformity

Mechanical Strength

In bleeding wound sites, the Fibrin Pad is exposed to blood pressure forces and must be capable of withstanding such forces until hemostasis is complete and physiologic hemostatic mechanisms become operative. The mechanical integrity of the Fibrin Pad is characterized by its --(b)(4)-----, i.e., the force required to tear the pad, and is primarily a function of the Matrix component.

Studies were conducted to evaluate the impact of the mechanical properties of the Matrix on those of the Fibrin Pad. Matrix samples prepared by the routine manufacturing process were compared with Matrix samples which were purposely weakened by partially degrading the Matrix (treated Matrix):

- -----

- -----

Fibrin Pad manufactured with treated Matrix exhibited lower --- (b)(4) -- when compared to Fibrin Pad manufactured with untreated Matrix thus suggesting that the Matrix is the main contributor to the --- (b)(4) --- of the product.

(b)(4)

(b)(4)

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

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

Content and Activity of Matrix and Drug Substances

(b)(4)

(b)(4)

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

Functional Performance

The functional properties of the Fibrin Pad are assessed by a series of *ex vivo* and *in vivo* tests which characterize the ability of the product to adhere to tissue and to achieve hemostasis.

In Vivo Functionality

Three well-established animal models of hemostasis were used in development and characterization of the Fibrin Pad: the rat kidney hemorrhage model, the swine aortotomy model, and the swine partial nephrectomy model. These models simulate clinical severe wound settings and therefore were used to assess the hemostatic efficacy of Fibrin Pad.

Physicochemical and Biological Properties Conclusion

The physical properties of the product are characterized by the --(b)(4)--, coating uniformity, and --- (b)(4)----- of the product. The chemical identity of the Matrix components is shown by the --- (b)(4)-- test methods. The identity and purity of the biologic components is verified by the ---

----(b)(4)-----; the potency of the drug substance is measured by the -----(b)(4)--- assay and the Thrombin Activity assay. The functional properties of the Fibrin Pad are characterized by the ----(b)(4)----- methods, which demonstrated the ability of the product to adhere to tissue and withstand pressure. The hemostatic performance of the product was demonstrated in live animal models, including the rat kidney hemorrhage model, the swine acute aortotomy model, and the swine partial nephrectomy model. Overall, the methods used indicate that the fibrinogen and thrombin active components remain essentially intact and functional within the Fibrin Pad drug product.

3.2.P.2.3 MANUFACTURING PROCESS DEVELOPMENT

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

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

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

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

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

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

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

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

8 Pages Determined to be Not Releasable: (b)(4)

(b)(4)

HISTORY OF TEST METHODS AND SPECIFICATIONS

Release and Stability

Descriptions of the release and stability analytical procedures for Fibrin Pad are presented in Module 3.2.P.5.2, Analytical Procedures. The analytical procedures and specifications have not changed during Fibrin Pad development for the following tests: appearance, ----(b)(4)-----, endotoxin, sterility, irradiation dose, package integrity ((b)(4)) test, --(b)(4)-----, visual inspection of foil pouch seal integrity, and --(b)(4)---. The following analytical procedures and/or specifications were changed during Fibrin Pad development and were validated:

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

(b)(4)

Thrombin Activity

(b)(4)

(b)(4)

3 Pages Determined to be Not Releasable: (b)(4)

The validation of the Fibrin Pad manufacturing process was conducted by manufacturing three consecutive production-scale Fibrin Pad batches using nominal process parameters and validated equipment in the Omrix FPPF production facility. These process validation batches - (b)(4) - were manufactured using the (b)(4) application of Drug Substances to the Matrix and were final sterilized by e-beam irradiation within the allowable dosage range of (b)(4). Intermediate materials with hold times were challenged to the maximum hold times. In-process control and characterization of intermediates as well as release testing of the final product were conducted, and these batches were included in stability studies. In-process acceptance criteria and limits were met for all steps of the manufacturing process. The results were comparable between the batches supporting consistency of the process. (b)(4)

The full Fibrin Pad Process Validation Report QA-R-FP-0014-00 is provided in Module 3.2.R.4, Regional Information.

All characteristics of the final product that was produced from the intermediates prepared within the process validation met the Fibrin Pad release specifications (Module 3.2.P.5.4, Batch Analyses) and the acceptance criteria in the approved stability plan (Module 3.2.P.8.1, Stability Summary and Conclusion).

(b)(4)

(b)(4)

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^a The Sponsor states that, per discussion with the Agency during the October 2009 Type B Pre-BLA meeting, a waiver for general safety test requirements is requested as specified in 610.11(c)(3) for “non liquid products other than freeze dried products” and is provided in Module 1.

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

^c

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

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

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

The stability specifications are identical to the release specifications except for----- --(b)(4)---
 ----, irradiation dose, and visual inspection of foil pouch seal integrity, which are not tested in
 stability studies. Instead, ----(b)(4)---- ----- (----(b)(4)-----) are
 included.

3.2.P.8.1 STABILITY SUMMARY AND CONCLUSIONS

The Sponsor requests the shelf-life for Fibrin Pad of 24 months when stored at 2 to 25°C.

Three batches of Fibrin Pad (used in the pivotal clinical study), which were manufactured according to the current Fibrin Pad manufacturing process, were put on long-term and accelerated stability studies:

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

Table 1 Fibrin Pad, status of stability studies for production-scale batches

Fibrin Pad Pivotal Batches				Fibrin Pad Process Validation Batches		
Batch	L11F284 ^a	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 12 months	Ongoing 12 months	Ongoing 12 months
Status of Study at ----- ----- (b)(4) -----	Completed	Completed	Completed	Ongoing 12 months	Ongoing 12 months	Ongoing 12 months

----- ----- (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.						

For clinical batches, 24-months stability data for thrombin activity, ----(b)(4)----, and --(b)(4)----- were subjected to statistical analysis. The projected shelf-life for all parameters extends beyond the requested dating period if based on the long-term storage conditions. However, 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)----- This was consistent with the results of ---(b)(4)----- analysis of this Lot for Fibrinogen when fibrinogen degradation products accumulated starting at (b)(4) months.

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

[(b)(4)]

Batch M06F164 represented a worst-case for ---(b)(4)--- as it was the only batch ---(b)(4)-----
----- . This trend was observed for both long-term storage
conditions at -----(b)(4)-----

Projections based on the data from the accelerated studies for this Lot do not support the 24-
months shelf-life.

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

[

(b)(4)

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

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

Reviewer's comment: The currently available stability data is not sufficient to support the
claimed shelf-life for the Fibrin Pad and up-to-date data for the long-term storage conditions for
the Process Validation Lots should be submitted to the BLA. Of note, Lots L11F284 and
M06F164 were used in the Pivotal Clinical Study 400-07-002 in which thromboembolic adverse

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

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

Reviewer's comment: Pre-existing animal efficacy data generated with Fibrin Pad material manufactured by the (b)(4) method appears applicable to the product manufactured by the (b)(4) method for Phase I clinical studies. Of note, the material used in the pivotal clinical study had Input dose: (b)(4)mg/sq.cm Fibrinogen;(b)(4)IU/sq.cm Thrombin, i.e., a (b)(4) content of Thrombin in comparison with the pre-clinical material.

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

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

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

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

[(b)(4)]

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

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

[(b)(4)]

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

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

RECOMMENDATION:

The submitted information demonstrates that the developed manufacturing process allows consistent production of the Fibrin Pad material with satisfactory hemostatic efficiency. Additional information is requested from the Sponsor to address a number of CMC concerns outlined in this memo under Reviewer's Comments and summarized in the Letter-ready comments below. I defer it to the Pharmacology/Toxicology and Clinical reviewers to comment whether the safety profile of the Fibrin Pad has been sufficiently studied.

Letter-ready Comments to the Sponsor:

1. Contents of Fibrinogen and Thrombin as presented in Table 1 Composition of Fibrin Pad (Module 3.2.P.1 Description and Composition of the Drug Product) are incongruent with those Table 1 Fibrin Pad Release Specifications (Module 3.2.P.5.1 Specifications). For example, the target Fibrinogen content of “7.8 mg/cm² measured as ----(b)(4)-----” may be confused with “the range ---(b)(4)--- mg/cm² measured as ----(b)(4)-----”. Therefore, please specify in a footnote comment to Table 1 Composition of Fibrin Pad that target values for Fibrinogen and Thrombin are the average values based on analysis of N lots of Fibrin Pad in respective assays.

2. Please explain how your dose optimizing studies address and exclude the overdosing of the biological drug substances that may lead to potential thrombogenicity of the Fibrin Pad. Also, please comment on how the established input dose ranges for Thrombin and Fibrinogen affect the performance of the Fibrin Pad.
3. Please describe in detail how you establish the in-process acceptance criteria for the -----

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

4. Please develop a Specification for the Matrix component of the Fibrin Pad (e.g., its -----
--(b)(4)-----). The proposed Specification may be set either as an acceptance range or as a lower limit threshold.
5. Please submit to the BLA Report Number FLC-013: *Verification of the Holding Time of* -
----- (b)(4) -----).
6. Please provide a risk assessment on the potential immunogenicity of the Fibrin Pad due to exposure of its components to --(b)(4)--- solvent and e-beam irradiation, with reference to specific sections of the BLA containing the relevant Study Reports.
7. Please submit to the BLA up-to-date stability data for the Fibrin Pad Validation Batches -
----- (b)(4) -----
8. In your stability studies, we note the trends for the ----- (b)(4)---- for Pivotal Lot L11F294 and in --- (b)(4)--- for Pivotal Lot M06F164 when compared to other lots. We also note that these 2 lots were used in Clinical Study 400-07-002 in which several adverse events had occurred. Please explain the aberrant stability trends, and comment on the potential correlation between these two observations.