


**FOOD AND DRUG ADMINISTRATION**

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: 5/14/10

From: Jennifer L. Reed, Ph.D.; CBER/OBRR/DH/LPD  
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To: File 125325 / 21

Through: Dorothy Scott, M.D.; CBER/OBRR/DH/LPD; HFM-345; 301-827-3016

Cc: Cherie Ward-Peralta; OBRR/DBA/RPMB; HFM-380; 301-827-9170

Subject: Review of Reply to IR: Immunogenicity assay development, quantitation of filaments in final product

Product: Alpha-1 Proteinase Inhibitor (Human) intravenous for chronic augmentation and maintenance therapy in individuals A1PI deficiency and emphysema

Submission Date: May 4, 2010

Manufacturer: Kamada, Ltd.

**Recommendations:**

1) A PMR for immunogenicity study final report to be provided no later than February 1, 2011 is recommended. As part of this PMR, Kamada should submit the validation final study report prior to testing clinical samples. [wording to be determined in collaboration with CRB]

The following comments can be forwarded to the Sponsor:

- 1) Please submit an amendment to this BLA stating that:
  - The release specification will be -----(b)(4)-----  
-----/vial of drug product.
  - Kamada will perform 100% visual inspection upon lot release, ----(b)(4)---  
-----.
- 2) Please submit a revised lot release protocol as an amendment to this submission reflecting new visual inspection criteria of -----(b)(4)-----.

3) Please commit to performing a -----(b)(4)-----  
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The final study report should be submitted as a PMC-final  
study report by February 1, 2011.

4) Please commit to performing a down-scale study which establishes the range of  
----- (b)(4) ----- consistent with removal of HIV and pseudorabies virus by  
nanofiltration. The final study should be submitted as a PMC-final study report by  
February 1, 2011, and if indicated, should include your modified ----- (b)(4) -----  
target range for full-scale production

5) ----- (b)(4) -----  
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6) In Table 2-4 of amendment 21, you submitted summary data for ----- (b)(4) -----  
----- in DP lots ----- (b)(4) -----  
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Please submit the individual vial data.

7) The operating pressure limits for nanofiltration should be ---- (b)(4) ----, based on  
downscale validation of virus removal. Please acknowledge that you have made this  
modification in your batch records.

### **Background**

On April 20<sup>th</sup> CBER sent an information request to the Sponsor regarding progress in  
developing a more sensitive immunogenicity assay. In addition, additional information  
was requested on the Sponsor's observation of protein filaments in Kamada-API final  
product. In this electronic submission the Sponsor provides replies, reviewed below.

### **Review**

***CBER Question 1: To aid in the ongoing review of your BLA submission, CBER requests an update on your activities toward refining the immunogenicity assay for Kamada-API. Please include assay development milestones and a working timeline. CBER would like to stress that a sensitive immunogenicity assay remains a high priority for this program.***

**Sponsor reply:** The Sponsor states that a significant effort continues to be made toward development of the immunogenicity assay. Current milestones are presented in a table:



Two (2) Pages Determined to be Non-Releasable: (b)(4)

------(b)(4)-----  
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**Question 3:** *In your current manufacturing process, bulk drug substance can be stored ------(b)(4)----- prior to being processed to drug product. Please confirm that you will validate the hold time for drug substance in your comparability protocol that evaluates drug substance manufactured from ------(b)(4)-----.*

**Sponsor's reply:** The Sponsor commits to validating the -(b)(4)- hold time for drug substance as part of the comparability protocol. Drug Substance batches prepared from ------(b)(4)----- will be entered into real-time and accelerated stability monitoring protocols, and data collected will be compared with stability data acquired from Drug Substance batches prepared from ------(b)(4)----- . The Sponsor commits to storing ------(b)(4)-----, then using this batch to manufacture one batch of Drug Substance and one lot of Drug Product, and monitor stability of these materials.

*CBER Comment: The answer is acceptable.*

**Question 4:** *Please confirm that you will establish upper and lower limits for mixing speed, mixing time, and -(b)(4)- contact time during the ----- -(b)(4)-----.*

**Sponsor's reply:** The Sponsor commits to studies to support limits for mixing speed, mixing time, and -(b)(4)- contact time, but then states that "These studies will be performed at either one or a combination of the following scales: laboratory, pilot, or full scale."

*CBER Comment: We could ask at the least that the mixing validation should include a full-scale batch.*

**Question 48:** *For nanofiltration, it appears that -(b)(4)----- is used as a critical control parameter and not ----- -(b)(4)----- . Please note that ------(b)(4)----- is one of the parameters that should be maintained in small scale validation studies and full scale manufacture (PDA Technical Report No. 41 "Virus Filtration"). Thus, please establish a range for ------(b)(4)----- consistent with small scale virus validation data.*

**Sponsor's reply:** Kamada states that ------(b)(4)----- will be held at -----(b)(4)----- . The Sponsor says the -----(b)(4)----- will be monitored.

*CBER Comment: Based on the downscale data the range should be -----(b)(4)-----.*

***Question 78: The flow diagram for -----(b)(4)----- Manufacture (Figure 2.3-1) provides critical operational parameters (e.g. -----(b)(4)-----) and process quality attributes (e.g. -----(b)(4)-----). However, the actual limits are not provided. Please provide actual numerical limits for all critical operational parameters and process quality attributes for the----- (b)(4)----- -----.***

**Sponsor's reply:** The diagrams were updated.

*CBER comment: This response is acceptable.*