



FOOD AND DRUG ADMINISTRATION  
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: 3/22/10

From: Jennifer L. Reed, Ph.D.; CBER/OBRR/DH/LPD  
HFM-345; 301-496-0625

To: File 125325 / 17

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:

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

Submission Date: October 23, 2008

Manufacturer: Kamada, Ltd.

**Recommendation:**

The following letter-ready comments can be faxed to the Sponsor.

1) -----(b)(4)-----  
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2) 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)-----.

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

**Background Information:**

On March 3, 2010, CBER communicated an information request to the Sponsor regarding drug product evaluation criteria. In the same communication, CBER included questions and recommendations regarding the Sponsor's proposed comparability protocol, which would demonstrate comparability of product manufactured from (b)(4) containing (b)(4). The Sponsor's replies to the information request were received electronically on March 18, 2010, and are reviewed below.

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**CBER comment:**

Lot 6116004 was reported in Table S.3.2-2 as having an average of (b)(4) filaments per vial. (b)(4) is a lot higher than what the Sponsor has reported previously.

**4. Please clarify whether (b)(4) from both source and recovered plasma will contain (b)(4) going forward.**

***If (b)(4) from both source and recovered plasma will contain (b)(4) going forward, please state in your Comparability Protocol that (b)(4) full-scale batches of Kamada-API from source (b)(4) containing (b)(4), and (b)(4) full scale batches from recovered (b)(4) containing (b)(4), will be manufactured.***

**5. Please clarify whether qualification studies of age (b)(4) containing (b)(4) have been performed. In the Comparability Protocol, you should manufacture a final container lot from (b)(4) containing (b)(4) which has been aged for the maximal amount of time you wish to claim, and enter the lot into your routine stability monitoring program.**

**6. Please provide validation data that you have collected in research scale and pilot scale for (b)(4) contact time, mix time, and mixing speed for (b)(4). The data set should include analysis of (b)(4). Please include validation of (b)(4) contact time, mix time, and mixing speed in your Comparability Protocol.**

7. In your Comparability Protocol, please modify your acceptance criterion for quality attributes for in-process intermediates and DS manufactured from (b)(4). Quality attributes should be comparable to quality attributes observed historically. The comparison should not be limited to lots submitted to support the BLA. You should show that

quality attributes for all in-process intermediates are comparable with historic results, and not limit your analysis to in-process intermediates downstream of (b)(4)-.

**Sponsor's reply:**

Comments 4-7 were addressed in the revised Comparability Protocol. Please see the revised Section 3.2.R.2 Comparability Protocol for -----(b)(4)-----.

CBER comment:

The Sponsor provides revised specific studies on page 8 of the new comparability protocol. The specific studies section acknowledges that both source and recovered plasma from (b)(4)- will contain -----(b)(4)----- going forward. This answers our question 4, above. The Sponsor proposes to manufacture (b)(4)- production runs from source plasma containing (b)(4)-, and (b)(4)- production runs from recovered plasma containing (b)(4)-, to demonstrate comparability of product. This is acceptable. The Sponsor also states that stability testing will be performed on (b)(4)- drug substance batches from source (b)(4)- containing (b)(4)-, and (b)(4)- drug substance batches from recovered (b)(4)- containing (b)(4)-. Long term stability and accelerated stability monitoring will be included. One drug product lot from source (b)(4)- containing (b)(4)- and one drug product lot from recovered (b)(4)- containing (b)(4)- will also be entered into the stability monitoring program. These plans are consistent with CBER's recommendations to the Sponsor.

Regarding (b)(4)- stability, the Sponsor proposes that -----(b)(4)----- during this comparability study will determine the shelf life of paste. The shelf life will be determined separately for recovered and source (b)(4)- containing (b)(4)-. This is in agreement with what we asked the Sponsor to do in question 5.

Manufacturing consistency will be established by consistent conformance with operational parameters, product quality attributes, and comparison of process performance (e.g. step yields) with historical data. This is in line with our request in question 7.

In question 6, we asked:

***Please provide validation data that you have collected in research scale and pilot scale for (b)(4)- contact time, mix time, and mixing speed for -----(b)(4)-----.***  
***The data set should include analysis of (b)(4)-. Please include validation of (b)(4)- contact time, mix time, and mixing speed in your Comparability Protocol.***

Mixing time, mixing speed, and length of (b)(4)- contact time had not been identified as critical parameters for the current manufacturing process. There is no information on the mixing time, mixing speed, or length of contact with (b)(4)- provided in the main body of the BLA, and none provided in the revised comparability protocol. Also there is no explanation regarding the lack of data regarding validation of these parameters in the revised comparability protocol, and no mention in the cover letter. Instead, on page 12 of the revised comparability protocol, the Sponsor states the following:

*The in-process control (IPC) limits will be the same as those that were established in validation of the current manufacturing process. The limits for the process quality attributes of the DS manufacturing process are described in Table.R.2-2. Process quality attributes will be compared to historical data accumulated to date for the current validated process. In addition,*

*the activity of -----(b)(4)----- will be monitored during contact with the ----(b)(4)-----*  
*----- in comparison to the current validated process.*

A reasonable approach may be to wait for the Sponsor to provide the -(b)(4)- data, then explicitly ask the Sponsor at that time to establish limits for mixing time, mixing speed, and -(b)(4)- contact time.