



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research

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**Date:** 10/16/09

**To:** To File (STN 125325)

**From:** Ewa Marszal, PhD; CBER/OBRR/DH/LPD, HFM-345, 301-402-4368

**Through:** Dorothy Scott, MD; CBER/OBRR/DH/LPD, HFM-345, 301-827-3016

**CC:** Cherie Ward-Peralta, RPM; CBER/OBRR/DBA/RPMB, HFM-380, 301-827-9170

**Applicant:** Kamada

**Product:** Alpha-1-Proteinase Inhibitor (Human)  
Proposed names: APIKAM (primary), GLASSIA (alternate)

**Subject:** **Mid-cycle Memo:** Chronic augmentation and maintenance therapy in individuals with congenital deficiency of alpha-1 proteinase inhibitor (A1-PI) and clinical evidence of emphysema

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**Recommendation:**

Letter-Ready comments are at the end of this review memo.

**Review**

This is an original BLA submitted by Kamada for their first to be licensed in the US product, plasma-derived  $\alpha_1$ -PI. The review is in progress.

All figures, tables, and attachments cited in this review memo are provided in the Attachments section.

**Manufacturer**<sup>1</sup>

Kamada Ltd., Beit Kama, Israel (A1PI), -----(b)(4)-----  
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<sup>1</sup> For address information and responsibilities see Attachments, pp. 1-4 – Table 2.3-2 and Table 2.3-30.



Container/Closure

----- (b)(4) ----- glass vials, 20 mm ---- (b)(4) ---- rubber stoppers ----- (b)(4) ----- seals with ---- (b)(4) ----- flip off caps. The stoppers are -- (b)(4) --.

*Comment: This is a liquid formulation and  $\alpha_1$ -PI can form -- (b)(4) --- protein aggregates. During the stability studies vials were stored in the upright and inverted position. No effect on product stability of the vial orientation was observed.*

Storage

2 – 8 °C (35 – 46 °F), ----- (b)(4) -----

Carton content

vial + sterile 5 µm filter needle

Batch/lot nomenclature (Tables S.2.2-1 and P.3.3-1, Attachments, pp.26, 27)

Starting material

----- (b)(4) ----- from Source or recovered plasma (----- (b)(4) -----) is obtained under contract from ----- (b)(4) ----- manufacture flow diagram – Figure 2.3-1, Attachments, p.7).

*Comment: I note that the - (b)(4) - is tested for ----- (b)(4) -----; however the acceptance criteria are not provided on the CoA (Attachments, p.8).*

*Also the level of parvovirus B19 in the recovered plasma pool is ----- (b)(4) -----, which as - (b)(4) - states on their CoA, results from assay sensitivity for an individual donation, - (b)(4) -. The limits for B19 in the source plasma are: ----- (b)(4) -----  
----- . This is inconsistent with our new Guidance for Industry: Nucleic Acid Testing (NAT) to Reduce the Possible Risk of Parvovirus B19 Transmission by Plasma-Derived Products, FDA/CBER, July 2009, which recommends that the B19 level in the manufacturing pool does not exceed  $10^4$  IU/mL.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm071592.htm>. Dr. Pei Zhang will handle this issue.*

Raw materials

Kamada stated that all raw materials are purchased from qualified suppliers and released by Quality Control against pre-established specifications.

*Comment: Supplier qualification program will be verified (See Letter-Ready Comments).*

Conformance lots and lots manufactured to demonstrate comparability of the Source and recovered plasma

3 conformance lots (- (b)(4) - from Source and - (b)(4) - from recovered plasma) and - (b)(4) - comparability lots (- (b)(4) - from Source and - (b)(4) - from recovered plasma) were manufactured. See Tables P.3.5-15 and P.3.5-18 (Attachments, pp.31, 32).

*Comment: I note that the conformance lots will expire before the submission will be approved. They were manufactured in March 2008.*

#### Kamada-API Drug Substance manufacture

Manufacture of Drug Substance (DS) involves dispersion of -----(b)(4)-----  
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-----, Figure 2.3-2 (Attachments, p.10), which undergoes nanofiltration, S/D treatment, and -----(b)(4)----- In-process controls are listed in Figure 2.3-3 (Attachments, p.11).

#### Critical process parameters and quality attributes

The critical operational limits and attribute limits are in Tables 2.3-3 and 2.3-4, respectively (Attachments, pp. 14, 15).

*Comment: I note that some ranges are broad and their full validation will be confirmed during further review (broad ranges highlighted in the table).*

*I note that the following parameters are not included on the critical process parameter and quality attribute list: -----(b)(4)-----*  
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----- (See Letter-Ready Comments).

#### Process design space

Kamada stated that process design space was established based on data from a number of different studies.

Two studies of process consistency at manufacturing scale involved -(b)(4)- sub-batches (-(b)(4)- from ---(b)(4)--- sourced from recovered plasma and -(b)(4)- sourced from -----(b)(4)----- from Source plasma) yielding -(b)(4)- DS batches. Multiple aspects of the manufacturing process, including operational parameters, yields, API specific activity, process and product related impurity removal, and bioburden and endotoxin removal were assessed. All batches met specification and representative conformance batches were subjected to additional characterization studies. All batches were placed on stability. All Drug Product (DP) lots manufactured from these batches met specification and were placed on stability.

Kamada stated that comparability of DS from the two types of -----(b)(4)----- source material as well as process consistency were demonstrated.

*Comment: The comparability report is currently under review.*

Kamada stated that a series of process robustness studies, using a Design of Experiment (DoE) approach and a validated laboratory scale model to investigate the influence of the

extremes of critical operational limits on process performance and product quality, were conducted. Process steps assessed were the -----(b)(4)-----

-----, Acceptance limits were established based on historical data from full scale manufacturing batches. In-process materials from full scale manufacturing were used for these studies, -----(b)(4)-----, and the suitability of each starting material -----(b)(4)-----

----- was confirmed. Process quality attributes that best represented the intended performance outcome for each step were monitored. The robustness of the viral elimination steps (nanofiltration and treatment with TnBP and Polysorbate 80) was studied within the scope of the viral clearance studies.

*Comment: Process parameter limits were not fully validated in the full scale. The small scale supporting data are currently under review.*

----- (b)(4) -----  
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Kamada stated that -----(b)(4)----- were performed using a validated laboratory scale model. Process quality attributes best representing the intended performance outcome for each step were monitored, with acceptance criteria for each step ----(b)(4)----

----- was established. Resin lifetime verification will be performed at manufacturing scale. SOP N-2G-016 “AAT Resin Lifetime – Evaluation of Product and process Related Attributes” is provided. The SOP covers -----(b)(4)----- steps and is limited to assessment of column performance based on evaluation of product and process related attributes.

Two retrospective analyses were performed to evaluate the efficacy of regeneration/cleaning and sanitization procedures for -----(b)(4)-----  
 ----- at full manufacturing scale. For -(b)(4)-, the efficacy of regeneration and sanitization was assessed through -----(b)(4)----- results. For ----(b)(4)----, the efficacy of cleaning and sanitization was assessed through -(b)(4)-  
 ----- . Kamada stated that the procedures described were shown to be effective. The review is ongoing.

### Hold times

Kamada stated that each process intermediate is further processed within -(b)(4)- of its production unless otherwise specified. Product intermediate may be ----(b)(4)---

----- Hold time studies tested the effect of the storage duration on the quality of the process intermediate at these two steps and at the S/D treatment step. Table S.2.4-3 provided in Chapter 3.2.S.2.4 lists the hold time duration and their limits for process intermediates (Attachments, p.25).

Hold time studies were performed to support holding of in-process intermediates. During routine manufacture, the -----(b)(4)----- is held for approximately --(b)(4)-- ----- and TnBP/Polysorbate 80 -----(b)(4)-----.

Operationally, a hold at the --- (b)(4) -- eluate should also be included in the hold validation studies.

Stability of the -----(b)(4)----- was assessed at pilot scale (-(b)(4)- of the full scale). All acceptance criteria were met over the test period of -(b)(4)-. Stability during -----(b)(4)----- was assessed at a qualified small scale, with acceptance criteria of -----(b)(4)-----

----- was assessed at pilot scale. Kamada stated that all acceptance criteria were met over the test period of -(b)(4)-.

*Comment: Kamada inappropriately refers to the hold times supported with small scale studies as to validated hold times (Table S.2.4-3). All hold times should be validated in the full scale. Nevertheless, Kamada stated that they will perform full scale validation during the course of the review. Also, the scale of the pilot scale is not clear. In Section 3.2S.2.5 p.166 Kamada states that pilot scale was -(b)(4)- of the full scale process and in Section 2.3.S.2.3 p. 17 Kamada states that the scale of early pilot runs was --(b)(4)--- ----- (see Letter-Ready Comment).*

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

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Kamada stated that the manufacturing data from a minimum of -(b)(4)- full scale production runs were trended and reviewed to determine whether the accumulated manufacturing experience gained since the design space was initially established would support adjustment of any of the operational parameters. The review included comparison of the range of operational parameters recorded during full scale production to the validated parameters established in laboratory and in pilot scale studies. Table S.2.5-55 (Attachments, pp.17-19) summarizes the operational limits validated by laboratory and

pilot scale studies, the operational limits in place during production of the full scale clinical and validation batches, the range of actual operational parameters recorded during full scale production of batches produced since 2005 and the operational limits submitted in this BLA based on this review.

*Comment: In the table, I highlighted the ranges that I would focus on during my review. One of the ranges requires explanation, the flow rate in -----(b)(4)----- step is vastly different from what was previously used in full scale manufacture (see Letter-Ready Comments).*

#### Pre-clinical lots

Lots used in the preclinical studies are shown in Table S.2.6-1 (Attachments, p28). The -(b)(4)-, manufactured in 2000, were pilot scale lots produced at a partial manufacturing scale starting with ca. -----(b)(4)------. The -(b)(4)- were manufactured at the current scale and the current formulation.

*Comment: I note that some of the earlier lots were formulated with -----(b)(4)-----.*

#### Clinical lots

Clinical lots are shown in Table S.2.6-2 (Attachments, p.29). They were manufactured by the full scale process.

*Comment: I note that all of them were manufactured from the recovered plasma.*

Prior to 2007, the API manufactured by Kamada was produced from -----(b)(4)----- manufactured by -----(b)(4)----- from recovered plasma. In 2007, Kamada completed a comparability study to demonstrate the acceptability of -----(b)(4)----- manufactured from the Source plasma (lots listed in Table S.2.6-3, Attachments, p.30). Kamada stated that the comparability study established that the products manufactured from the two plasma sources are comparable in terms of quality, safety, purity, stability and physicochemical characteristics. Kamada stated that, in addition to these comparability batches, the subsequent conformance batches were also manufactured using either -----(b)(4)----- manufactured from either source material and serve as additional evidence of their comparability.

*Comment: The review of comparability is ongoing.*

#### Control of Drug Substance

Kamada-API DS specifications and release tests are listed in Table 2.3-6 (Attachments, p.20).

*Comment: I note that DS -----(b)(4)-----.*

Justification of specifications for Kamada-API DS is in Table 2.3-7 (Attachments, p.21) and evolution of the DS specifications is shown in Table 2.3-10 (Attachments, p.24).

----- (b)(4) ----- of Phase II/III clinical batches are shown in Table S.4.5-1 (Attachments, p.34).

----- (b)(4) -----  
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DS release test results for the conformance batches are shown in Table 2.3-11 (Attachments, p.35). DS release test results for Phase II / III Clinical Batches are in Table 2.3-12. The ----- (b)(4) ----- in those lots was in the range of --- (b)(4) --- and supports the specification for the ----- (b)(4) ----- and for the ----- (b)(4) -----.

#### Analytical methods

Kamada stated that wherever appropriate the analytical methods are performed as per ----- (b)(4) ----- The majority of the analytical methods used for the DS are the same as those used for the DP. Table 2.3-8 presents the analytical methods (Attachments, pp.22-23).

#### Drug product

#### Development

Kamada stated that during clinical development, ----- (b)(4) -----  
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----- (b)(4) -----  
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#### Compatibility

Compatibility of Kamada-API with the container closure system and the filter needle was assessed by determining the effect of the components on the product quality as measured by API activity, protein concentration and ----- (b)(4) ----- Possible extractables and leachables from the container closure system were also investigated. The effect of vials and stoppers on product quality was studied through the various stability studies performed. Most studies were performed on vials in both the upright and inverted orientations. Kamada stated that no significant differences were seen. No evidence of penetration of microbial contamination or of chemical or physical impurities was observed.

Using -(b)(4)- lots of API and -(b)(4)- different infusion volumes, the compatibility of ----- (b)(4) ----- were evaluated. Studies were performed with each filter needle; product quality was evaluated using routine release tests for protein concentration, activity by ----- (b)(4) ----- . Analyses performed up to -(b)(4)- hours postfiltration. Kamada stated that differences between the two filter needles were negligible. Kamada discussed results from extractables and leachables from the container closure components assessed by the component manufacturers.

Flow chart of API DP manufacturing process is in Figure P.3.3-1 (Attachments, p. 13).

----- (b)(4) -----  
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 ----- (b)(4) -----  
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#### Critical process parameters and quality attributes

Critical operational parameters and critical process quality attributes during DP manufacture are in Table 2.3-31 (Attachments, p.16). There are 3 critical steps involved: ----- (b)(4) -----.

*Comment: Operational limit for endotoxin of --- (b)(4) ---, which is measured at -(b)(4)- of the final target volume appears inconsistent with the limit of ---- (b)(4) ---- in the final container (see Letter-Ready Comment).*

#### Process consistency

Kamada tested process consistency by analysis of -(b)(4)- lots of Kamada-API in two independent studies comprising -(b)(4)- lots manufactured from source material originating from Source plasma and -(b)(4)- lots manufactured from source material originating from recovered plasma. Storage times for the DS batches used in these studies ranged from --(b)(4)--- (Table P.3.5-18, Attachments, p.32). The traceability of these lots is outlined in Table P.3.5-15 (Attachments, p.31).

Kamada stated that the consistency of the process was demonstrated; no impact of source material or time in storage on drug product quality was observed. The review of the study is ongoing.

#### Media fill

Media fill process simulations were performed using ----- (b)(4) ----- . Vials were incubated for a minimum of ----- (b)(4) -----, followed by a minimum of ----- (b)(4) ----- . Following visual inspection, the growth promotion capability of vial contents was confirmed using organisms defined in the -(b)(4)- as well as environmental isolates. The procedure and acceptance criteria are defined in

Kamada SOPs. Per agreement with FDA, the simulation studies for the -----(b)(4)----- will be completed during the initial stages of the BLA review process. The data will be available for review at the pre-approval inspection.

### Shipping

The shipping configuration and conditions for Kamada-API DP were based on stability data under accelerated and combination conditions. The configuration was required to maintain a product temperature between ---(b)(4)--- simulations were performed; -(b)(4)----- Kamada stated that the shipping configuration was shown to maintain product temperature between -----(b)(4)-----, sufficient time for delivery to the final destination.

*Observation not related to the manufacturing process: Subject/lot number information appears not to correlate with the study protocol (Attachments, pp. 36, 37) (see Letter-Ready Comments).*

### Recommendation

IR should be sent to Kamada.

## **LETTER-READY COMMENTS**

1. Please explain the “Listing of Subjects receiving test drug(s) investigational” (Section 5.3.5.1.3, Appendix 16.1.6). Lot assignment appears to be inconsistent with the study protocol. Some patients appear to receive exclusively Prolastin. Some patients are stated to be on Prolastin; however, the number of lot assigned indicates that Kamada-API was used.
2. Please provide copies of contractual agreements with laboratories involved in raw material, product in-process intermediate and final container testing. Please provide an SOP describing your audit policy.
3. Please provide an SOP describing your raw material supplier qualification program.
4. Please provide a list of raw materials used in the Kamada-API purification process and indicate the quality of each material and testing that is performed.
5. Please provide a table with all process control parameters (not only critical) and all quality attributes. Please note that all process parameter ranges should have two-sided limits. In the table, please include time of each operation.
6. Please provide a table similar to Table S.2.5-55 containing operating parameters for the manufacture of the Drug Substance and Drug Product for the clinical lots, lots manufactured during product comparability study (recovered plasma vs. source plasma) and for the conformance lots. For the clinical lots, please provide observed parameter ranges, for the comparability and conformance lots, please provide individual results. Also, please provide a table with all in-process product quality attributes observed for the lots mentioned above with product quality attributes ranges for the clinical lots and individual results for the comparability and conformance lots.
7. Please explain the -----(b)(4)----- for the -----(b)(4)----- step (Table S.2.5-55). The proposed range has not been covered during the full scale manufacture. Please comment.

8. We note that -(b)(4)- time is not listed as a critical process parameter in the ----(b)(4)--- step. Please comment.
9. -----(b)(4)-----  
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10. 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.
11. Please clarify whether you -----(b)(4)----- nanofiltration and -----(b)(4)----- ----- is used if this operation is performed.
12. We note the lack of critical product attributes after the -----(b)(4)-----, which is performed to -----(b)(4)----- . Please establish specifications or justify the lack of thereof.
13. Operational limit for endotoxin of -----(b)(4)-----, which is measured at -(b)(4)- of the final target volume, appears inconsistent with the limit of -----(b)(4)--- in the final container. Please tighten the limit or justify.
14. Please provide equipment flow diagram with indication of sampling points and all tests performed at each sampling point.
15. Please clarify whether single product -----(b)(4)--- that is proposed in this submission was validated in the full scale manufacture. Please note that --- (b)(4)--- should be validated in the full scale and the --(b)(4)--- lots should be placed on stability.
16. Please clarify what amount of -----(b)(4)----- was used in the pilot scale. Section 3.2S.2.5 p.166 and Section 2.3.S.2.3 p. 17 appear to provide conflicting information, -(b)(4)- of the full scale and -----(b)(4)-----, respectively.
17. Please provide a list of all pilot and full scale lots manufactured thus far and the year of their manufacture. Please include lots, manufacture of which was not completed. If such lots exist, please provide the reason for stopping the manufacturing process.
18. Please provide a list of deviations observed during the manufacture of -(b)(4)- comparability lots and conformance lots. Also, please provide summaries of the investigations.