



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

Date: November 23, 2009

To: STN: 125325.0

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Applicant: Kamada

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

Subject: Mid-cycle Review (Viral Validation)

Recommendation

The following Information Request needs to be sent to the sponsor:

1. You have provided the data of robustness studies for PPV. Please provide data to support that the viral clearance by nanofiltration is robust for clearance of other enveloped and non-enveloped viruses under the worst-case conditions.
2. Please provide justification for not including both -----(b)(4)----- as critical parameters in your study for the robustness of viral clearance for PPV at the step of nanofiltration.
3. In your submission, plasma testing for manufacturing of Kamada-APITM includes ---(b)(4)--- tested in -----(b)(4)----- . Please provide validation data for such an in-process NAT testing. Within the submission, please be sure to include the following information:
 - 1) The sensitivity of -(b)(4)- NAT for -----(b)(4)----- and the threshold level of -(b)(4)- to exclude those positive plasma donations from getting into the -----(b)(4)-----.
 - 2) A copy of the SOP for -(b)(4)- NAT describing sample preparation, sample input volume, sequences and map locations of the primers and probes used, and cycling conditions.
 - 3) -(b)(4)- analysis of all -----(b)(4)----- and probes to demonstrate that all -(b)(4)- genotypes can be efficiently detected.
 - 4) The yield of -----(b)(4)----- donations since the implementation of NAT assays for -(b)(4)- per annual basis. Please identify the genotype(s) if known.
 - 5) The sensitivity of -(b)(4)- NAT for -----(b)(4)----- and the threshold level of ---(b)(4)--- set, if any.
 - 6) A copy of the SOP describing the management procedures for those positive donations (i.e,

beyond the threshold level) of Source Plasma and recovered plasma to be excluded from manufacturing.

Summary

This submission by Kamada for the product of Alpha-1 Proteinase Inhibitor (Human) was received by the CBER/FDA on September 30, 2009 as a BLA. In this submission, the firm provided viral safety data to support the approval of the BLA. These studies include 1) Plasma screening; and 2) Manufacturing procedures that are intended for virus clearance.

CMC Review - Viral Safety

1. Material origin

The starting material for API is -----(b)(4)----- that is manufactured from human plasma by -(b)(4)- ----- in the FDA licensed facility. Either Recovered Plasma or Source Plasma is used for the manufacture of -----(b)(4)----- . Recovered Plasma is separated from Whole Blood whereas Source Plasma is collected by plasmapheresis; both are collected from healthy donors in the FDA approved blood or plasma collection centers.

Assessment of donor suitability and procedures for collection of blood or plasma are in accordance with the requirements of 21CFR Part 640. Prior to donation, the suitability of a donor is determined by a donor questionnaire and physical examination. In addition, testing for viral markers is carried out. Each donation is labeled with a unique donation number, which allows traceability and recall if necessary. Following collection, the plasma is frozen by cooling rapidly according to 21CFR Part 640.

2. Plasma testing for manufacturing of Kamada-APITM

Plasma Screening

Test	Test Performed on:		
	Individual Donation	Mini-pool (512 samples)	Manufacturing pool
HBsAg	(b)(4)		
HIV 1 & 2-Ab			
HCV-Ab			
HCV RNA			
HIV RNA			
(b)(4)			
B19V DNA			
<i>Other Tests</i>			
(b)(4)			

¹ For Recovered Plasma only

(b)(4)

Note: Parvovirus B19 (B19) in the manufacturing pool is set not to exceed 10^4 IU of B19 DNA per mL.

Reviewers' comments on -(b)(4)- NAT testing in -----(b)(4)-----:

In the submission, plasma testing for manufacturing of Kamada-APITM includes --(b)(4)-- tested in -(b)(4)- ----- . An Information Request was conveyed to the firm regarding the validation data of such an in-process NAT testing. Within the submission,

following information was recommended to be included:

- 1) The sensitivity of (b)(4)- NAT for screening (b)(4)- and the threshold level of (b)(4)- to exclude those positive plasma donations from getting into the (b)(4)-.
- 2) A copy of the SOP for (b)(4)- NAT describing sample preparation, sample input volume, sequences and map locations of the primers and probes used, and cycling conditions.
- 3) (b)(4)- analysis of all (b)(4)-specific primers and probes to demonstrate that all (b)(4)- genotypes can be efficiently detected.
- 4) The yield of (b)(4)-reactive donations since the implementation of NAT assays for (b)(4)- per annual basis. Please identify the genotype(s) if known.
- 5) The sensitivity of (b)(4)- NAT for (b)(4)- and the threshold level of (b)(4)- set, if any.
- 6) A copy of the SOP describing the management procedures for those positive donations (i.e, beyond the threshold level) of Source Plasma and recovered plasma to be excluded from manufacturing.

3. Viral removal and inactivation during the manufacturing process

The starting material for API is (b)(4)- manufactured from human plasma by (b)(4)-. Initial purification of API from (b)(4)- is accomplished by (b)(4)- chromatographic steps and a (b)(4)- step. (b)(4)- and then undergo nanofiltration (NF), treatment with solvent/detergent (S/D) (b)(4)- yield the drug substance (DS). (b)(4)- and is aseptically filled to produce the drug product (DP).

(b)(4)-

[(b)(4)]

The manufacturing steps for viral clearance are validated in small-scale: 1. Nanofiltration (NF) – for the removal of both enveloped and non-enveloped viruses; 2. Treatment by Solvent and Detergent (S/D) for inactivation of enveloped viruses.

Operating limits and values related to viral clearance during process validation

Claimed reduction factors (Log₁₀) by manufacturing process of Kamada-API

Process Step	Enveloped Viruses				Non-Enveloped Viruses	
	HIV-1	PrV	BVDV	WNV	HAV	PPV
NF	> 5.59	> 5.57	> 5.74	ND	> 4.99	4.56
S/D	> 6.41	> 6.14	> 5.61	> 6.32	N/A	N/A
Global RF	> 12.00	> 11.71	> 11.35	> 6.32	> 4.99	4.56

N/A - Not Applicable. The S/D treatment is not relevant for non-enveloped viruses.

ND- Not Done

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5. Nanofiltration

Challenge studies were performed by ----- (b)(4) ----- using five different viruses (three lipid-enveloped and two non-enveloped) to validate the effectiveness of nanofiltration using the - (b)(4) - 15 Nanofilter in removing potential viruses during the API production process.

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

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

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

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

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

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---(b)(4)---
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Reviewers' Comments on S/D treatment

Data provided in this BLA support that the S/D treatment effectively inactivates all the enveloped viruses tested.

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

In the -(b)(4)- studies, the S/D treatment effectively inactivates viruses within -----(b)(4)-----
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