



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

To: STN: 125613/0

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Applicant: Kamada Ltd.

Product: Rabies Immune Globulin (Human)
Proposed Brand Name: KEDRAB

Subject: Executive Summary and Final Review – Kamada BLA: Viral Clearance

Recommendation

Approval

Executive Summary

To support the viral clearance and viral inactivation for the KEDRAB manufacturing process Kamada provided laboratory viral (b) (4) study data. (b) (4) is the contract laboratory that conducted the viral clearance validation studies. The study's design and results were acceptable.

The starting material is human plasma from donors who have been hyper-immunized with rabies vaccine. Individual plasma units are tested for hepatitis B surface antigen (HBsAg) and for antibodies to hepatitis C virus (HCV) and human immunodeficiency virus types 1 and 2 (HIV-1/2), as well as Nucleic Acid Testing (NAT) for hepatitis B virus (HBV), HCV and HIV-1. Each plasma unit must be non-reactive (negative) in all tests. Plasma is also tested by in-process NAT procedures for HAV and parvovirus B19. For HAV each plasma unit must be non-reactive. For parvovirus B19 the limit in the manufacturing pool is set not to exceed 10^4 IU per mL. All plasma collection centers are FDA licensed. All test kits are FDA licensed.

There are three steps from manufacturing process that Kamada claims to have viral removal/inactivation effects:

1. Solvent/detergent (S/D) treatment with a mixture of tri-(n-butyl) phosphate (TnBP) and Octynoxol 9;
2. Heat treatment (pasteurization) step;
3. Nanofiltration (NF) step.

Following is the Log₁₀ Virus Reduction table from the package insert:

Process Step	Enveloped Viruses				Non-enveloped Viruses	
	HIV-1	BVDV	PRV	WNV	EMCV	PPV
S/D treatment	>4.99	>5.70	>4.38	>5.46	Not tested	Not tested
Heat treatment	>6.21	>5.67	Not tested	>6.33	3.30	Not tested
Nanofiltration	Not tested	Not tested	>6.58	Not tested	>7.66	3.41
Global Log₁₀ Reduction Factor	>11.20	>11.37	>10.96	>11.79	>10.96	3.41

Background Summary

Kamada Ltd. submitted a BLA for Kamada-HRIG, Solution for Injection. It is human immunoglobulin intravenous. The proposed indication is for passive, transient post-exposure prophylaxis of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and in combination with a rabies vaccine.

Dr. Michael Kennedy is the chair of this BLA submission. My review will focus on viral clearance section of this BLA.

1. Risk assessment for TSE transmission

Scientific literature provided the basis of potential inactivation and removal of TSE via manufacturing process of Kamada-HRIG.

Validation studies that are similar to Kamada-HRIG reported the potential of overall 12 log₁₀ overall clearance of TSE:

Table 1: Results of Prion Protein Clearance Studies

Process Step	Plasma Product Studied	Reported vCJD Log ₁₀ Reduction	Reference
DEAE-Sepharose Chromatography	Factor IX Factor VIII	> 3	Foster et al, 2000 Foster et al, 2004
Depth Filtration	IgG	> 4	Van Holten and Autenrieth, 2003
Nanofiltration	Albumin	> 4.93	Tateishi et al, 2001
Overall Log ₁₀ Reduction		> 11.93	

The risk from vCJD infection via blood cannot be predicted. Based the risk assessment, the US Public Health Services concluded that the risk to patients receiving factor VIII and von Willebrand factor concentrates was likely to be extremely small and the vCJD risk from other plasma products was likely to be as or smaller that for FVIII. Screening and exclusion of plasma donors in addition to donor traceability systems also contribute to the safety of the starting material. The potential of Kamada-HRIG manufacturing process based on scientific publication could reduce the risk further.

2. Testing of (b) (4) Materials

Kamada-HRIG drug product (DP) is manufactured from anti-rabies hyper immune human plasma via (b) (4). Only (b) (4) plasma is used for manufacture.

Donor suitability is determined by donor questionnaire and physical examination in addition to testing for viral markers. Donations are accepted if parvovirus B19 (B19V) levels are 'non-elevated'; for (b) (4) samples the cut-off limit applied is not more than (b) (4) copies/ml and in the manufacturing pool a limit of not more than 10⁴ copies/ml is applied. The results for all other viral markers are required to be negative.

Table 2: Plasma Screening

Test	Test Performed on:	
	Individual Donation	Manufacturing pool
HBsAg	X	(b) (4)
HIV 1 & 2-Ab	X	(b) (4)
HCV-Ab	X	(b) (4)
HCV RNA		(b) (4)
HIV RNA		(b) (4)
HBV DNA		(b) (4)
HAV RNA		(b) (4)
B19V DNA		(b) (4)
Other Tests		(b) (4)

¹ Testing is performed on (b) (4) of (b) (4) samples using the (b) (4)

² Testing is performed on (b) (4) of (b) (4) samples using the (b) (4)

³ On the day of the first medical examination or plasmapheresis, whichever comes first and at least every 4 months thereafter.

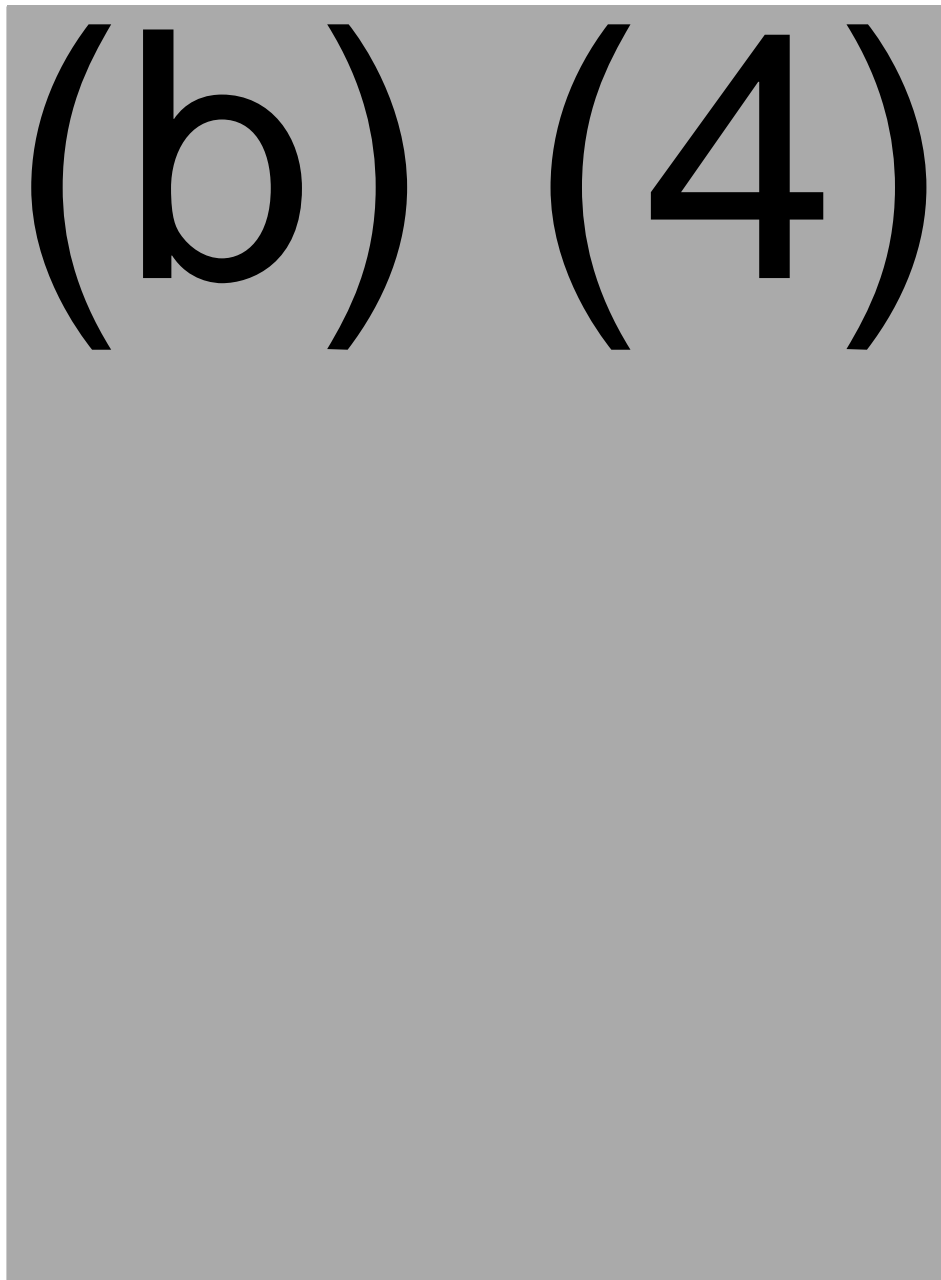
3. Virus removal and inactivation during the manufacturing process

1. Designated viral removal and inactivation steps

The process steps validated for virus removal are as **Figure 1**:

- Step (b) (4): Solvent/Detergent (S/D) treatment for inactivation of lipid-enveloped viruses.
- Step (b) (4): Heat Treatment (HT, also known as Pasteurization) for the inactivation by denaturation of heat-labile viruses.
- Step (b) (4): Nanofiltration for the removal of both lipid-enveloped and non-enveloped viruses by size exclusion.

Figure 1: Flow Chart of the Manufacturing Process of Kamada-HRIG Drug Substance



3.1.1 Solvent/Detergent (S/D) Treatment

Tri-n-butyl phosphate (TnBP), (b) (4) v/v, and Octoxynol 9 (Triton X-100), (b) (4) w/w @ (b) (4)

(b) (4)

(b) (4)

(b) (4)

3.1.2 Heat Treatment (HT)

(b) (4)

(b) (4)

2.1.3 Nanofiltration

(b) (4)

(b) (4)

4. Viral clearance validation studies

3.1 Scale down of the process

Scale-down models were established for each viral clearance step for viral (b) (4) validation studies. Critical parameters were compared between full production scale and scale down models. Intermediates generated from both were tested for potency and protein profiles to ensure the mimicking.

4.1.1 Solvent detergent treatment

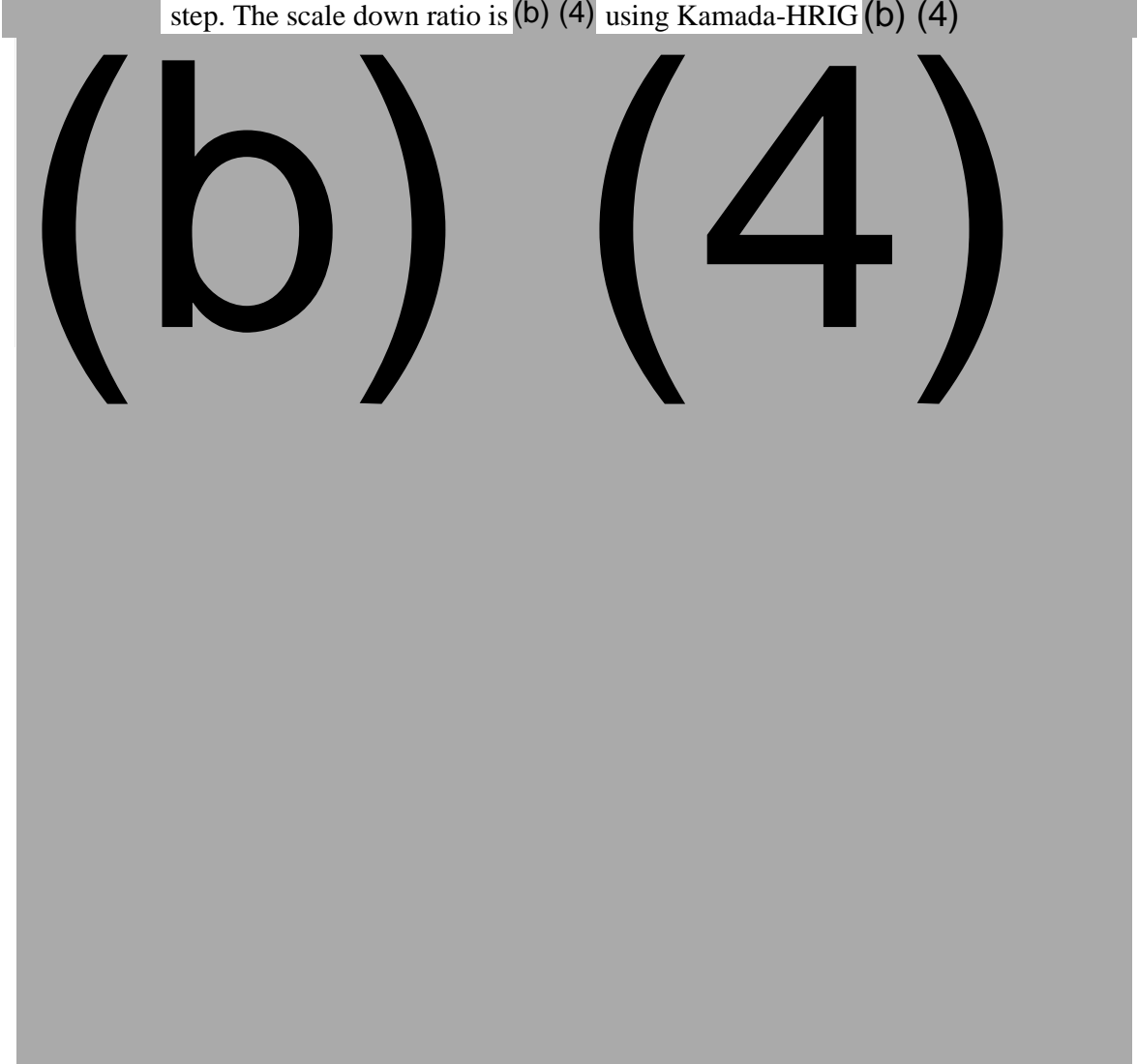
S/D in process material cannot be properly evaluated in the presence of the solvent detergent, the subsequent (b) (4) is included as part of the scale down model.

A linear scale down factor of (b) (4) was used. The (b) (4) were evaluated in the viral (b) (4) studies. In process material from Kamada-HRIG (b) (4) was processed in (b) (4) scaled down S/D treatment runs (including S/D removal by (b) (4)). The performance of scaled down model was compared with full scale production by potency and protein characteristic results.

1 page has been determined to be not releasable: (b)(4)

4.1.2 Heat treatment

The starting material was withdrawn from a full scale production run at the end of the (b) (4) step. The scale down ratio is (b) (4) using Kamada-HRIG (b) (4).



4.1.3 Nanofiltration

Material was withdrawn from the full scale manufacturing process after the (b) (4) step and from the (b) (4). The scale down factor is (b) (4) for the filter area. In process material from Kamada-HRIG (b) (4) was processed in (b) (4) scale-down nanofiltration runs. (b) (4) and (b) (4) tests were passed for each filter prior usage.

(b) (4)

In process material from Kamada-HRIG (b) (4) was used for all the small scale virus (b) (4) studies. Sample storage and shipment conditions were tested to ensure the quality of samples to (b) (4) – the contract testing laboratory for viral (b) (4) studies. Testing assays including:

(b) (4)

3.2 Selection of viruses for validation studies

Viruses and model viruses representing different sizes, with and without envelope, of DNA or RNA, of different viral families should be chosen for (b) (4) studies.

(b) (4)

3.3 Validation studies conducted by (b) (4)
(b) (4) (formerly (b) (4))
Located at (b) (4)

Positive and negative controls were included in all studies. Toxicity and interference of intermediate/test samples to testing cell lines and viruses titers were evaluated by comparing serum free media. A negative control (b) (4) was run in parallel in all (b) (4) studies. Robustness studies using (b) (4) are evaluated for S/D treatment and Heat treatment. Robustness study for nanofiltration was tested using (b) (4).

Table 10: Manufacturing Steps Evaluated

Virus	Solvent/Detergent	Heat treatment	Nanofiltration
(b) (4)	(b) (4)	(b) (4)	(b) (4)

¹ Virus used for robustness testing

3.3.1 Solvent detergent treatment

Production scale S/D treatment is Tri-n-butyl phosphate (TnBP), (b) (4) v/v, and Octoxynol 9 (Triton X-100), (b) (4) w/w @ (b) (4). (b) (4)

To target the worst case conditions of the process, Solvent /Detergent viral validation studies were carried out (b) (4)

Table 11: Solvent/Detergent Concentrations in Challenge Studies

	Triton X-100 (% w/v)	TnBP (% v/v)
Production Conditions	(b) (4)	
Studied Range ¹	(b) (4)	

¹ Including robustness studies

(b) (4)

Robustness study used (b) (4) at the worst condition of S/D at (b) (4)

The effect of different protein concentrations and buffer conductivity was studied.

(b) (4)

Protein concentration or conductivity appeared not to have any big impact on the (b) (4) reduction as (b) (4) .

For kinetic study, samples were taken at (b) (4) and at time points up to and including (b) (4) , for evaluation of the kinetics of viral inactivation. A control with (b) (4) was included. A sharp decrease of viable virus occurred at T0 and no detectable viable virus in any subsequent samples at (b) (4) .

Conclusions:

S/D treatment is considered effective and robust in inactivate/removal of enveloped viruses under production condition mimicked by scaled-down model. Log reduction factors claimed are:

(b) (4)

3.3.2 Heat treatment

Heat treatment conducted at production scale is @ (b) (4) for at least (b) (4) in the presence of (b) (4) as a stabilizer followed by a (b) (4) step to (b) (4). Viral validation studies were carried out at (b) (4) in the presence of (b) (4) at an average concentration of $3^{(b) (4)}$. Since (b) (4) is a protein stabilizer, high concentrations may stabilize viruses as well. Therefore, (b) (4) was used as worse case conditions. (b) (4) are also used for worse case conditions.

(b) (4)

(b) (4)

Kinetic studies chose (b) (4) . Samples were taken after (b) (4)

For Study

31731.01 the subsequent samples were taken (b) (4)

. A control, consisting of (b) (4)

was also prepared and heated to (b) (4) .

(b) (4) inactivation showed a rapid decrease of viable virus during the (b) (4) of heat treatment. After (b) (4), no detectable virus was in (b) (4) of the sample. (b) (4) showed rapid inactivation by heat treatment. No virus detectable for sample at (b) (4) . (b) (4) inactivation showed a steady decrease of viable virus over the (b) (4) course with still detectable virus by the end of (b) (4) treatment.

Conclusions: The heat treatment is considered effective for various viruses represented. Robustness studies showed effectiveness when treatment conditions of protein concentrations levels outside the target values in Kamada-HRIG manufacturing process. Other than (b) (4), remaining tested viruses were not detectable after (b) (4) treatment. Log reduction factors claimed are:

(b) (4)

(b) (4)

3.3.3 Nanofiltration

At production scale, nanofiltration is using (b) (4) at pH of (b) (4) @ (b) (4), operating pressure of (b) (4) psi. It is conducted in the (b) (4).

(b) (4) viruses were tested for challenge studies. In each study, the stock virus solutions were (b) (4)

Validation studies were carried out under standard conditions at the pH of (b) (4), at the temperature of (b) (4) C and the pressure of (b) (4) psi. The volumes passed through the (b) (4) filters were in the range of (b) (4) ml/m² of nanofilter.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

In study No 31599.01 part 3, samples were tested at protein concentration of (b) (4) mg/ml and (b) (4) mg/ml with (b) (4) under standard pH range of (b) (4) and temperature of (b) (4)°C.

(b) (4)

In Study No 312153.01, various pH ((b) (4)) and temperature ((b) (4) °C) conditions were tested. The pressure is under the higher end of (b) (4) psi as worse case.

(b) (4)

Both studies results showed effectiveness of this nanofiltration step for (b) (4) clearance under conditions near or outside the critical production ranges.

Conclusions: Effectiveness and robustness of the nanofiltration step for Kamada-HRIG is relatively validated. Following log reduction factors are claimed:

(b) (4)

(b) (4)

Overall following LRF are claimed:

(b) (4)

Information Requests and Kamada responses

1. FDA IR (February 13, 2017)

1. Please provide following (b) (4) assay procedure from contract lab (b) (4)
 - a. (b) (4) Procedure (b) (4)
 - b. (b) (4) Procedure (b) (4)
 - c. (b) (4) Procedure (b) (4)
 - d. (b) (4) Procedure (b) (4)
 - e. (b) (4) Procedure (b) (4)

(b) (4) submitted above protocols by February 24, 2017.

Reviewer's comments: After reviewing (b) (4) procedures of above, the virus titer measurement and calculations were assured to be properly conducted.

Appendix

1. Description of manufacturing process and process controls
2. 3.2.A.2 Adventitious Agents Safety Evaluation
3. Study No 31599.01 part 2 robustness study of solvent detergent treatment
4. Study No 31599.01 part 2
5. Study No 31731.01
6. (b) (4) virus titer testing procedures