



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

To: File BLA STN 125613/0

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Applicant: Kamada Ltd.

Product: Human Rabies Immune Globulin, Solution for Injection
Trade Name: KEDRAB®

Subject: Final Review: Original Biological License Application – Raw Materials, Extractables & Leachables and Stability

Recommendation

This original BLA submission is recommended for approval based on the assigned topics.

Executive Summary

This Discipline Review memorandum covers assigned CMC sections of the original Biologics License Application (BLA) submission from Kamada Ltd., for Human Rabies Immune Globulin, Solution for Injection, KEDRAB (HRIG). The CMC sections I reviewed were raw materials, extractables & leachables and stability. Kamada's manufacturing control on plasma, drug product excipients, primary packaging materials and processing reagents (chemicals, (b) (4), filtration membranes and filters) as well as their assessments and studies on extractables & leachables were acceptable and adequate. The Drug Substance (DS) stability results supported Kamada's proposed DS shelf life of (b) (4) at (b) (4) with currently set DS release specifications. The Drug Product (DP) stability results supported Kamada's proposed DP shelf life of 30 months at 5±3°C with currently set DP release specifications. Note that (b) (4) were not included in the test for (b) (4). Setting specification for (b) (4) and its implementation in (b) (4) DP lot release and DP stability will be fulfilled as a Post Marketing Commitment.

Background Summary

This submission was received from Kamada as an original BLA on August 29, 2016, for KEDRAB, a human rabies immune globulin product, also referred as HRIG. Kamada-HRIG is indicated 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.

Approximately (b) (4) of frozen hyperimmune human Anti-Rabies plasma is processed into (b) (4). The purification process includes (b) (4). Virus inactivation and reduction is ensured by heat treatment, solvent/detergent treatment and nanofiltration. The final product is formulated using glycine as the excipient and filled in configurations of 2 mL and 10 mL solution. The product is supplied in single-use (b) (4) clear glass vials sealed with (b) (4) or (b) (4) stoppers and (b) (4) flip-off cap. Kamada proposes a shelf life of 30 months at 5 ± 3 °C for HRIG drug product.

The Pre-BLA meeting was held on April 15, 2016. The following comments related to product consistency and stability were communicated with the Sponsor:

1. The Appearance acceptance criteria – product that is opalescent or may contain some granular deposit are generally regarded a non-desirable outcome and may be indicative of product quality issues such as (b) (4).
2. The Protein Concentration acceptance criterion of (b) (4) in HRIG Drug Product Specifications is too broad. Most low concentration IG products have tighter protein concentration specifications.
3. The (b) (4) for (b) (4) for both (b) (4) and HRIG drug product should be increased from (b) (4) to $\geq 95\%$.
4. FDA stated that the currently licensed RIG products were licensed quite a long time ago and do not necessarily represent current standards needed for approval.
5. FDA stated the hyper-immune IG monographs in the (b) (4) are outdated. FDA does not consider these monographs valid.
6. FDA asked Kamada to eliminate opalescence and to characterize particulates to improve manufacturing consistency.

Raw Materials

I. Plasma

Hyperimmune anti-Rabies human plasma used in manufacturing Kamada-HRIG is obtained as (b) (4) plasma exclusively from (b) (4), FDA licensed plasma collection centers in the USA under US license number 1876. (b) (4) to which Kamada signed Quality Agreement for Supply of Human Source Plasma.

1. Plasma screening tests

Kamada performs the HRIG potency test on the manufacturing pool according to SOP N-1P-5348-02/8 which is done by (b) (4). The manufacturing pools are screened by Nucleic Acid Amplification Test (NAT) methods for HCV RNA and B19V DNA by the (b) (4). Serological markers for HBsAg and HIV 1 & 2-Ab will be tested by (b) (4) upon commercial use of the Kamada-HRIG product.

The table below summarizes the tests to be performed on donors, plasma pool and manufacturing pool. In Amendment STN 125613.10, Kamada requested to withdraw the serological test for HCV Ab at the manufacturing plasma pool which was listed as a test item in the original submission. Justifications for removing the testing of HCV Ab on the plasma manufacturing pool are as follows which are acceptable.

- Since January 2008, the (b) (4) has been revised to remove the requirement for HCV serology testing on plasma manufacturing pools.
- The requirements for serology HCV antibody testing on the manufacturing plasma pool is not found in the FDA documents referenced below. FDA approves serology test kits for individual plasma unit testing only. The sensitivity is validated at the plasma unit level.
- Plasma manufacturing pools are currently HCV tested using validated nucleic acid amplification technology (NAT). The test for serology anti-HCV has become redundant due to the mandatory performance of HCV NAT testing of all plasma pools.

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


(b) (4)

2. Plasma receipt, storage and release

Upon successful completion of the plasma bottle inspection, all bottles are transferred to a storage cage and released by the Kamada Quality Unit. SOP TR-N-7P-080 *Shipment, Reception, Storage and release of Plasma and Plasma Fractions* is used for plasma reception and handling which is outlined below. Kamada also provided validation study of overseas shipping of Hyperimmune IgG (b) (4) plasma by (b) (4) container.

Control Measure	Description
Documents supplied with plasma	<p>The following are provided by the plasma manufacturer and are required for release of plasma:</p> <ul style="list-style-type: none"> • Certificate of Analysis (CoA) • Packing list which includes the number of bottles, total plasma volume and total number of boxes. • Test results: according to the approved specifications of the plasma. • Documentation of temperature which reflects the cold chain from the time the plasma was packaged through its shipping period and until arriving at Kamada.
Parameters verified upon receipt of plasma container	<ul style="list-style-type: none"> • Temperature • Estimation of quantity of dry ice remaining • Container type • Container identification number • Closure of the container • General condition of the plasma • Details concerning of temperature recorders
Release requirements	<p>Release of the plasma by Kamada's Quality Unit for manufacturing, according to a SOP which requires the following but is not limited to:</p> <ul style="list-style-type: none"> • Verification that the required NAT and serological tests were performed on the individual donations and (b) (4) of the plasma donations and that the results comply. • Verification that at least (b) (4) days elapsed / will elapse from the last bleed date to the scheduled manufacturing date. • Verification that the temperature data representing the cold chain are in order and comply with specifications and deviations that occurred were investigated.
Verification performed by Kamada	<p>The QA Representative together with the Warehouse Worker verify the following:</p> <ul style="list-style-type: none"> • That numbering as appears on the cartons complies with the numbers in the packing lists. • That the bleed number on each bottle appears in the packing list of that particular carton by opening every carton box and inspecting each bottle individually.

(b) (4)



(b) (4)

II. Non-active Ingredients

The chemical raw materials and primary packaging materials are controlled by SOP TR-N-1G-009. The auxiliary materials are controlled by SOP TR-N-1G-008. Majority of the filters (nanofilters, (b) (4)) used in manufacturing HRIG are single use filters (see detail information in Table 18 of Chapter 3.2.S.2.3). Kamada holds Quality/Service agreements with all Raw Material suppliers which include the obligation to notify Kamada of any change that may impact the quality of the product supplied to Kamada. All non-active raw materials used in manufacturing HRIG are of (b) (4) grade and their release specifications are based on the relevant current (b) (4) monograph (see tables below). No animal derived source materials are used. Currently the non-active raw materials are tested by either the QC laboratory or an approved contract laboratory. Some of the tests are part of routine raw material batch release and are performed on every incoming batch of non-active raw material (see the table below). Testing according to the complete monograph is performed in the following cases:

- As part of the approval of a new non active raw material supplier. In this case (b) (4) batches are tested.
- For approved suppliers, testing of batches is performed periodically based on analysis of experience gained since initial purchase of each raw material.
- In cases of a major change notification received from the supplier.

List of Chemicals Used in the Manufacture of Kamada-HRIG

Reagent/Material	Kamada Testing Grade	Purpose in Process	Testing Intervals
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Glycine		Buffer preparation	
(b) (4)		(b) (4)	
(b) (4)		(b) (4)	
(b) (4)		(b) (4)	
(b) (4)		(b) (4)	
(b) (4)		(b) (4)	
Tri n-Butyl Phosphate (TnBP)		S/D treatment solvent	
Octoxynol-9 (Triton X-100)		(b) (4), S/D treatment detergent, (b) (4)	
(b) (4)		(b) (4)	

(b) (4)

(b) (4)

The final container closure system used in the manufacturing of HRIG drug product is summarized below:

Glass vials:

1. (b) (4), colorless glass vials for 2 ml DP by (b) (4)
2. (b) (4), colorless glass vials for 2 ml and 10 ml DP by (b) (4)

Rubber stoppers:

1. (b) (4) rubber stoppers by (b) (4)
2. (b) (4), bottom-side (b) (4) rubber stoppers by (b) (4)
(b) (4) is applied only to the top surface of the rubber stopper.

III. Excipients

1. Glycine

“(b) (4) grade” Glycine from (b) (4) is used in the final product formulation. A CoA for each delivery is provided by the manufacturer using (b) (4). Glycine is tested for (b) (4) batch at Kamada according to the current (b) (4) monograph, except for Glycine concentration. Glycine concentration is determined by (b) (4) monograph for Glycine, with the exception that the (b) (4) method is based on (b) (4). Glycine complies with the current Glycine (b) (4) monograph requirements.

2. Water for Injection (WFI)

“(b) (4) grade” is used in the final product formulation. WFI is purified at Kamada. The WFI system is routinely sampled and tested according to the specifications described in the (b) (4) monograph.

Extractables & Leachables

Upon information request (see responses in Amendment 15 and Amendment 29), Kamada outlined the current items in contact with process intermediates, drug substance and drug product during the manufacturing process stream of the HRIG. They provided their estimates on the potential risk associated with each item according to the proximity of each item to the HRIG drug substance and drug product solutions and to the contact duration and contact surface area of each item with intermediates, drug substance and drug product. In addition, other relevant parameters like the item's wash steps, the item turnover and life time as determined in the manufacturing process were evaluated. Finally, the document also prioritizes the extractables & leachables studies based on the risk level each item introduces to the product quality. Kamada's assessment on the risk level of the items used in the manufacturing process of HRIG to the product quality appears to be acceptable.

The highest risk ranking was associated with the primary container-closure system of the HRIG drug product, (b) (4) glass vial and rubber stoppers. The potential for extraction of chemicals from the

pharmaceutical glass vials was assessed by the vial manufacturers, (b) (4), or by Kamada through a contract laboratory. The extractables identified from the vials do not provide evidence of a toxicological risk to a person receiving a single dose of HRIG. The extractables studies on rubber stoppers were performed by (b) (4), respectively. The extractables obtained from both stoppers are well below any safety concern levels of each elemental impurity permitted for HRIG. (b) (4) leachables studies were performed on the primary container closure system: (b) (4)

Stability

I. Drug Substance

Kamada commits to use the following policy for the drug substance (DS) stability testing:

(b) (4)

(b) (4)

(b) (4)

The stability of DS was tested under the following conditions:

(b) (4)

(b) (4)

The following product attributes were tested:

(b) (4)

Freeze and thaw stability studies, high temperature stress stability testing, combined temperature stability testing and photostability testing were performed on the Drug Product (DP) lots (b) (4). The rationale for relying on the DP data was as follows:

- (b) (4) DP are both stored in (b) (4) glass containers.

- The solution composition for the (b) (4) DP is identical, with the exception that (b) (4) .
- The container surface to volume ratio in the DP is much greater than the ratio for (b) (4) and as such represents the “worst case” of the two products.

Kamada proposed that the DS can be stored for up to (b) (4) at (b) (4) and provided (b) (4) worth of long-term stability data for lots (b) (4) to support their claim. (b) (4) was deliberately held for (b) (4) before being used in the formulation of Drug Product (DP) lots. (b) (4) DP lots produced from this (b) (4) , lots (b) (4) were put up for long term and accelerated stability testing.

The presented test results of long term DS stability meet the DS acceptance criteria set by Kamada. The DS stability studies showed that (b) (4) is the primary stability indicator. For the accelerated testing, the results are all within the DS acceptance criteria except that one potency result of batch (b) (4) was (b) (4) IU/mL at (b) (4) time point which is lower than the set criteria of (b) (4) IU/mL.

According to Kamada’s “Stability Study Summary Report of (b) (4) Conformance Drug Substance” SR-00163, in 2013, following change control #4105, the (b) (4) Potency specification for the DS release was increased from NLT (b) (4) IU/mL to NLT (b) (4) IU/mL in order to confidently support the (b) (4) shelf life of the DS. This is mainly due to analytical testing variability. However, Kamada implemented the change only as an internal limit while the DS release specification remained NLT (b) (4) IU/mL throughout the whole DS shelf life.

II. Drug Product

Kamada commits to place future lots of Kamada-HRIG DP, at a rate of (b) (4) stability program under long term conditions. When changes are made to the DP manufacturing process or container closure system, or when a major change is made to the Kamada-HRIG drug substance, Kamada commits to place Kamada-HRIG DP lots on accelerated and long term stability testing. The number of lots put up for stability testing will be defined as part of the process validation/comparability protocol supporting the change, based on a risk assessment of the manufacturing change. The ongoing lots included in the stability program for which data will be reported during the review phase and post-approval. Kamada commits to report any real-time stability failures to the Agency within (b) (4) of occurrence. Kamada will submit the Final Study Report for the on-going and future lots placed in stability program.

The DP stability was tested under the following conditions:

- Long term testing: Storage at 5±3 °C, for 36 months
- Accelerated testing: (b) (4)
- Stress testing: (b) (4)
- Combined temperature (at 5±3 °C and 25 (b) (4) °C) testing:
 - Long term storage (35 months) at 5±3 °C followed by up to four weeks storage at 25 (b) (4) °C.

The following items were tested. The stability acceptance criteria are the same as the specifications at release.

Test	Stability Acceptance Criteria
Clarity and Degree of Opalescence	The solution is clear to opalescent
Degree of Coloration	The solution is colorless to pale yellow
Visible Particles	May contain some protein particles
Sub-Visible Particles	For monitoring
Anti-Rabies Potency	NLT 150 ^{(b) (4)} IU/ml
Molecular Size Distribution	(b) (4)
pH	5.0-6.0
Sterility	Sterile
Package Integrity	Meets Requirements

Kamada proposed a shelf life of 30 months for Kamada-HRIG at 5±3°C. To support this claim, Kamada provided 36 month worth of long-term stability data for lots (b) (4). These^{(b) (4)} lots were made after the change in pH release specification from (b) (4) to 5.0-6.0. (b) (4) of the Kamada-HRIG lots stated above were put up for additional long term stability testing to support a parallel qualification of a new rubber stopper manufactured by (b) (4) and a new vial manufactured by (b) (4). Lot (b) (4) was formulated from a DS batch that was held for (b) (4) prior to formulation. Kamada also provided on-going stability data for lots (b) (4). The complete list of the lots in stability program can be found in Appendix II.

For the DP stability results in this submission, DP were (b) (4)

Kamada will place the^{(b) (4)} lot manufactured with the container closure combination of (b) (4) glass vials – (b) (4) rubber stopper on stability.

No trend was observed for all the parameters. All real time stability results obtained were well within the current stability acceptance criteria. Note that the provided DP stability data do not cover the full protein concentration range which is set as (b) (4) (final container specification). The final amount of IgG content in DP is controlled by the potency rather than its protein concentration. Low protein concentration could affect DP stability especially when it is close to the low end at (b) (4). The results of the parallel qualification of a new rubber stopper manufactured by (b) (4) and a new vial manufactured by (b) (4) show that the changes in the container closure have no effect on the Kamada-HRIG stability profile and shelf life. The stability data of HRIG under stress conditions indicate that HRIG is stable after (b) (4). HRIG is (b) (4) which can be avoided by (b) (4). HRIG appears to be stable when stored at 25^{(b) (4)} °C for up to 4 weeks during its shelf life.

Note that in the initial submission, the (b) (4) only included (b) (4) in the lot release specifications and in the stability program for (b) (4) DP. (b) (4) were not included at all. (b) (4) IgG will lead to a decrease in

potential efficiency of the product. The presence of IgG (b) (4) might indicate the presence of proteases in the finished product. Hence (b) (4) is a well-established stability indicator for immune globulin products, especially for long term storage. In Amendment 32, Kamada agreed to set the specification for (b) (4) after an improved (b) (4) method is validated as a PMC.

In Kamada's stability report SR-00164 "Stability Study Summary Report- Kamada-HRIG Conformance Drug Product Lots (pH 5.0-5.6)", following change control #14082 in 2015, the Anti-R potency shelf life specification was updated from (b) (4) IU/ml to '150^{(b) (4)} IU/ml, the confidence limits (p=0.95) of the estimated potency are not less than (b) (4) and not more than (b) (4)'. The Anti-Rabies potency specification for Phase I clinical product was set as NLT 150 IU/ml. The package insert of HRIG states that each carton of Kamada-HRIG contains a single use vial containing 2 mL or 10 mL of ready to use solution with a potency of 150 IU/mL. In Amendment 19, Kamada agreed to set the anti-Rabies potency as "150^{(b) (4)} IU/ml" for final container release and stability.

According to the stability report SR-00164, an untypical (b) (4) was detected in the (b) (4) test result in a few stability study test points (Deviation PR-3580). Kamada has identified the (b) (4) as (b) (4). In their medical risk assessment (Amendment 19), Kamada listed (b) (4) concentration in HRIG (b) (4), human plasma ((b) (4)), fresh frozen plasma (FFP) (1 unit = (b) (4) per 200ml), (b) (4) in 10 mL DP for 20 IU/Kg, 75Kg patient ((b) (4)) and maximum safe amount of (b) (4) ml FFP). Kamada stated that the amount of (b) (4) in FFP treatment (400 mL) is 3 times higher than HRIG treatment to a 75Kg patient. FFP is given usually 2 units (400 mL) with no safety issues. HRIG is given intramuscular and lower amount of (b) (4) will get into the blood stream than by intravenous route which is counted as the worst case scenario. Kamada concluded that the amount of (b) (4) found in HRIG will not pose any risk to patients. Evi Struble (OTAT/PDB) was consulted for any toxicological concerns regarding this issue. She concluded that the amount of (b) (4) after HRIG administration would not be vastly different than what the exposure may be from IGIV preparations, and so it would be acceptable in terms of safety.

Information Request Questions

First IR (sent on Jan-12-2017. Kamada responded in Amendment 10):

1. Please confirm that the conformance lots (b) (4), are consecutive lots.
2. Please provide the final stability study reports for the following Drug Substance lots, along with the stability raw data in Excel format: (b) (4).
3. Please provide the final stability study reports for the following Drug product lots along with the stability raw data in Excel format:
 - a. Conformance lots: (b) (4)
 - b. Phase I clinical lots: 7313011 and 5213008
4. Please provide an update on your ongoing stability studies for Drug Product and submit any further final-product stability data that have become available.
5. For the Drug Product stability study:
 - a. Please justify why the Anti-Rabies Potency specification was changed from "NLT 150 IU/ml" (for Phase I clinical lots) to "150^{(b) (4)} IU/ml, the confidence limits (p=0.95) of the estimated

potency are not less than (b) (4) and not more than (b) (4) ” (for conformance lots and comparability lots).

- b. The Anti-Rabies Potency of the lot (b) (4) was below 150 IU/ml and out-of-specification at 24-month time point. Please explain.
 - c. Lot (b) (4) was used as a control in the Kamada-HRIG (b) (4) Study. However, its Anti-Rabies Potency test result was below 150 IU/ml and out-of-specification. Please explain.
6. Product (b) (4) was determined as one of the primary product stability indicating attributes. Please justify why (b) (4) is not included in the Stability Study Test Program for (b) (4) Drug Product, and in the Drug Product Release Specifications.
 7. Please justify why “Protein Composition” is not included in the Stability Study Test Program for Drug Substance and Drug Product.

Second IR (sent on Jan-18-2017. Kamada responded in Amendment 10 and Amendment 20):

1. In the document 3.2.S.2.3,
 - a. On page 13, please specify the SOP identification number for receiving the hyperimmune anti-Rabies plasma at Kamada.
 - b. On page 14, please specify the SOP identification numbers for plasma release by Kamada’s Quality Unit and for Kamada’s (b) (4) .
2. Please provide the short supply agreement for the (b) (4) plasma, which should include: collection, freezing, storage, and shipment conditions for (b) (4) plasma for further manufacturing.
3. Please provide the manufacturing plasma pool and (b) (4) testing SOPs.
4. Please submit your plasma inventory hold, (b) (4) , and traceability procedure(s) or SOP(s).
5. Please submit the SOP(s) on testing, rejection, and release of Raw Materials which include but are not limited to (b) (4) , filters, (b) (4) glass bottles and caps, final product vials, stoppers, (b) (4) , glycine, (b) (4) tri n-butyl phosphate, triton X-100 and (b) (4) .
6. Please submit documentation of agreements with Raw Material suppliers, which specify that Kamada will be notified of any changes to the material.

Third IR (sent on Feb-21-2017. Kamada responded in Amendment 14 and Amendment 15):

1. Please provide your extractables and leachables assessments. Please indicate the location or submit or cross-reference the extractables and leachables reports for the following materials but not being limited to:
 - a. (b) (4)
 - b. Nanofilter
 - c. (b) (4)
 - d. (b) (4)
 - e. (b) (4) Drug Product container and stopper
2. Kamada-HRIG batch numbers:
 - a. Please provide a batch tree clearly indicating ALL the Kamama-HRIG lots you have been manufactured since clinical Phase II/III lots, including all Drug Substance (DS) batch numbers and Drug Product (DP) batch numbers, the relationship between the batches of DS and DP, and information on their disposition.
 - b. In the response to Q3b of FDA December 22, 2016 Information Request, please clarify why the sequential fill numbers in the provided list of DP lots are not consecutive.

Forth IR (sent on Mar-06-2017. Kamada responded in Amendment 19, Amendment 21 and Amendment 28):

1. For the Stability Study Report SR-00163:
 - a. What was the change control #4105? Please provide details.
 - b. Please provide detail justification and raw data on why the (b) (4) potency specification at release was increased from NLT (b) (4) IU/mL to (b) (4) IU/mL.
 - c. Please provide the document RM-00102 Risk Assessment Concerning the Anti-R Drug Substance Shelf Life.
 - d. Please provide investigation report for Deviation PR-5141 explaining in detail how the (b) (4) was identified being the (b) (4) used for sampling and dispensing the DS solution. Please provide the corresponding CAPA.
 - e. For the OOS-014/12
 - i. Please clarify to which (b) (4) batch the OOS-014/12 occurred.
 - ii. Why this OOS was not reported when it was first observed?
 - iii. Please provide detail investigation report for Deviation OOS-014/12, along with its corresponding CAPA.
2. For the Stability Study Report SR-00164:
 - a. What was the change control #14082? Please provide details.
 - b. Please provide detail justification and raw data on why the DP potency shelf life specification was changed from NLT (b) (4) IU/mL to 150 (b) (4) IU/ml, the confidence limits (p=0.95) of the estimated potency are not less than (b) (4) and not more than (b) (4).
 - c. For Deviation PR-3580:
 - i. Please provide detail investigation report for Deviation PR-3580, along with its corresponding CAPA.
 - ii. Please provide your risk assessment regarding the finding of the (b) (4) in the final container product.
3. In the ongoing stability study updates provided in your response to Question 4 of FDA January 12, 2017 Information Request:
 - a. What was the lab error for the anti-Rabies potency at 9-month time point for lot (b) (4)? Please provide detail investigation report.
 - b. On page 19, the Kamada-HRIG shelf life anti-Rabies potency specification was changed to 150 (b) (4) IU/mL from (b) (4) IU/mL. You stated that “A result of (b) (4) IU/mL was not considered an out of specification result at the time of release, since it met the previous shelf life specification, NLT (b) (4) IU/mL”. It is unacceptable to use outdated specification for current ongoing stability study. Please re-evaluate your ongoing stability study using the most current specification.
4. It appears that the anti-Rabies potency tests are done in two labs: Kamada QC (b) (4) and (b) (4).
 - a. Please provide the comparability report.
 - b. Please clearly indicate which steps' samples are tested by Kamada QC and which ones are tested by (b) (4).
 - c. Please provide a table indicating which lots of DS and DP were tested by Kamada QC and which lots were tested by (b) (4).
 - d. Please provide all SOPs related to the anti-Rabies potency testing: SOP 1106, SOP 1105, SOP 1108, SOP 02-02.1.08/ CVS-11, SOP 02-02.1.06, SOP 02.81-02, and SOP N-1 G-028.
5. Please include (b) (4) in DP Release Specifications and in Stability Study Test Program for DS and DP. Please set up (b) (4) specification and provide test results of (b) (4) for the Phase I clinical lots, Phase II/III lots, conformance lots and comparability lots. (b) (4) is a

well-established DP stability indicator, especially for long term storage. The presence of IgG (b) (4) might indicate the presence of (b) (4) in the finished product. (b) (4) IgG may lead to a decrease in potential efficiency of the product.

6. Regarding your (b) (4) and manufacturing plasma pool screening tests for markers of infection:
 - a. Please provide your current (b) (4) testing methods for HCV RNA, HIV RNA, HBV DNA, HAV DNA and B19V DNA, and your current manufacturing pool testing methods for (b) (4) .
 - b. What methods will be used for serological markers for HBsAg and HIV 1 & 2-Ab by (b) (4) ?
7. Please specify which computerized inventory system is used for plasma (b) (4) ? Please clarify how the integrity between donor list and actual plasma units is verified.
8. Please provide a detail list of the chemical raw materials and primary packaging materials used in manufacturing HRIG which are controlled by SOP TR-N-1G-009. Please include this information into Section 3.2.S.2.3.
9. Please provide a detail list of the auxiliary materials used in manufacturing HRIG which are controlled by SOP TR-N-1G-008. Please include this information into Section 3.2.S.2.3.
10. Please provide a list of filters (nanofilters, (b) (4) filters, (b) (4) filters) used in manufacturing HRIG including the following information but not being limited to: model, manufacturer, usage, validated life time and a representative copy of CoA. Please include this information into Control of Materials.
11. According to your response to Question 6 of FDA January 18, 2017, Kamada holds Quality/Service agreements with Raw Material suppliers which include the obligation to notify Kamada of any change that may impact the quality of the product supplied to Kamada. Please provide a copy of all the agreements.

Fifth IR (sent on May-31-2017. Kamada responded in Amendment 27, Amendment 28 and Amendment 29):

1. In the response to Q5 of FDA March 6, 2017 IR (Amendment 21), Table 4: (b) (4) Test Results, Phase II/III, Conformance and Comparability Lots, the contents of (b) (4) for the lots presented on page 10 are significantly lower than those on page 11. The lots on page 10 were manufactured from 2011-2013 and the lots on page 11 were manufactured from 2015-2016. Please comment on this difference.
2. We disagree with your Extractables & Leachables assessment stated in your responses to Q6 of FDA February 21, 2017 IR (Amendment 15): “The (b) (4) nanofilter and the (b) (4) were not required for leachables studies...”. Leachables from those materials are directly related to product safety and should be well studied. Please submit or cross-reference the Extractables & Leachables Study Reports for (b) (4)
3. Please provide the missing page 6/38 of “rep-vl-101217-gr-report.pdf”.
4. Please submit or cross-reference the extractable study reports for the DP final container closure system: (b) (4) glass vials, (b) (4) glass vials, (b) (4) stoppers and (b) (4) stoppers.

Sixth IR (communicated in the teleconference held on Aug-10-2017. Kamada responded in Amendment 32):

1. Please include the following into Section 2.1 Stability Commitment under 3.2.P.8.2 Post Approval Stability Protocol and Stability Commitment:

- Kamada commits to report any real-time stability failures to the Agency within (b) (4) of occurrence.
- Kamada commits to place the (b) (4) lot manufactured with the container closure combination of (b) (4) glass vials – (b) (4) rubber stopper on stability.
- For the on-going stability studies and future lots placed in stability program, Kamada commits to submit a final stability report within (b) (4) months of completing the study as a Product Correspondence.

Appendix I

Drug Substance Batches Placed on Stability Testing

Reason Manufactured	Drug Substance Batch No.	Manufacturing Date	Batch Size (Kg)	Stability Study	Data Presented	Status
Conformance batch	(b) (4)					
Clinical phase II/III study Conformance batch + hold time validation						
Clinical phase II/III study Conformance batches						
Conformance batch						

Appendix II

Drug Product Batches Placed on Stability Testing

Drug Product Lot No.	Fill Volume (ml)	Manufacturing Date	Use of Lots	Drug Substance Batch from Which the Drug Product was Manufactured	Stability Study	Data Presented (months)	Status
(b) (4)	10	(b) (4)	-Comparability lot, (b) (4)	(b) (4)	Long term	9	On-going
					(b) (4)		Completed
	10	(b) (4)	-Comparability lot, (b) (4)	(b) (4)	Long term	12	On-going
					(b) (4)		Completed
	10	(b) (4)	-Comparability lot, (b) (4)	(b) (4)	Long term	12	On-going
					(b) (4)		Completed
	2	(b) (4)	-Comparability lot, (b) (4)	(b) (4)	Long term	12	On-going
					(b) (4)		Completed
	2	(b) (4)	-Comparability lot, (b) (4)	(b) (4)	Long term	12	On-going
					(b) (4)		Completed
	10	(b) (4)	Routine lot used for stress stability study	(b) (4)	Stress: Stability at	(b) (4)	On-going
	10	(b) (4)	- Conformance lot – lower pH - Additional supplier for (b) (4) filter	(b) (4)	Long term	36	Completed
					(b) (4)		Completed
					Stress:	(b) (4)	Completed
	2	(b) (4)	- Conformance lot – lower pH; - Hold time validation; - Phase II/III Clinical lot; - Re-validation of contractor for sterilization of rubber stoppers (b) (4)	(b) (4)	Long term	36	Completed
					(b) (4)		Completed
					Stress:	Not applicable	Completed
					Stress: Stability at	(b) (4)	Completed
					Stress: (b) (4)		Completed
(b) (4)						Completed	

Drug Product Lot No.	Fill Volume (ml)	Manufacturing Date	Use of Lots	Drug Substance Batch from Which the Drug Product was Manufactured	Stability Study	Data Presented (months)	Status
(b) (4)	2	(b) (4)	- Conformance lot – lower pH; - Formulation at end of (b) (4) shelf-life; - Parallel qualification of new rubber stoppers (b) (4)	(b) (4)	Long term	36	Completed
					(b) (4)		Completed
					Stress: (b) (4)		Completed
	10		- Conformance lot – lower pH - Phase II/III Clinical lot - Parallel qualification of new vials ((b) (4)) and new rubber stoppers (b) (4)).		Long term	36	Completed
					(b) (4)		Completed
						(b) (4)	Completed
	2		- Conformance lot – lower pH - Parallel qualification of new rubber stoppers (b) (4)).		Long term	36	Completed
					(b) (4)		Completed
					(b) (4)		Completed
	2		- Phase I Clinical lot		Long term	36	Completed
					(b) (4)		Completed
	10		- Phase I Clinical lot		Long term	36	Completed
					(b) (4)		Completed