



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
Division of Manufacturing and Product Quality

**To:** Administrative File, STN 125613/0

**From:** Pankaj (Pete) Amin, Senior Reviewer, CBER/OCBQ/DMPQ/MRB2

**Through:** CDR Qiao Bobo, Ph.D., RAC, Branch Chief, CBER/OCBQ/DMPQ/MRB2  
John A. Eltermann, Jr., OCBQ, DMPQ, Division Director

**Subject:** Kamada 125613/0 BLA – Final Review Memo, Recommend Approval

**Location:** Kamada Ltd., Beit Kama, MP Negev, Israel

**License Number:** 1826

**Action Due:** 08/29/2017

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**Review Recommendation**

Based on the information provided in the BLA and in the amendments (responses to information requests), the pre-license inspection (PLI), and the firm's corrective actions implemented in response to the inspectional observations, I recommend approval of this BLA with the following PMC regarding the implementation of (b) (4) during the CCIT test method validation:

*Kamada commits to perform validation of the container closure integrity test for each stopper and vial combinations (4 ml and 13.5 ml size vials and stoppers, from each of two vendors) with the inclusion of a (b) (4). Kamada will submit a final validation report.*

- *Study Completion Date: November 30, 2017*
- *Final Report Submission: December 29, 2017*

**Inspection**

Dr. Ewa Marszal, Arie Menachem and I performed a pre-license inspection of Kamada from March 26-31 and April 2-4, 2017. The location of the manufacturing facility is as follows: Kibbutz Beit Kama, Negev, Israel. The FEI number is 1000630279. A FDA Form 483 with six inspectional observations was issued to Kamada on April 5, 2017. Kamada provided responses to the 483 observations on the June 6, 2017 and the responses were found adequate as described in a separate memo.

## Summary

On August 29, 2016, Kamada Ltd submitted a BLA (under STN 125613) for Kamada- HRIG (Human Rabies Immune Globulin). This product is to be used for post-exposure prophylaxis of rabies infection in combination with a rabies vaccine. The (b) (4) is derived from human plasma of healthy adult donors immunized with rabies vaccine. Anti-rabies immunoglobulins from plasma are enriched using (b) (4) steps. Viral inactivation of the plasma is achieved using solvent/detergent (S/D), heat treatment, and nanofiltration. The DP is a sterile, nonpyrogenic liquid provided at a potency of 150 IU/ ml in 4 ml and 13.5 ml glass vials. The Drug Product (DP) is formulated with 0.3 M glycine at a pH range of 5.0 – 6.0. The dosage proposed is one intramuscular administration of 20 international units (IU) per kilogram.

## Name of Biological Product

Rabies Immune Globulin (Human), proprietary name: KEDRAB

## Indication

Passive, transient post- exposure prophylaxis of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and in combination with rabies vaccine.

## BLA Application Summary

Date of Application: August 29, 2016

Date of Receipt: August 29, 2016

Action Due Date: August 29, 2017

US License Number: 1826

RPM: Jiahua Qian, OTAT/DRPM

Chair: Michael Kennedy, OTAT/DPPT

## Product History

The formulation of Kamada- HRIG proposed for approval in the US is (b) (4) to the formulation of the product distributed in Israel since 2012. It is also approved in El Salvador, India, Israel, Mexico, Russia, Thailand, Australia, Georgia, and South Korea. To date, Kamada-HRIG has been administered to more than 250,000 individuals worldwide. According to Kamada, there have been no adverse reaction reports associated with the clinical use of the Kamada-HRIG product.

Kamada provided a description of the HRIG product. The HRIG preparation is a sterile, non-pyrogenic, aqueous solution of human anti-rabies immunoglobulin (not less than 95% protein as IgG). It has a labelled potency of 150 IU/ml. Kamada-HRIG final product contains 0.3M Glycine as a stabilizing agent, and does not contain any preservative. (b) (4) is used for the pH adjustment of the final product.

Kamada states that the active ingredient, Human Rabies immunoglobulin enriched plasma, is a glycoprotein expressed by human plasma white blood cells occurring naturally in the environment and administered intramuscularly only once, at the beginning of anti-rabies prophylaxis treatment.

The starting material for Kamada-API is a hyper-immune plasma containing a high titer of anti-Rabies antibodies from healthy human donors immunized with Rabies vaccine. Approximately (b) (4) plasma is

processed into (b) (4). The manufacture of the (b) (4) involves (b) (4) S/D Treatment (b) (4), Heat Treatment (b) (4) Nanofiltration (b) (4).

Aseptic filling is carried out in an ISO Class (b) (4) room with (b) (4) filter coverage. Critical parameters ((b) (4)) are continuously monitored and controlled. Samples are collected throughout the filling process. The DP is tested and released against the specifications. The final Kamada-HRIG DP formulation is filled into (b) (4) glass vials and sealed with (b) (4) rubber stoppers or (b) (4) rubber stopper pending visual inspection, which is performed manually. Complete or partial lots are labeled and packaged, as needed, and returned to 2 – 8 °C storage pending release and shipment.

Kamada claimed a categorical exclusion from the requirement to file an Environmental Assessment for Kamada-HRIG [Kamada Human Rabies Immune Globulin] under U. S. Federal regulation 21 CFR 25.31(c). According to Kamada, HRIG will be administered instead of other registered HRIG products. Kamada explained that the use and disposal of this product will not significantly alter the concentration or distribution of the protein, its metabolites, or degradation products in the environment. Kamada concluded that Kamada-HRIG will have no significant impact on the overall quantity of human rabies immunoglobulins in the environment.

#### Review comment:

Kamada request for categorical exclusion is acceptable; however, the statement “no extraordinary circumstances exist” was not included as part of the request for categorical exclusion (See IR question below).

#### **Manufacturing Facilities**

##### Manufacture address

Kamada Ltd.  
Beit Kama  
MP Negev 8532500  
Israel

FEI Number 1000630279  
DUNS Number 649062486

#### **Manufacturing Site Responsibilities**

Regarding the DS, this manufacturing site is responsible for (b) (4). For the DP, this site is responsible for manufacturing, warehouse, quality control testing (microbiological and sterility), labeling, packaging, lot release, and stability testing.

#### **Kamada Facility Location**

Kamada's manufacturing facility is located at Kibbutz Beit Kama, Industrial Park, Israel, which is within a one hour drive from Ben Gurion Airport. Kamada's Head Office is located in the Kiryat Weizmann Science-Based Industrial Park. Head Office operations includes management, marketing, regulatory affairs, research and development and clinical operations.

**Facility Diagram**

Manufacturing Support Services are distributed between (b) (4)

Kamada provide a facility diagram in the BLA as follow:

(b) (4)

(b) (4)

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(b) (4)

(b) (4)

Review comment:

This Kamada facility is FDA licensed for the manufacture of Glassia (under STN 125325/0). Kamada reported no additional major facility changes (since the 2010 facility inspection) except a few changes to (b) (4). HRIG product uses the same production, warehouse, and QC labs areas that were previously approved for Glassia.

**Floor Diagrams**

The manufacture of the HRIG DS takes place in the (b) (4). Floor diagrams for (b) (4) were provided in the submission. Approximately (b) (4) of hyper-immune human plasma containing a high titer of Anti-Rabies antibodies is processed into (b) (4). The following diagram describes the (b) (4) process flow as provided in the BLA.

**Drug Substance Flow Diagram**

(b) (4)

Manufacturing is performed in production suites that are served by HVAC systems, which are designed to supply air via HEPA filters at the point of entry to controlled rooms in the production facility, achieving the appropriate room classifications relative to clean room operations and associated controlled environments. The facility has a total of (b) (4) Air Handling Units (AHUs) providing segregated air to the following manufacturing areas; (b) (4)

. HVAC distribution, room classifications, and pressure cascade information were provided in the BLA and were found to be adequate.

#### **Drug Substance – In-Process Control**

Kamada provided a list of various in process tests that performed during each of manufacturing process as described in the following table.

#### **List of In-Process Tests**

The following in-process tests are performed during DS manufacturing:

(b) (4)

(b) (4)

As indicated in the above table, (b) (4)

The manufacture of the HRIG DP takes place in the (b) (4). Floor diagrams for (b) (4) were provided in the BLA. The formulation and filling suite (b) (4) used for Kamada-HRIG DP has a HVAC system that serves only this suite. A separate HVAC system supplies the air to the vial preparation room. Each AHU is designed to supply air at the required temperature and (b) (4). The following diagram describes the process flow for the DP as provided in the BLA.

**Drug Product Flow Diagram**

(b) (4)



The formulation room is ISO Class (b) (4), the vial preparation room is ISO Class (b) (4) with an internal ISO Class (b) (4) and the filling room is ISO Class (b) (4). The filling room has 100% HEPA filter coverage. The critical physical parameters in the clean rooms ((b) (4)) are continuously monitored and controlled. (b) (4) are positive with respect to the external environment for protection of the product. Kamada monitors process quality attributes and process parameters throughout the formulation and filling process.

### **Warehouse**

Incoming raw materials are received, documented, and quarantined by the Warehouse Department ((b) (4)). The Quality Unit releases raw materials after testing to confirm material identity and quality, per pre-established specifications. Segregation between released and quarantined raw materials in the warehouse is performed electronically via the ERP system.

The Finished Goods Warehouse is located in (b) (4). Finished goods status and release is controlled through the ERP system. Finished product release designation is controlled via the ERP system and not by physical segregation of quarantined product from released product. Kamada's Responsible Pharmacist releases product for distribution after the Quality Unit has reviewed and approved the manufacturing records.

Kamada utilizes (b) (4) facility ((b) (4)) as an alternative controlled temperature warehouse for storage of (b) (4) finished DP. Kamada states that this facility is an FDA approved facility. All shipments to (b) (4) are controlled using Kamada's ERP system. Product release and distribution to Kamada's authorized markets is performed solely by Kamada's responsible pharmacist, according to Kamada's SOPs. Shipment of Kamada's DPs to and from the (b) (4) facility is performed using validate refrigerated trucks. At this warehouse, product is stored in a qualified and validated cold storage warehouse (2-8°C).

### **Review comment:**

The computer system (EPR) used for inventory control; however, a computer system validation summary was not provided in the BLA and was requested via IR. The shipping validation for the final DP was provided in the BLA and was found to be adequate (shipping validation is covered in a later part of this memo). The cold storage warehouse was stated as being validated, though this validation was not provided in the BLA. Kamada stated in response to an IR that they last audited this vendor warehouse facility on 09/11/2016 (IR was sent on 07/28/2017 and response received via email from on 7/28/2017).

### **Multi Product Facility**

The Kamada facility is a multi-product production facility. Design of the manufacturing facility provides for separate controlled areas to prevent cross-contamination include separation of downstream formulation and fill activities from upstream protein purification manufacturing operations and segregation of manufacturing areas by different AHUs. Kamada manufactures products on a campaign basis. Equipment used in a manufacturing process is either product dedicated or has a validated cleaning procedure (which included testing to verify that the cleaning procedure meets pre-designated criteria for (b) (4) residuals, microbial bioburden, and bacterial endotoxins). The following list of the products manufactured at the Kamada facility was provided in BLA:

### List of Products Manufactured by Kamada

Group	DP Trade Name	Active Substance	Location of Manufacture
1	GLASSIA®; Ventia™; Respikam™	Alpha-1 Proteinase Inhibitor <sup>1</sup>	Human plasma derived products manufactured, formulated and filled in (b) (4)
	KamRAB; Rebinolin™	Anti-Rabies IgG <sup>2</sup>	
	KamRh <sub>o</sub> -D I.M	Anti-D I.M IgG	
	KamRh <sub>o</sub> -D I.V	Anti-D I.V IgG	
	Transferrin	Transferrin <sup>1,3</sup>	
2	Heparin Lock Flush	Heparin sodium	Porcine derived <sup>4</sup> product formulated and filled in (b) (4)
	Kamacaine	Bupivacaine HCl	Chemical solution formulated and filled in (b) (4)
3	Snake Antivenom Immunoglobulin	Anti-Snake Venom	Equine-derived <sup>5</sup> product manufactured in (b) (4) and formulated and filled in (b) (4)

<sup>1</sup> Derived from US FDA or EU Licensed Plasma only; <sup>2</sup> Derived from US FDA Licensed Plasma only; <sup>3</sup> Not for human use; <sup>4</sup> Active pharmaceutical ingredient manufactured in (b) (4); <sup>5</sup> The equine plasma is collected from horses that are under the Israeli Ministry of Health veterinary control and are immunized against all zoonotic equine viruses present in Israel

According to Kamada, human derived plasma products are produced in the (b) (4). Heparin lock flush and Kamacaine active pharmaceutical ingredients are purchased from approved suppliers and (b) (4) is not prepared in the Kamada facility. Only formulation and filling is performed for these products. Filling and finish of these DPs takes place in (b) (4) on a separate filling line and equipment (filling (b) (4)). The equine Anti-Snake Venom (b) (4) is manufactured in the (b) (4) and DP is formulated in formulation and (b) (4). All Kamada products are manufactured on a campaign basis with segregation of manufacturing operations.

All product contact equipment used in the production of DP is product dedicated. Potentially porous product contact materials such as (b) (4) used in the production of Kamada HRIG in (b) (4) DP production are dedicated based upon the plasma origin (i.e., either from US or EU).

Kamada validated the effectiveness of cleaning and sanitization/sterilization methods. Validation studies including (b) (4), and maximum hold time storage before cleaning/sterilization and hold time after cleaning/sterilization before use. Kamada states that the SIP conditions for the formulation and filling (b) (4) were validated for heat (b) (4).

Kamada implemented several levels of control via facility design and established methods to include segregation of operations and cleaning to mitigate potential risk of contamination of HRIG DS and DP by adventitious agents, viral contamination, and product cross-contamination. Implemented measures including use of dedicated equipment, transfer line and filling equipment for downstream Processes, validated cleaning procedures for dedicated and non-dedicated equipment; and several layers of containment based on facility design, processes, and operational SOPs.

Kamada implemented controls to prevent contamination or cross-contamination of areas or equipment includes, but is not limited to (1) facility design, control and monitoring, (2) personnel training, qualification and monitoring, (3) sanitization procedures, control and monitoring, (4) equipment qualification and validation, (5) control of raw materials, and (6) manufacturing process controls and validation. Facility design, control, and monitoring information are provided in the submission and found to be reasonable for the stated purpose.

Review comment:

The Kamada facility is an FDA licensed multiproduct facility, and all of the products listed in the above table were previously reported in approved BLAs or supplements. Kamada products are produced in manufacturing campaigns, with only one product being produced at a given time in a manufacturing area and any shared equipment having validated cleaning procedures. Kamada provided information in the BLA that was found to be adequate to support a multi-product facility.


**Room Classifications**

Kamada provided information regarding the manufacturing areas room classification. (b) (4)



**Drug Substance Equipment**

(b) (4)



Reviewer comment:

Cleaning validation is reviewed in a later part of this memo.

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Review comment:

The information Kamada provided regarding room classification, room identification, and equipment used was found to be adequate. However, the BLA contained inadequate information regarding cleaning validation for shared equipment and this information was therefore requested (see IR question below).

**Drug Product Equipment**

All of the product contact equipment, (b) (4) used in the manufacture of DP is product dedicated. Critical equipment used in the production of the DP includes but is not limited to (b) (4).

Kamada uses an (b) (4) vial washer to clean the glass vials (4 ml and 13.5 ml) prior to delivery into the (b) (4). Validation study results for the vial washer were provided in the BLA and found to be adequate (reviewed in a later part of this memo). Small equipment and (b) (4) are washed in a central washing area. After (b) (4) are cleaned, they are subjected to either (b) (4) sterilization. Subsequent to cleaning and sterilization, equipment is stored in a clean storage room.

The following tables describes the equipment used in the DP manufacturing areas, and include the room classification, process operations, room number, equipment description, equipment cleaning method, and equipment status (shared or dedicated equipment).

(b) (4)

(b) (4)

(b) (4)

### **HVAC System**

Manufacturing is performed in production suites that are served by HVAC systems that are designed to supply air via HEPA filters at the point of entry to controlled rooms in the production facility, achieving the appropriate room classifications relative to clean room operations and associated controlled environments. The facility has (b) (4) AHUs providing segregated air to the manufacturing areas. Each AHU is designed to supply air at a (b) (4). Kamada describes the (b) (4) for each of the production rooms as follow:

(b) (4)

Review comment:

It was not clear (in the above table), why the first viral elimination area ((b) (4) area?) was kept at a (b) (4) compare to gowning room. An IR (question #7) was requested on May 22, 2017 for clarification, Kamada provided adequate justification regarding (b) (4) between different production areas to prevent cross contamination. (Please see IR #7 response in this memo for IR question and Kamada's response to IR below).

**Formulation and Filling Room** (b) (4)

(b) (4)

**Filling Operation** (b) (4)

(b) (4)

**Formulation and Filling Room** (b) (4)

(b) (4)

As noted in the tables, all production rooms are kept at (b) (4) compare to less clean area. Information provided in the above tables for the room classification and (b) (4) appears to be adequate (air travel from clean to less clean areas).

**HVAC Validation**

The HVAC system validation (IQ, OQ, and PQ) was initially performed between July 2007 and July 2008. During the HVAC validation, the design requirements for (b) (4) were confirmed. In addition, the environmental monitoring (EM) results established that the HVAC system design was sufficient to consistently meet the (b) (4) DP production rooms. Additional requalification was performed in 2009, 2010, and April 2011.

In 2015, the filling line conveying system was adjusted for filling of the HRIG product into 4 ml and 13.5 ml vials. Kamada performed an additional environmental requalification following this change (no change was performed to the filling room HVAC system or any facility modification). During this qualification, the production areas were cleaned and disinfected according to relevant SOPs. Testing (at (b) (4)) was performed under (b) (4) conditions for (b) (4) consecutive work days (Phase I). Testing involved both (b) (4), with all sites being tested (b) (4). In addition, (b) (4) testing was performed for (b) (4) days (Phase I). A summary of Phase I test results provided in the table below:

**Summary of Phase I Test Results**

Assay	No. Sampling Days	No. Sampling Sites	Total No. Samples	Test Results
(b) (4)				



(b) (4)

All tests met established limits for the Phase I testing. A summary of Phase II test results provided in the table below:

**Summary of Phase II Test Results**

Assay	No. Sampling Days	No. Sampling Sites	Total No. Samples	Test Results
(b) (4)				

<sup>1</sup> A total of (b) (4) operators were sampled with each sampled at (b) (4) sampling sites.

The EM data show that the HVAC systems provide good control over (b) (4) after the minor adjustments implemented along the filling line conveying system. Based on provided data, it was concluded that the qualification was successfully completed.

**(b) (4) Requalification**

Kamada implemented a (b) (4) for the HRIG product filling (4 ml and 13.5 ml vials). This change was previously approved under STN 125325/218. Kamada provided the summary of the requalification (Phases I and II) as shown in the following tables. During the Phase I qualification, (b) (4) days of EM monitoring ((b) (4)) was performed. During the Phase II qualification, (b) (4) days of monitoring was performed.

**Summary of Phase I Test Results**

Assay	No. Sampling Days	No. Sampling Sites	Total No. Samples	Test Results
(b)	(b)	(b)	(4)	(b)

The results provided for the Phase I filling room requalification was met for all test samples demonstrating that the filling room met the established clean room standard.

#### Summary of Phase II Test Results

Assay	No. Sampling Days	No. Sampling Sites	Total No. Samples	Test Results
(b)	(b)	(b)	(4)	(b)

The Phase II requalification studies were also successfully completed. The information provided appears to be acceptable.

#### Review comment:

A Phase III Long Term Validation study for (b) (4) DP was performed and demonstrated that the HVAC system met the design requirements for (b) (4). The EM results established that the HVAC system design was sufficient to consistently meet the (b) (4) DP production rooms. The HVAC requalification information was found to be acceptable. During the PLI, additional HVAC system information was covered. The (b) (4) are routinely measured for (b) (4) using (b) (4). Testing for (b) (4) is performed (b) (4) using (b) (4).

#### Environmental Monitoring Program

The routine EM program consists of testing for (b) (4) [REDACTED]. Kamada provided an EM program summary for the manufacturing areas including descriptions of the production area, room classification and test frequency ((b) (4) [REDACTED] monitoring) in the BLA. The testing frequency for the (b) (4) [REDACTED] is summarized in the following tables.

(b) (4)

Kamada routinely reviews of the (b) (4) [REDACTED] data ((b) (4) [REDACTED]). In addition, the monitoring system is equipped with a local alarm. Kamada provided information regarding physical data review frequency that was found to be reasonable.

The action alert and action limits for viable for the EM program are provided in the following table.

(b) (4)

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(b) (4)

Review comment:

Kamada established the filling room monitoring frequency based on the FDA aseptic processing guidance document recommendations. Regarding the production areas (ISO (b) (4) areas), I noted that (b) (4) monitoring is performed (b) (4) and was based on the risk assessment study.

**Environmental Monitoring Non-Viable Alert and Action Limits**

The non-viable monitoring alert and action limits and monitoring frequencies in the production areas are described in the following tables.

(b) (4)

Review comment:

Information provided regarding EM test points and test frequencies appears to be based on currently approved ATT product, which uses the same production areas. Based on the good product history (no product sterility failure since 2010 for license product that uses same EM program/procedures), the information provided was to be found acceptable. Additional EM information was evaluated during the PLI. The rationale for the EM monitoring locations was requested as part of an IR (see question below).

### Environmental Monitoring Alert/Action Limit Procedures

Kamada described the actions taken when limits are exceeded in the filling room suite (ISO (b) (4)). According to Kamada, if an action limit excursion is obtained for (b) (4), the investigation includes additional testing surrounding the site where the result was obtained. In addition, evaluation of the integrity of the HEPA filters at that location, evaluation of the status of the return air grills, evaluation of the activities that were on-going in the room at the time of testing, evaluation of the results for other testing performed in the filling room at the time that the original test sample was taken, and corrective action based upon the findings of the investigation. If an action limit excursion is obtained for (b) (4), testing is performed at the site on (b) (4) consecutive workdays. If an action limit excursion is obtained for (b) (4), at least (b) (4) additional (b) (4) samples are taken from the area surrounding the site where the action result was obtained. In addition, an investigation is initiated and the microbe is identified. If a reversal of the pressure cascade occurs between the filling room and an adjacent area of lower quality ISO classification (ISO Class (b) (4)), filling operations are stopped immediately, all open vials are discarded, the filling room is decontaminated, additional sampling is performed, and filling needles are replaced with a newly sterilized set.

Kamada also described the actions taken when limits are exceeded in the (b) (4) production areas (ISO (b) (4)). If an action limit excursion is obtained for (b) (4), testing is performed at the site on (b) (4) consecutive work days. If an action limit excursion is obtained for (b) (4), at least (b) (4) additional (b) (4) samples are taken from the area surrounding the site where the result was obtained. If the results for the additional testing are all within the limit, an investigation is conducted to identify the potential source of contamination. If one of the results is outside of the limit, further actions are taken with the aim of identifying the source of contamination and neutralizing it. Actions taken will include, for example, additional testing, identification of the contaminating organism(s), and additional cleaning of the area or production room. Actions taken as an outcome of a reversal in the pressure cascade are dependent on the rooms or areas involved, if the reversal is identified at the time it occurred, and the activities taking place in the production areas that are impacted. Most actions are based on execution of different levels of cleaning.

### Environmental Monitoring Trending Data

Kamada provide a summary of 2015 EM test results for formulation and filling suites as follow:

Production Room	ISO Class.	Assay	No. Tests	No. Alert Results	No. Action Results	Percent Excursions
(b) (4)						

(b) (4)

The gowning room trending data demonstrated no alert or action level excursions. A very low level of the (b) (4) monitoring excursions was also noted.

Production Room	ISO Class.	Assay	No. Tests	No. Alert Results	No. Action Results	Percent Excursions
(b) (4)						



The formulation room and formulation gowning room EM data trending demonstrated overall good control during the time period for which data was provided.

Production Area	ISO Class	(b) (4)					
		No. Tests	No. Action Limit Excursions	Percent Excursions	No. of Tests	No. Action Limit Excursions	Percent Excursions
(b) (4)							(4)

Kamada summarized the (b) (4) test results and (b) (4) for the ISO (b) (4) and ISO (b) (4) production areas and HRIG formulation and filling areas. The results included the number of samples tested, number of action limit excursions recorded and the percent excursions relative to the number of samples tested. Overall, the frequency of excursions was less than (b) (4), indicating that the (b) (4) levels are well controlled.

## **WFI System**

(b) (4)



### **WFI System Validation**

The WFI system Installation and Operation qualification was performed in 2007. The qualification including Phases I and II, was performed between June and July 2007. Phase III was performed from July 2007 until June (b) (4). During Phase I, intensive (b) (4) sampling was performed for (b) (4) consecutive work days. During Phase II, (b) (4) sampling was performed for at least (b) (4) weeks. Phase III (long-term testing) was performed to confirm that the quality of the WFI was not adversely affected by long-term use and/or season changes. At the end of this period ((b) (4) months), a trend analysis of the data was performed and concluded that procedures established for operation and maintenance of the WFI production and distribution systems ensure that WFI in the (b) (4) and WFI pulled from the different use points consistently meet all test specifications. Subsequent to the initial validation study, additional requalification was performed in 2010 and 2011. Kamada provided a WFI system requalification (PQ) qualification summary as follow:

### **WFI – PQ Results/Phase III**

(b) (4)

Few (b) (4) deviations were noted (September 2010 to 2011), and Kamada has taken corrective actions to address these deviations. Kamada provided the WFI qualification summary data that were collected after these corrective actions taken (September 2011 to December 2011) as follows:

### **Routine Monitoring Summary – WFI (2015)**



(b) (4)

WFI testing results for 2015 showed only one action limit excursion (out of (b) (4) total assays performed) for (b) (4). The investigation concluded that the action limit excursion was caused due to limited access to the sampling valve, the test result was returned to (b) (4) with the next sampling. All other tests met the requirements. Based upon the data provide, it can be concluded that the WFI system was working under control.

#### **Routine WFI Monitoring**

Kamada provided the current WFI monitoring limits. The chemical and microbial attributes for WFI is based on the (b) (4). The WFI routine monitoring program alert and action limits and test frequency summarized in the table below:

#### **WFI Current Quality Attributes**

(b) (4)

#### **Routine Monitoring Frequency – WFI**

(b) (4)

#### Review comment:

I have no additional comments regarding WFI system validation or routine monitoring program. They appear to be acceptable.

#### **Computer Systems**

Kamada uses (b) (4) computer systems for the control of manufacturing and quality operations and its function as follow.

#### **(b) (4) Application**

(b) (4) monitors and controls production activities. The (b) (4) application controls and receives data from instrumentation/ equipment via (b) (4).

**(b) (4) Application**

(b) (4) is an Enterprise Resource Planning (ERP) system. The (b) (4) ERP System supports core business processes to include supply chain management. CGMP related activities controlled by (b) (4) ERP include control of quarantined and released materials, forward and reverse traceability of raw materials used in production, traceability of marketed finished goods, and calibration and preventative maintenance scheduling and procedures.

**(b) (4) Application**

(b) (4) is an off the shelf software package designed for the pharmaceutical industry. The (b) (4) software is utilized for quality related functions to include management of standard operating procedures (SOPs), and batch production and control records.

**(b) (4) Application**

(b) (4) is an off the shelf software package is utilized for management of Change Control, Audits, Customer Complaints, Deviations and CAPA processes.

**(b) (4) Application**

(b) (4) is an off the shelf software package for Laboratory Information Management System and utilized for management of laboratory processes, control of test samples, and to summarize results for different tests.

Kamada states that the validation of computer systems and software packages in use at Kamada were performed according to Kamada's Computerized System Validation Policy. This computer validation policy was prepared, based on the (b) (4) FDA Guidance for Industry (21 CFR Part 11). A risk assessment was performed to determine required validation activities. Each computer system was assigned one of (b) (4) categories based upon the level of product quality concern and determined the required validation activities.

Review comment:

Computer validation summary was not provided in the BLA, and therefore additional information was requested as part of IR question (see comment below).

**Cleaning Validation**

Kamada provided a summary of the cleaning methods used in the production areas. (b) (4)

[REDACTED]

[REDACTED]

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

Kamada provided justification for the acceptance criteria that were observed during the cleaning validation. The cleaning validation acceptance criteria based on the WFI specification or test method detection limit. No concern was noted regarding provided justification of acceptance criteria that were observed during the cleaning validation.

**Routine Monitoring- Cleaning Verification**


Kamada provided the routine cleaning verification summary, cleaning verification is performed following routine production runs. The following tables provide a list of cleaning monitoring tests, acceptance criteria and frequency of these tests for the routine monitoring performed between production runs and campaign.

(b) (4)

(b) (4)


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

(b) (4)



### **Glass Vial Cleaning**

The rubber stoppers used for closure of the glass vials are purchased cleaned and sterilized from the manufacturer. The vials undergo the cleaning process including the (b) (4)



The vials (b) (4)




### Review comment:

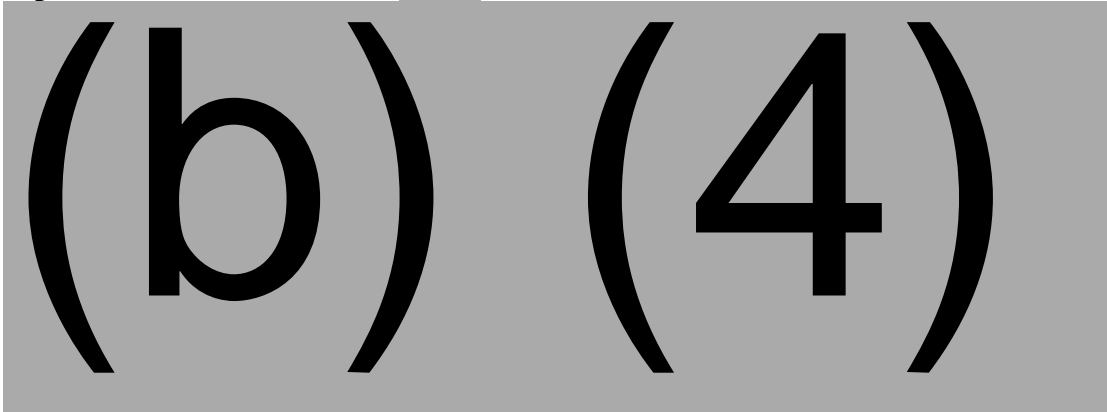
The vial washing validation summary is described in a later part of this memo.

S/D (b) (4) Study

(b) (4)



### **Operation Conditions of the (b) (4) Runs**



All (b) (4) runs met operation limits for (b) (4)  
The following table summarized the (b) (4) during the validation.

**Distribution of the (b) (4)**

(b) (4)

The (b) (4) validation demonstrated that all results were within the operational limits ((b) (4) ) for each time point and throughout the S/D treatment, and indicated that the (b) (4) . The following table summarizes the (b) (4) during the validation.

(b) (4)

The validation data indicated that the results were within the operational limits ((b) (4) ) for both (b) (4)

Based on this validation, Kamada concluded that (b) (4) during the S/D treatment ensures validated conditions throughout the (b) (4) .

**Container Closure – (b) (4)**

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(b) (4)

(b) (4)

**Shipping Validation - Hyperimmune Anti-Rabies Plasma**

The starting material in the manufacturing of Kamada-HRIG is hyperimmune plasma containing a high titer of anti-Rabies antibodies, obtained from healthy human donors immunized with Rabies vaccine. The source plasma is collected by plasmapheresis at blood collection centers licensed by the FDA for the manufacture of blood and blood components and are subject to periodic inspections by the FDA. Overseas shipment of hyper immune Anti-Rabies plasma from an approved USA plasma supplier to Kamada is performed by air transport using (b) (4) freezing containers supplied by a shipping company. The plasma manufacturer confirms that all plasma for Kamada-HRIG manufacturing is stored at (b) (4), following plasma collection. During transport the plasma is kept at (b) (4).

(b) (4)

Shipping Validation (b) (4) Freezing Container

(b) (4)

Shipping Validation (b) (4)

Freezing Container

(b) (4)

Based on the shipping validation results, Kamada confirmed that when utilizing the operational and procedural controls, the temperature requirement of (b) (4) or lower was maintained. All the results met the acceptance criteria.

#### **Sterilization Validation**

Kamada uses (b) (4) for sterilization of product contact equipment. The following table provides brief (b) (4) make and model information.

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

#### **Filling Weight Consistency**

Uniformity of filling validation for Kamada-HRIG DP filled in formulation and filling (b) (4) was conducted to allow filling of Kamada-HRIG DP in 4 ml and 13.5 ml vials following adjustments in formulation and filling (b) (4). The aim of the uniformity of filling studies was to demonstrate consistency and homogeneity of each DP lot in terms of product quality and filling homogeneity following filling of the lots.

#### **Filling Process Consistency**

Uniformity of Filling in formulation and filling (b) (4) was demonstrated. (b) (4) lots were tested (b) (4) in 4 ml vials and (b) (4) in 13.5 ml vials). Samples were withdrawn prior to filling (formulation sample) and at preset points throughout the filling process in accordance with the validation protocol. Samples were tested and results analyzed per the protocol. The (b) (4) lots are described in the following table.

### Filling Uniformity Lots

Lot No.	Manufacturing Date	Presentation (ml)	Formulation weight (Kg)	Lot Size (vial #)
(b) (4)				

Kamada performed uniformity validation using (b) (4) lots of 4 ml presentation and (b) (4) lots of 13.5 ml presentation. Results for one of the lots are provided in the following table.

### Uniformity of Filling Results of Kamada-HRIG Drug Product Lot (b) (4)

Test	Appearance	Bacterial Endotoxins (b) (4)	Glycine Concentration (mM)	Protein Concentration by (b) (4)	pH	(b) (4)		Extractable Volume (ml)
Specification	The liquid preparation is clear to opalescent, and colorless to pale yellow solution. May contain some particles	(b) (4)	(b) (4)	(b) (4)	5.0-6.0	(b) (4)	(b) (4)	(b) (4)
(b) (4)					5.3	(b) (4)		
					5.4			
					5.3			
					5.4			
					5.4			
					5.4			
					5.4			
					5.4			
					5.4			
					5.4			
					5.4			
					5.4			
					5.4			
					0			
					1			
					Yes			


Below the LOQ of the method which is currently (b) (4)

As indicated in the above tables, test results for endotoxin, glycine concentration, pH, (b) (4), and extractable volume for the samples collected during the filling process demonstrated product

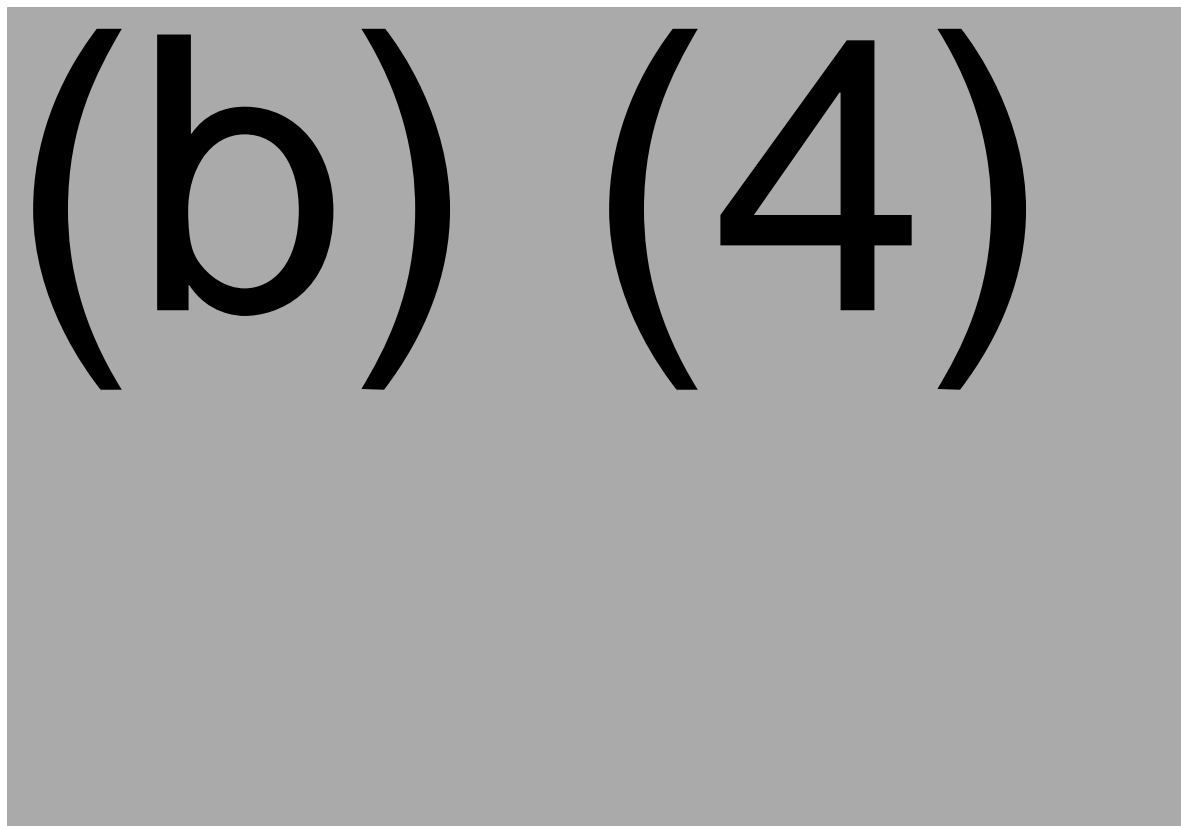
uniformity. All test results for all DP lots included in the uniformity of filling studies met the acceptance criteria and confirmed the homogeneity of the DP in the formulation (b) (4) and filling process. Kamada concluded that the formulation step was validated for homogeneity by the uniformity of filling validation for the range of (b) (4) .

#### **Shipping Validation Final Product**

Kamada challenged the shipping procedure to maintain a product temperature range of (b) (4) from the start of packaging to arrival of the DP at its final destination. The validation included (b) (4)



The shipping validation acceptance criteria includes verification that no individual data logger exceeded the temperature range of 2°C to 8°C for more than (b) (4) nor exceeded the range of (b) (4) at any time from the start of the packaging until the arrival to the destination. Results of the shipping runs are provided in the following tables.



Kamada reported that no individual data logger exceeded the temperature range ((b) (4) ) at any time from the start of the packaging until the arrival to the destination.

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

## Container Closure Drug Product

Kamada provided detailed information on DP CCS including specifications, dimensional drawings, and representative certificates of quality for each CCS component.

### Glass Vials

Kamada states that the vial used for the DP is manufactured by (b) (4). The vial is made of clear, colorless (b) (4), approximately 4 ml and 13.5 ml in size, and compliant with the current (b) (4) requirements for (b) (4) glass. Kamada provided a letter of authorization for (b) (4) for (b) (4) and (b) (4) for (b) (4) for the 4 ml and 13.5 ml vials. The 4 ml vials are filled with 2 ml of DP while the 13.5 ml vials are filled with 10 ml of DP.

Kamada provided a vial dimension specification of the 4 ml vials and 13.5 ml vials in the BLA. Kamada verified the vial dimension specification for the each lot of incoming vial based upon the vendor provided certificate of analysis. Kamada provided a COA, which include a specification for the vial neck finish diameter, opening diameter, microbial limit test, and chemical tests specification and results. Specifications for the glass vials are shown in the following table.

**Table 1:** (b) (4) Glass Vials – QC Specifications

Test	Specifications	Method
(b) (4)		

#### Review comment:

Kamada provided summary of QC specification as part of acceptance criteria that Kamada implemented for the glass vials. The provided information is considered to be adequate.

(b) (4)



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(b) (4)

(b) (4)

(b) (4)

### Rubber Stoppers

The vials are stoppered with (b) (4) mm or (b) (4) mm (nominal) dark gray (b) (4) (rubber compound (b) (4) ) or (b) (4) (rubber compound (b) (4) ) rubber stoppers. Kamada provided approved stopper vendor information shown in the following section.

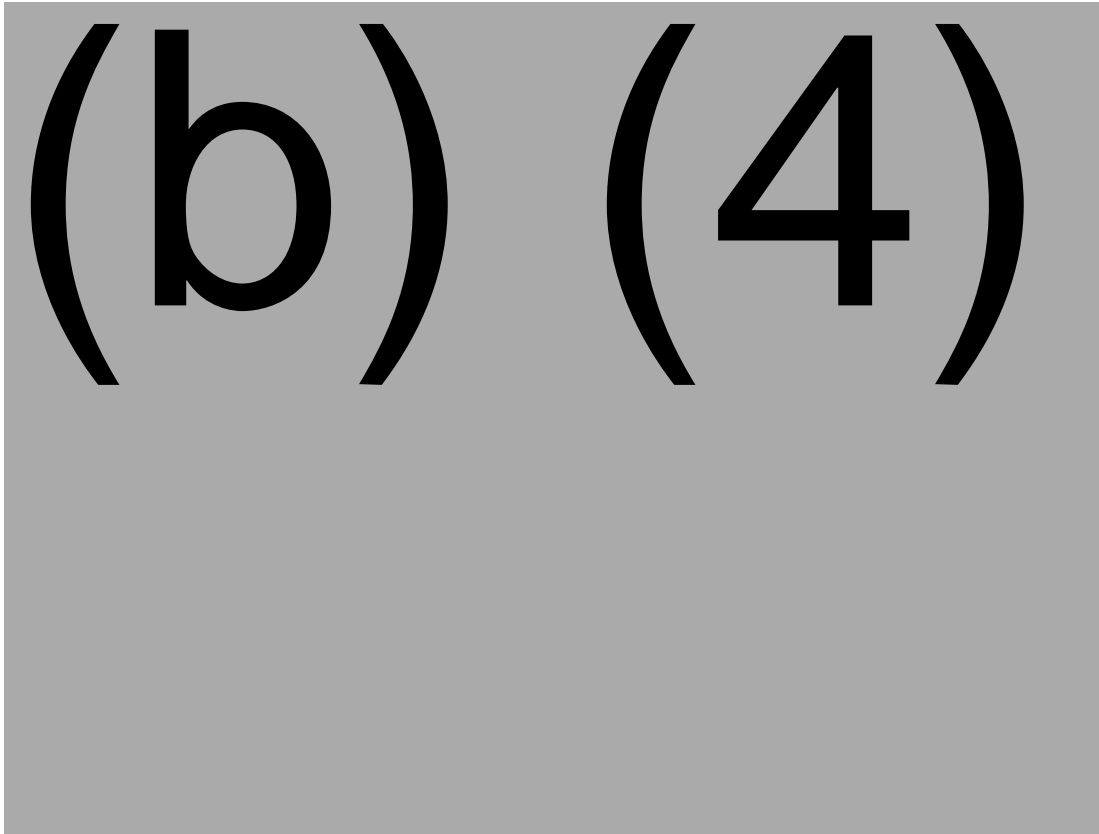
### Stopper Suppliers

The manufacturers' addresses are provided below:

(b) (4)

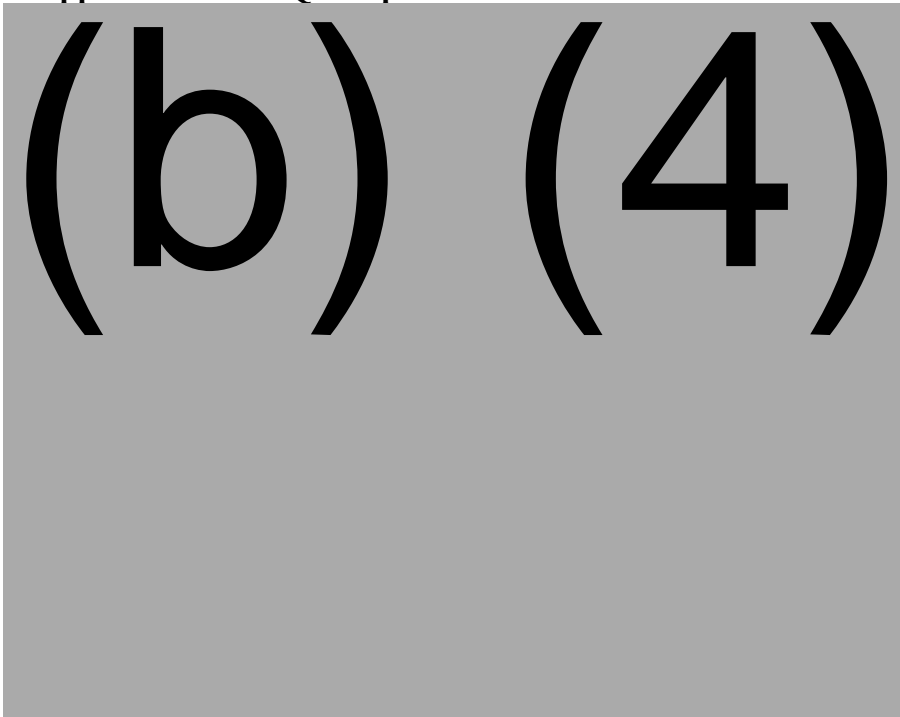
The rubber stoppers conform to the current (b) (4) stoppers and are manufactured with compliance to current (b) (4). In addition, the rubber stoppers meet the requirements for biological activity tests according to current (b) (4). The (b) (4) rubber stoppers purchased pre-sterilized by (b) (4) or sterilized by a local contractor (b) (4). The (b) (4) rubber stoppers are purchased as pyrogen free and are sterilized by (b) (4) by (b) (4).

Kamada samples each delivery of stoppers, which are tested for release by the Kamada QC laboratory. Kamada provided a vendor supplied Certificate of Analysis (COA) as shown in the following table.



The vendor provided COA includes the sterility, endotoxin, various physical and chemical tests results. Kamada also prepares QC reports for each lot of stopper received and conforms the specifications listed in the following table.

## Stoppers - Kamada QC Report



Each incoming stopper delivered lot is sampled and tested (by Kamada QC unit) before release for production use.

### Sterilization of Rubber Stoppers

The rubber stoppers used for stoppering the Kamada-HRIG final product vials are sterilized by (b) (4). The stoppers supplied by (b) (4) are provided sterilized to Kamada. In addition, a contractor in (b) (4) was validated for performance of (b) (4) for stoppers supplied by (b) (4).

The stoppers supplied by (b) (4) are irradiated by a validated and approved contractor, (b) (4). Sterilization validation studies were performed on the rubber stoppers from both (b) (4).

Kamada provided the sterilization validation of (b) (4) rubber stopper by (b) (4). The study consisted of both establishment of the (b) (4). The study was performed on (b) (4) mm rubber stoppers.

### (b) (4) Rubber Stoppers- (b) (4)

Validation of sterilization by (b) (4) was performed and included the establishment of the sterilization dose in order to determine the minimum (b) (4) necessary to provide the required SAL. Furthermore, dose mapping was performed in order to identify the (b) (4) within the product load using a predetermined loading pattern and to select the (b) (4) monitoring locations for routine processing.

The rubber stoppers are received by Kamada and shipped to (b) (4) packed in double bags and then in a cardboard box.

Initial (b) (4) level before sterilization was determined. The test was performed on samples from (b) (4) different batches of rubber stoppers for each size of rubber stopper as summarized in the table below.

#### (b) (4) Results for Stoppers

(b) (4)

Based on the (b) (4) level of (b) (4), a (b) (4) would be required to achieve a SAL of (b) (4) (according to standard (b) (4)).

A verification (b) (4) study was performed at (b) (4). Based on the initial stopper (b) (4) results of (b) (4), the (b) (4) would be required to achieve a SAL of (b) (4) (according to standard (b) (4)). The results of the verification dose study are provided in the following table.

#### (b) (4) Verification Results

Parameter	Acceptance Criteria	Test Results	Meet Requirements
(b) (4)			

A (b) (4) mapping study was performed on the (b) (4) mm rubber stoppers package configuration as a representative of the (b) (4) mm rubber stoppers. Since the density of the (b) (4) mm rubber stoppers is higher by (b) (4), it represents a worst-case in terms of (b) (4) distribution and minimal expected level of (b) (4).

The rubber stoppers were subjected to a routine (b) (4) process at (b) (4). The (b) (4) process (b) (4) the stopper packages to a (b) (4), as measured by the routine monitoring (b) (4). The (b) (4) mapping study results are provided in the following table.

**(b) (4) Mapping Results**

(b) (4)

The validation acceptance criterion was met for the minimum (b) (4) required to obtain an SAL of (b) (4). Based on (b) (4) -mapping runs, the (b) (4) expected range in a routine process was (b) (4). The validation concluded that the minimum (b) (4) accepted in the (b) (4) mapping (b) (4) was higher than the minimum sterilization (b) (4) for the rubber stoppers (b) (4) required to obtain an SAL of (b) (4) for the bioburden of (b) (4). The maximum (b) (4) expected in routine process ((b) (4)) was lower than the maximum (b) (4) authorized by the manufacturer ((b) (4)).

**(b) (4) Stoppers - (b) (4) Sterilization Requalification**

Kamada provided information on a routine on-going requalification study for the (b) (4) stopper (b) (4) sterilization. The requalification study included the (b) (4) audit and the (b) (4) mapping study. Results are provided in the following tables.

**(b) (4) Mapping Results**

(b) (4)

**(b) (4) Verification Results**

(b) (4)

The minimum (b) (4) was (b) (4) during the (b) (4) mapping study and was more than minimum (b) (4) to achieve an SAL of (b) (4) based on the (b) (4) load of (b) (4). The sterilization (b) (4) did not exceed the verification (b) (4) by more than (b) (4) and there was no positive unit resulted for all unit tested. The requalification study concluded that sterilization process of (b) (4) rubber stoppers at (b) (4) was valid and was re-qualified.

#### (b) (4) - (b) (4) Sterilization Validation

Kamada provided the (b) (4) sterilization information for the (b) (4) rubber stopper. The sterilization process of (b) (4) rubber stoppers was performed at (b) (4). The stopper (b) (4) study identified bioburden load of (b) (4) for the (b) (4) stopper as shown in the following table.

#### (b) (4) Results for Stoppers

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

Based on the (b) (4) load, the (b) (4) verification determined the sterilization (b) (4) for the rubber stoppers ((b) (4) ) required to obtain an SAL of (b) (4) for the (b) (4) of (b) (4) according to standard (b) (4). A verification dose study was performed and the results are provided in the following table.

#### (b) (4) Verification

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

A (b) (4) mapping study identified a minimum (b) (4) of (b) (4) and maximum (b) (4) of (b) (4). The (b) (4) mapping study results are summarized in the following table.

**(b) (4) Mapping Results**

(b) (4)

The validation concluded that the minimum (b) (4) accepted in the (b) (4) mapping ((b) (4) ) was higher than the sterilization (b) (4) for the rubber stoppers ((b) (4) ) required to obtain an SAL of (b) (4) for the (b) (4) of (b) (4) according to standard (b) (4) . The maximum radiation (b) (4) accepted from the (b) (4) mapping was (b) (4) , which was not more than (b) (4) maximum (b) (4) authorized by the manufacturer.

The requalification study for the (b) (4) stopper included a (b) (4) audit and (b) (4) mapping study. The (b) (4) results for (b) (4) stopper before sterilization is provided in the following table.

**(b) (4) Results for Stoppers**

(b) (4)

(b) (4)

**(b) (4) Verification Results**

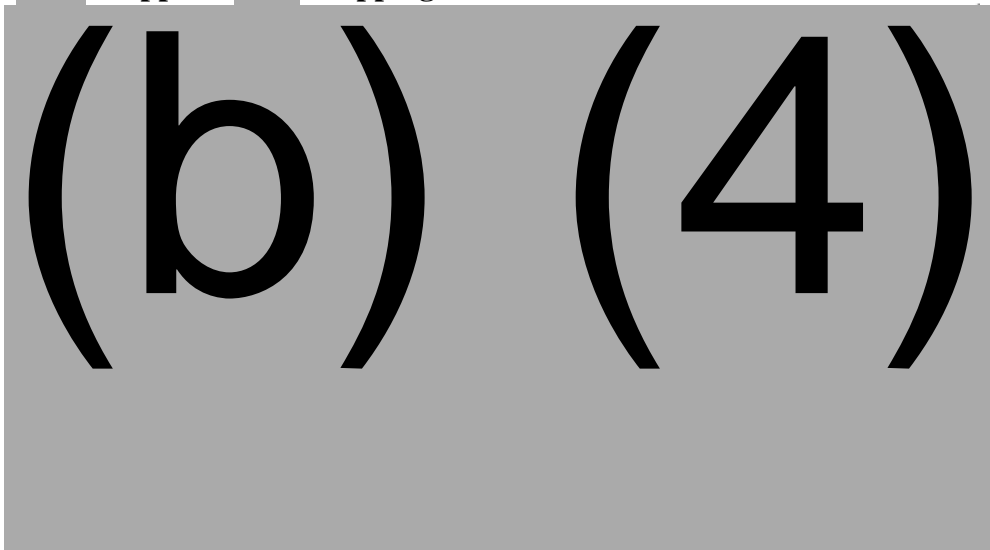
(b) (4)

The sterilization (b) (4) did not exceed the verification (b) (4) by more than (b) (4) and there was no positive unit resulted for all unit tested.

The (b) (4) mapping results are shown in the following table.



## (b) (4) Stopper – (b) (4) Mapping



The minimum (b) (4) was (b) (4) during the (b) (4) mapping study was more than minimum (b) (4) required to achieve an SAL of (b) (4) based on the (b) (4) load of (b) (4). The maximum (b) (4) accepted from the (b) (4) mapping was (b) (4), which was lower than (b) (4), which was the maximum (b) (4) authorized by the manufacturer. The sterilization (b) (4) did not exceed the verification (b) (4) by more than (b) (4) and there was no positive unit resulted for all unit tested. Based on the (b) (4) mapping, the limits for minimum and maximum position were set at (b) (4).

The requalification study concluded that sterilization process of (b) (4) rubber stoppers at (b) (4) was valid and was re-qualified.

### Flip-Off Overseal

The overseal (cap) used for the DP is a (b) (4) mm (for the 4 ml vial) or (b) (4) mm (for the 13.5 ml vial) (b) (4) seal with a flip-off (b) (4) cap purchased from (b) (4) or (b) (4). Kamada compared the vendor provided certificates of quality (received with the (b) (4) mm and (b) (4) mm (b) (4) seals) to the reference certificates in the QC laboratory. If found compatible, the (b) (4) seals are released for use. Dimensional drawings of the (b) (4) mm and (b) (4) mm (b) (4) seals and flip off caps were provided in the BLA. The (b) (4) seal and flip off cap is a non-functional secondary packaging component which is not in direct contact with the Kamada-HRIG DP.

### Container Closure Integrity Testing – Drug Product

The glass vials used for Kamada-HRIG DP are sealed hermetically with rubber stoppers and (b) (4) seals with flip-off caps to prevent contamination or loss of contents. Container closure integrity testing (CCIT) was performed as part of stability studies to demonstrate no penetration of contamination. The accumulated stability study results for both CCIT and sterility show no evidence of penetration of microbial contamination or of chemical or physical impurities.

### CCIT/Stability

Kamada validated the package integrity using a method based upon (b) (4). The container closure integrity was determined by (b) (4).

A qualification of the package integrity test was performed which included an established (b) (4) level for Kamada-HRIG samples by testing (b) (4) samples from (b) (4) different Kamada-HRIG lots (total of (b) (4) samples) (b) (4) by (b) (4) of the samples. Testing was performed by (b) (4) analysts on (b) (4) different days using (b) (4) different (b) (4).

The qualification study established a (b) (4) level for IgG samples as part of determination of the limit of detection. This was performed by testing (b) (4) samples from (b) (4) different IgG lots (total of (b) (4) samples). (b) (4) Testing was performed by (b) (4) analysts on (b) (4) different days using (b) (4) different s (b) (4). The results are shown in the following table.

(b) (4)

The acceptance criteria of the signal to (b) (4) ratio between IgG (b) (4) samples and blank samples was set as (b) (4).

(b) (4)

### Review comment:

An IR was requested for lack of (b) (4) during CCIT validation (see IR question #14a below).

The results are provided in the following table.

(b) (4)

(b) (4)

**Long-Term Stability – CCIT Test Results Drug Product**


Kamada provided a long-term stability test results for the CCIT test as shown in table below.

(b) (4)

The accelerated stability results for the CCIT and sterility test results provided for the DP tested with the new vial (from (b) (4) ) and the new stopper (from (b) (4) ) and passed the sterility and CCIT test.

### **Bioburden Testing**



Kamada performed the microbial limit test per the current (b) (4) . The (b) (4) method validation was performed to verify that IgG (b) (4) samples do not inhibit microbial growth. The validation study was carried out using (b) (4)



(b) (4)



(b) (4)



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As indicated in the above table, Kamada monitored (b) (4) throughout the manufacturing process. The information provided was found to be acceptable for the product microbial quality monitoring during the (b) (4) manufacturing process. Kamada provided the results obtained for the (b) (4) conformance batches shown in the following table.

(b) (4)

(b) (4)

#### **Sterility Testing**

The (b) (4) procedure is used for sterility testing of the Kamada- HRIG DP. The sterility test was tested for bacteriostasis and fungistasis by challenge with (b) (4). The validation met the pre-set acceptance criteria. It was concluded that the test process was valid for use in sterility testing of Kamada-HRIG DP. All DP conformance batches were tested for sterility (product release test) and all of the batches met the sterility test acceptance criterion.

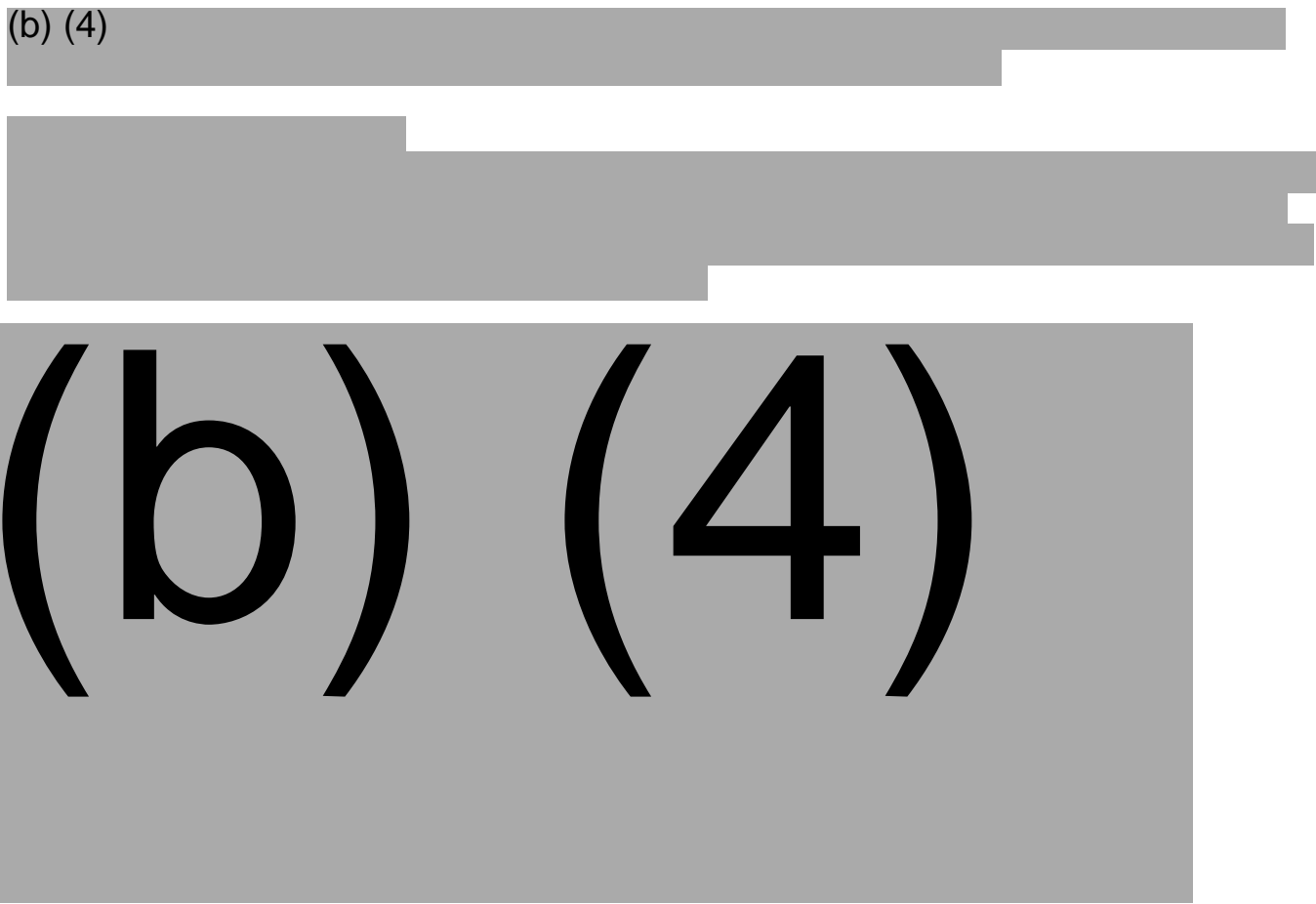
#### Review comment:

Please note that the sterility method validation was reviewed in detail by DBSQC reviewer assigned to this BLA. My review was for the sterility test was information only; however, I verified that all conformance lots DP batches met sterility test requirement and there were no sterility failures reported.

(b) (4)

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(b) (4)



The level of (b) (4) was monitored at several steps in the manufacturing process. All of the results were within the operational limits set for the in-process steps. The results demonstrate that (b) (4) levels are consistently low throughout the manufacturing process and the values obtained are comparable.

## **Review of the Response to the Information Request**

### **Question 1**

*Regarding Environmental analysis (Section 1.12.14)*

*Regarding your request for a categorical exclusion from environmental assessment, please clarify if, to your knowledge, any extraordinary circumstances exist that require submission of an environmental assessment, as referred to in 21 CFR 25.15 (d).*

### **Response to Question 1**

Kamada revised the statement to include the following: "To Kamada's knowledge no extraordinary circumstances exist that would significantly affect the quality of the human environment" as per 21 CFR 25.15(d). Kamada added the revised statement to section 1.12.14 Environmental analysis.

#### Review comment:

Kamada's response is adequate.



## Question 2

*Reference to Facilities and Equipment (3.2.A.1), Table #3 (pages 17, 18, 19, 20, and 21): We noted that BLA includes the retrospective (sanitization and (b) (4)) validation data from the batches produced between (b) (4) for the (b) (4) and (b) (4) systems used in the process. However, cleaning and sanitization validation data were not provided in the BLA for all other shared equipment (for example (b) (4)) used in the (b) (4) process.*

- a. Please provide cleaning and sanitization validation report for these shared equipment. If these cleaning and sanitization validation were previously submitted to the FDA (for the GLASSIA product) then, please provide reference where this information was submitted in the BLA 125325/0 and justify why requalification was not needed for the additional HRIG product (for the BLA 125613/0).*
- b. Please provide recent cleaning and sanitization summary data ((b) (4) and (b) (4)) to demonstrate efficacy of cleaning and sanitization of the (b) (4) and (b) (4) steps.*

## Response to Question 2a

Kamada provided the cleaning validation summary in the response. Kamada confirmed that the shared equipment cleaning validations were completed as part of the Glassia (ATT) supplement STN 125325/120, which was used in the (b) (4) manufacturing process. This supplement was approved on 07/23/2014.

Kamada states that the cleaning verification for AAT or Glassia ((Alpha-1 Proteinase Inhibitor (Human) Intravenous)) and Kamada-HRIG products was performed during routine production. The cleaning verification was performed on the shared and the dedicated equipment used during the production of each one of the products.

According to Kamada, the cleaning verification was completed for the equipment and production accessories used in the GLASSIA (b) (4) manufacturing process in 2012. During this period, Kamada-HRIG was already manufactured using equipment shared with GLASSIA. Therefore, the cleaning validation submitted in the GLASSIA BLA 125325/0 (document Rep-VL-100648B-PQ), was relevant for both products. Kamada provide the copy of this cleaning verification report as part of the response. This report concluded that all equipment and production accessories used in the GLASSIA (b) (4) manufacturing process tested after production run met all of the acceptance criteria.

Kamada provided a cleaning verification report (document Rep-VL-100993-PQ) which concluded that equipment used in the HRIG (b) (4) manufacturing process were cleaned after HRIG production runs and verified that all samples collected after cleaning met the acceptance criteria. In addition, a periodic cleaning verification was performed in 2016 for the equipment used during the Glassia manufacturing process (document Rep-VL-100648\_PQ) and all of the acceptance criteria were met.

In addition, Kamada performed a cleaning validations for shared small equipment (in 2011), described in document Rep-VL-100552-PQ, the shared (b) (4) systems (in 2013), described in document Rep-VL-100383C-PQ (which was provided in the GLASSIA BLA), and the (b) (4) transfer line (in 2016),

described in document Rep-VL-07745B-PQ. Kamada reported successful completion of this cleaning validations.

Review comment:

Kamada provide all cleaning validation reports and these reports verified that validations were successfully completed with same acceptance criteria listed in this memo. Kamada's response verified that all shared equipment-cleaning validation was previously successfully completed. Moreover, all of the routine requalification studies were completed successfully.

**Response to Question 2b**

Kamada provided the most recent cleaning and sanitization data for the (b) (4) systems and the (b) (4) systems. The (b) (4) systems and the (b) (4) cleaning and sanitization summary data (for Kamada-HRIG batches produced from (b) (4)) provided is shown in the following tables.

Table 3: Cleaning and Sanitization Summary Data – (b) (4)

(b) (4)
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Table 2: Cleaning and Sanitization Summary Data – (b) (4) Systems

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

Regarding the (b) (4) systems, one deviation MDR-19020 was noted for a (b) (4) result for the “(b) (4) before use” sample. The root cause was identified as operator error. In addition, the sample was taken from the (b) (4) instead of the sampling location as stated in the SOP. Even though it was a single (isolated) event, a CAPA was issued to find a convenient sampling procedure to prevent recurrence of this kind of deviation.

Review comment:

Overall, the (b) (4) and the (b) (4) cleaning and sanitization data demonstrated that the specifications were met for all (b) (4) batches, except for the one deviation was noted (summarized above). Overall, cleaning and sanitizations procedures remained effective based upon the provided (b) (4) months of data. Kamada’s response is adequate.

**Question 3**

*Reference to Facilities and Equipment (3.2.A.1), Table #4 (page 23) It was not clear, if following equipment were previously qualified for the FDA license product (GLASSIA). Please provide brief qualification history and requalification summary of the (b) (4), the filling machine (b) (4) and the (b) (4).*

**Response to Question 3**

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

(b) (4)

#### **Question 4**

*Reference to Facilities and equipment (section 3.2.A.1), Table #43 (page 73)*

*List of products manufactured by Kamada provided in the table 43. We noted that Heparin lock flush (Heparin sodium), Kamacaine (Bupivacaine HCL), and Anti-snake venom products are formulated and aseptically filled in the building (b) (4). Please describe precaution taken to prevent contamination and /or cross contamination between the many products that will be processed in the same formulation and filling areas.*

#### **Response to Question 4**

Kamada provided the following clarification. Kamada-HRIG is filled in formulation and filling (b) (4) located in Building (b) (4) while their Anti-snake product is filled in formulation and filling (b) (4) also located in Building (b) (4). Kamada pointed out several design and procedures control that are in place to minimize any risk of contamination by other products as shown below.

- Use of dedicated equipment, transfer lines and filling equipment for downstream processes
- Validated cleaning procedures for dedicated and non-dedicated equipment
- Several layers of containment based on facility design, processes and operational SOPs
- Production performed on a campaign basis, with a strict segregation of manufacturing operations

- Only one Kamada DP processed in formulation and filling (b) (4) at a given time using dedicated (b) (4) and filling equipment for Kamada-HRIG
- Production process flow and material process flow unidirectional
- The (b) (4) product dedicated and have validated cleaning validations
- Dedicated equipment appropriately marked to ensure clear identification of them as being product dedicated
- Manufacturing equipment cleaned with (b) (4) to reduce the risk of cross-contamination between products
- Procedures require workers (or other personnel) entering into the filling room to use a new sterile gown each time they enter the room with different gown colors used per room operation type
- No filling performed at the same time in the (b) (4) formulation and filling (b) (4)
- In-Process limits and DP release specifications set to ensure proper execution of contamination control steps
- Monitoring programs in place to enable early detection of potential sources of contamination
- Quality system in place to ensure compliance with the defined procedures and operations

Review comment:

The multiproduct provided information appears reasonable and therefore the response is adequate.

**Question 5a**

*Reference to Facilities and Equipment (3.2.A.1), Table #66 through Table #71 provided (b) (4) validation summary. Following information was not found in the BLA.*

- Please provide when these validations were performed (validation history), and summary of most recent qualification (If applicable)*

(b) (4)

7 pages have been determined to be not releasable: (b)(4)

(b) (4)

The minimum load item for the qualification of (b) (4) was the (b) (4) (in the same location as in the maximum (b) (4)), which is the most difficult item to sterilize ((b) (4)).

Review comment:

Kamada provided the rational for worst-case locations, (b) (4) monitoring location and (b) (4) diagrams for (b) (4). The response is adequate.

**Question 5c**

*Reference to Facilities and Equipment (3.2.A.1), Table #66 through Table #71 provided (b) (4) validation summary. Following information was not found in the BLA.*



3 pages have been determined to be not releasable: (b)(4)

(b) (4)

Review comment:

Kamada provided the information regarding the (b) (4) which was found to be adequate. The response is acceptable.

**Question 7**

*Reference to Facilities and Equipment (3.2.A.1), Table 19 (Page 43):*

*Please describe, containment between pre and post viral inactivation production areas. It appears that virus elimination rooms kept at (b) (4) pressure (for example room (b) (4) ) from the surrounding production rooms (b) (4) .*

**Response to Question 7**

Kamada explained that the containment between the pre- and post-viral inactivation production areas is achieved by segregation of airflow and (b) (4) cascade. Each suite has its own dedicated HVAC unit and recirculated air return to the specific unit to achieve airflow segregation. A (b) (4) cascade is used to protect clean areas from adjacent or surrounding less clean areas. A (b) (4) containment control concept is used to protect the process core, which is the cleanest area that is located in the middle and is surrounded by less clean areas. The airflow between different areas prevents contamination to the

cleaner areas based upon the (b) (4) differences. Airlocks are located at the entrance of viral eliminations rooms. These airlocks were used for maintaining the (b) (4) cascade and prevent cross-contamination. Airlocks with different (b) (4) cascade regimes include cascade airlocks, sink airlocks and bubble airlocks.

Kamada stated that the (b) (4) viral elimination room ((b) (4)) is in (b) (4) compared to the gowning room ((b) (4)) with (b) (4) of (b) (4) and the air-lock room ((b) (4)) prior to the gowning room, which has a (b) (4) of (b) (4). Therefore, air from the (b) (4) room could only flow in one direction, towards the airlock ((b) (4)).

The (b) (4) virus elimination room ((b) (4)) maintains a (b) (4) of (b) (4) compared to the sink airlock ((b) (4)) with a pressure of (b) (4). Therefore, air always flow from the (b) (4) towards the sink airlock. Kamada explained that there is an interlock system used to avoid an opening of two or more doors that are linked to the same clean area or airlocks. Every suite is validated to ensure that the supplied air is capable of maintaining the predetermined acceptance criteria. Periodical physical tests are performed for production suites to ensure that physical parameters were within the acceptance criteria necessary for each clean room in accordance with its classification. The tests performed include: (b) (4)

Review comment:

Kamada's response is adequate

**Question 8**

*Reference to Facilities and Equipment (3.2.A.1), Validation of HVAC system (Page 45 and 46):  
Please provide the acceptance criteria that were validated for (b) (4)*

**Response to 8**

The required validated acceptance criteria for airflow (b) (4) tests are shown in the following table.

**HVAC Validation Parameters**

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

These acceptance criteria were used for all three phases of the HVAC validation.

Review comment:

Kamada's response is adequate

**Question 9a**

*Reference to Facilities and Equipment (3.2.A.1), Routine Environmental Monitoring (2.2.8):*

- a. *Please provide a routine environmental procedure (SOPs) that are currently in use in the HRIG production areas including rationale for selecting sampling locations and test frequencies listed in these procedures.*

**Response to Question 9a**

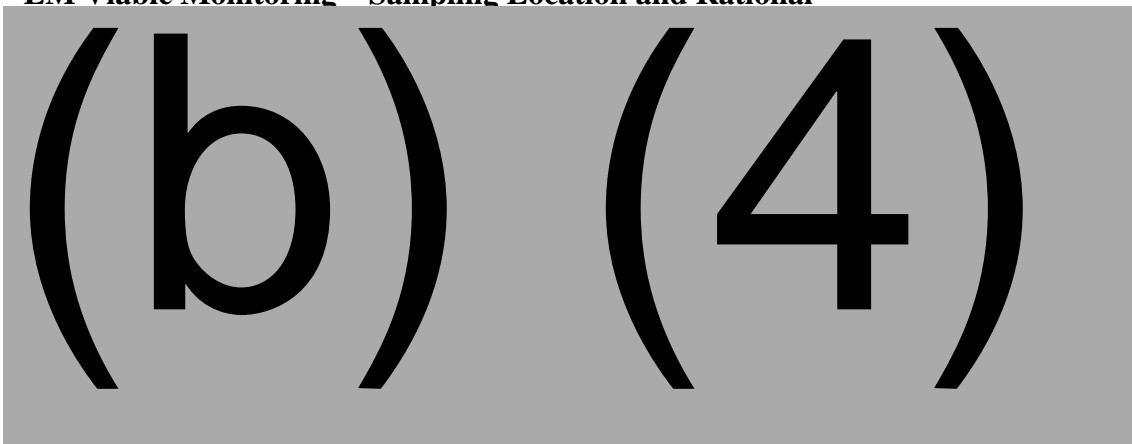
The routine environmental procedures (SOPs) that are currently in use in the Kamada-HRIG production areas are as follows:

- TR-N-2G-008 Physical Monitoring of Clean Rooms
- TR-N-2G-009 Microbial and Physical Monitoring of Filling Rooms
- TR-N-2G-010 Microbial Monitoring of Clean Rooms

Kamada provide a rational for EM sampling selection. Kamada applied a risk-based approach. The highest risks for the environmental locations were sampled and these samples received the greatest attention. Environmental samples were representative of the environment from which they were collected. The method of sampling was selected in accordance with the measured parameters and sample criticality. The sampling locations included where equipment and personnel movement occurs frequently.

The frequency of monitoring was determined by the criticality of the activities performed in the area and the regulatory requirements. Areas where the potential for product exposure was greater required a higher frequency of monitoring to ensure close control over the microbial status of the area. Kamada provided the rationale for sampling locations and test frequencies for viable air borne samples presented in the table below.

**EM Viable Monitoring – Sampling Location and Rational**



2 pages have been determined to be not releasable: (b)(4)

(b) (4)

Review comment:

Kamada's rationale for the EM sample selection seems to be reasonable. Kamada's response is adequate.

**Question 9b**

*Reference to Facilities and Equipment (3.2.A.1), Routine Environmental Monitoring (2.2.8):*

- b. Please provide most recent (b) (4) months of the routine EM monitoring data summary for the HRIG production areas.

**Applicant Response to Question 9b**

Kamada provide (b) (4) months of routine environmental monitoring results for the Kamada-HRIG production areas including the buffer preparation areas, corridor formulation and filling suite, and (b) (4) areas. All of the samples met acceptance criteria.

Review comment:

Kamada's response is adequate

### Question 10a

Reference to Facilities and Equipment (3.2.A.1), (b) (4) (page 69):

a. Please provide the (b) (4) utilities brief qualification history.

### Response to Question 10a

#### (b) (4) System Qualification History

According to Kamada, the distribution of (b) (4) system is located in the (b) (4) part of the plant within a built and enclosed area. The (b) (4) is distributed to the use points in the (b) (4) manufacturing areas through (b) (4). The pressure in the batteries is monitored by the (b) (4) system. In a case of a low pressure, an alarm is triggered.

Installation Qualification (IQ) was performed on 2008 and included testing of system drawings, calibration, equipment qualification (valves, pressure regulators etc.), technical file testing etc.

Operational Qualification (OQ) was performed on 2009 and included pressure tests at use points to ensure that pressure is maintained within the prescribed limits and testing of the (b) (4) system for low (b) (4) pressure alarm.

In 2016, a system for automatic replacement of the (b) (4) batteries (between the working and the backup batteries) was installed. The system was validated and the validation included (b) (4).

In 2017, a new (b) (4) distribution line was installed in room (b) (4) close to (b) (4) (from an existing use point in the room close to (b) (4)). The change was validated and the change control included testing of drawings and testing of the (b) (4) line for slope, surface quality and pressure test.

#### (b) (4) System Qualification History

(b) (4) supply system consists of (b) (4). (b) (4) is distributed to appropriate use points in (b) (4). (b) (4) being exposed to the product (b) (4).

The (b) (4) supply system was qualified according to IQ and OQ protocols. The last PQ for the (b) (4) system was performed from December 2010 to January 2011. The PQ study included sampling (b) (4) a week for (b) (4) weeks for (b) (4) for the validation period by the (b) (4) system. (b) (4) use points in rooms (b) (4) in the production facility and (b) (4) use point in the production facility were sampled for (b) (4). (b) (4) content was sampled in the exit of the (b) (4) production system. The acceptance criteria for the qualification study were as follows:

(b) (4)

(b) (4)

(b) (4)

Requalification is performed every (b) (4) month and the requalification study includes testing for (b) (4).

Review comment:

Kamada's response is adequate

**Question 10b**

*Reference to Facilities and Equipment (3.2.A.1), (b) (4) (page 69):*

- b. Please provide the routine monitoring parameters, acceptance criteria, and test results summary performed during the conformance lots.*

**Response to Question 10b**

Kamada stated that the (b) (4) is supplied to the manufacturing facility in batteries containing (b) (4) is released for production by the QC according to relevant SOP as detailed in table below.

(b) (4) **Acceptance Criteria**

(b) (4)



Test results summary performed during the conformance lots for (b) (4) is provided in the table below.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

Review comment:

Kamada's provided information for the (b) (4) that was found to be adequate.

**Question 11**

*Reference to Facilities and Equipment (3.2.A.1), Table 42 - Computer system validation (page 72). Regarding the computer system that control critical manufacturing process ((b) (4) computer systems) listed in the table #41, Please provide a validation summary of parameters monitored, test performed and validation summary report (PQ only).*

**Response to Question 11**

(b) (4)

(b) (4) is the central Enterprise Resource Planning (ERP) System in Kamada. (b) (4) is an integrated ERP System, designed to manage the entire business activities processes. This system is used for control of quarantined and released materials in the raw materials and finished goods warehouses, forward and reverse traceability of raw materials used in production, traceability of marketed finished goods; and calibration and preventative maintenance scheduling and procedure. Kamada provided following IQ/OQ information:

During IQ, installation preparations (such as creation of virtual machine servers, minimum hardware and software requirements verification, etc.) were performed. In addition, installation of the different environments (testing, production) and installation of the different servers ((b) (4) ) were completed.

During OQ, the operational testing of each module includes (b) (4)

During the PQ, following tests were performed:

(b) (4)

Kamada noted that additional minor changes were implemented due to change control request as the addition of the logistic center.

Review comment:

Kamada's response is adequate

#### **(b) (4) System**

The (b) (4) system is a (b) (4) system, which enables the collection, display and analysis of real time data during manufacturing and response of the system to operator instructions. The system is also used to monitor and control plant utilities such as WFI and purified water production and distribution. The current (b) (4), and it was validated between August to October 2009. The main tests performed in the validation were as follows:

(b) (4)

The applications built using the (b) (4) system are managed separately and were validated separately. Each application has its own set of documents (URS, FS, STP, STD, PQ, and STR) as required, according to the application level of concern.

Kamada provided the (b) (4) test results summary lists. All of the tests met the acceptance criteria.

#### Review comment:

Kamada response is adequate

#### **Question 12**

*Media fill (Section 3.2.P.3.5):*

*Table# 11 provided the media fill summaries, however detailed information was not provided for these media fill runs regarding the interventions (normal and non-routine interventions) that were performed, number of personnel who participated during the media fill, number of aseptic additions performed, and line speed for each media fill that was used. In addition, information was not included regarding the aseptic activities performed (weight check, shift change, operator breaks, gowning changes), media growth promotion study results, number vials incubated, number of units excluded before and after incubation, and the number of defective units found during each media fill runs. Please provide this information for each media fill listed in the Table # 11.*

#### **Response to Question 12**

Kamada provided the following details regarding the aseptic activities performed: In order to mimic an intervention, a (b) (4) is performed at the beginning of the filling procedure on (b) (4) vials using a (b) (4) within the filling suite. The vials are taken out using (b) (4). For the routine filling process, the (b) (4) procedure is performed outside of the filling suite.

(b) (4)

The gowning procedure for the filling room is according to the relevant SOP. Each entrance to the filling room must be in a new sterile gown and when an operator exits the filling room, the gown is sent to the laundry followed by sterilization. The operator changes his gloves in the gowning room in case he performed an intervention that may contaminate his gloves or prior to critical aseptic activities (e.g., (b) (4)).

The table below summarizes the media fills activities performed for the validation of the filling process in formulation and filling (b) (4). This table provides the following additional information for each media fill run: number of vials incubated, number of vials excluded following incubation, normal routine and non-routine interventions, number of personnel who participated during the media fill, number of aseptic additions, line speed for each media fill and growth promotion study results.

#### Media Fill Study Details

Media Fill No.	Date	No. Vials Filled	No. Vials Incubated	No. Vials Excluded after Incubation	Vials Volume	No. Contaminated Vials
(b) (4)						

### Media Fill Study Details

Media Fill No.	Filling Duration (h)	Routine Interventions	Non-Routine Interventions	Number of Personnel who Participated	Number of Aseptic Additions	Line Speed (bottles/min)	Growth Promotion Study (Pass/Fail)
(b) (4)							

#### Review comment:

Kamada provided MF detail above, it verified that no contaminated vial was found and all incubated vials was discarded.

The table below describes the normal interventions simulation performed for each media fill.

#### Media Fill - Interventions

No.	Intervention	Comments
(b) (4)		

Kamada provided justification for the intervention performed during the media fill and found reasonable.

The table below describes the number of vials excluded before incubation of each media fills and the reasons for not incubating the vials.

**Vials Excluded from Incubation for Each Media Fill**

Media Fill No.	No. of Vials Excluded Before Incubation	The Reason for not Incubating the Vials
(b) (4)	(4)	

The table below describes the non-routine interventions simulation performed for each media fill.

**Media Fill Non-Routine Interventions**

Media Fill No.	No. of Non-Routine Interventions	Non-Routine Interventions
(b) (4)	(4)	

Review comment:

Kamada provided additional information for the media fill study submitted in the BLA and this information was found to be adequate.

**Question 13**

(b) (4) – Container closure (3.2.S.6, Page 6):

(b) (4)

**Response to Question 13**

(b) (4)

(b) (4)

Review comment:

Kamada response is adequate to support using the validated (b) (4) for the (b) (4).

**Question 14**

*Reference to container closure integrity test (Section 3.2.P.8.1, Page 19 to 22):*

- a. Please verify inclusion of the (b) (4) that was tested during the CCIT validation ((b) (4)) submitted in the BLA.
- b. Please clarify if CCIT study was performed for each stopper and vial combinations ( 2 ml and 10 ml size vials and stoppers, from each of two vendors) to assure that the product remains integral through expiration dating.

**Response to Question 14a**

Kamada states that the validation of CCIT integrity ((b) (4)) submitted in the BLA did not include a (b) (4). Kamada currently is performing a CCIT validation to all container closure combinations, which includes a (b) (4). Kamada is committed to submit the reports to the FDA by December 2017 as a PMC.

Review comment:

I note that the CCIT using the (b) (4) method submitted in the BLA did not include a (b) (4) and Kamada is committed to submit the reports to the FDA by December 2017 as a PMC (see below).

**Response to Question 14b**

According to Kamada, the CCIT is part of the stability plan and is performed on each CCS combination (refer to Table 2 in Section 3.2.P.8.2 of the BLA). Stability results for the (b) (4) combinations are found in Section 3.2.P.8.3 of the BLA as follows:

Vial Fill Volume	Stoppers	BLA Location
2 ml	(b) (4)	Table 2 Section 3.2.P.8.3
10 ml		Table 2 Section 3.2.P.8.3
2 ml		Table 3 Section 3.2.P.8.3
10 ml		Table 4 Section 3.2.P.8.3

Review comment:

Kamada confirmed that all CCS combinations were tested for the CCIT during the stability testing. Kamada's response is acceptable.



### Question 15

(Section 3.2.P.7- page 9, 1.2.4.1):

Regarding (b) (4) stoppers sterilized by a contractor in (b) (4). Please provide a kamada approved sterilization protocol and validation summary report for the (b) (4) mm and (b) (4) mm stoppers.

### Response to Question 15

Kamada provided an approved protocol of the sterilization of the (b) (4) stoppers ((b) (4) mm and (b) (4) mm) by (b) (4) (document TR-VL-100466-PQ). In addition, a validation report and requalification report were provided.

### Summary (b) (4) Stopper Sterilization Validation Protocol

Rubber stoppers used for the filling of Kamada products are sterilized by (b) (4) by (b) (4). The rubber stoppers are (b) (4) by a (b) (4). The rubber stoppers are packed in double plastic bags, and the bags are packed in cartons. The initial and periodic (b) (4) mapping will include (b) (4) -mapping runs.

The density of (b) (4) mm rubber stopper packages is higher than the density of (b) (4) mm rubber stopper packages. The (b) (4) mm rubber stopper packages are therefore worst-case concerning (b) (4) and minimum expected (b) (4) level. Therefore, (b) (4) -mapping runs of (b) (4) mm rubber stopper packages were carried out. (b) (4) additional (b) (4) -mapping run of (b) (4) mm rubber stopper packages was carried out to verify that the (b) (4) is within the same range as that of the (b) (4) mm rubber stoppers.

Periodic (b) (4) mapping was conducted (b) (4) every (b) (4) years. (b) (4) audit was conducted (b) (4) for (b) (4) rubber stoppers lot of the (b) (4) rubber stopper sizes.

Kamada provided validation reports containing the same validation studies and validation results/conclusion that was submitted in the BLA (see stopper validation section of this memo).

### Review comment:

I verified that the (b) (4) stopper sterilization by (b) (4) (vendor) was performed using the Kamada approved protocol and the vendor provided validation report including the stopper routine requalification protocol and report was reviewed and approved by the Kamada quality unit. The proposed frequency and use of (b) (4) rubber stopper lot for the (b) (4) rubber stopper sizes is acceptable. Kamada's response is adequate.

### Additional Information Request:

Following additional clarification request was made on August 9, 2017, regarding (b) (4) validation:

### Question 1

Reference to Facilities and Equipment (3.2.A.1), Table #66 and Table #67 provided

(b) (4) summary. Following information was not found in the BLA. Please provide following information:

a) Date of original validation and/or most recent requalification

- b) (b) (4) used during Validation (most requalification or initial validation)
- c) Calculated lethality for each validation run (most requalification or initial validation)

**Response to Question 1**

Kamada provided the following response on 09/14/2017:

Original (b) (4) validations and most recent requalification dates for (b) (4) and for (b) (4) are detailed below in Table 1 and in Table 2 respectively.

(b) (4)

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

(b) (4)

**Kamada PMC**

Kamada provided following PMC commitment (email communication from Kamada on 08/17/2017):

Kamada commits to perform validation of the container closure integrity test for each stopper and vial combinations (4 ml and 13.5 ml size vials and stoppers, from each of two vendors) with the inclusion of a (b) (4). Kamada will submit a final validation report.

- Study Completion Date: November 30, 2017
- Final Report Submission: December 29, 2017

**Final Review Summary**

Based upon the information provided in the BLA and response to the IR, and provided during the PLI, approval of this BLA is recommended.