

**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Division of Biological Standards & Quality Control, Office of Compliance & Biologics Quality,
Center for Biologics Evaluation & Research, Food & Drug Administration, 1401 Rockville Pike, Rockville, MD 20852

MEMORANDUM

Date: March 21, 2017

RE: Administrative File for STN: 125613/0

From Noel Baichoo, DBSQC

Through Muhammad Shahabuddin, DBSQC
James Kenney, Acting Director, DBSQC
William McCormick, Director, DBSQC

Cc Jiahua Quian, RPM

Applicant: Kamada Ltd

Subject: Review of Analytical Methods for Purity, Identity and Potency used for testing
Human Rabies Immune Globulin (Human) product Kamada-HRIG: KEDRAB

Recommendation: Acceptable

Summary:

A new BLA was submitted for human anti-rabies immunoglobulin (HRIG). This document constitutes the Primary Review Memo from DBSQC for the following analytical methods and their validations, as used for lot release.

1. (b) (4) Test to (b) (4) Rabies Virus Neutralizing Antibodies (SOP 1120)
2. Identification of Human IgG by (b) (4) (SOP N-IP-5344-17)
3. Determination of Protein Composition in IgG Product by (b) (4) (SOP N- 1189)

Review of these methods and their validations led to an Information Request (IR), which was submitted on November 21, 2016. The response was received on December 1, 2016. The response was reviewed and included in the memo.

Conclusion: On the basis of the review of the original submissions and amendments, the assays listed above were approvable for quality control testing.

Background:

On August 29, 2016, Kamada Ltd submitted a BLA (STN 125613) for a Drug Product (DP) Kamada-HRIG (Human Rabies Immune Globulin). This product is used for post-exposure prophylaxis of rabies infection in combination with a rabies vaccine. The Drug Substance (DS) is derived from (b) (4). Anti-rabies immunoglobulins from plasma are enriched using (b) (4) steps. Viral inactivation of the

plasma is achieved using solvent-detergent, heat treatment and nanofiltration. The DP is a sterile, nonpyrogenic liquid provided at a potency of 150 IU/ ml in 2 ml and 10 ml glass vials. The DP is formulated with 0.3 M glycine at a pH range of 5.0 – 6.0.

Documents Reviewed:

This is an electronic submission. Information submitted and reviewed includes:

- 125613/0 - 5.3.1.4 IS#2.3/v1 Partial Validation Report of the (b) (4) Test to (b) (4) Rabies Virus Neutralizing Antibodies – Modified (b) (4)-fold method
- 125613/0 - 5.3.1.4 IS#2.8/v1 Validation Report of the (b) (4) Test to (b) (4) Rabies Virus Neutralizing Antibodies-Modified (b) (4)-fold method.
- 125613/0 - 5.3.1.4 SOP#1120.00 The (b) (4) to (b) (4) Rabies Virus
- 125613/0 - 3.2.S.4.3 Rep-VL-100891-AM Qualification Report of Kamada RIG Product Potency Testing in (b) (4)-Fold (b) (4) Assay by (b) (4)
- 125613/0 - 3.2.P.5.2 Analytical Procedures [Protein Identity by (b) (4)]
- 125613/0 - 3.2.P.5.3 Rep-VL-06520-AM, Version 2: Qualification Report for Identification of Human IgG by (b) (4) according to SOP N-IP-5344-17
- 125613/0 - 3.2.P.5.2 Analytical Procedures [Protein Composition]
- 125613/0 - 3.2.P.5.3 Rep-VL-03002-AM Report: Determination of Protein Composition in IgG Product by (b) (4)
- 125613/0.6 - Response to FDA Information Request, received 11/21/2016

Review Narrative:

1. Potency

Potency was determined using a quantitative method for determining the (b) (4) of anti-rabies antibodies present in DP, (b) (4). The proposed specifications are for potency to be not less than (b) (4) not less than 150 IU/ml for DP.

Method:

(b) (4)



(b) (4)



Method Validation:

Results of accuracy, precision, linearity, quantitation limit, dilutability and robustness of the method were evaluated to validate the method. Three validation reports IS#2.8/v1, IS#2.3/v1 and Rep-VL-100891-AM documented aspects of these parameters. Validation was performed in accordance with ICH Guideline Q2(R1).

IS#2.8/v1 investigated accuracy, precision, linearity, quantitation limit and robustness. Specificity and sensitivity were covered in the report by referring to published peer-reviewed articles rather than experimental studies. IS#2.3/v1 investigated accuracy, linearity, precision, robustness and the lower limit of quantitation of the assay after changes in location and reagent lots. Rep-VL-100891-AM investigated accuracy and precision of the assay using DP, (b) (4) samples.

Accuracy in validation report IS#2.8/v1 was determined by analysis of (b) (4) reference standard (b) (4). Potencies of (b) (4) IU/ml were used. (b) (4) determinations per concentration were performed. Acceptance criteria were for the measured value to be (b) (4) of the theoretical value. Measured values ranged from (b) (4) of the theoretical values fulfilling the criteria.

In validation study IS#2.3/v1, accuracy was determined using replicate analysis of the (b) (4) standard rabies immune globulin reference standard at (b) (4) IU. The standard was (b) (4)

Each concentration was determined (b) (4) times. Measured values were compared to theoretical values. Acceptance criteria were for the measured values to be within (b) (4) of the corresponding theoretical values. Differences between theoretical and measured values ranged from (b) (4). These differences were within the acceptable range, but were just above the lower limit. The reason given for this was the SRIG (b) (4) used to calculate the accuracy samples was on the higher end of the expected acceptance range ((b) (4)) causing the IU/ml to be lower. The accuracy determination was considered to be near the extreme end of the expected % recovery, but still within the acceptable range.

In document Rep-VL-100891-AM, accuracy was determined for (b) (4) DP (lots (b) (4)) and (b) (4) samples. This study compared values obtained from the (b) (4) to those obtained from the (b) (4). The values obtained during development were considered the theoretical values. Acceptance criteria for potency values for lots at (b) (4) to be within (b) (4) of the theoretical values were fulfilled by ratios ranging from (b) (4).

Precision was determined in validation report IS#2.8/v1 as repeatability and intermediate precision. One measure of repeatability was determined using (b) (4) replicates of reference standard sera ((b) (4), (b) (4)) to a single potency in the (b) (4) IU/ml range. Results were presented as (b) (4). Acceptance criteria for %CV to be (b) (4) were met with a value of (b) (4). Repeatability was also determined using one potency level in each of (b) (4) ranges ((b) (4)) along with negative serum as a control. Each potency level was tested in (b) (4). Acceptance criteria for %CV to be (b) (4) were met with a maximum value of (b) (4) among the samples and (b) (4) for negative serum. In validation study IS#2.3/v1, repeatability was determined using (b) (4) measurements of a (b) (4) of (b) (4) reference standard. Normal human serum from (b) (4) was used for (b) (4) and as a negative control. Acceptance criteria for %CV to be (b) (4) were met with a %CV of (b) (4) for (b) (4) values. Additional repeatability studies were done using samples at (b) (4) in the same assay. The (b) (4) samples were from known positive sera from the (b) (4). The highest %CV measured was (b) (4), which was within the (b) (4) acceptance criteria.

Intermediate precision in validation report IS#2.8/v1 was determined using reference standard (b) (4) at (b) (4) potency ranges ((b) (4)). Each sample was tested (b) (4) times in separate assays. Results were presented as (b) (4) values. Acceptance criteria for %CV to be (b) (4) were met by a maximum value of (b) (4).

Intermediate precision in validation study IS#2.3/v1 was determined using samples at (b) (4) in separate assays. Reference standard was used for the (b) (4) level while a known positive sample from (b) (4) were used for the other levels. The highest %CV observed was (b) (4), which was within the acceptance criteria of (b) (4). In addition to the (b) (4) assays, studies determining repeatability and intermediate precision were also performed measuring IU/ml for information only. The studies measuring IU/ml displayed higher %CV values than those determining (b) (4) values. The %CV for intermediate precision values for low and moderate IU/ml showed %CV higher than the acceptance criteria of (b) (4). The Sponsor stated the IU/ml values were for information only and not considered in the validation criteria.

In document Rep-VL-100891, precision as repeatability was determined using DP lot (b) (4) and (b) (4). (b) (4) replicates of each sample were analyzed. Acceptance criteria for RSD (b) (4) were met with values of (b) (4) for DP and a maximum of (b) (4) for the (b) (4) lots.

Specificity was not experimentally determined by the Sponsor. A peer reviewed publication ((b) (4)) was cited to demonstrate specificity and sensitivity of the assay. The study in this publication compared the (b) (4) to a Mouse Neutralization Test published by (b) (4). The mouse assay measured the ability of rabies antisera to prevent lethal infection of mice with five weanling mice being used for each dilution of sera.

In the (b) (4) study, CVS-11 Rabies virus and a collection of sera samples were tested using both methods. Results from the mouse assay were available after two weeks, while those of the (b) (4) . A total of (b) (4) sera samples were tested in the study with (b) (4) of the results showing agreement between the two methods. For (b) (4) samples, the (b) (4) assay produced a positive result at dilutions of sera, which were detected as negative by the mouse method. While some sera samples were detected as positive by the (b) (4), but negative by the mouse method, no sera were detected as positive by the mouse method and negative by (b) (4). The authors interpreted this observation as showing the (b) (4) to be more sensitive than the mouse assay. No pre-immune sera were detected as positive by the (b) (4). A specificity of (b) (4) and sensitivity of (b) (4) were reported based on results in the study.

Linearity in validation report IS#2.8/v1 was determined using (b) (4) potency levels (b) (4) from U.S standard rabies immune globulin (b) (4). Each level was measured in duplicate and the assay was repeated (b) (4) times. The measured (b) (4) at each level was plotted against the theoretical value. Acceptance criteria were for the correlation coefficient R to be (b) (4) and for at least (b) (4) samples to have a CV (b) (4) with the lower limit of quantification allowed to have a CV (b) (4). The maximum CV observed for all samples was (b) (4). A correlation coefficient of (b) (4) was observed. Together these results fulfilled the acceptance criteria.

Detection limit was determined in validation report IS#2.8/v1 as the lower limit of quantification, which was defined as the (b) (4). Additionally, measurement of this potency should have a precision of (b) (4) and an accuracy of (b) (4). Data from accuracy and precision studies using reference standard (b) (4) were used in this determination. The potency fulfilling these criteria showed an average (b) (4) of (b) (4) corresponding to (b) (4) with a precision of (b) (4) and accuracy of (b) (4). In revalidation report IS#2.3/v1, (b) (4) reference standard was assayed for the lower limit of quantification using potencies of (b) (4) at (b) (4) replicates per level. Acceptance criteria for this parameter were for it to be the lowest potency at which the %CV (b) (4) and at which the potency of sera is clearly identifiable from negative serum. The (b) (4) values obtained for (b) (4) were indistinguishable from negative serum. A lower LOQ of (b) (4) was determined with a precision of (b) (4) fulfilling the acceptance criteria. Results measuring IU/ml instead of (b) (4) values were also presented for information purposes. These results confirmed those presented as (b) (4) values. An addendum to IS#2.3/v1 (IS#2.7/v1) showed the recovery of the LLOQ at (b) (4) to be (b) (4). This relatively low recovery was attributed to increased variation at the lower level of sample and due to the method being a (b) (4) assay.

(b) (4) was determined in validation report IS#2.3/v1. This parameter was defined as the ability to obtain accurate results with (b) (4) samples. Known positive samples from (b) (4) with potencies at (b) (4) were used. These were used (b) (4) and (b) (4) at (b) (4) in assay media. Acceptance criteria were for differences between (b) (4) observed values and (b) (4) expected values to be (b) (4). The largest (b) (4) difference obtained was (b) (4), which is within the limit.

Robustness in validation report IS#2.8/v1 was investigated with respect to changes in technician, cell passage number, virus neutralization time, and length of the infection. Reference (b) (4) was used in these studies. (b) (4) different analysts, (b) (4) different (b) (4), virus neutralization times of (b) (4) and (b) (4), and assay infection times of (b) (4) and (b) (4) were compared. (b) (4) replicate measures of the reference (b) (4) were determined for each parameter change. The median (b) (4) for the reference standard was compared using one way analysis of variance. No statistically significant differences were found due to these variations.

Validation of accuracy, precision, linearity, quantitation limit, dilutability and robustness of the method described in the document is acceptable.

2. Identity

Identity for (b) (4) is determined using the (b) (4) method, which was also used for potency. This method was used as a (b) (4) assay to identify a (b) (4) lot as being anti-rabies. The method and its validation are reviewed in the potency section above. Acceptance criteria for (b) (4) are for the lot to be active against rabies virus.

Identity for DP is determined by (b) (4). This method is used to identify a DP lot as being human IgG. Acceptance criteria for this assay are for the position of the main component of the sample to correspond to that of the human IgG standard.

Method.

(b) (4)



Method Validation

Validation of this method is described in Section 3.2.P.5.3 in Rep-VL-06520-AM, Version 2: Qualification Report for Identification of Human IgG by (b) (4). According to SOP N-IP-5344-17. Specificity and robustness were determined in this study. Validation was performed in accordance with ICH Guideline Q2(R1).

(b) (4)



(b) (4)

Validation of specificity and robustness of the method described in the document is acceptable

3. Protein Composition

Protein composition of the DP was determined by (b) (4) . In this type of (b) (4) . This method was performed according to (b) (4) . This method is described in Section 3.2.P.5.2 in Analytical Procedures - 2.4.1 – Protein Composition. The Sponsor used a commercial kit ((b) (4)), which uses (b) (4) . Specifications for release are for the (b) (4) to IgG to have (b) (4) of the total (b) (4) .

Method

(b) (4)

Method Validation

Validation of this method is described in document REP-VL-03002-AM and Section 3.2.P.5.3. - 3.1.7. - Protein Composition. Specificity, precision, limit of detection and robustness were investigated for this assay. Validation was performed in accordance with (b) (4) .

(b) (4)

Information Request and Review

The following Information Request (IR) was submitted to the Sponsor on November 21, 2016. The response was received on December 1, 2016.

IR:

1. In Section 4 of Rep-VL-03002-AM Report: Determination of Protein Composition in IgG Product by (b) (4)", reference is made to (b) (4) images attached to forms VL-03002-AM/1, VL03002-AM/2 and VL-03002-AM/3. These (b) (4) are not attached to the electronic validation report. Please provide the images of these (b) (4) in a quality where all relevant (b) (4) are visible.
2. In Section 3.2.P.5.3 document: Validation of Analytical Procedures, it is difficult to see (b) (4) corresponding to (b) (4) in figures 15 and 16. Please provide these images at a quality where the (b) (4) is visible as stated in the document or provide (b) (4) evidence of the (b) (4) presence.

Response

The Sponsor provided the images requested

Review of Response

In the (b) (4) provided for lots (b) (4) the (b) (4) at (b) (4) were visible. This result showed (b) (4) present at levels of least (b) (4) can be distinguished from IgG in this assay.

Precision was determined as repeatability and intermediate precision. Repeatability was investigated using results from the specificity study. Each of the (b) (4) lots examined for specificity was run in (b) (4) for a given day. Passing results were obtained for each replicate for each lot tested supporting precision of the method.

Intermediate precision was determined for differences in analyst and day of performance. The (b) (4) lots analyzed for specificity were investigated by (b) (4) analyst on (b) (4) different days and by (b) (4) analyst on a (b) (4) day. Passing results were obtained for each lot tested.

Detection limit was determined from the (b) (4) ratios of IgG to (b) (4) used in determinations of specificity and precision. These were (b) (4) of (b) (4) in the sample. The limit of detection was determined to be (b) (4), since this was the lowest percent of (b) (4) and was also visible in the (b) (4) used.

Robustness was determined with respect to sample application time, (b) (4) kit lot. Lots (b) (4) of anti-rho D IgG were used for these studies. No anti-rabies IgG DP lots were used in robustness studies. Application times tested were (b) (4) Performance with lots (b) (4) of the (b) (4) kit were compared. For each combination of conditions used, the (b) (4) was visible and could be identified.

Validation of specificity, precision, limit of detection and robustness of the method described in the document is acceptable.