



To: Review Committee Chair, STN 125613/0

From: Leslyn Aaron, Biologist, LACBRP, DBSQC, OCBQ

Through: Lokesh Bhattacharyya, PhD, Chief, LACBRP, DBSQC, OCBQ  
James Kenney, PhD Acting Division Director, DBSQC/OCBQ

Sponsor: Kamada Ltd.

Product: KamRAB, Human Rabies Globulin (HRIG), Solution for Injection

Subject: Review Memo for Biological License Application for Quality Control Lot-Release Test Method for the (b) (4) for KamRAB, Human Rabies Globulin (HRIG), Solution for Injection.

Recommendation: Approval

### Summary of Review

This document constitutes the review memo for the Biological License Application (BLA), for STN 125613/0, submitted by Kamada Ltd. for the (b) (4) method used to perform a (b) (4) assay to measure pro-coagulant activity due to (b) (4) in Kamada-HRIG (b) (4). The validation was performed by (b) (4) on behalf of the sponsor, Kamada. (b) (4) will also perform this assay routinely as part of routine lot release. Based on the information submitted, the method can be approved as the Quality Control Lot-Release Test Method for the (b) (4) for Kamada-HRIG, Solution for Injection.

### Background

Kamada-HRIG drug product is a sterile, nonpyrogenic liquid preparation enriched with antirabies human immunoglobulins (not less than 95% protein as IgG) and is indicated for passive, transient postexposure prophylaxis (PEP) of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and in combination with a rabies vaccine. It should be administered as part of the PEP regimen in patients exposed to animals suspected of being rabid, provided the patient was not vaccinated with rabies vaccine at an earlier date.

It has a labeled potency of 150 IU/mL. The product is stabilized with 0.3 M Glycine at a pH range of 5.0-6.0 and does not contain preservatives. Kamada-HRIG is supplied in 2 mL and 10 mL (b) (4) glass vials as a ready-to-use solution.

## Submitted Information and Documents

Information reviewed includes:


- 125613/0 – 3.2.S.4.1 Specification
- 125613/0 – 3.2.S.4.2 Analytical Procedures
- 125613\0 – 3.2.S.4.5 Justification of Specifications
- 125613/0./14 – 3.2.S.5 Reference Standards or Materials
  - ✓ TM-10054-1 – (b) (4) Method for IgG.
- 125613\0 – 3.2.S.4.3 Validation of Analytical Procedures
  - ✓ AMVR-20160616-01 Method Validation Report – Validation of the (b) (4) Assay Test Method for (b) (4) Drug Product (b) (4).
- 125613/0.020 – Response to FDA Questions Received April 6, 2017
- 125613/0.29 - Response to FDA Questions Received June 29, 2017
- 125613/0.32 – Response to FDA DBSQC Questions Received on August 10, 2017

### (b) (4) **Method for IgG (TM-10054-1)**

The (b) (4) assay method is used to measure pro-coagulant activity due to (b) (4) in Kamada-HRIG (b) (4). The test is performed as a release test on (b) (4) for further processing to DP. The acceptance criterion is to be established after at least (b) (4) of product are evaluated.

### Method

(b) (4)



### Method Validation

The method validation report (AMVR-20160616-01) describes evaluation of the validation parameters, Accuracy, Precision (Repeatability and Intermediate Precision), Linearity, Limit of Quantification (LOQ), Specificity, Range and Robustness. This is a method for the quantitation of a product-related (b) (4); therefore, the validation

characteristics studied are appropriate. Data for system suitability are also presented in the report.

In this validation, (b) (4) lots of (b) (4) and (b) (4) lots of drug product (DP) [(b) (4)] and the same lots (b) (4) with a known amount of commercial (b) (4) and (b) (4) with the same lot to create (b) (4) levels ((b) (4) mU/mL) of activity, which covered the range of the method, were studied. Each (b) (4) level as well as the (b) (4) drug product (b) (4) of each lot was tested in (b) (4) by (b) (4) analysts.

To evaluate the accuracy of the method the (b) (4) studied. Each (b) (4) sample was tested by (b) (4) analysts, each in (b) (4). In the initial DP evaluation, the (b) (4) mU/mL DP (b) (4) generated results outside the range of the standard curve. The measured (b) (4) value of the highest level studied ((b) (4)) was greater than the (b) (4) value of the highest point on the Standard Curve. As the QC samples for the affected run were within specification, the results for the DP levels were determined by extrapolation of the standard curve. Kamada believes as accuracy of the method is determined based on the % recovery and not the measured activity (mU/mL), the (b) (4) level result would have no impact on the validation results. In the results presented, the 90% confidence limits for the mean percent (%) recovered at each (b) (4) level were within 70% - 130%. However, as the Reference Standard ranged from 0.03125 – 2.0 mU/mL we do not agree that results obtained from data-points outside of the standard curve are acceptable. An IR was submitted on April 6, 2017 to the sponsor requesting (b) (4) recovery results from samples (b) (4) to the final (b) (4) levels within the standard curve range to demonstrate accuracy of the (b) (4) Method for IgG.

The precision of the assay (repeatability and intermediate precision) of the assay was evaluated by analyzing “normalized” results of each measurement at each (b) (4) level of the (b) (4) drug product. The results of the accuracy study were used in this assessment. The normalized results are calculated as follows:

(b) (4)

The pooled results of (b) (4) analysts performing independent tests were evaluated. In the drug product Repeatability evaluation, the % RSD values ranged between (b) (4) and the Intermediate Precision values ranged between (b) (4). In the (b) (4) Repeatability evaluation, the % RSD values ranged are between (b) (4) and the Intermediate Precision values ranged between (b) (4).

Repeatability and intermediate precision of the (b) (4) DP (b) (4) samples were also evaluated from the results of the measured activity (mU/mL). For DP, within run RSD ranged between (b) (4) and between run RSD for DP ranged between (b) (4). For (b) (4), RSD within run ranged between (b) (4) and between run RSD ranged between (b) (4).

As the sponsor used “normalized” result values from the (b) (4) levels of DP (b) (4) to assess precision of the method an IR was submitted on April 6, 2017 requesting the sponsor provide reportable result values (mU/mL) within the range of the range of the assay to demonstrate precision of the method.

Linearity was evaluated from the geometric mean (GM) activity (mU/mL) value of each measured level of (b) (4) drug product. The samples used to evaluate accuracy were used in the linearity study. The results of the linearity study indicated that the plot of the measured (b) (4) activity versus the (b) (4) activity across the range of the assay showed  $R^2$  values of (b) (4). The sponsor did not provide data to demonstrate linearity of the standard used in the (b) (4) Method for IG. The plot presented by the sponsor shows correlation between measured and expected activities, which represents accuracy of the method, not linearity. Also, results above (b) (4) mU/mL are above the range of the standard curve, hence not valid. An IR was submitted on April 6, 2017 requesting the sponsor to provide linearity data within the range of the standard curve from linear regression analyses of the plots of response ((b) (4)) vs concentration for both standard and sample, and evaluation of parallelism between the standard and sample (b) (4) curves.

The Limit of Quantification (LOQ), (b) (4) mU/mL for the drug product and (b) (4) mU/mL for the (b) (4), of the method was inferred from the linearity, accuracy and precision data. However, as discussed above, the results of the linearity, accuracy and repeatability studies provided by the sponsor were deemed unacceptable. An IR was submitted on April 6, 2017 requesting the sponsor to reevaluate the LOQ of the method based on the results of the re-evaluation of linearity, accuracy and precision.

The specificity for the method was assessed by (1) comparing DP (b) (4) samples (b) (4) with (b) (4) to the same lots of (b) (4) DP (b) (4), (2) evaluating the results of the assay buffer ((b) (4)) and (3) passing the acceptance criteria for accuracy, linearity and precision. The ratio of (b) (4) drug product to (b) (4) drug product is between (b) (4)-fold and (b) (4)-fold. The assay buffer results evaluated were less than the LOQ. Also, results of the accuracy, linearity and precision studies met their respective acceptance criteria.

The range of the method should be inferred from the linearity, accuracy and precision data submitted in AMVR-20160616-01. As the results of the linearity, accuracy and repeatability studies are deemed unacceptable, an IR was submitted requesting the sponsor to reevaluate the range of the assay based on the results of reevaluation of linearity, accuracy and precision.

Robustness of the of the (b) (4) assay was evaluated by analyzing the results of accuracy, precision and linearity studies performed by multiple analysts, instruments and varying lots of reagents. However, accuracy, linearity and precision of a method do not demonstrate robustness. An IR was submitted to the sponsor requesting data to demonstrate the effect of small deliberate changes of critical method parameters, such as (b) (4) to assess robustness.

During the execution of the method validation, samples were qualified for System Suitability. Three vials each of High Level Quality Control samples (HQC) and Low Level Quality Control sample (LQC) were evaluated in each validation run. The measurement of (b) (4) of LQC was determined to be an outlier and excluded from the determination of the acceptance criteria. All other results support the defined acceptance criteria defined in the test method (TM -100054-01).

### Information Requests

The information requests referenced below were submitted to the sponsor on April 6<sup>th</sup> 2017, June 29<sup>th</sup> 2017 and August 10<sup>th</sup> 2017. The sponsor's response was received on April 26<sup>th</sup> 2014 as Amendment 125613/0.20, July 17<sup>th</sup> 2017 as Amendment 125613/0.29 and August 16<sup>th</sup> as Amendment 125613/0.32 respectively. The IRs and review of the responses are detailed below:

- a. IR dated April 6, 2017 (Question 1a): You indicated that the Standard used in your assay procedure TM-10054 was developed with (b) (4) and calibrated against the current (b) (4) primary reference standard. Please provide the qualification report.

Review of Response: The sponsor provided a copy of the qualification protocol; not the requested qualification report. An additional IR was sent to the sponsor on June 29, 2017 requesting the qualification report.

IR dated June 29, 2017 (Question 1): You indicated that the Standard used in your assay procedure TM-10054 was calibrated against the current (b) (4) primary reference standard. In our previous IR (sent on April 6<sup>th</sup>) we requested that you provide the calibration (qualification) report for the Standard used in validation of TM-10054. However, you provided the qualification protocol. Please provide the qualification report, as previously requested.

Review of Response: In Amendment 125613/0.29 Kamada provided Report 20170523-02, Requalification of (b) (4) Standard for (b) (4) Assay. For the qualification, (b) (4) measurements of (b) (4) vial of (b) (4) measured against the (b) (4) were presented. The GM mean and % Geometric Relative Standard Deviation (GRSD) were calculated. The GM activity is within the (b) (4) range of the CofA of the standard. Also, analysis of the measured activity at (b) (4) for the (b) (4) standard show no adverse trend. The results of the (b) (4) requalification study for Reference Standard (b) (4) used in this validation and tested as detailed in Qualification Protocol, PR-10028 (Qualification Requalification and Stability Monitoring of (b) (4) Reference Standard), is acceptable.

- b. IR dated April 6, 2017 (Question 1b): In TM-10054 you indicated that the Reference Standard levels ranged from (b) (4) mU/mL, while in AMVR-20160616-01 you presented results of (b) (4) samples (b) (4) with (b) (4) mU/mL of (b) (4) for the evaluation of the method accuracy. Any potency above (b) (4) mU/mL is outside of the range of the standard curve, and, therefore, outside the scope of quantitation using the standard curve. Please provide (b) (4) recovery

results with samples (b) (4) to the final (b) (4) levels within the standard curve range to demonstrate accuracy of your method.

**Review of Response:** In Amendment 125613/0.020 the sponsor explained that test samples are (b) (4) -fold in sample diluent then tested. The potency values presented in AMVR-20160616-01 is the “Adjusted Result”. The “Adjusted Result” is the measured (b) (4) activity multiplied by the test sample (b) (4) factor. Therefore, all but one set of the results presented in AMVR-20160616-01 are within the range of the Reference Standard Curve and are valid. In the one instance where the drug product potency value ((b) (4) mU/mL) is outside the standard curve range. The results for the DP levels were determined by extrapolation of the standard curve. We do not agree with the sponsor’s method of assessment of the (b) (4) recovery or that they demonstrated accuracy of the method. On June 29, 2017 an additional IR was submitted to the sponsor.

**IR dated June 29, 2017 (Question 3):** In section 9.2 of the validation report, AMVR-20160616-01, the accuracy of the method is assessed by (b) (4) reference standard into (b) (4) lots of drug product ((b) (4) ) and (b) (4) lots (b) (4) , and (b) (4) with the same lot of DP/(b) (4) to create (b) (4) concentration levels. The results of (b) (4) analysis of each level of DP (b) (4) measured by (b) (4) analysts are presented. We do not agree with your method of assessment of the (b) (4) recovery or that you demonstrated accuracy of your method. When we recalculated recovery from your results using the equation,

(b) (4)

all activities being expressed in mU/mL (reportable results), our results show that your recoveries range from (b) (4) , for (b) (4) out of (b) (4) results you have reported for the drug products, which shows that you failed to demonstrate the method accuracy for the drug product. Please provide results by (b) (4) (b) (4) lot each of your drug product (DP) with (b) (4) different concentrations of your standard, which covers your assay range, and measure the activities of (b) (4) and (b) (4) samples in terms of the reportable results and calculate percent recovery at each concentration level using the above mentioned equation.

**Review of Response:** In Amendment 125613/0.29, Report 20170711-02 the sponsor presented results from the assessment of a (b) (4) lot of (b) (4) and (b) (4) with (b) (4) reference standard to create (b) (4) levels of activity (b) (4) U/mL) , which cover the range of the assay. Each (b) (4) level was tested in (b) (4) across (b) (4) independent runs by (b) (4) analysts. The mean results of the (b) (4) recovery of the (b) (4) levels ranged between (b) (4) and (b) (4) and the (b) (4) CI of Mean %Recovery range, (b) (4) falls within the (b) (4) acceptance criteria.

- c. **IR dated April 6, 2017 (Question 1c):** You assessed the precision (repeatability and intermediate precision) of your method using “normalized” results from your accuracy study. “Normalized” result is not your reportable result. Precision should be evaluated based on the reportable results. Furthermore, the results of your accuracy study are unacceptable because most of the data were obtained above the range of the standard curve. Thus, your assessment of precision is also

unacceptable. Please provide results of repeatability and intermediate precision over the range of your assay method based on the reportable results using representative samples, whose measured activities are within the range of the assay standard curve.

**Review of Response:** The sponsor responded that to increase the power of the validation design as well as to confirm the precision of the method across different lots of DP (b) (4), the data were normalized. Normalization was required as the different DP lots of (b) (4) had different levels of endogenous (b) (4) activity. Therefore, normalization of the data increased the power of the design as results across DP lots (b) (4) could be pooled. Also, normalization of the data allowed an assessment of precision across DP lots (b) (4). Results for the (b) (4) samples of (b) (4) DP lots were not normalized. Normalized results were calculated as detailed before.

However, the statement regarding statistical power is not acceptable nor are the results because they were obtained at activity levels above the range of the standard curve. An additional IR was submitted on June 29, 2017.

**IR dated June 29, 2017 (Question 4):** In your validation report (AMVR-20160616-01), you indicated that the samples were (b) (4) mU/mL of (b) (4) for (b) (4). Hence, these results could not be combined with other results for evaluation of precision at different concentration levels. Thus, you reported results from (b) (4) sample assayed by (b) (4) analysts, each in (b) (4) in terms of reportable results, and the results from a (b) (4) sample assayed by (b) (4) analyst, also in (b) (4), at each concentration level. We do not agree that these results permit determination of RSD for the evaluation of repeatability and intermediate precision. Repeatability should be assessed from reportable results from (b) (4) lot each of the (b) (4) the drug product each at (b) (4) concentration levels, which covers the assay range, with (b) (4) replicates at each concentration level or a minimum of (b) (4) determinations at (b) (4) of the target concentration of the test method. Intermediate precision should be reported by overall RSD based on combined reportable results from repeatability studies at least by (b) (4) analysts on (b) (4) different days. However, you have not reported results that demonstrate repeatability and intermediate precision of your assay, as required. Please provide results obtained in the manner described above and with the calculations of RSD in each case.

**Review of Response:** In Amendment 125613/0.29, Report 20170711-02, to demonstrate precision, the sponsor presented results from a (b) (4) lot of (b) (4) with (b) (4) reference standard to create (b) (4) levels of activity, which cover the range of the assay. Each (b) (4) level as well as the (b) (4) was tested in (b) (4) across (b) (4) independent runs by (b) (4) analysts.

**Repeatability:** The GRSD values at each (b) (4) level are between (b) (4), which met the acceptance criteria of (b) (4).

**Intermediate Precision:** (b) (4) analyst measured (b) (4) replicates of each (b) (4) level and (b) (4) analyst measured (b) (4) replicates of each (b) (4) level. The %GRSD of all measurements at each (b) (4) level ((b) (4) measurements total) were evaluated and ranged from (b) (4). The results were within the predefined acceptance criteria, (b) (4) GRSD.

- d. IR dated April 6, 2017 (Question 1d): You did not provide data on the evaluation of linearity of your standard and did not demonstrate parallelism between the standard curve and the sample (b) (4) curve. Please provide linearity data from linear regression analyses of the plots of response vs concentration for both standard and sample and evaluation of parallelism between the standard and sample (b) (4) curves. Please note that all data should be obtained within the range of your standard curve.

Review of Response: The sponsor states that while the validation did not specifically evaluate the linearity of the standard curves generated with the (b) (4) Reference Standard, the method does require that all standard curves have a  $R^2$  value of greater than or equal to (b) (4). The results of the reference standard from (b) (4) replicate assays indicates  $R^2$  values greater than or equal to (b) (4).

However, the sponsor did not provide data on parallelism between the standard and the (b) (4) samples. An additional IR was submitted June 29, 2017 requesting data to demonstrate parallelism between the standard and the sample and (b) (4) curve.

IR dated June 29, 2017 (Question 5): You have reported linearity by plotting geometric mean in mU/mL vs (b) (4) in mU/mL. Linearity should be determined by plotting response vs concentration/activity. From your submission, it is not clear to us what the unit of your response is however generally; it is measured in (b) (4) for this assay. Please submit your linearity results from plots of response vs concentration/activity.

Review of response (Amendment 125613/0.29): The sponsor provided a plot of the response (nM) vs. activity (mU/mL) and explained that the results of the calibration curve is used to convert the level of (b) (4) generated by a sample to units of (b) (4) activity. The (b) (4) software used in the test method automatically collects the sample results ((b) (4) ) and calculates all parameters of the (b) (4) and expresses the results in nanomolar (nM) of (b) (4). Consequently, sponsor is unable to provide requested data.

In all (b) (4) runs the  $R^2$  values were reported as (b) (4), which met the acceptance of  $R^2$  (b) (4). The equation of the linear regression and the residual sum of squares were presented as supporting information. However, the data submitted did not include results from plots of response vs concentration/activity (mU/mL).

An additional IR was submitted August 10, 2017 requesting linearity results from plots of (b) (4) (response) vs mU/mL (measured activity).

IR dated August 10, 2017 (Questions 1): In the IR sent on June 29th, 2017 we requested you provide data on linearity by plotting response vs concentration/activity (mU/mL). You have reported linearity by plotting geometric mean of the measured activity (mU/mL) vs (b) (4) activity (mU/mL). Such a plot provides correlation between known and measured activities, hence accuracy but not linearity. Please submit your linearity results from plots of (b) (4) (response) vs mU/mL (measured activity).

Review of Response: The sponsor responds that, as the output from the (b) (4) system is (b) (4) rather than (b) (4), and as the (b) (4) is calibrated against the (b) (4) reference standard, it is appropriate using

the (b) (4) system to assess linearity by plotting the response ((b) (4)) vs. (b) (4) activity (mU/mL). In Amendment 125613/0.32, the results of a single lot of (b) (4) to (b) (4) levels of activity ((b) (4) U/mL) and the (b) (4) sample were assessed. Each (b) (4) level was tested in (b) (4) across (b) (4) independent runs by (b) (4) analysts. The sponsor presented plots of (b) (4) versus the (b) (4) activity (mU/mL). The results of the linearity study indicated that the plots of the (b) (4) response ((b) (4)) versus the (b) (4) activity (mU/mL) showed  $R^2$  values of (b) (4). The results met the defined acceptance criteria, (b) (4).

IR dated June 29, 2017 (Question 6): In the IR sent on April 6th, 2017 we requested you to provide data on the evaluation of linearity of your standard and sample to demonstrate parallelism between the standard the sample (b) (4) curves. You responded that “the response function of the standard curve generated with the (b) (4) reference standard is nonlinear. The concentration-response relationship is fitted to a 4-parameter logistic model. While the validation did not specifically evaluate the linearity of the standard curves generated with the (b) (4) Reference Standard the method does require that all standard curves have a  $R^2$  value of greater than or equal to (b) (4).” Please refer to ICH Q2 (R1) to note that linearity does not necessarily mean that the standard and sample (b) (4) curves will have to be straight lines. Please submit data to show that they are parallel, as requested. [You may consult standard literature on the demonstration of parallelism of 4-parametric fit curves.]

Review of Response: The (b) (4) responses of the DP (b) (4) samples referenced in AMVR-20160616-01 (Validation of the (b) (4) Assay Test Method for 1 (b) (4) Drug Product (b) (4)) were compared to the responses of the Reference Standard (RS) and fitted to a 4-parameter logistic model. The p-value hypothesis ( $p > 0.05$ ) and equivalence testing were applied to assess parallelism. The results of this analysis show that the dose response curves for the RS and samples are not parallel. However, if the response ((b) (4)) of the assay (b) (4) is subtracted from the response at each level of the standard and the response ((b) (4)) of the (b) (4) sample is subtracted from the response of each level of the (b) (4) samples, the results are comparable. The results show lack of matrix interference, but not linearity. An addition IR was submitted to the sponsor on August 10<sup>th</sup> 2017.

IR dated August 10, 2017 (Question 2): In the IRs sent on April 6th, 2017 and June 29, 2017 we requested you to provide data on the evaluation of linearity of your standard and sample to demonstrate parallelism between the standard the sample (b) (4) curves. Please note that linearity does not necessarily mean that the standard and sample (b) (4) curves will have to be straight lines to demonstrate parallelism. Please plot response ((b) (4)) vs measured activity (mU/mL) for your standard and sample to show that they are parallel, as requested in our previous IR.

Review of Response: The sponsor provided results of the Reference Standard and a (b) (4) lot where the assay buffer and the (b) (4) sample responses are

subtracted from the measured response at each (b) (4) level. The sample response at each (b) (4) level within the range of the standard curve is comparable to the response of the reference standard.

- e. IR dated June 29, 2017 (Question 7): Please reevaluate the range of your assay based on the results of reevaluation of linearity, accuracy and precision and submit results for review.

Review of Response: As the (b) (4) test will only employ the (b) (4) samples the range of the method was inferred from the linearity, accuracy and precision results of the (b) (4) lots presented in the method validation report (AMVR-20160616-01). In AMVR-20160616-01, the sponsor demonstrated that the method can adequately measure (b) (4) between (b) (4) mU/mL.

- f. IR dated August 10, 2017 (Question 3): Please reevaluate the range of your assay based on the results of reevaluation of linearity, accuracy and precision and submit results for review.

Review of Response: The sponsor responded “(b) (4) laboratory uses the (b) (4) method and therefore it is not possible to assess linearity, accuracy and precision by plotting response ((b) (4) ) vs. measured activity (mU/mL)”. As the (b) (4) test will only employ the (b) (4) samples the range of the method was inferred from the results of the (b) (4) lots presented in the method validation report (AMVR-20160616-01). In AMVR-20160616-01, the sponsor demonstrated that the method can adequately measure (b) (4) between (b) (4) mU/mL.

- g. IR dated April 6, 2017 (Question 1f): You reported LOQ value is well above the lowest point of your standard curve. LOQ is the lowest concentration/potency at which measurements can be made with adequate accuracy and precision. Therefore, LOQ cannot be above the lowest point of the standard curve. Please reevaluate LOQ of your assay based on the results of evaluation of linearity, accuracy and precision and provide the results for review. Your results should demonstrate that LOQ is the lowest point of the assay range and the criteria for accuracy and precision are met at the LOQ.

Review of Response: Kamada responded that the response function of the standard curve generated with the (b) (4) reference standard is nonlinear and as such feels that it is appropriate to have anchor points below the LOQ and outside the range of quantification to facilitate the fitting of the curve. This is not acceptable. Another IR was submitted.

IR dated June 29, 2017 (Question 8): Please reevaluate LOQ of your assay based on the results of evaluation of linearity, accuracy and precision and provide the results for review. Your results should demonstrate that LOQ is the lowest point of the assay range and the criteria for linearity, accuracy and precision are met at the LOQ.

Review of Response: The sponsor reaffirms that LOQ of the method, inferred from the linearity, accuracy and repeatability data of (b) (4) lots of (b) (4) submitted in AMVR-20160616-01, is (b) (4) mU/mL. As linearity was not adequately addressed in the response, an IR submitted on August 10, 2017 to the sponsor requesting they reevaluate the LOQ of the method.

IR dated August 10, 2017 (Question 4): In response to our IR dated April 6, 2017 (Question 1f), you have reported that the LOQ is well above the lowest point of your standard curve. LOQ is the lowest concentration/potency at which measurements can be made with acceptable accuracy and precision. Therefore, measurements made below LOQ cannot be reliable and the lowest point of the standard curve cannot be lower than the LOQ. Please revise your assay procedure in TM-10054: (b) (4) Test Method for IgG assay such that LOQ is the lowest point of the standard curve. Also, revise your assay range accordingly in your method validation report AMVR-20160616-01.

Review of Response: Kamada restated that the results of (b) (4) lots of (b) (4) presented in AMVR-20160616-01 demonstrate that the LOQ is (b) (4) mU/mL. The LOQ determination specifically applies to the KamRAB, Human Rabies Globulin (HRIG), Solution for Injection (b) (4) and not the method.

- h. IR dated April 6, 2017 (Question 1g): You have presented the results of the accuracy study as evidence of robustness of your assay method. However, accuracy of a method does not demonstrate its robustness. Please provide data to demonstrate effect of small deliberate changes of critical method parameters, such as (b) (4), as appropriate, to show assessment of robustness of your method.

Review of Response: The sponsor presented results obtained during the development of the method to demonstrate robustness. Robustness was evaluated by varying (i) sample (calibration curves and QC samples) (b) (4); and (ii) elapsed time after addition of (b) (4) and prior to dispensing the substrate reagent. Varying sample (b) (4) or elapsed time after (b) (4) did not significantly affect the results of the (b) (4) activity. All results presented were within the acceptance criteria;  $R^2$  (b) (4), HQC – (b) (4) mU/mL and LQC – (b) (4) mU/mL.

- i. IR dated June 29, 2017 (Question 2): Validation report AMVR-20160616-01 indicates that the validation studies were performed by (b) (4). Will the lot release testing be performed routinely at this facility only? If this test may be performed at any other facility (other than (b) (4)), please provide data from reproducibility and comparability studies to demonstrate that the (b) (4) Assay is transferred/transferrable to the other facility where this assay may be performed.

Review of Response (Amendment 125613/0.29): Kamada intends to use the same laboratory, (b) (4), which preformed the development and validation of the assay for routine testing. Therefore, no tech transfer is required. The sponsor's response is acceptable.

**Recommendation**: Based on the review of documents submitted and the responses to the information requests it is concluded that the (b) (4) Method for IgG is adequately validated and is suitable for testing of Kamada Ltd.'s Human Rabies Immune Globulin drug substance.