



MEMORANDUM

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Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To: Biologics License Application Submission Tracking Number 125613/0

Subject: (b) (4) for Kamada-HRIG (Human Rabies Immune Globulin)

Through: Lokesh Bhattacharyya, Ph.D., Acting Director, CBER/OCBQ

Applicant: Kamada Ltd.

Submission Received by CBER: August 29, 2016

Summary:

A new BLA was submitted by Kamada for Human Rabies Immune Globulin (HRIG). This document includes the Primary Review Memo from DBSQC for the analytical method of (b) (4) in Kamada-HRIG and its validation, which is proposed to be used for quality control of (b) (4) drug product (DP).

This reviewer found the analytical procedure is currently evaluated for the determination of (b) (4). (b) (4) percent is combined as part of (b) (4), which is not acceptable because (b) (4) are well-established as IgG stability indicator and (b) (4) percent should be determined separately with a specification. A Post Market Commitment (PMC) is proposed by the sponsor to submit an improved (b) (4) method for the determination of

(b) (4) with full validation by
October 31, 2017.

Background

Kamada-HAIG product is for the use of passive, transient post-exposure prophylaxis of rabies infection. Kamada-HRIG DP is a sterile, nonpyrogenic liquid preparation enriched with antirabies immunoglobulins. It is supplied in 2 mL and 10 mL (b) (4) glass vials as a ready-to-use solution for intramuscular administration.

Documents Reviewed

Original submission STN 125613/0 dated August 29, 2016

- Cover letter
- 2.2 Introduction
- 3.2.S.4.1 Specifications
- 3.2.S.4.2 Analytical procedures
- 3.2.S.4.4 Batch analyses
- 3.2.S.5 Reference Standard or Materials
- 3.2.P.1 Description and composition of the drug product
- 3.2.P.5.1 Specifications
- 3.2.P.5.2 Analytical procedures
- 3.2.P.5.3 Validation of analytical procedures
- 3.2.P.5.4 Batch analyses
- SOP (N-1P-5344-02): Determination of (b) (4) of Immunoglobulins by (b) (4)
- Validation report (Rep-VL-100887-AM, version2): Validation Report of (b) (4) Test by (b) (4) Analysis for IgG

Amendment 11, dated February 7, 2017

- Responses to FDA Questions Received on Jan. 26, 2017
- Updated SOP (N-1P-5344-02): Determination of (b) (4) of Immunoglobulins by (b) (4)
- Validation Protocol (TR-VL-100887-AM): Validation of (b) (4) Analysis in Anti R Samples

Amendment 17, dated April 4, 2017

- Completion of Responses to FDA Questions Received on Jan. 26, 2017
- Validation report (Rep-VL-103050-AM, version 1): Validation Report of (b) (4) Test for IgG Samples by (b) (4)

Amendment 21, dated May 5, 2017

- Response to FDA Questions Received on April 4, 2017 and Question 5 Received on March 6, 2017
- Updated SOP (N-1P-5344-02): Determination of (b) (4) of

Immunoglobulins by (b) (4)

Amendment 28, dated July 13, 2017

- Response to FDA Questions Received on May 26, 2017

Amendment 30, dated July 31, 2017

- Post-Marketing Commitments

Amendment 31, dated August 03, 2017

- Response to FDA Questions Received on August 1 and August 2, 2017

Amendment 31, dated August 15, 2017

- Response to CMC comments received on August 9, 2017

Review Narrative

Method and Validation

Method

(b) (4)



The proposed specifications for (b) (4) DP are (b) (4)



Validation

The method is validated by evaluating specificity, accuracy, precision, linearity, range and robustness for the (b) (4) and by evaluating specificity, accuracy, precision, linearity, range and limit of quantitation (LOQ) for (b) (4). (b) (4) is not evaluated because they are considered as part of (b) (4) and no specification for (b) (4) was proposed.

The specificity was assessed by (b) (4)

Accuracy for (b) (4) is evaluated by (b) (4)

The repeatability was evaluated by performing (b) (4) independent measurements of (b) (4) and (b) (4) lots of DP samples. (b) (4)

The linearity was demonstrated by analyzing (b) (4) of a (b) (4) DP sample. Plot of (b) (4) versus protein concentration shows a correlation coefficient (b) (4) and (b) (4) for (b) (4) and (b) (4) (b) (4), respectively, which meet the acceptance criterion of (b) (4). The range is determined to be protein concentration of (b) (4) mg/mL based on the outcome of accuracy, precision and linearity studies.

The LOQ of (b) (4) is determined to be (b) (4) in the (b) (4) of (b) (4) samples containing (b) (4) with (b) (4) independent measurements. (b) (4) of the

sample with (b) (4) is between (b) (4) and (b) (4), which meet the acceptance criterion of (b) (4).

Robustness of the assay was evaluated by (b) (4). Results show no effect on (b) (4) (b) (4) results. (b) (4) DP samples are stable for up to (b) (4) hours at (b) (4) temperature.

First Information Request (IR) and Response Review

A DBSQC IR was sent to the sponsor on Jan. 26, 2017 after initial review. The responses were received on Feb. 7 and Apr. 4, 2017 in amendments 11 and 17, respectively.

1. Please make following change to your SOP N-1P-5433-02 and submit for review:
 - a. Please setup an acceptance criterion for resolution between IgG monomer and (b) (4) in section 6.
 - b. Add a typical sample (b) (4) in the SOP.
 - c. Define the (b) (4) dimension in section 4.
 - d. What type of (b) (4) did you use, (b) (4)? If (b) (4) is used, please describe the details to show each (b) (4) with necessary zoomed-in figure.

Review of the response

- a. In the response, the sponsor stated that they set acceptance criterion for the (b) (4) between the IgG monomer and (b) (4) in section 6.1.2.1. A further IR was sent to the sponsor to ask a resolution criterion as system suitability check because (b) (4) alone cannot ensure adequate (b) (4) resolution because of the potential of (b) (4).
 - b. A representative (b) (4) of Kamada-HRIG sample is added to the updated SOP as an appendix. The response is satisfactory.
 - c. Though the sponsor included a (b) (4) data sheet from (b) (4) manufacturer as one of the appendixes, it is still not clear the specific (b) (4) of the (b) (4) used for this assay. A follow-up IR was sent to the sponsor in the second IR.
 - d. The sponsor provided a new SOP (TR-N-1G-042) "Policy for (b) (4) Use". In the section 7.22, (b) (4) of a (b) (4) is described, which states that (b) (4) is not allowed. However, (b) (4) parameters may be changed by authorized employees. The response is acceptable.
2. Please provide appropriate data to show that the molecular forms larger than the (b) (4) of your proteins in (b) (4) DP are not (b) (4) or (b) (4) by the (b) (4) under the proposed (b) (4) condition.

Review of the response

The request data was not provided in the response. A follow-up IR emphasizing our concern was sent to the sponsor in the second IR.

3. Regarding the validation report of (b) (4) Test by (b) (4) Analysis for IgG (Rep-VL-100887-AM, Version2):
 - a. Please provide the validation protocol (PR-8567) cited in page 8 of the validation report in order to check the deviations.
 - b. We do not agree with your experimental design for the determination of the limit of quantitation (LOQ) of the aggregates in section 5.3, in which you (b) (4) the (b) (4) DP samples to create (b) (4) equivalency for (b) (4) at (b) (4). Such estimation doesn't reflect the real LOQ situation during the sample analysis because the reportable result for aggregate is in (b) (4) rather than (b) (4). Please use a few (b) (4) DP samples with aggregates (b) (4) close to the LOQ for (b) (4) determination if you choose to use (b) (4) as LOQ acceptance criterion. Also, provide the accuracy and precision data at the LOQ. Alternatively you may plot (b) (4) of (b) (4) against their respective (b) (4) at levels close to anticipated LOQ by using the equation (b) (4), where (b) (4).
 - c. Please provide your results to demonstrate the linearity of (b) (4) components by plotting their respective (b) (4) against protein concentration with the linear regression analyses.
 - d. You provide the accuracy evaluation for the combined (b) (4) for (b) (4) DP samples in section 5.5. Please provide accuracy data for the (b) (4) components.
 - e. Please express the assay ranges for the individual components in protein concentrations based on the outcome of linearity, accuracy and precision.

Review of the response

- a. The requested protocol was provided. The response is satisfactory.
 - b. The LOQ was recalculated based on the suggested (b) (4) approach and summarized in the method validation, which is discussed above. The response is satisfactory.
 - c. The requested plots were provided in the response and summarized in the method validation above. The response is satisfactory.
 - d. The accuracy data for (b) (4) were provided in the response and discussed above. The response is satisfactory.
 - e. The assay range was provided in the response and discussed above. The response is satisfactory.
4. It is well known that IgG products contain small amount of fragments as product-related impurity. However, the fragments were not evaluated in your SOP and in the validation report. Please provide experimental data for the assessment of fragments in your (b) (4) DP.

Review of the response

The sponsor explained that the proposed (b) (4) procedure is not able to detect any fragment (b) (4) from (b) (4) DP samples or in the in-house Kamada-HRIG reference standard, (b) (4). A (b) (4) Kamada-HRIG sample shows a fragment (b) (4) at the (b) (4). However, the results from (b) (4) clearly show at least (b) (4) fragment (b) (4) in original Kamada-HAIG samples and a few additional (b) (4) in the (b) (4) sample. (b) (4) analysis using a (b) (4) revealed the presence of IgG fragments from both (b) (4) in the in-house Kamada-HAIG reference standard. Thus, the proposed (b) (4) method is not sensitive enough to detect fragment (b) (4).

This reviewer performed the analyses of (b) (4) lots of the DP samples using a DBSQC developed (b) (4) method as part of testing in-support of this BLA. Our results showed higher (b) (4) compared to those from the sponsor (CBER's (b) (4) versus sponsor's (b) (4)) and (b) (4) of fragments in these samples (details in DBSQC test memo from Hsiaoling Wang, dated Mar. 29, 2017).

Second IR and response review

The 2nd IR was sent to the sponsor on April 4, 2017 and the responses were received on May 5, 2017 in the amendment 21.

1. In response to question 1a of our IR dated Jan. 26, 2017 you indicated that (b) (4) is considered as indication of (b) (4) between IgG monomer and the (b) (4). We do not agree that (b) (4) alone can ensure adequate (b) (4) because of the potential of (b) (4). Please revise your SOP and establish acceptance criterion for the resolution based on your historical data, as requested in our previous IR.

Review of the response

An acceptance criterion of (b) (4) between the (b) (4) and the (b) (4) no less than (b) (4) has been added to the system suitability check in updated SOP (N-1P-5344-02, version 7) based on (b) (4) historical data. The response is satisfactory.

2. In response to question 1c, you have not provided the (b) (4) in the section 4 of SOP N-1P-5344-02. The appendix N-1P-5344-02/2 is a data sheet from (b) (4) manufacturer, which has (b) (4) different (b) (4) for (b) (4). Please update your SOP to specify the (b) (4) that you use for this test, as requested in our previous IR.

Review of the response

The (b) (4) is specified in the section 4 of the updated SOP (N-1P-5344-02, version 7). The response is satisfactory.

3. In response to question 2, you did not provide experimental data to demonstrate that (b) (4) in your (b) (4) DP samples are not (b) (4) under the proposed (b) (4) conditions. For this IR, our concern is whether the result of (b) (4) reflected the percent of (b) (4) actually present in samples ((b) (4) DP). It has been widely reported in the literature that the (b) (4) of (b) (4) interacts with the sample leading to, in many instances, (b) (4) resulting in underestimation of (b) (4) because (b) (4) conditions is not adequate to overcome the (b) (4). Please provide experimental data to demonstrate that the (b) (4) percent in your product is not underestimated under your proposed (b) (4) conditions.

Review of the response

The sponsor provided data from (b) (4) experiments to evaluate the potential loss of (b) (4) under the proposed (b) (4) condition.

- a) Measurements from (b) (4) of the same sample:
(b) (4). The sponsor reasoned that, if the (b) (4) would (b) (4) loss should be more significant at (b) (4), which would result in a lower (b) (4) content for the more (b) (4) samples. The results show that (b) (4) remained essentially unchanged over the range (b) (4) mg/mL protein for (b) (4) samples, which indicate there is no (b) (4) of the (b) (4) by the (b) (4).
- b) Accuracy evaluation from sample containing different (b) (4):
(b) (4) samples were prepared by (b) (4). The sponsor reasoned that, if the (b) (4) would (b) (4) loss should be more significant for the sample containing lower (b) (4) level, which would reflect in (b) (4) values. The measured (b) (4) levels for samples with different (b) (4) showed recovery of (b) (4), respectively, which indicated no (b) (4) of (b) (4).
The data demonstrate that the (b) (4) from the Kamada-HAIG samples are not (b) (4) under proposed separation condition. The response is satisfactory.

Third IR and response review

The 3rd IR was sent to the sponsor on May 26, 2017 after internal meeting among the CMC reviewers from OBRR/OTAT and DBSQC/OCBQ and the responses were received on July 13, 2017 in the amendment 28. Discussion about the (b) (4) method and (b) (4) (b) (4) was part of a conference call with the sponsor held on June 8, 2017 to clarify FDA standing on the method choice, corresponding validation requirements and (b) (4) integration principles.

1. For your (b) (4) testing method:

- a. A confirmatory test conducted in FDA laboratory on Feb. 2, 2017 using the FDA developed method showed that the results of six lots (Table 1) are different from the data submitted in your COA or IR response to Q5 in Amendment 21. The (b) (4) obtained by FDA laboratory show (b) (4) of (b) (4) (b) (4) of a representative sample shown in Appendix A).

Table 1. (b) (4) results of CBER and the Kamada's

Samples	(b) (4)							
	Kamada CoA	Kamada response to Q5 (Amendment 21)	CBER	Kamada CoA	Kamada response to Q5 (Amendment 21)	CBER	Kamada response to Q5 (Amendment 21)	CBER
Reference	1.6		3.6	98.4		95.6		0.7
RA5131115	0.2	0.5 (12 months)	0.8	99.8	96.7 (12 months)	98.5	2.8 (12 months)	0.7
RA5141115	0.1	0.6 (12 months)	0.8	99.9	96.5 (12 months)	98.4	2.9 (12 months)	0.8
RA3151115	0.3	0.4 (10 months)	0.6	99.7	96.6 (10 months)	98.6	3 (10 months)	0.8
RA3161215	0.2	0.3 (23 months)	0.5	99.8	96.8 (23 months)	98.7	2.9 (23 months)	0.7
RA3020216	0.0	0.5 (?* months)	0.5	100.0	96.2 (?* months)	98.7	3.1 (?* months)	0.8
RA3050513	0.2	0 (36 months)	0.6	99.8	100 (36 months)	98.6	0 (36 months)	0.8

*?: The storage period is not specified

Appendix A: Extended (b) (4) of a typical drug product (Lot: RA3020216)



Please test the same six lots using the referenced FDA method and evaluate whether the FDA method provides better (b) (4) of (b) (4) in these lots.

- b. Your current (b) (4) specifications include quantification of (b) (4). Please explain how the (b) (4) of (b) (4) is performed.
- c. After a discussion with FDA on the (b) (4) method of (b) (4) is finalized, please revalidate your (b) (4) method and provide a final method

validation report including method analysis of accuracy, precision, linearity, range and LOQ for (b) (4). It is acceptable to re-analyze the raw data used in the validation report Rep-VL-100887-AM.

- d. In Report RD-4270 “Investigation of uncharacteristic (b) (4) of KamRAB and KamRho-D reported in deviation (b) (4)” you concluded that (b) (4) was better to achieve better resolution; however, it appears that the concentration that you are using is (b) (4) (SOP N-1P-5344-02; effective date February 12, 2017). Please comment.
- e. In the SOP (N-1P-5543-02), you included (b) (4) of an immunoglobulin reference sample, a heat treated drug product lot. However, you did not establish acceptance limits of (b) (4). Please provide the limits for this sample based on your historical data.

Review of the response

- a. The sponsor tested the (b) (4) method with (b) (4) different (b) (4) using (b) (4) different (b) (4) for the six lots samples mentioned in the IR. The results confirmed that FDA method provides better (b) (4) and resulted in higher (b) (4) percentages than the proposed method. The results of the ((b) (4)) and (b) (4) percentages were affected by the (b) (4) method employed. At the moment, the sponsor has not decided what will be the final (b) (4) of the methods. But they committed that a fully validated improved method would be submitted by the end of October, 2017 as a PMC.
 - b. The (b) (4) are defined as all (b) (4) after (b) (4) until the end of (b) (4), which include (b) (4).
 - c. As indicated in the response 1a, it will be included in the full validation report by the end of October, 2017.
 - d. The sponsor considered that the improvement in (b) (4) by increasing the (b) (4) concentration was not significant enough to trigger a change in the method. The (b) (4) condition will be finalized in the PMC that the sponsor has committed.
 - e. (b) (4) is used for (b) (4) check in the SOP. The limits for the reference control were not established for the current method. The sponsor committed to establish the limits for the improved method in the response dated Aug. 03, 2017.
2. In response to setting a specification for (b) (4) in your response to Q5 in Amendment 21, you amended the specifications to be (b) (4) and the (b) (4) summed up to 100%. No specification for (b) (4) in numerical limit was set. Please set the specification in numerical limit for (b) (4) based on your historical stability data. Please note that the results for the (b) (4) should be obtained by calculating the (b) (4), not by subtracting the content of the (b) (4) from 100%.

Review of the response

In response, the sponsor stated that a specification for (b) (4) will be set at (b) (4). However, this change is outside the scope of the current method and validation, because (b) (4) are part of (b) (4). A new specification of (b) (4) will be re-established using an improved test method with sufficient data in the PMC.

Fourth IR and response review

The 4th IR was sent to the sponsor on Aug. 2, 2017 and the response was received on Aug. 4, 2017.

Please establish acceptance criteria for the limits of (b) (4) percentages for (b) (4), for your in-house immunoglobulin reference sample based on your historical data and submit for review.

Review of the response

The sponsor is committed to have established limits for (b) (4) for the in-house immunoglobulin reference as part of the method validation for an improved (b) (4) method. The response is satisfactory.

Post Marketing Commitment

Kamada commits to perform validation of an improved (b) (4) method and determine the (b) (4) specifications accordingly.

A final validation report as well as the method SOP and specifications will be submitted to FDA by October 31, 2017, as a CBE-30 Supplement. In case a method different from that provided by CBER is chosen for the validation, a full characterization of the (b) (4) will be performed.

The final method specification will include (b) (4).

The submission will include the acceptance criteria for (b) (4).

Conclusion

The analytical procedure of (b) (4) in HRIG by (b) (4) is evaluated for the determination of (b) (4). An improved method is still under evaluation and a PMC has been committed to complete the full validation by the end of October, 2017.