



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

To: File BLA STN 125613/0

From: Olga Simakova, Ph.D., OTAT/DPPT/PDB

Through: Michael Kennedy, Ph.D. (Team Lead), OTAT/DPPT/PDB

CC: Jiahua Qian, Ph.D., RPM, OBRR/RPMS

Applicant: Kamada Ltd.

Product: Human Rabies Immune Globulin [HRIG] Injection
KEDRAB

Subject: Final CMC Review: Original Biological License Application – Analytical Methods,
Reference Standards and Reference Materials

Recommendation

Approval recommended with the following PMC related to the analytical methods:

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 different (b) (4) than the (b) (4) will be 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)

Study Completion Date: September 29, 2017

Final Report Submission: October 31, 2017

Executive Summary

This Discipline Review memorandum covers assigned CMC sections of the Original Biologics License Application (BLA) submission from Kamada Ltd. for Rabies Immune Globulin (Human), which was received by FDA CBER on August 29, 2016. I reviewed the following (b) (4)

Drug Product analytical procedures and their validation studies: Clarity and Degree of Opalescence; Degree of Coloration; Visible Particles; Subvisible Particles; Identification by (b) (4); Protein Identity; Anti-Rabies Potency; Protein Concentration; Protein Composition; (b) (4) Concentration; (b) (4) Concentration; Triton X-100 (Octoxynol 9) Concentration; Tri-n-Butyl Phosphate

Concentration; IgG subclasses; (b) (4)

(b) (4) reviewed by DBSQ (with other lot release tests) are shortly covered in this memorandum. In general, the information provided by Kamada for these methods and reference standards in this BLA submission and in their responses to our Information Requests was sufficient and acceptable to support the licensure of KEDRAB.

Background Summary

On August 29, 2016, Kamada Ltd submitted a BLA STN 125613 for a Drug Product Kamada-HRIG (Human Rabies Immune Globulin), KEDRAB. KEDRAB is used for post-exposure prophylaxis of rabies infection in combination with a rabies vaccine. KEDRAB is manufactured from hyperimmune human plasma of healthy adult donors with high titers of rabies-specific antibodies collected in US plasma centers. KEDRAB is a sterile, non-pyrogenic aqueous solution of anti-rabies immunoglobulins ($\geq 95\%$ protein as IgG) provided at a potency of 150 IU/ ml in 2 ml and 10 ml glass vials; stabilized with 0.3 M glycine and has pH of 5.0 – 6.0. DP is manufacture (b) (4) with 0.3M glycine from a Total Protein Concentration of (b) (4) mg/ml to (b) (4), followed by (b) (4) and filling into final containers.

DBSQC reviewed following lot release tests and method validations: Clarity and Degree of Opalescence, Degree of Coloration, Visible Particles, pH, Identification by (b) (4), Anti-Rabies Potency, Protein Concentration (b) (4), (b) (4), Residual TnBP, Residual Triton X-100, Bacterial Endotoxin, Microbial Limit Test, Extractable volume, Protein Identity, Glycine Concentration, Protein Composition, Sterility, and Pyrogenicity.

(b) (4) was reviewed by DBSQC and Mikhail Ovanesov, Ph.D. of OTAT/DPPT/HB provided consult (see below).

The above listed analytical procedures and their validation studies were reviewed by several assigned reviewers of DBSQC/OCBQ (see their Discipline Review memos).

Serological and nucleic acid tests of viral markers in plasma pool were reviewed by Lilin Zhong of OTAT/DPPT/PDB.

My CMC review focuses on the product perspective of the Analytical Procedures and their Validation Studies (except for pH, Glycine Concentration, Residual Triton X-100, Residual TnBP, Extractable volume, Sterility, Microbial Limit Test, Pyrogenicity, and Bacterial Endotoxins, which were solely reviewed by DBSQC reviewers). (b) (4) is shortly covered in this review mostly regarding to other reviewed methods ((b) (4)) and specifications.

Review Summary

1) Analytical Methods

The summary of analytical methods used in analysis of Kamada-HRIG (b) (4) is in Appendix 1 and methods used in analysis and release of Kamada-HRIG Drug Product are listed in Appendix 2 (resubmitted in Amendment 31, received August 4, 2017).

a) Release testing

i) Summary of Release Tests and Acceptance Criteria for (b) (4) DP

The updated test parameters, analytical procedures and acceptance criteria for Kamada-HRIG (b) (4) testing are provided in Appendix 3 (resubmitted in Amendment 32, received August 15, 2017).

The majority of the analytical methods used (b) (4) for the Drug Product (DP), and are listed in Appendix 4 (resubmitted in Amendment 31, received August 4, 2017). Most of the analytical tests require (b) (4) sample prior to testing (the same (b) (4) to prepare DP is used).

During the review cycle of this original BLA, the following tests/ specifications were added or significantly modified by Kamada: Clarity and Degree of Opalescence, Degree of Coloration, Visible Particles, Subvisible Particles, and (b) (4) Concentration.

ii) General Characteristics Tests

- **Appearance; Clarity and Degree of Opalescence; Degree of Coloration; Visible Particles for (b) (4) DP**

At the time of this BLA submission, only a general appearance test performed during visual inspection was used as (b) (4) DP release test; the provided SOP for appearance testing of solutions was not detailed enough without any information regarding color and opalescence standards, the specification for the number of observed particles, the degree of coloration and opalescence. The (b) (4) DP were originally assessed, prior to other tests, in terms of clarity and color by only a subjective visual evaluation performed without using any standards. Individual tests for different aspects of Appearance were added (Clarity and Degree of Opalescence; Degree of Coloration; Visible Particles). Specifications for Clarity and Degree of Opalescence (the solution is clear to slightly opalescent), Degree of Coloration (the solution is colorless to pale yellow) and Visible Particles (may contain some protein particles) were added to (b) (4) DP release specifications (see IRs below).

The Degree of Coloration of KEDRAB is evaluated according to (b) (4) . (b) (4) DP samples are visually inspected by comparison to (b) (4) and Color reference reagent (b) (4) from (b) (4) .

The test to determine the Degree of Opalescence and Clarity in liquids is based on (b) (4) . (b) (4) DP samples are visually inspected by comparison to (b) (4) and reference opalescence standards prepared from (b) (4) solution and (b) (4) solution (the instructions how to prepare (b) (4) standards of opalescence are included in SOP TR-N-IP-0001-27). Tested sample is evaluated as slightly opalescent if its opalescence is (b) (4) .

The presence of Visible Particles is tested by visual inspection of (b) (4) DP samples to detect visible granulates or fibers that originate from the product itself or visible filament shaped particles not originating from the product itself.

Information on qualification of these procedures was not provided.

IR sent February 21, 2017; responded in Amendment 14, received March 16, 2017

Question 3: We recommend the use of a quantitative assay to determine the degree of opalescence as a part of the Appearance Test. Please consider adding the degree of opalescence to the Appearance Test for (b) (4) DP. Please clarify if any reference opalescent suspensions are used in the Appearance Test. If no reference standard is used, please include it into the method for (b) (4) DP Appearance test. Also, clarify the following:

- (a) Number of tested vials per batch for (b) (4) DP
- (d) Since the nature of the Appearance test is subjective, explain how are the training, supervision and confirmation of observation provided.
- (e) Please provide a copy of form N-1P-0001-01/1 and SOP N-1P-0001-54.

Reviewer's comment to Kamada's response: Kamada added reference standards to the updated Degree of Opalescence and Degree of Coloration tests; however the SOP was not sufficiently detailed. For the Degree of Coloration test, (b) (4) samples of (b) (4) DP are tested. For the degree of opalescence test, (b) (4) sample of (b) (4) DP is tested. Kamada sufficiently described qualification and re-qualification of their analysts performing the Appearance tests. Also, percentage of colorless and opalescent samples and solution with particles were provided as requested. For further modifications of SOP, Appearance tests specifications and requested improved control strategy, see IRs below.

IR sent May 5, 2017; responded in Amendment 23, received May 11, 2017

Question c: The statement “May contain some particles” is unacceptable as part of acceptance criterion for “Appearance”. More detailed comments are being prepared.

Reviewer’s comment to Kamada’s response: Kamada refers to results of their investigation of the nature of the visible particles concluding that the particles are composed of proteinaceous particles. Kamada proposes to monitor the proteinaceous particles as a process trend parameter rather than a release parameter. Kamada clarified the numerical control strategy which was further reconsidered as well as the proposed visible particle limits and other issues related to Appearance testing. More details are provided in reviewer’s comment under Amendment 27.

IR sent May 31, 2017; responded in Amendment 27, received July 12, 2017

Question 15: The Degree of Coloration Test with the Acceptance Criteria “The solution is colorless to yellow (b) (4)” was added during the review cycle of this BLA. The Acceptance Criteria for Appearance Test are “The liquid preparation is clear to opalescent, and colorless to pale yellow solution. May contain some particles”.

- a. Please justify the addition of (b) (4) color specification for the solution for (b) (4) DP (b) (4).
- b. What is the percentage of drug product vials with (b) (4) color?

Reviewer’s comment to Kamada’s response: Kamada clarified that the Kamada-HRIG product is colorless to pale yellow ((b) (4)). Wording was changed accordingly in the newly provided SOP N-1P-5344-21: Evaluation of degree of Coloration of IgG Samples (for details see below).

Question 16: Please make SOPs for the Evaluation of Degree of Coloration, Appearance test and Clarity and Degree of Opalescence more detailed e.g. include specification regarding (b) (4) and instructions about (b) (4) the sample especially for particle and clarity evaluation.

- a. Please justify why the acceptance criteria in the Evaluation of degree of Coloration in IgG Drug Product SOPs is listed as none.
- b. What is the procedure in the case the product color is other than colorless (only “colorless” or “other option” is listed under product color section of Appearance of Solution Test TR-N-1P-0001-01/1)?
- c. You provided a manufacturer and catalog number of reference color solutions (SOP N-1P-5344-21) or that similar reference can be used. Please either list all color reference reagents to be used or remove the expression “or similar”.

Reviewer’s comment to Kamada’s response: Kamada updated the SOPs as requested. The appearance evaluation of KEDRAB involves the following updated or new SOPs; the specific tests replaced the general Appearance method (TR-N-1P-0001-01) which included the color, clarity and particles count:

*TR-N-1P-0001-05 – Testing of Visible Particles in Solutions (a specific SOP for particles count). This SOP was updated by adding the word “protein” in front of the word “particles” as requested (resubmitted in Amendment 31 on August 4, 2017).

*N-1P-5344-21 – Evaluation of degree of Coloration of IgG Samples (a specific SOP for color identification using the specific color standard). This SOP still refers to the general Appearance method (SOP TR-N-1P-0001-01) which was replaced (Kamada was notified about it).

*TR-N-1P-0001-27 – Clarity and Degree of Opalescence (a specific SOP for determining the clarity of the solution)

Due to the changes in the appearance evaluation SOPs, the Question 16b is not relevant anymore.

Question 18: In Amendment 23 (May 11, 2017), in response to question c, you proposed to control and monitor the proteinaceous particles as a process trend parameter rather than a release parameter. Regarding your proposal, please clarify the following:

- a. It is not clear whether you proposed to analyze (b) (4) vials and (b) (4) vials from the 2 mL and the 10 mL presentations, respectively or adjust the number based on the lot size. Please clarify.

- b. You proposed to report the results for each lot in the following manner:

(b) (4) visible proteinaceous particles / vial – percent of vials

(b) (4) visible proteinaceous particles / vial – percent of vials

(b) (4) visible proteinaceous particles / vial – percent of vials

Above (b) (4) proteinaceous particles / vial – with a limit of (b) (4) of the tested vials. Exceeding the limit would result in testing a larger number of vials ((b) (4) vials for 10 ml and (b) (4) vials for 2 ml) and if the result again exceeds the limit an investigation would be open.

At the same time you presented data for (b) (4) product lots in which case no vials with the presence of more than (b) (4) particles were observed. Please reconsider the proposed numerical control strategy and justify the proposed limits.

Reviewer's comment to Kamada's response: Kamada clarified that the proteinaceous particles would be analyzed on a fixed number of vials from each volume presentation; (b) (4) vials and (b) (4) vials from the 2 ml and the 10 ml presentations, respectively. Kamada proposed the following tightened limit: Above (b) (4) proteinaceous particles / vial – with a limit of (b) (4) vial of the tested vials, ((b) (4) of the inspected vials). In the case that the obtained number of vials containing above (b) (4) visible proteinaceous particles per vial exceeds the process limit, the test will be repeated on a larger sample size with the limit being also (b) (4) of the inspected vials.

IR sent August 9, 2017; responded in Amendment 32, received August 15, 2017

- Please provide a current SOP for visible particle testing for KedRAB, i.e., the method described in Amendments 23 and 27 (dated 5/11/17, 7/10/17), in response to comments “c” and 18, respectively. Please clarify how samples are selected for testing.
- Method description (3.2.S.4.2.1.3.3) says that (b) (4) vials are analyzed together and the time for evaluation is at least (b) (4) against each background; is this sufficient for particulates counting; how was this validated? How/when this method is used for KedRAB?
- The SOP in 3.2.S.4.2 is not clear.
It says for DPs: “(b) (4) vials shall be tested, unless otherwise specified in the applicable protocol”, for (b) (4) samples unless otherwise specified – again, is this method used for KedRAB?
- When more data are available, a numerical final container specification should be developed.

Reviewer's comment: SOP TR-N-3A-034 describing the visible particles testing performed at the (b) (4) stage is provided. Kamada confirmed that the current visible particles limit will be re-evaluated after examining (b) (4) additional Kamada-HRIG lots (the limit is currently NMT (b) (4) vial containing (b) (4) proteinaceous particles). SOP N-1P-0001-05: Testing of visible particles in solutions was updated and includes more details regarding number of tested samples and information that just (b) (4) vial at a time will be evaluated. Kamada commits to perform a qualification study for the revised procedure which will be performed prior to executing the revised SOP. Kamada confirms that (b) (4) vials shall be tested for DP (b) (4), for release test unless otherwise stated; (b) (4) samples shall be tested for (b) (4) 10 ml and 2 ml respectively. At this point, this control strategy is sufficient.

IR sent August 1, 2017; responded in Amendment 31, received August 4, 2017

Reviewer's comment to sponsor's response: Kamada changed the specification of “Visible Particles” for (b) (4) DP to “May contain some protein particles” and also corrected the error in “Clarity and Degree of Opalescence” specification for (b) (4) DP as requested.

Reviewer's comment: SOPs for Clarity and Degree of Opalescence; Degree of Coloration; and Visible Particles were modified and clarified; and standards for color and opalescence were added as requested. These methods for established Pharmacopeial tests are acceptable for (b) (4) DP Kamada-HRIG evaluation.

- **Subvisible Particles for DP**

Kamada included Subvisible Particulate Matter test in KEDRAB DP by (b) (4) into DP release and stability testing as requested in IR sent May 31, 2017. The method performed according to SOP TR-N-IP-5348-06 (updated SOP submitted in Amendment 32 on August 15, 2017) is based on (b) (4) and is currently used for monitoring of DP without formal limits. Kamada uses (b) (4) solution ((b) (4)). Particle count is conducted for (b) (4) and (b) (4) particles. Environmental testing should be performed prior to sample testing and acceptance criteria for the environment test are (b) (4) particles/^{(b) (4)} mL for particles (b) (4). Standard results should comply with the standard CoA. Requested information on subvisible particulate characterization and counts was provided in Amendment 14 (received March 16, 2017).

IR sent August 9, 2017; responded in Amendment 32, received August 15, 2017

- o Why is the product (b) (4) for the analysis (3.2.P.5.2 in the method description in the section and also in SOP N-IP-5348-06 in Section 3.2.P.5.2)? (b) (4) samples before analysis is not recommended for samples containing proteinaceous particles. How this was validated?

Reviewer's comment: Kamada modified the Subvisible Particles procedure and the (b) (4) of samples will not be performed (updated SOP was provided). Kamada committed to submit a qualification for a (b) (4) solution by September 30, 2017 as a Product Correspondence.

Overall, since Subvisible Particles test for DP was added at the end of the review cycle and it is currently used only for trending, the test is acceptable as described in the limited form provided and without validation.

- **Identification by Bio-**(b) (4)

(b) (4)

iii) Identity Tests

- **Protein Identity for DP**

Kamada determines KEDRAB DP identity by (b) (4) when DP lots are confirmed as human immunoglobulins. The test is based on (b) (4). Acceptance criteria for Protein Identity for DP are that the (b) (4). This identity test uses (b) (4). The SOP (submitted in Amendment 28, received July 13, 2017) includes information on the following reference standards: (b) (4). The test is considered valid and the DP sample is confirmed to be human IgG if (b) (4).

Validation (validation report Rep-VL-06520-AM Version 2: Qualification Report for Identification of Human IgG by (b) (4)) was performed according to (b) (4). The specificity of the method was proofed by (b) (4).

(b) (4)

. The method is robust for the IgG DP formulated in pH ranges from (b) (4). (b) (4) deviations were reported in the validation report: The qualification tests were performed before the qualification protocol was assigned; and the test forms on which the primary qualification tests were recorded were lost.

Reviewer's comment: Since the qualification assays were performed according to the test SOP, and all required samples were tested and the scanned pictures of (b) (4) were saved, the reported deviations are not considered to affect the method qualification. The robustness and specificity of the method for the identification of Kamada's Ig DP were found to be properly validated. The method can be used to test Protein Identity for Kamada-HRIG DP.

IR sent August 1, 2017; responded in Amendment 31, received August 4, 2017

Question 4: Regarding the Protein Identity test:

- a. Please confirm that the test is performed after (b) (4) and include this information into Section 2.2 under 3.2.P.5.2 Analytical Procedures section and the SOP N-IP-5344-17.
- b. Please clarify how your Protein Identity test distinguishes KEDRAB from all other products manufactured by Kamada. If the assay is not specific to KEDRAB, please implement a specific assay.

Sponsor's response: Kamada has revised the identity testing for release to include Protein Identity as well as Identification by (b) (4), both will be performed on filled vials of the drug product. Kamada's SOP for performing laboratory tests states that release test should be performed on filled vials of the tested product unless otherwise mentioned.

Reviewer's comment: I agree with the addition of (b) (4) test among the Identity Tests to distinguish KEDRAB from other Kamada's products. However, the identity tests should be performed after (b) (4) in compliance with the 21 CFR 610.14, not (b) (4) as performed by Kamada. In response to our IR sent August 9, 2017, received in Amendment 32 (August 15, 2017), Kamada confirmed to change the procedure and to perform the identity testing after (b) (4).

- **Identification by (b) (4) for DP – for detailed review see below**

Kamada determines KEDRAB DP Identity by (b) (4)

. Acceptance criteria for Identification by (b) (4) is for the DP lot to be active against Rabies virus.

iv) Content Tests

- **Anti – Rabies Potency for both DS and DP**

Kamada determines the potency of KEDRAB by (b) (4) method (which is also used as (b) (4) test for (b) (4) DP). The method quantitatively measures the (b) (4) of anti-rabies antibodies in (b) (4) DP samples. The specification for (b) (4) 150^{(b) (4)} IU/mL for DP. Multiple discrepancies were noticed regarding the Acceptance Criteria for Anti-Rabies Potency throughout the submission. The issue was properly addressed (the final clarification is in Amendment 16, received March 30, 2017).

Kamada's potency assay is based on the modified version of the method described in the (b) (4) to improve the precision of the measurement. Kamada uses (b) (4)-fold steps in the (b) (4) series modified by (b) (4) as described in SOP 1120.00: The (b) (4) Test to (b) (4) Rabies Virus Neutralizing Antibodies - Modified (b) (4)-fold (b) (4) method. The test measures the dose of immunoglobulin required to (b) (4)

(b) (4)

SOP 02-02.1.08, SOP 02-02.1.06, SOP 02-02.1.03 (replaced the last version of 02.81-02).

Validation reports with addendum monitored accuracy, precision, linearity, lower limit of quantitation, and robustness of the method (IS#2.3/v1: Partial Validation Report of the (b) (4) Test to (b) (4) Rabies Virus Neutralizing Antibodies – Modified (b) (4)-fold method 2014; IS#2.8/v1: Validation Report of the (b) (4) Test to (b) (4) Rabies Virus Neutralizing Antibodies-Modified (b) (4)-fold dilution method 2007; Rep-VL-100891-AM: Qualification Report of Kamada RIG Product Potency Testing in (b) (4)-Fold (b) (4) Assay by (b) (4), version 4). Accuracy was determined by analysis of different potencies of reference standard (b) (4). Also, potency values of the same DP (b) (4) samples measured in (b) (4) and in the (b) (4) were found comparable. LOQ of (b) (4) IU/ml was determined. Robustness testing included different technicians performing the assay, number of (b) (4), variation in virus neutralization time ((b) (4)) and the length of the (b) (4). Specificity and sensitivity of (b) (4) have been demonstrated by cited publications. Only minor deviations (data entry errors, one document used for presentation instead of two) were reported.

IR sent February 21, 2017; responded in Amendment 16, received March 30, 2017

Question 4: Please update the related BLA sections to list the DP potency in the same way. Potency in the range of “150 (b) (4) IU/ml, the confidence limits ($p=0.95$) of the estimated potency are not less than (b) (4) and not more than (b) (4)” is listed as proposed for marketing e.g. in Table 1 in “3.2.P.5.4 Batch Analysis”. However, potency (b) (4) 150 IU/ml is listed in Acceptance Criteria e.g. in Table 1 in “3.2.P.5.1 Specifications”. The range for potency - “the confidence limits ($p=0.95$) of the estimated potency are not less than (b) (4) and not more than (b) (4)” “is too broad and should be tighten.

4b: Please clarify: (b) (4) used for (b) (4) – is it (b) (4) (as listed in “3.2.S.4.2 Analytical Procedure) or (b) (4) (as listed in SOP N-1P-5348-02)?

Reviewer’s comment: Kamada corrected the potency acceptance criteria to “150 (b) (4) IU/ml, the confidence limits ($p=0.95$) of the estimated potency are not less than (b) (4) and not more than (b) (4)”. More information regarding the change of Anti-Rabies potency release specification and detailed justification for the DP potency shelf life specification change from (b) (4) IU/ml to 150 (b) (4) IU/ml is provided in Amendment 19 (received April 21, 2017) and reviewed by Lu Deng, Ph.D. of OTAT.

Kamada clarified that (b) (4) method performed at (b) (4), described in Chapter 3.2.S.4.2, is the same as performed at the (b) (4), described in SOP N-1P-5348-02 with the only difference between the laboratories which is the (b) (4) used. The (b) (4)

(b) (4). More details regarding the two testing facilities are provided in the response to the IR sent March 6, 2017:

IR sent March 6, 2017; responded in Amendment 19, received April 21, 2017

Question 4: It appears that the anti-Rabies potency tests are done in two labs: (b) (4)

a. Please provide the comparability report.

b. Please clearly indicate which steps' samples are tested by (b) (4) and which ones are tested by (b) (4).

Reviewer's comment to Kamada's respond: Kamada clarified that (b) (4) performed the (b) (4) assay only during the developmental stages of the product for US market. Kamada started to perform the (b) (4) assay at (b) (4) since the manufacturing of the conformance lots produced in (b) (4) during the years 2(b) (4). (b) (4) is the only laboratory that will perform all (b) (4) testing (b) (4) DP for Kamada-HRIG commercial lots for the U.S. market. The provided comparability study for the (b) (4) and the (b) (4), Rep-VL-100891-AM was found acceptable.

Reviewer's comment: Validation parameters evaluated in provided validation reports were found to be acceptable and the method can be used as Anti – Rabies Potency test or both Kamada-HRIG (b) (4) DP and also as identification test by (b) (4) for (b) (4) DP.

- **Protein Concentration for (b) (4) DP**

The total protein concentration in (b) (4) DP is measured by (b) (4)

The discrepancies regarding the specification for DP were solved in Amendment 14 (see below). Determination of protein concentration by (b) (4) in KEDRAB is performed based on the SOP N-1P-0001-04. Method precision, intermediate method precision, repeatability, detection and quantitation limits, range, robustness, linearity, and accuracy were evaluated and results described in Rep-VL-100884-AM, Version 3: Validation Report for the Determination of Protein Concentration by (b) (4) in Kamada Immunoglobulins Samples. The range of the method is as (b) (4). Even though the quantitation limit of the test was proved to be (b) (4), the linearity did not cover this value of (b) (4), therefore the method's quantitation limit is set up at (b) (4). Robustness of the test was covered by testing different (b) (4) samples of varying protein concentration and using different (b) (4). One deviation from the validation protocol was noted when different samples were analyzed instead of the repeated testing of the same sample.

Reviewer's comment: The described deviation does not affect the results of the validation study which is found to be acceptable. This procedure was found acceptable for testing Protein Concentration for (b) (4) DP.

IR sent February 21, 2017; responded in Amendment 14, received March 16, 2017

Question 5: Please verify the specification for protein concentration. Based on "3.2.P.5.4 Batch Analysis" and "Justification of Specification 3.2.P.5.6" "The specification of (b) (4) mg/mL (b) (4) was implemented recently as supported by conformance lots results see Table 3 in Chapter 3.2.P.5.4". However, a range of (b) (4) is listed in other parts of the submission.

Reviewer's comment to Kamada's response: Kamada verified and corrected the protein concentration specification to (b) (4) mg/ml (b) (4) as requested.

v) Purity & Impurities

- (b) (4) DP – reviewed by DBSQC

Kamada determines the (b) (4) based on (b) (4), in accordance with SOP N-1P-5344-02, version 7 (Determination of (b) (4) of Immunoglobulins by (b) (4); most recently updated in Amendment 21, dated May 5, 2017). The test is performed according to (b) (4)

Standard used in (b) (4): Human Immunoglobulin Biological Reference Preparation (BRP) (b) (4) with (b) (4) mg/ml protein concentration.

Originally, Kamada focused on determination of aggregates level and the (b) (4) method missed (b) (4) described as (b) (4) from the main (b) (4). When (b) (4) were revealed on the c(b) (4) of the (b) (4) immunoglobulin sample, the (b) (4) SOP had to be updated. Also, changes in specifications were requested by the FDA (see IRs below). The most recent validation study report for the (b) (4) assay by (b) (4) for IgG (Rep-VL-103050-AM) using the new (b) (4) instrument was provided in Attachment 17 (received April 4, 2017; it replaced the prior validation report submitted in Amendment 11 (received February 10, 2017; Rep-VL-100887-AM, Version 2, where old (b) (4) instruments were used). Multiple IRs regarding the method, SOPs, validation, and specifications were requested by both the product and DBSQC reviewers. The most recent IRs and Kamada's commitment to improve the (b) (4) method, its validation and modification of specifications are noted below.

IR sent August 1, 2017; responded in Amendment 31, received August 4, 2017

Question 1: In regard to “(b) (4)”:

a. We agree to using your current validated method of “(b) (4)” for (b) (4) DP with the following specifications:

(b) (4)

DP: (b) (4)

(b) (4)

b. Please resubmit your PMC with the following language:

“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 the FDA by October 31, 2017 as a CBE-30 supplement.”

c. We recommend calling the specification for the (b) (4) species “Fragments” instead of (b) (4) for the following reasons:

- A specification for “Fragments” is a well-established IgG stability indicator

- A numerical value set as a specification for the total amount of these proteins will represent the limit for IgG fragments

- The levels of the (b) (4) in the product are low and thus an individual determination of these impurities appears unnecessary at this time.

Sponsor's response: Kamada clarified that the specification for (b) (4) will include:

(b) (4)

(b) (4)

(b) (4) (IgG fragments and (b) (4)

Kamada will define the specification for the (b) (4) species as IgG fragments using numerical value following the improved method validation.

Reviewer's comment: Since the commitment to include (b) (4) is not acceptable, additional IR was sent to Kamada:

IR sent August 9, 2017; responded in Amendment 32, received August 15, 2017

- Whichever (b) (4) method is chosen, it should be fully validated
- The current specification should be based on the currently validated method
 - since the method was validated for (b) (4), the specification should include only these species
 - the specification for the (b) (4) species will be established after a new method is validated
- A specification for (b) (4) should be established; the level of (b) (4) is an important stability indicator and the specification for (b) (4) should demonstrate how much increase of (b) (4) takes place during the shelf life.
- Postmarketing commitment submitted in Amendment 31 dated 8/4/17 should be modified.
 - Information that the specification will include (b) (4) should be added.
 - If more time for the method development/validation is needed, the date of the submission of the Final Report can be changed.

Response: Kamada amended the (b) (4) specifications to be used with the currently validated method as follows:

(b) (4)

(b) (4)

A new specification will be established after validating a new method and will be adjusted to include a specification for (b) (4). The limits will be revised based on the validation results.

Reviewer's comment: Kamada committed to perform a full validation for the new (b) (4) method. The updated PMC includes a commitment to establish an (b) (4) specification which will include (b) (4) as requested.

- Since (b) (4) (also known as (b) (4)) was noticed on (b) (4) (see above), Kamada included (b) (4) release testing.

IR sent June 8, 2017; responded in Amendment 29, received July 17, 2017

Question 2: Please provide information on the development of an (b) (4) assay for (b) (4). If the assay has already been developed and if the product testing results are available, please provide an SOP and available test results.

Reviewer's comment: Kamada provided results of (b) (4) concentration in (b) (4) which were in the range of (b) (4) mg/ml. Kamada uses commercial (b) (4) kit made by (b) (4) to quantify (b) (4) concentration in (b) (4). The results are currently used for trending and the acceptance criteria will be determined. SOP N-5P-025 for Detection of Human (b) (4) by (b) (4) is based on the (b) (4) instructions with some modifications. The (b) (4) readings should be below the (b) (4) ng/mL IgG standard ((b) (4) is part of the kit) and within the calibration curve linear range ((b) (4) ng/ml). Based on the Validation report Rep-VL-103101-AM: Validation of (b) (4) for (b) (4), the assay seems to be specific, accurate and precise (intra-assay and inter-assay precision tested) with limited robustness. (b) (4)

(b) (4). LOQ of the method was set to (b) (4) ng/ml. The linearity of the assay was established within the range of (b) (4) ng/ml.

Deviations: In the accuracy study, (b) (4) ng/ml was used as (b) (4) instead of (b) (4) ng/ml. This deviation does not affect the validation study results, since the calculations were adjusted accordingly. Also, during the validation of the intra-assay precision a high %CV was obtained in one of the (b) (4) tested. The intra assay precision test was repeated with passing results (clarified in the IR below).

IR sent August 9, 2017; responded in Amendment 32, received August 15, 2017

a. Was the SOP N-5P-025 updated based on robustness study finding that (b) (4) proposed in the Validation report Rep-VL-103101?

b. What was the result of intra assay precision test repeat after a high %CV was obtained during the validation of the intra-assay precision (Investigation NO. PR20943MDR)?

c. What (b) (4) factor was used for the (b) (4) analyzed?

d. Does the antibody used in the (b) (4) kit recognize (b) (4) as seen on (b) (4)? If only (b) (4) is detected by the (b) (4), which (b) (4) is recognized?

Kamada was also informed that establishing final container specification would require a full method validation including test kit batch to batch variability

Response: Kamada updated SOP N-5P-025 as requested. Kamada committed to supplement the method validation to include a test kit batch to batch variability and submit the report in the Annual Report with (b) (4) concentration results from future batches. A (b) (4) was used for the (b) (4) analyzed during the validation. Kamada stated that the test will be performed only on Kamada-HR (b) (4) samples. The (b) (4) used in the (b) (4) kit is (b) (4), therefore it is expected to (b) (4).

Reviewer's comment: Kamada's responses are acceptable. This procedure is currently used for trending only and as such it is found acceptable for (b) (4) concentration testing of (b) (4) DP. Kamada committed to determine the specification for (b) (4) when accumulated data collected from future manufactured batches (at least (b) (4) batches) is available. The results will be submitted in an Annual Report.

- **Protein Composition for DP**

Proteins present in the tested sample are fractionated by (b) (4) as described in SOP N-1P-5344-03: (b) (4) (the SOP also includes information on preparation of the reference standard, (b) (4). The testing is performed according to (b) (4).

The acceptance criteria for Protein Composition for DP is that the (b) (4) of the tested sample is (b) (4). Kamada uses (b) (4) kit for (b) (4) by (b) (4). The proteins (b) (4). The purity of IgG samples is evaluated according to (b) (4).

Results of testing Specificity, Precision, Intermediate Precision, Detection Limit and robustness were provided in Validation Rep-VL-03002-AM: Determination of Protein Composition in IgG Product by (b) (4). Robustness of the method for changes in (b) (4).

(b) (4) was validated. Kamada set up the limit of detection of (b) (4) at (b) (4). Requested (b) (4) images referenced in Rep-VL-030002-AM were submitted in better quality in Amendment 6 (received December 5, 2016).

Reviewer's comment: Based on the provided validation study report, the criteria for all validation parameters were met.

b) (b) (4) testing

The methods used in analysis of (b) (4) are summarized in Appendix 5. The SOPs and method validations for most of the (b) (4) assays for (b) (4) are provided in 3.2.S.4.3 and in Amendment 28, received July 13, 2017 as a response to IR sent May 31, 2017. In addition to the assays reviewed above, the following tests are used by Kamada for in-process testing:

- (b) (4)

- **Triton X-100 (Octoxynol 9) Concentration** (b) (4)

The concentration of Triton X-100 is measured in the (b) (4) samples after the addition of (b) (4)

Validation report Rep-VL-LAB-09: Validation of the identification of Triton X-100 Raw Material and its Determination in Immunoglobulins in (b) (4) Material summarizes results of system and method precision, intermediate method precision, accuracy, linearity, specificity, range and robustness testing of Triton X-100 concentration; and of specificity testing of the identification of Triton X-100 raw material. The method is linear within the range of (b) (4) Triton X-100. The range is between (b) (4) Triton X-100 in the (b) (4) sample. The robustness testing included measurements under (b) (4) and these changes did not affect the method. One out of three modifications in (b) (4) did not pass the validation criteria (no SOP update was needed).

Reviewer's comment: Based on the testing results provided in Rep-VL-LAB-09, the validation of the assay for Triton X-100 concentration and identification of Triton X-100 raw material is acceptable.

The method is acceptable for Triton X-100 concentration measurement and identification of Triton X-100 in Raw Material.

- **Tri-n-Butyl Phosphate (TnBP) Concentration** (b) (4)

The method for measuring TnBP concentration is based on a test developed by the (b) (4). TnBP is determined by (b) (4).

Based on SOP N-1P-0001-31: Determination of Tri n-Butyl Phosphate (TnBP) (b) (4) in Protein Containing Solutions by (b) (4), the (b) (4) samples from the S/D viral inactivation step should be tested within (b) (4) weeks from sampling. Results of Precision, Accuracy, Specificity and Stability of sample solution testing for TnBP Concentration method were provided in Rep-VL-100349-AM, Version 3: Validation Report for the Determination of Tri n-Butyl Phosphate (TnBP) in IgG Solutions. Results of Robustness (variations in (b) (4)), Linearity and System Precision testing were used from validation report Rep-VL-100406-AM: Determination of Tri n-butyl Phosphate (T'nBP) in Alpha-1 Antitrypsin Solutions (other Kamada's product) by (b) (4) Method. Since the test procedure is the same as for Kamada HRIG, Kamada considers the validation results for Alpha-1 Antitrypsin applicable for IgGs. Two deviations from the validation protocol were noted: Accuracy tests were performed on sample (b) (4) with different levels of TnBP and therefore the test range was limited; specificity tests were performed on samples (b) (4) reagents addition.

Reviewer's comment: Based on the testing results provided in Rep-VL-100349-AM and Rep-VL-100406-AM, the validation of the assay for TnBP Concentration is acceptable. The reported deviations do not affect the conclusions of validation study. TnBP Concentration method can be used for evaluation of TnBP concentration in the in-process samples.

- **IgG subclasses** ((b) (4) DP)

Kamada uses (b) (4) kits manufactured by (b) (4) to determine the IgG subclasses IgG1, IgG2, IgG3 and IgG4 (the company web page lists the kit as IgG Subclass (b) (4) – the same code is listed in Kamada's SOP; FDA Analytical ID Code is (b) (4)) as described in SOP N-5P-390: Determination of Human Blood Plasma Protein Concentrations by the (b) (4) Method. The SOP is based on the manufacturer's instructions (included in Kamada's validation report RD-1710).

The (b) (4) kit uses conventional (b) (4) technology, with a sensitivity of approximately (b) (4) mg/mL. The principle of the assay is (b) (4).

The results of precision studies of the kit and the (b) (4) variation evaluated by the manufacturer using serum samples containing various concentrations of the respective IgG subclasses are included in Kamada's validation report RD-1710: Qualification of the (b) (4) Method for Determination of IgG Subclasses Concentration in IgG (b) (4) DP samples. This report also describes qualification studies of specificity of the (b) (4) method using the (b) (4) kits performed by Kamada.

Reviewer's comment: Based on the provided qualification report for the (b) (4) method using the (b) (4) kit (procedure one described in the kit is used), the specificity of the determination of all four IgG subclasses seems to be acceptable for testing Kamada's manufacturing samples. Even so the range of recoveries of control (b) (4) for IgG3 and IgG4 ((b) (4)) was wider

and more variable in comparison to IgG1 and IgG2 ((b) (4)), as noted by Kamada since IgG3 and IgG4 are minor components among the IgG subclasses, the observed higher variability does not affect the IgG subclasses determination. ((b) (4)) kit can be used to determine the IgG subclasses IgG1, IgG2, IgG3 and IgG4 in the Kamada HRIG samples.

- ((b) (4))

- ((b) (4))

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

(b) (4)

(b)
(4)

2) Reference Standards and materials

- a) Reference Standards used in analytical methods for testing the Kamada-HRIG (b) (4)
DP samples are listed below. The specific standards are described under the review of the specific analytical methods.
- i. Anti-Rabies Potency: (b) (4)
 - ii. Glycine concentration: Glycine (b) (4) Reference Standard or working standard calibrated against USP reference standard (b) (4) to a concentration of (b) (4) mM
 - iii. (b) (4)
 - iv. Residual Triton X-100: Triton® X-100 (b) (4) Reference Standard
Limit of quantitation verification standard - (b) (4) Octoxynol 9 in (b) (4)
 - v. Residual TnBP: Tri-n-butyl phosphate (b) (4) Reference Standard or working standard derived from TnBP (b) (4) calibrated against (b) (4) reference standard (b) (4)
 - vi. Bacterial Endotoxin: (b) (4) Technique: control standard endotoxin diluted in (b) (4). The standard endotoxin stock solution is prepared from a control standard endotoxin that has been calibrated against the International Standard (e.g. endotoxin standard (b) (4)).
(b) (4) Method: The standard endotoxin stock solution is prepared from a control standard endotoxin that has been calibrated against the International Standard (e.g. endotoxin standard (b) (4)). The standard endotoxin stock solution is (b) (4) with (b) (4) to (b) (4) concentrations of (b) (4) EU/ml.
 - vii. Clarity and Degree of Opalescence: Reference opalescence standards prepared from (b) (4) solution and (b) (4)
 - viii. Degree of Coloration: Color reference reagent (b) (4)
 - ix. pH: buffers at pH (b) (4) and (b) (4)
 - x. Triton X-100 (Octoxynol 9) Concentration: Standard stock solutions: (b) (4) ppm Triton X-100 (Octoxynol 9) in (b) (4)
 - xi. Tri-n-Butyl Phosphate (TnBP) Concentration: Standard Calibration curve of TnBP: (b) (4) TnBP in diluent [(b) (4)].
 - xii. (b) (4)
 - xiii. (b) (4)
 - xiv. (b) (4)
 - xv. (b) (4)
 - xvi. Protein Identity by (b) (4) : (b) (4) ; Human IgG standard - the following can be used:
Human IgG Std; or
Human IgG Std by (b) (4) and Control ((b) (4));
or IgG reference house standard

- xvii. Protein Composition: A sensitivity standard composed of (b) (4) % protein from which (b) (4) % is IgG ((b) (4) mg/ml, in-house IgG reference) and (b) (4) is (b) (4)
- xviii. Subvisible Particles: (b) (4) solution ((b) (4))
- xix. IgG subclasses and (b) (4) Concentration: Control sample is calibrated against the international reference preparation (b) (4)

b) Kamada HRIG Reference House Standard (RHS)

- i. Preparation: (b) (4)
- ii. Usage: To verify consistency of the IgG manufacturing process in comparability studies and as a standard for the following analytical methods: (b) (4) of Kamada-HRIG DP; (b) (4) of Kamada-HRIG (b) (4); (b) (4) analysis of Kamada-HRIG (b) (4); IgG subclasses by (b) (4) of Kamada-HRIG (b) (4); and Protein composition of Kamada-HRIG DP
- iii. RHS lots: The current Kamada-HRIG standard (b) (4) (manufactured in (b) (4) from a Kamada-HRIG DP lot # (b) (4) that was also a clinical lot in the Phase II/III study and one of the 2013 conformance lots) replaced lot # (b) (4) (manufactured in (b) (4) from (b) (4)).
- iv. Characterization: Identification by (b) (4); Protein concentration by (b) (4); IgG concentration by (b) (4); related (b) (4) by (b) (4); IgG protein profiles by (b) (4); Identification by (b) (4); IgG fragments identification by (b) (4); IgG subclasses by (b) (4); Purity by (b) (4); Process-related (b) (4) - Residual protein (b) (4) level determination by specific methods (e.g. (b) (4)).
- v. New standard qualification: Release DP specifications and additional qualification testing listed in Appendix 6 have to be met. Comparative study has to demonstrate that the biochemical and physicochemical characteristics of the new RIG-RHS are within the range of results of the previous RHS and the accumulated data for Kamada-HRIG (DP (b) (4)).
- vi. Stability: RHS is tested (b) (4) every (b) (4) months over the (b) (4) year, and every (b) (4) months thereafter.