



From Alfred V. Del Grosso, DBSQC/OCBQ

To STN 125613/0

Through Lokesh Bhattacharyya, Acting Director DBSQC/OCBQ

Product Human Rabies Immune Globulin, Solution for Injection, Kamada-HRIG

Sponsor Kamada Ltd.

Subject Primary Discipline Review Memo for Biological License Application for Quality Control Lot-Release Test Methods for the (b) (4) Drug Product for Kamada-HRIG

Summary of Review

This BLA is for approval of human rabies immune globulin, Kamada-HRIG, indicated for passive, post-exposure prophylaxis of rabies infection. The product is indicated to be given immediately following possible rabies exposure. This document is the Primary Review Memo from DBSQC for the following analytical methods and validations, as intended for use in product lot release:

1. Clarity and Degree of Opalescence – (b) (4) DP
2. Degree of Coloration – (b) (4) DP
3. Visible Particles – (b) (4) DP
4. pH – (b) (4) DP
5. Protein Concentration (b) (4) – (b) (4) DP
6. Glycine Concentration – (b) (4) DP
7. Residual TnBP – (b) (4) DP
8. Residual Triton X-100 (Octoxynol 9) – (b) (4) DP
9. Extractable Volume – DP

Conclusion: On the basis of the review of the submitted method descriptions and validation and qualification studies, the assays listed above are approvable for lot release purposes.

Background

On August 29, 2016, Kamada Ltd submitted a BLA (STN 125613) for a Drug Product (DP) Kamada-HRIG (Human Rabies Immune Globulin). This product is used for post-exposure prophylaxis of rabies infection in combination with a rabies vaccine. The (b) (4) derived from human plasma of healthy adult donors immunized with rabies vaccine. Anti-rabies immunoglobulins from plasma are (b) (4). Viral inactivation of the plasma is achieved using solvent-detergent, heat treatment and nanofiltration. The DP is a sterile, non-pyrogenic liquid provided at a potency of 150 IU/ ml in 2 ml and 10 ml glass vials. The DP is formulated with 0.3 M glycine at a pH range of 5.0 – 6.0. Drug Product manufacture from the Drug Substance consists of dilution with 0.3M glycine from a Total Protein Concentration of (b) (4), followed by sterile filtration and filling into final containers.

Submitted information reviewed:

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

125613/0 – 3.2.S.4.1 Control of Drug Substance – Specification

125613/0 - .3.2.S.4.2 Control of Drug Substance – Analytical Procedures

- Analytical Procedures (Kamada-HRIG, Kamada Ltd.)
- SOP N-1P-0001-04 Determination of Protein Concentration and Optical Absorption using (b) (4)
- SOP N-1P-0001-12 Determination of pH in Protein Solutions
- SOP N-1P-0001-32 Determination of Tri-n-Butyl Phosphate (TnBP) in Protein Solutions by (b) (4) (Limit Test)
- SOP N-1P-5344-10 Limit Test of Triton X-100
- SOP N-1P-5344-21 Evaluation of Degree of Coloration of IgG Samples
- SOP TR-N-1P-0001-01 Appearance Testing of Solutions
- SOP TR-N-1P-001-27 Determining Clarity and Degree of Opalescence of Liquids
- SOP TR-N-1p-5344-23 Glycine Concentration Testing Using the (b) (4) Method
- SOP N-1P-001-05 Testing of Visible Particles in Solutions

125163/0 – 3.2.S.4.3 Validation of Analytical Procedures

- Validation of Analytical Procedure (Kamada-HRIG, Kamada Ltd.)
- Rep-VL-03087-AM Report Determination of Glycine Concentration in IgG Product by (b) (4)
- Rep-VL-08444-AM Report Determination of TnBP Residues (Limit Test) in Protein Containing Solutions by (b) (4) Validation
- Rep-VL-100988-AM Report: Qualificaiton of pH Testing of Anti R Samples

- Rep-VL-1009960AM Report: Validation Report for (b) (4) Method for Determination of Glycine Concentration
- Rep-VL-101009-AM Report: Validation of the Test for Determination of Residual Triton X-100 in Anti R Samples
- Rep-VL-100884-AM Report: Validation Report for the Determination of Protein Concentration by (b) (4) in Kamada Immunoglobulins (IgG) Samples

-
125163/0 – 3.2.P.5.1 Control of Drug Product – Specification(s) (Kamda-HRIG, solution for injection)

125163/0 – 3.2.P.5.2 Control of Drug Product – Analytical Procedures

- Analytical Procedures (Kamada-HRIG, Solution for Injection)
- SOP TR-N-1P-0001-011 Determination of Extractable Volume in Drug Product Vials

125163/0 – 3.2.P.5.3 Validation of Analytical Procedures

- Validation of Analytical Procedures (Kamada-HRIG, Solution for Injection)
- Rep-VL-05128-AM Report: Determination of Volume of Injection in Containers
- Rep-VL-100689-AM Report: Qualification of the Method for Determination of Extractable Volume in Drug Product Vials Through (b) (4)

1. Clarity and Degree of Opalescence

This test is applied to (b) (4) Drug Product. Samples are visually inspected by comparison to (b) (4) and reference opalescence solutions according to (b) (4). Specifications for (b) (4) DP are that “the solution is clear to slightly opalescent”. SOP TR-N-1P-001-27 “Determining Clarity and Degree of Opalescence of Liquids” was provided in the initial submission.

Method

(b) (4)

Method Validation

Information regarding qualification of this procedure was not submitted.

Conclusions

As a common and established Pharmacopeial test, this procedure is acceptable for evaluation of (b) (4) Drug Product.

2. Degree of Coloration

This test is applied to (b) (4) Drug Product. Samples are assessed in terms of color by visual inspection according to (b) (4). Specifications for (b) (4) DP are that “the solution is colorless to pale yellow”.

Method

(b) (4)

Method Validation

Information regarding qualification of this procedure was not submitted.

Conclusions

As a common and established Pharmacopeial test, this procedure is acceptable for evaluation of (b) (4) Drug Product.

3. Visible Particles (Appearance)

This test is applied to (b) (4) Drug Product. Samples are assessed by visual inspection in order to detect visible product particles (granulates or fibers) that originate from the product itself or visible filament shaped particles of a source other than the product itself. Specifications for (b) (4) DP are “May contain some protein particles”.

(b) (4)

Method

(b) (4)

Method Validation

Information regarding qualification of this procedure was not submitted.

Conclusions

This procedure is acceptable for evaluation of (b) (4) Drug Product.

4. pH

pH is (b) (4) determined using a (b) (4) Drug Product specification is 5.6 – 6.0.

Method

(b) (4)

Method Validation

pH determination was qualified as described in “Validation of pH testing in Anti R samples” VL-100988-AM. For (b) (4) Kamada Rabies IG samples, pH was determined with a total of (b) (4) measurements on at least (b) (4) working days, by (b) (4) analysts using (b) (4). All measurements were within (b) (4) pH of the average for each tested sample.

Conclusion

This procedure is acceptable for evaluation of (b) (4) Drug Product.

5. Protein Concentration

Total protein concentration is determined by (b) (4) Testing is in accordance with (b) (4) Drug Product Specification is stated as (b) (4).

Method

(b) (4)

Method Validation

Method validation was described in Doc. VL-100884-AM. Characteristics evaluated included (b) (4)

(b) (4)

(b) (4)

Conclusion

While the evaluations of (b) (4) are expressed in terms of analytical response rather than analyte level, the ability to quantitate Total Protein at (b) (4) DP levels has been adequately demonstrated. This procedure is acceptable for evaluation of (b) (4) Drug Product.

6. Glycine Content

Determination of Glycine in (b) (4) DP is performed by a (b) (4) method using (b) (4)

The procedure is based on (b) (4) . Specifications for Glycine are (b) (4) Kamada-HRIG (b) (4) Drug Product.

Method

(b) (4)

Method Validation

Validation of the method for Glycine content was described in Rep-VL-100996-AM.

Characteristics of (b) (4) were evaluated. Samples used for validation purposes included (b) (4)

(b) (4) lots, (b) (4) DP lots and (b) (4) process intermediate sample. (b) (4)

(b) (4)

Conclusion


While (b) (4) across the full claimed range of (b) (4), or (b) (4) for IgG samples (b) (4) fold has not been fully established, adequacy in the (b) (4) used to evaluate (b) (4) DP samples has been demonstrated. This procedure is acceptable for evaluation of (b) (4) Drug Product samples.

7. Triton X-100 (Octoxynol 9) Limit Test

Determination of Triton X-100 (Octoxynol 9) as a Limit Test is performed by (b) (4) with detection by (b) (4). The method is based on the (b) (4). Specification for residual Triton X-100 in (b) (4) Drug Product is (b) (4).

Method

(b) (4)



Evaluation of system suitability includes (b) (4)




The Limit Standard ((b) (4)) is (b) (4) should be (b) (4). Sample (b) (4) should not exceed (b) (4) the (b) (4) of the (b) (4) Limit Standard. Since the sample is diluted 1:5, this evaluates that the sample contains (b) (4) Triton X-100.

Method Validation

As a Limit Test, validation characteristics of (b) (4) were evaluated. Validation was documented in report Rep-VL-101009-AM.

(b) (4)



Conclusion

This procedure is acceptable as a Limit Test for Triton X-100 at the (b) (4) specification level in Kamada-HRIG (b) (4) Drug Product.

8. Tri-n-Butyl Phosphate (TnBP) Limit Test

Residual Tri-n-Butyl Phosphate is determined by a limit test using (b) (4) detection. (b) (4) test samples are (b) (4). Specification for residual TnBP in (b) (4) Drug Product is (b) (4).

Method

(b) (4)

The (b) (4) identified as TnBP for the (b) (4) samples and (b) (4) samples is calculated. The residual amount of TnBP is determined from the (b) (4) of (b) (4) relative to those of (b) (4) samples. The preparation of the (b) (4) sample complies with the test, if the (b) (4) of the (b) (4) samples is (b) (4) of the standard (b) (4).

The ratio of average TnBP (b) (4) in the (b) (4) samples to that in the (b) (4) samples is calculated. In case the ratio is (b) (4), the residual amount of TnBP in the sample is reported as (b) (4). If this ratio is (b) (4), the residual amount of TnBP in the sample is (b) (4). In this case the test is to be repeated with (b) (4) samples. The standard working solution is (b) (4) TnBP in (b) (4). The (b) (4) solution is (b) (4) TnBP in (b) (4) into (b) (4) of sample ((b) (4)). The calculations are repeated but this time using the (b) (4) standard solutions.

Method Validation

As a Limit Test, validation characteristics of (b) (4) were evaluated. Validation was documented in report Rep-VL-08444-AM.

(b) (4)

Conclusion

This procedure is acceptable as a Limit Test for TnBP at the specification level (b) (4) in Kamada-HRIG (b) (4) Drug Product.

9. Determination of Volume of Injection (Extractable Volume)


The method is described in the (b) (4)

. Product

Specification is NLT 2 mL for 2 mL vials and NLT 10 mL for 10 mL vials. The method is described in SOP TR-N-1P-0001-011.

Method

Determination of the extractable volume is accomplished by (b) (4)



Method Validation

Separate validation studies were performed for evaluations by the (b) (4) method, Rep-VL-05128-AM, and by the (b) (4) method, Rep-VL-100689-AM. Both were performed using (b) (4) as the test article.

For the evaluation of accuracy and precision using the (b) (4) was (b) (4) with an accuracy of (b) (4). (b) (4) replicates were tested per the SOP and accuracy and precision determined. For the 2 ml vials, recovery of (b) (4) met the criteria of (b) (4); Intermediate Precision of RSD (b) (4) met the (b) (4) criteria. For 10 ml vials, recovery of (b) (4) met the criteria of (b) (4) and Intermediate Precision of (b) (4) met the criteria of (b) (4).

Qualification of the (b) (4) method was similar. For the 2 ml vials, recovery of (b) (4) met the criteria of (b) (4); Intermediate Precision of RSD (b) (4) met the (b) (4) criteria. For 10 ml vials, recovery of (b) (4) met the criteria of (b) (4) and Intermediate Precision of (b) (4) met the criteria of (b) (4).

Conclusion

This procedure is acceptable as for the determination of extractable fill volume of Kamada-HRIG Drug Product.