



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

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To: To File (BLA STN 125613/0)

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Applicant: Kamada Ltd.

Product: Rabies Immune Globulin (RIG)
Trade name: KamRab

Subject: Final Review: BLA for Rabies Immune Globulin, CMC (b) (4)
Studies

Recommendation

The (b) (4) study sections of this BLA are approvable with the PMC listed below.

Postmarketing Commitment (PMC)

(#2 in Approval Letter)

Kamada commits to perform full scale validation on (b) (4) additional full scale lots, (b) (4) of the critical operating parameter ranges and times, including the (b) (4) for the (b) (4) step, with in-process testing for (b) (4) at each manufacturing step.

Kamada will submit a validation protocol outlining the operating parameters for each lot, and (b) (4) tests along with the acceptance criteria, as a Post Marketing Commitment – Product Correspondence prior to manufacture of these lots. The final report will be submitted as a Post Marketing Commitment – Final Study Report by August 31, 2018. These lots will be placed on stability and a final stability report will be submitted as a Post Marketing Commitment – Final Study Report by February 28, 2022.

Final Protocol Submission: October 31, 2017

Study Completion Date: June 29, 2018

Final Report Submission: August 31, 2018

Final Stability Report Submission: February 28, 2022

Executive Summary

Kamada-HRIG is a human rabies immune globulin product 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. The dosage proposed is one intramuscular administration of 20 international units (IU) per kilogram.

Kamada-HRIG (b) (4) is manufactured from human hyperimmune plasma of healthy adult donors who have been immunized with rabies vaccine and have developed high titers of rabies antibody. The manufacturing process includes (b) (4) and three viral inactivation steps: solvent-detergent (S/D) treatment, heat treatment and nanofiltration. Kamada-HRIG drug product is a sterile, nonpyrogenic liquid preparation enriched with antirabies immunoglobulins (not less than 95% protein as IgG). 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.

My review focus is on the (b) (4) steps and (b) (4) validations. The main review issue with the (b) (4) validation is that the process validation report contains only small scale robustness studies that were performed with material non-representative of the intermediate from the routine manufacturing process. E.g., the (b) (4). The use of equivalent in-process material is especially important for the DEAE column because it is the main (b) (4) step. Kamada agreed to repeat the (b) (4) robustness study and agreed to narrow their operating ranges to those which were used in the conformance lots, as the robustness studies performed with the altered starting material did not adequately cover the originally-submitted broader operating ranges. Additionally, the (b) (4) are not measured at each manufacturing step, mainly the (b) (4), to allow for the full assessment of purification aspect of the (b) (4). A PMC for the manufacture and characterization of (b) (4) additional conformance lots is included in the approval of this BLA.

The initial (b) (4) studies are also not fully adequate in that they did not use a protein solution and did not examine product impact of (b) (4). Kamada agreed to repeat the (b) (4) studies with protein solution and assess the product impact of (b) (4).

CMC Review

1. My review's focus is on (b) (4) steps and (b) (4) studies.
 - a. Please refer to the attachment for the manufacturing Flow Chart and Process Narrative.
2. (b) (4)
 - a. General overview
 - i. There are (b) (4) steps in the Kamada HRIG manufacturing process: (b) (4).
(b) (4)
(b) (4) The process validation submitted for the (b) (4) steps included only small-scale robustness studies, and (b) (4) and cleaning studies. More information about full scale conformance lots and development studies was obtained through multiple information requests. More information is needed regarding the consistency of the (b) (4) operating parameters, mainly of the main (b) (4) step ((b) (4)), in the removal of (b) (4). The robustness study for the (b) (4) will be repeated post-approval. Additionally, Kamada committed to manufacturing (b) (4) additional conformance lots to monitor the removal of (b) (4) throughout the process and confirm the operating parameter consistency at the (b) (4) ends of the operating range.
 - b. Step 2: (b) (4)
 - i. The purpose of this step is to change the (b) (4) of the intermediate.

- ii. (b) (4)
- iii. Kamada provided the following documents for this step:
 - 1. Protocol VL-0347-PQ – Small Scale Robustness (b) (4) – Protocol
 - 2. Rep-VL-0347-PQ – Small Scale Robustness (b) (4) – Final Report
 - a. (b) (4)
 - b. Multiple IRs were sent to address the appropriateness of this material. Finally, it was decided that since this step is not a (b) (4) step, Kamada narrowed the operating parameters to those used during the manufacture of the lots listed in the BLA, and Kamada will manufacture (b) (4) additional conformance lots for additional characterization, the (b) (4) study may be sufficient.
 - 3. (b) (4) Studies – Process Validation, Section 5.2.1
 - a. Kamada submitted a study for up to (b) (4) consecutive batches of (b) (4) cycles each. The (b) (4) performance was analyzed every (b) (4) run. The data were acceptable.
- c. Step 4: (b) (4)
 - i. This step is the main (b) (4) step during the Kamada-HRIG manufacturing process.
 - ii. (b) (4)
 - iii. Kamada provided the following documents for this step:
 - 1. Protocol VL-03034-PQ – Small Scale Robustness (b) (4) – Protocol
 - 2. Rep-VL-03034-PQ – Small Scale Robustness (b) (4) – Final Report
 - a. (b) (4) The treatment of the starting material is not representative of the actual manufacturing conditions; therefore, Kamada was asked to repeat the study. Kamada agreed to this.
 - 3. (b) (4) Studies – Process Validation, Section 5.2.2
 - a. Kamada submitted a study for up to (b) (4) consecutive batches of (b) (4) cycles each. The (b) (4) performance was analyzed every (b) (4) run. The data are acceptable.
 - iv. Kamada also found that the (b) (4) lot affects the (b) (4) (Study report RD-4368 Characterization of (b) (4) During the Anti-R Manufacturing Process). New (b) (4) lots are tested against a reference (b) (4) lot and must result in (b) (4) at this step.
 - v. Kamada also had a (b) (4) issue (Deviation GED-060/12) before this step which involved batch (b) (4) that was also challenged with (b) (4) of (b) (4) (Rep-VL-100817-PV). Kamada stated that the duration of the (b) (4) step did not have an impact on the (b) (4). Kamada cited (b) (4) other small scale hold time studies for the (b) (4) step where the

(b) (4) was stable up to (b) (4). Kamada was asked to repeat this (b) (4) hold time in the PMC involving the manufacture of (b) (4) additional conformance lots. To correct this deviation, Kamada changed the collection of (b) (4) at the end of the (b) (4) step. They replied that they have had (b) (4) incident since the correction due to inappropriate (b) (4) removal. The (b) (4) issue was addressed in the August 10, 2017 telecon and Kamada agreed to investigate all (b) (4) incidents as deviations.

- d. Step 6: (b) (4)
- i. The purpose of this step is removal of S/D reagents
 - ii. The S/D-treated material is (b) (4) to remove the S/D reagents and (b) (4). The (b) (4).
 - iii. Kamada provided the following documents for this step:
 1. Protocol VL-03090-PQ – Small Scale Robustness (b) (4) – Protocol
 2. Rep-VL-03090-PQ – Small Scale Robustness (b) (4) – Final Report
 - a. The study was done with (b) (4) S/D-treated material. The material was (b) (4). This material is not fully representative of the manufacturing process.
 - b. As for the other robustness studies, multiple IRs were sent to address the appropriateness of this material. Finally, it was decided that since this step is not a purification step, Kamada narrowed the operating parameters to those used during the manufacture of the lots listed in the BLA, and Kamada will manufacture (b) (4) additional conformance lots for additional characterization, the robustness study may be sufficient.
 3. (b) (4) Studies – Process Validation, Section 5.3.3
 - a. Kamada submitted a study for up to (b) (4) consecutive runs. The (b) (4) performance was analyzed every (b) (4) run. The data are acceptable.
- e. Step 8: (b) (4)
- i. The purpose of this step is (b) (4) (after heat treatment)
 - ii. The (b) (4) heat-treated solution is (b) (4) onto a (b) (4) to remove the (b) (4) and other (b) (4). (b) (4)
 - iii. Kamada provided the following documents for this step:
 1. Protocol VL-05066-PQ – Small Scale Robustness (b) (4) – Protocol
 2. Rep-VL-05066-PQ – Small Scale Robustness (b) (4) – Final Report
 - a. The study was performed with heat-treated starting material that was (b) (4). The material was (b) (4). This material is not fully representative of the manufacturing process.
 - b. As for the other robustness studies, multiple IRs were sent to address the appropriateness of this material. Finally, it was decided that since this step is not a (b) (4) step, Kamada narrowed the operating parameters to those used during the manufacture of the lots listed in the BLA, and Kamada will manufacture (b) (4) additional conformance lots for additional characterization, the robustness study may be sufficient.
 3. (b) (4) Studies – Section 5.3.4

- a. Kamada submitted two studies: the first study validated the (b) (4) up to (b) (4) runs, and the second study for up to (b) (4) consecutive runs. The data are acceptable.
- f. (b) (4) Studies – Section 5.4.1
 - i. The (b) (4) and sanitization conditions were studied as follows:
 - 1. (b) (4) analysis of (b) (4) after equilibration as an indication of contamination by adventitious agents.
 - 2. (b) (4) testing of the (b) (4) solution for protein residuals.
 - ii. The (b) (4) data were acceptable.
 - iii. The (b) (4) had multiple (b) (4) results. OOT-008/12 was opened to investigate this.
 - 1. (b) (4)
 - 2. (b) (4)
 - 3. (b) (4)
 - 4. Kamada supplied additional (b) (4) data spanning (b) (4) years in Table 29, in the response to Question 8h, February 21, 2017 IR (Amendment 15, 3/2317) to show that the (b) (4) was functioning properly following the CAPA. The results were acceptable

3. (b) (4) Studies

- a. General overview
 - i. Most of the (b) (4) studies for homogeneity were not performed with protein solution representative of the material at the indicated step. Additionally, product-impact studies were not performed for the (b) (4), the volume in (b) (4) and how it relates to (b) (4) formation. Kamada agreed to repeat the (b) (4) studies post-approval to address these issues.
- b. Step 1: (b) (4) of pooled plasma - (b) (4) validation for (b) (4) : Rep-VL-101099-PQ.
 - i. Homogeneity study was conducted on (b) (4) which is used to collect plasma after opening and emptying the plasma bottles. Qualification was performed during (b) (4) routine productions of IgG with total solutions weights of (b) (4) at a (b) (4) rate of (b) (4). Protein concentration was collected and tested from (b) (4) locations in the (b) (4) minutes after initiation of (b) (4). All results met the predefined acceptance criteria of (b) (4) RSD between samples.
- c. Step 2: Intermediate process material from the (b) (4) cycles pooling and (b) (4) validation for (b) (4) (b) (4) : Rep-VL-07708C-PQ.
 - i. (b) (4) contains the protein solution from the (b) (4). (b) (4) validation for (b) (4) was performed by testing the ability of the (b) (4) in the (b) (4) in WFI. (b) (4) weights were used ((b) (4)) with (b) (4) rates ((b) (4)), and the (b) (4) concentration was measured after (b) (4) minutes from the initiation of the (b) (4). Acceptance criteria were met after (b) (4) minutes for both (b) (4) rates for the (b) (4) weight and after (b) (4) minutes for both (b) (4) rates for the (b) (4) weight. It was concluded that the routine parameters would be (b) (4) of (b) (4) at a (b) (4) for not less than (b) (4) min.
- d. Step 5: Solvent and Detergent (b) (4) Validation
 - i. The step is performed with (b) (4) min (b) (4) and (b) (4) hours treatment (b) (4).
 - 1. This open ranges for this step were adjusted in response to Question 8 December 22, 2016 IR (Amendment 9)

- ii. Kamada measured the TnBP concentration and (b) (4) during (b) (4) runs mimicking worst case manufacturing conditions: (b) (4). In all of the 3 worst-case runs, the TnBP concentration and (b) (4) were within the operational limits throughout the study in both the (b) (4) at all measured time points and locations.
 - e. Step 7: (b) (4) addition/(b) (4) until dissolution: (b) (4) validation for (b) (4) : Rep-VL-07345-PQ/A1 (an ongoing qualification is performed every (b) (4) years)
 - i. (b) (4) in WFI using (b) (4). Sampling was held at (b) (4) locations (b) (4) minutes after initiation of the (b) (4). Acceptance criteria for reaching the (b) (4) concentration with (b) (4) RSD was achieved at both (b) (4) minutes of (b) (4). It was concluded that the routine parameters would be (b) (4) of (b) (4) WFI with (b) (4) at a (b) (4) for not less than (b) (4) minutes after (b) (4) addition.
 - f. Step 7: Constant (b) (4) after Heat Treatment: (b) (4) validation for (b) (4) : Rep-VL-07708B-PQ.
 - i. (b) (4) constant (b) (4)
 - ii. Following the heat treatment, the protein solution containing the (b) (4) is (b) (4) to (b) (4) prior to entering the next step of (b) (4). (b) (4) validation for (b) (4) was performed by testing the ability of the (b) (4) in the (b) (4) in WFI. (b) (4) weight were used (b) (4) with (b) (4) rates ((b) (4)), and the (b) (4) concentration was measured after (b) (4) minutes from the initiation of the (b) (4) at three locations. Acceptance criteria were met for both (b) (4) rates for the (b) (4) and after (b) (4) minutes for both (b) (4) rates for the (b) (4). It was concluded that the routine parameters would be (b) (4) at a (b) (4) for not less than (b) (4) minutes.
 - g. (b) (4) during hold times: Kamada did not perform (b) (4) validations during the hold time steps. Kamada stated they will perform a (b) (4) validation which will address these steps.
 - i. (b) (4) - (b) (4) performed in intermediate product (b) (4) at (b) (4) in order to maintain the solution homogeneity achieved in the previous step, pH adjustments of the (b) (4).
 - ii. (b) (4) - (b) (4) is performed in intermediate product (b) (4) at (b) (4) in order to maintain the solution homogeneity achieved in the previous step, (b) (4)
 - iii. Steps 9 to 10: After nanofiltration (b) (4) - (b) (4) is performed in intermediate product (b) (4) in a velocity of (b) (4) following the Nanofiltration step.
4. Additional CMC findings during the review of IR responses:
- a. Broad Process Operating Parameters
 - i. Kamada was asked to narrow their Operating Parameter ranges to those used during the Conformance batches and batches submitted in support of the BLA. They did so in the answer (7/12/17 in Amendment 27) to Question 1a from the May 31, 2017 IR.
 - ii. The narrowed ranges are acceptable; however, Kamada was asked to commit to a PMC to manufacture additional (b) (4) Conformance lots at the (b) (4) of each range with additional characterization.
 - b. (b) (4) study
 - i. In the response to one of the IR questions, we found that Kamada does not have a (b) (4) study or number of uses limit for their (b) (4). They were asked to perform this in the August 10, 2017 telecon, to which they agreed.
 - c. Replacement of filters ((b) (4))

- i. In the response to Question 7i ((7/12/17 in Amendment 27) from the May 31, 2017 IR, Kamada stated that as part of production process of the (b) (4) and the (b) (4) steps, a filter replacement is allowed according to batch production instructions.
 - ii. We also noticed that this applies to the nanofilter as stated in the Master Batch Record (tr-p-539/547 version 17, pg. 22 of 36, section 9.2).
 - iii. During the August 10, 2017 teleconference, we informed Kamada that filter replacement is not acceptable as part of routine manufacturing process, unless it is sufficiently validated. During this telecon and in a written response by e-mail (8/9/17) to Dr. Ewa Marszal, Kamada agreed that until a validation is performed and submitted to the Agency as a supplement, a filter replacement due to (b) (4) will be designated as a deviation with instructions for quality assessment, additional characterization, placement on stability, etc.
5. Information Requests (IRs) - The summary of my IRs is listed below.
 - a. May 31, 2017 IR (Responses received in Amendment 27, 7/10/17 and Amendment 28, 7/13/17)
 - i. Kamada submitted a table of narrowed process operating parameters to reflect those used during the conformance lot manufacturing and other lots submitted in support of the BLA. The narrowed process parameters are acceptable; however, further assessment of the process parameters will be made following the review of the data submitted post-approval in PMC#2.
 - ii. Kamada explained the (b) (4) robustness studies as they relate to the purpose of each (b) (4) step. Kamada committed to repeating the (b) (4) robustness study as this is the main (b) (4) step. The other studies will not be repeated. The answer is satisfactory since Kamada also narrowed their operating parameter ranges to those used in the manufacturing of lots submitted in the BLA and will manufacture (b) (4) additional conformance lots at the (b) (4) of the process parameter range as a PMC.
 - iii. We found that Kamada allows filter changes at certain filtration steps if the flow rate is (b) (4). The nanofiltration step is one of the filtration steps involved. This issue was addressed at the August 10, 2017 teleconference. We explained that a change of filter is not acceptable unless adequately validated. Kamada agreed to change all instances of filter replacement to a deviation-triggering event and perform applicable quality review until such a process is validated.
 - b. February 21, 2017 IR (Responses received in Amendment 14, 3/16/17, Amendment 15, 3/23/17, and Amendment 16, 3/30/17)
 - i. We requested additional information regarding (b) (4) process validation and development studies. Additional (b) (4) studies data and information regarding certain deviations were also requested.
 - c. December 22, 2016 IR (Responses received in Amendment 9, 1/20/17)
 - i. We requested additional information regarding process validation parameters and (b) (4) studies.
6. Teleconferences:
 - a. August 10, 2017. We informed Kamada that filter replacement is not acceptable as part of routine manufacturing process, unless it is sufficiently validated to show that product quality is not affected. This would include, but not limited to: validation of the sheer force of aggregation on the product quality, processing time, and (b) (4) assessment. Kamada stated that they would submit a protocol for filter replacement in response to the PMC where (b) (4) additional conformance lots will be made. Kamada agreed that a filter replacement due to (b) (4) will be designated as a deviation with instructions for quality assessment, investigation into the root cause, additional characterization, placement of the affected lot on stability, etc.

- b. Late Cycle Meeting, June 8, 2017. Kamada acknowledged our IR from May 31, 2017. We did not have any major issues at that time; however, we informed them that we may request 2 additional conformance lots based on the IR response.
 - c. Midcycle, February 23, 2017. No major issues were identified. An IR was sent February 21, 2017 for more clarification.
7. Commitments made during the review process that are not included in the Approval Letter:
- a. Response (received 7/12/17 in Amendment 27) to Question 1 May 31, 2017 IR.
 - i. “The (b) (4) step is the main (b) (4) step of the manufacturing process and therefore the study for this step will be reevaluated and will be performed again.”
 - ii. “Kamada confirms that coagulation factors content throughout the manufacturing process will be evaluated in future qualification batches”
 - b. Kamada commits to conduct (b) (4) validation for (b) (4) for the different weight ranges at each (b) (4) step for homogeneity and to avoid foaming, using a protein solution. The study will be performed using a protein solution and the impact of (b) (4), on product attributes such as aggregation, fragmentation, etc., will be evaluated. Kamada will submit a final validation report and amended batch records.

Final Protocol Submission: March 30, 2018

Final Report Submission: June 29, 2019