

DEPARTMENT OF HEALTH & HUMAN SERVICES



Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: Administrative File: Submission Tracking Number (STN) -
BL 125325-0
Alpha-1-Proteinase Inhibitor (Human)

Firm: Kamada Ltd. (License # 1826)

From: David Doleski, Team Leader, CBER/OCBQ/DMPQ/MRB2
Randa Melhem, Ph.D, CSO, CBER/OCBQ/DMPQ/MRB2
Jennifer Schmidt, CSO, CBER/OCBQ/DMPQ/MRB2

Through: Chiang Syin, Ph.D., Chief, CBER/OCBQ/DMPQ/MRB2

Subject: Mid-Cycle Review Memo

Action

Due Date: April 1, 2010

Recommendation:

An Information Request should be sent to the sponsor to address questions that arose during the review of this BLA.

Questions:

Sterilization/Sanitization:

1. Please provide the following information regarding your steam in place (SIP) validations:
 - a. Please indicate the organisms (genus/species) and D-value of your biological indicators.
 - b. Since you have listed multiple size vessels which are used in your drug substance manufacturing, please indicate which vessels were validated with respect to SIP. If not all of the vessels were validated (i.e. a matrix approach was used), please provide data and/or a justification as to why the vessels selected were worst case.
 - c. We note that for each vessel type, you used a different number of thermocouples and biological indicators. Please provide a diagram of each vessel type and

indicate the locations of thermocouples and biological indicators within the vessel. In addition, please provide rationale for these locations used (e.g. worst case).

- d. Please provide the acceptance criteria for Minimal Accumulated Lethality.
 - e. Please provide a summary of all deviations associated with the SIP validation.
2. You state on page 62 of section 3.2.A.1 that your filling machine (-(b)(4)-) is CIP/SIP; however, we note that your SIP validation information (e.g. Table A.1-39) did not address this equipment. Please clarify if your filling machine equipment is SIPed or autoclaved and provide a detailed summary of the sterilization validation.
3. Please provide a detailed summary of the autoclave used for sterilization of product-contact equipment. This information should include:
- a. The model number and location of the autoclave within the facility.
 - b. A detailed summary of the autoclave load validations including:
 - i. Number of runs.
 - ii. Description of biological indicator (e.g. organism and D-value).
 - iii. Number and placement of thermocouples.
 - iv. Number and placement of biological indicators.
 - v. Rationale for placement of thermocouples and biological indicators as representative or worst case locations.
 - vi. Acceptance criteria and results from runs.
 - vii. A list of equipment, quantity present, and placement within the sterilizer for each load.
 - c. A list of deviations associated with the validation.
4. The section on sterilization and depyrogenation is difficult to understand with respect to the equipment being used (references to both a -----(b)(4)-----), the containers being sterilized or depyrogenated (references to both -----(b)(4)-----), and the purpose of the cycles (references to both sterilization and depyrogenation). Therefore, please provide spreadsheet tables that include, but are not limited to, the following:
- a. All equipment used for sterilization or depyrogenation.
 - b. Types of container closure systems (bottles, vials, caps) that are sterilized or depyrogenated.
 - c. Sizes of container closure systems involved.
 - d. Container closure materials (type of glass or plastic).
 - e. Stage of the manufacturing process for which the containers are used
 - f. Intended purpose of the cycles (depyrogenation, sterilization, or both)
 - g. Validation load size

- h. Routine production load size
 - i. Cross-reference to the table numbers provided in the submission.
 - j. Please present the information in a manner that will allow us to easily connect all of the related aspects of the validation and/or the routine processes.
5. Please address whether any of the product storage containers are reusable.
6. For the validation studies, please provide spreadsheet tables that include, but are not limited to, information regarding:
- a. Number of empty chamber (mapping) runs,
 - b. Loaded chamber runs (for different containers),
 - c. Acceptance criteria (time, pressure, temperature range,
 - d. Accumulated lethality,
 - e. Log reduction in endotoxins or spores
 - f. Actual data obtained from the studies (time, temperature, pressure, etc.)
 - g. Indication of whether the criteria were met.
7. Please provide diagrams to explain the placement of thermocouples, biological indicators (spores), and endotoxin within the loads or the chambers. Please provide the rationale for the selection of those locations.
8. (b)(4)-----

9. For all manufacturing equipment that contacts the products and is sanitized or sterilized, please provide sanitization or sterilization hold times and data to support the hold times.

Needle Assembly:

10. We note that you intend to market the product with a 5µm filter needle purchased from either -----(b)(4)------. Please provide letters of authorization from the needle manufacturer allowing us to review the Master Files for these products. Alternatively, please provide the method of sterilization, sterility assurance level, residual levels (if applicable), and radiation dose (if applicable).

Clean in Place (CIP):

11. For the CIP system that are used for production equipment:

- a. Please provide a detailed description of the CIP system itself, including an explanation of whether it is one system or multiple systems.
 - b. Please identify the equipment cleaned by each skid.
 - c. Please provide a detailed summary of the validation of the CIP process for production equipment. This should include, but not be limited to: the size of vessels tested; type of substance used for soiling, rationale for the use of the substance used as soilant; the locations of the swab or rinse samples; rationale for the locations tested; and any data resulting from the studies.
 - d. Please clarify if the solutions used for the CIP are used once or used for multiple CIP cycles. If the solutions are reused, please indicate the frequency in which the solutions are changed.
 - e. Please indicate whether there is segregation between the cleaning of pre and post viral inactivation process equipment. If so, please elaborate on this segregation.
 - f. Following the CIP of equipment, please explain the timeframe in which SIP must be performed (i.e. -(b)(4)-). Please explain the process that will occur if hold times are exceeded. Specifically address whether the CIP is repeated or whether a WFI rinse is performed.
 - g. You state that both CIP and SIP are performed manually. Please explain what aspects of the CIP and SIP are performed manually.
12. Please explain the rationale for spraying of equipment with -----(b)(4)-----
----- and indicate whether you have performed any studies to assess the effect of long time exposure of the vessels to ----(b)(4)----. If so, please provide a detailed summary of that data.
13. Please provide validation data to demonstrate that the use of ----(b)(4)---- is effective for bioburden and endotoxin control.
14. For the manual cleaning of equipment:
- a. Aside from ----(b)(4)----, please indicate what testing performed after manual cleaning to assure that the equipment is clean (----- (b)(4) -----
-----). Please provide a detailed summary of the qualification of the manual cleaning process.
 - b. Please provide the dirty hold time and the clean hold time for manually cleaned equipment along with data to support those hold times.
 - c. -----(b)(4)-----

(cleaning validation following facility upgrade) you state that the acceptance criteria for -----(b)(4)----- Please explain this discrepancy.

15. Please provide detailed summaries of any sanitization effectiveness studies that were performed.
16. For routine cleaning of the facility, please provide a detailed summary of any qualifications performed. Additionally, please indicate the frequency of routine cleaning, the cleaning regime between campaigns, or after routine maintenance, after spills, contamination, or environmental monitoring excursions.

Vial Washing:

17. For the vial washing, please provide the acceptance criteria for the allowable levels of -----(b)(4)--- residuals, Sodium residuals, particle residuals, vial bioburden, and endotoxin residuals.

Media Simulations:

18. We note your statement regarding the January 2009 pre BLA meeting with us with respect to media fill simulation studies for a new -(b)(4)----- and new -----(b)(4)----- that was to be completed during the BLA review process.
- a. Please provide the media fill simulation studies if such information is available.
- b. Additionally, please provide detailed summaries of media fill studies that were performed prior to the installation and qualification of the new -----(b)(4)--- and new -----(b)(4)-----, as there was likely to have been media fill studies prior to filling the clinical and conformance lots.

------(b)(4)-----:

19. Batch Record (Form TR-P-518/500-08) for Manufacturing Batch Number -(b)(4)- contains Lot numbers for the -----(b)(4)----- However, the genealogy of each finished product lot is unclear since batch records were not provided for all conformance lots.
- a. Therefore, please provide chart with all conformance lot numbers, and the associated -----(b)(4)----- lot numbers.
- b. Additionally, if there are any other lot numbers for different stages of the process (e.g. drug substance), please provide the associated lot numbers of those as well.
20. You have provided one Certificate of Analysis (COA) from -(b)(4)- for -----(b)(4)----- lot number -----(b)(4)----- However, COAs from other lots do not appear to have been provided.

- a. Please provide COAs for the other -----(b)(4)----- lots that may have been used to manufacturing your conformance lots.
 - b. For the COA for lot number -----(b)(4)----, the test results for bioburden and coliform are reported as "All results meet established limits." Please provide the actual release test results for each lot of -----(b)(4)----- that was used to manufacture conformance lots.
 - c. Please indicate if any other test result information is routinely provided from -(b)(4)- to Kamada for these lots other than the COAs.
21. The flow diagram for -----(b)(4)----- Manufacture (Figure 2.3-1) provides critical operational parameters (e.g. -----(b)(4)-----) and process quality attributes (e.g. -----(b)(4)-----). However, the actual limits are not provided. Please provide actual numerical limits for all critical operational parameters and process quality attributes for the -----(b)(4)-----.

Review Details:

The following section was written by Randa Melhem:

Note: I reviewed the cleaning/ disinfection of the facilities. My comments/questions are in italics and they cover both review and inspection issues.

Section 3.2.A.1

Kamada states that following use, large or fixed equipment is cleaned in place (CIP). Samples are collected for verification of cleaning. If the equipment is not used within a validated time period, it is sprayed with -----(b)(4)----- . Prior to use, the equipment is -----(b)(4)-----, or it is sanitized by washing with -----(b)(4)----- . A similar procedure is followed for small equipment.

Both CIP and SIP are performed manually.

Comments

CIP: *It is not clear in the submission how many CIP skids are available. Please provide the number of skids, and clarify if the specific skids are used for cleaning specific equipment.*

1. *Is there segregation between the cleaning of pre and post viral inactivation process equipment.*

2. *Please clarify if the reagents used for the CIP are re-circulated or single use? What is the frequency of changing the reagents?*
3. *Please explain the spraying of equipment with -----(b)(4)------. Have you performed any studies to assess the effect of long time exposure of the vessels to -(b)(4)-.*
4. *You state that both CIP and SIP are performed manually. Please explain.*

------(b)(4)-----

5. ------(b)(4)-----

------(b)(4)-----

Comments:

The manual cleaning section does not provide specific details such as the wash or rinse times of the equipment to assure that the manual cleaning is validated and consistent.

6. *Please state which tests, -(b)(4)- are performed on the final rinse to assure that the equipment is clean – do you perform -(b)(4)-----? Do you perform any -----(b)(4)------. Have the manual cleaning procedure been validated?*
7. *Please provide the validation for the dirty hold time and the clean hold time for manually cleaned equipment. Please provide the sterile hold time for the autoclaved manually cleaned equipment.*
8. *Is there segregation between the cleaning of pre and post viral inactivation process.*

P67/94 Rationale for the Cleaning Procedures

Kamada states that the rationale for their cleaning procedures is as follows:

------(b)(4)-----

9. *There should not be any product residues in shared equipment – whether of similar of different nature. The cleaning procedure should be validated to remove any product and cleaning agent residues.*

------(b)(4)-----

10. *Please provide validation data to demonstrate that the use of ----(b)(4)----- is effective for bioburden and endotoxin control.*

P65/94 Equipment Cleaned in Place and Steamed in Place

Kamada states that samples of the final rinse water are withdrawn for verification of -(b)(4)- (acceptance limit of -(b)(4)-).

*However in **table A.1-36 (p68/94)** (cleaning validation acceptance criteria), they state that the acceptance criteria for rinse water -(b)(4)- is -(b)(4)-; and in **table A.1-37** (cleaning validation following facility upgrade) they state that the acceptance criteria for rinse water --- (b)(4) ---.*

11. *Please explain.*

P.69/94 Cleaning validation

In the submission, Kamada states that they have performed studies on different vessels at least three successive times and the results met the acceptance criteria.

However they do not provide any specific information – sizes of vessels tested; type of protein solution used for soiling, and why it is worst case solution; number of swabs they took of each vessel tested, and whether they are worst case location.

12. *Please provide the validation report for CIP.*

Kamada states that they validated the clean hold time prior to SIP = up to -(b)(4)-.

13. *Please provide the dirty hold time validation studies.*

14. *Please provide validation for the sterile hold time after SIP.*

P. 72/94 Validation of washing for vials (final container)

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

Note: The endotoxin level in the experiments (after washing the vials) is <0.1 EU/vial, yet the acceptance criteria is -(b)(4)-.
The bioburden in the experiments after washing is <1cfu/vial; yet the acceptance criteria is -(b)(4)-.

Recommendation: *an alert limit set closer to the experimental value.*

P 77/94. Validation of the depyrogenation cycle

----- (b)(4) -----

Comment

*In the validation, ----- (b)(4) ----- were sterilized in each run – is the number of BIs, TCs, and EIs enough to represent the load. Do they have to address worst case locations (do they have to determine the worst case locations)?
They did not report any deviations in their validation studies of the depyrogenation tunnel.*

P88/94. Cleaning and Sanitization Procedures, Control and Monitoring

Kamada states that

- Sanitization of the manufacturing areas is performed and monitored according to a written program.
- Surface sanitization is performed using validated sanitization agents.
- Sanitization during cleaning of production vessels and equipment by treatment with ----- (b)(4) ----- was validated for efficacy of viral inactivation and control of bioburden.

Comment:

15. *I am not sure where they presented the protocols and validation studies to determine sanitization effectiveness; and how they determined the effectiveness of the sanitization agents. Please provide the validation studies.*

In the submission they do not provide any validation for the cleaning of the facility, the frequency of routine cleaning in the different areas, the cleaning regime between campaigns, or after maintenance, spillage, contamination, EM excursions. Do they do cleaning followed by disinfection, do they use sporicides, etc... and how frequently? Do they rotate the cleaning reagents/disinfectants?

16. *Please provide cleaning validation and routine cleaning protocol of the facility.*
17. *Please address the clean hold of a room: if routine cleaning of a room is not performed as required, then no further processing activity should occur in that room until cleaning has been completed.*

Cleaning and sanitization of columns and ----(b)(4)---- are presented in 3.2.S.2.2 pp18-22; and in section 3.2.S.2.5 pp 157-164

Regeneration, sanitization procedures as well as storage and equilibration conditions for the columns have been defined based on accumulated experience during product development.

The following section was written by Jennifer Schmidt:

Please note: As requested, I have reviewed information pertaining to the sterilization of equipment used in the manufacture of Alpha-1-Proteinase Inhibitor (Human) produced in the Beti Kama, Israel facility. The sterilization of equipment related to the manufacture of the -----(b)(4)----- from human plasma by -----(b)(4)-----
----- was not reviewed.

Summary

Purpose of Submission: This application is for new biologic Kamada – API (Alpha-1 Proteinase Inhibitor) which is a multifunctional serine protease inhibitor (serpin) purified from human plasma. The product is manufactured by Kamada, Ltd. at their facility at Beti Kama, Israel. Kamada-API is supplied as a ready to use sterile solution for intravenous infusion. Each single dose vial contains 50 ml of a 2% solution of active API in -(b)(4)- sodium phosphate buffer containing -(b)(4)- sodium chloride. A 5µm filter needle is provided. Kamada-API is indicated for chronic augmentation and maintenance therapy in individuals with congenital deficiency of alpha-1proteinase inhibitor (API) and clinical evidence of emphysema.

Contents of Sterilization information: The following sections were reviewed for sterilization information:

- “Quality Overall Summary”
- Section 3.2.A.1 “Facility and Equipment”

Conclusion: The provided information is insufficient and a request for additional information should be provided to the firm.

Sterilization Review

Drug Substance (DS):

Equipment related to manufacturing (DS):

----- (b)(4) -----

----- (b)(4) -----

[--(b)(4)--]

[--(b)(4)--]

[--(b)(4)--]

One (1) Page Determined to be Non-Releasable: (b)(4)

----- (b)(4) -----

----- (b)(4) -----

Drug Product (DP):

Equipment related to manufacturing:

The firm states that all product equipment, utensils and flexible tubing used in the production of DP is product dedicated. The following table was presented on page 62 of section 3.2.A.1

[--(b)(4)--]

From the review of this table we are unclear if filling machine equipment was SIP. This is a concern since their SIP validation information did not address the filling machine **(See Information Request Question)**. The SIP validation for the formulation vessel and the filling vessel are addressed in the information above for the Drug Substance.

Container closure:

As referenced in the “Quality Overall Summary,” the final container closure consists of sterile, deoxygenated, (b)(4)- glass vials which are closed with (b)(4)- rubber stoppers and aluminum overseal fitted with a flip-off (b)(4)- cap.

- (b)(4)- rubber stoppers: purchased from (b)(4)- . A sample vendor certificate of quality was provided (p. 79)

Stoppers are sterilized by (b)(4)- by the vendor. Each lot of stoppers are tested by Kamada and released by Quality control specification. The review of the C of A indicated (b)(4)- meeting standard EN-11137. Kamada uses the stoppers as purchased with no further processing step.

- (b)(4)-

- Overseal: The overseal appears to be non-sterile and supplied by (b)(4)- (p. 79)

- Filter needle: In addition to the primary container closure system, a sterile single use stainless steel filter needle with polypropylene hub, epoxy needle attachment and 5 µm particulate depth filter is included. The filter needle purchased from (b)(4)- is included as a packaged component. (b)(4)- Certificate of Compliance were provided. The review of the C of A for both these vendors provided insufficient sterilization information and only stated the devices meet QSRs (**See recommendation 1**).