

## 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, Branch 2, CBER/OCBQ/DMPQ

**Through:** Chiang Syin, Ph.D., Chief, Branch 2, CBER/OCBQ/DMPQ

**Subject:** **Final Review Memo:** Recommend Approval

### **Action**

**Due Date:** July 1, 2010

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### **Recommendation:**

Based on the information in the BLA, the amendments (responses to information requests), the pre-license inspection, and the firm's corrective actions to the inspectional observations, I recommend approval of the BLA.

### **Inspection:**

A CBER pre-license inspection of Kamada was performed by Dr. Ewa Marszal, and myself during the period of February 3-4 and 7-11, 2010. The location of the manufacturing facility is as follows: Kibbutz Beit Kama, Negev, Israel. The FEI number is 1000630279. A FDA Form 483 with 13 inspectional observations was issued to Kamada on February 11, 2010. Kamada provided responses to the 483 observations on the following dates: February 25, 2010; April 1, 2010; May 17, 2010; June 8, 2010; and, June 28, 2010. Additionally, there were telecons and less formal e-mail updates.

### **Background:**

For review comments on the original BLA, please see the mid-cycle review memo from Jennifer Schmidt, Dr. Randa Melhem, and myself. The original BLA was difficult to understand and lacked details with respect to data generated from the validation studies. However, this was addressed through Kamada's amendments. Additionally, we (Dr. Marszal and I) performed a pre-license inspection, where issues were covered in great detail.

Product Presentation:

Alpha-1-Proteinase Inhibitor (Human) is a sterile, stable, ready to use, liquid preparation of purified alpha-1-proteinase inhibitor (API), also known as alpha-1-antitrypsin (AAT), derived from human plasma. It is formulated as a 2% solution of API in phosphate-buffered saline and is presented in single-use vials containing 50 ml of ready-to-use solution. It is presented in -----(b)(4)---- glass vials, closed with -----(b)(4)----- rubber stoppers (------(b)(4)-----) and ---(b)(4)--- seals with -----(b)(4)----- flip-off caps. A 5µm filter needle is provided in the presentation.

Manufacturing Process:

The starting material for Kamada-API is -----(b)(4)-----, derived from either Source Plasma or Recovered Plasma by -----(b)(4)----- and obtained under contract from -(b)(4)-. Release specifications for -----(b)(4)----- are agreed between -(b)(4)- and Kamada, and appear on the -(b)(4)- Certificate of Analysis. Released -----(b)(4)----- is shipped to Kamada according to a validated shipping procedure.

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Aseptic filling, is carried out in an ISO -(b)(4)- room with -----(b)(4)----- . Critical parameters (non-viable particulates, differential pressure, temperature, relative humidity) are continuously monitored and controlled. Samples are collected throughout the filling process. Kamada- drug product is tested and released against the specifications. The filled vials are sealed with sterile -----(b)(4)----- stoppers, capped with -----(b)(4)----- overseal with a flip-off cap and stored at 2 – 8 °C pending visual inspection, which is performed manually. Complete or partial lots are labeled and packaged, as needed, and returned to 2 – 8 °C storage pending release and shipment.

Validation Studies:

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**December 9, 2009 IR / January 11, 2010 Amendment:**

**58. Please provide the following information regarding your steam in place (SIP) validations:**

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The biological indicators used for SIP validation studies are certified to meet the current -----(b)(4)----- for steam sterilization and -----(b)(4)-----  
----- . They contain at least -----(b)(4)-----  
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Table 58-1 summarizes the properties of two representative lots of biological indicators that were used in the SIP studies.

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**Reviewer Comments:** Kamada's response is acceptable.

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**c. Please provide a summary of all deviations associated with the SIP validation.**

There were three deviations total: one was a broken BI vial (no data possible); and, two pertained to momentary drop in temperature.

**Reviewer Comments:** Kamada's response is acceptable. During the inspection, I covered the drops in temperature, and this resulted in a 483 item (see EIR).

**59. 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.**

The filling machine equipment is --- (b)(4) ---. A summary of the sterilization validation performed for the loads containing filling equipment is provided in response to question 60.

**Reviewer Comments:** Kamada's response is acceptable. In this response, Kamada neglected to mention that the ----- (b)(4) ----- . During the inspection, I discovered this fact, and it became a 483 item (see EIR).

**60. 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;**

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**Reviewer Comments:** Kamada's response is acceptable.

61. The section on sterilization and depyrogenation is difficult to understand with respect to the equipment being used (references to both -----(b)(4)-----), the containers being sterilized or depyrogenated (references to both -----(b)(4)-----), and the purpose of the cycles (references to both -----(b)(4)-----).

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;**

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**Reviewer Comments:** Kamada's response is acceptable.

**b. Types of container closure systems (bottles, vials, caps) that are sterilized or depyrogenated;**

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Closure System	Component	Sterilization Process	Depyrogenation Process	Performed by
Final Container	50 ml Glass Vial Rubber closure Aluminum seal and flip		(b)(4)	Kamada supplier
	(b)(4)			Kamada

**Reviewer Comments:** Kamada's response is acceptable.

**c. Sizes of container closure systems involved;**

Kamada-API drug product is filled in a single container closure system.

**Container closure materials (type of glass or plastic);**

Container Component	Description	Supplier
<b>Glass Vial</b>	50 ml clear, colorless ---(b)(4)--- glass vial, classified as Glass (b)(4)	(b)(4)----- -----
<b>Rubber Stopper</b>	20 mm (nominal) dark gray ----- (b)(4) ----- rubber stopper conforming to ----- (b)(4) -----	----- (b)(4) -----
<b>Flip off overseal</b>	20 mm Aluminum seal with flip off cap	----- (b)(4) -----

**Reviewer Comments:** Kamada's response is acceptable.

**d. Stage of the manufacturing process for which the containers are used;**

----- (b)(4) ----- . The drug product is filled in the glass vials. Process intermediate material in the drug substance and drug product production process is stored in - (b)(4) - ----- .

**Reviewer Comments:** Kamada's response is acceptable.

**e. Intended purpose of the cycles (depyrogenation, sterilization, or both);**

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**Reviewer Comments:** Kamada's response is acceptable.

**f. Validation load size;**

Please see the response to Question 63 in reference to the dry heat oven and tunnel. Please refer to the response to Question 60 in reference to the autoclave loads.

**Reviewer Comments:** Kamada's response is acceptable.

**g. Routine production load size;**

The autoclave loads for sterilization of the filling equipment are set loads with a fixed location for each item. The validation was performed accordingly. ----- (b)(4) -----  
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**Reviewer Comments:** Kamada's response is acceptable.

**h. Cross-reference to the table numbers provided in the submission;**

**Reviewer Comments:** Kamada provided the information. The response is acceptable.

**i. 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.**

**Reviewer Comments:** Kamada's response is acceptable.

**62. Please address whether any of the product storage containers are reusable.**

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**Reviewer Comments:** Kamada's response is acceptable.

**63. 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.**

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**64. 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.**

**Reviewer Comments:** Kamada's response is acceptable. The diagrams were provided, and the thermocouples, biological indicators (spores), and endotoxin indicators were well-distributed throughout the loads.

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**c. Any information that supports these approaches.**

The information is presented above in response to the specific questions.

**Reviewer Comments:** Kamada's response is acceptable.

**66. 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.**

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**Reviewer Comments:** Kamada's response is acceptable.

**Needle Assembly:**

**67. 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).**

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Sterilization Information for 5µm Filter Needle Manufactured by -----(b)(4)-----  
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**Clean in Place (CIP):**

**68. 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.**

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**Reviewer Comments:** Kamada's response is acceptable.

**b. Please identify the equipment cleaned by each skid.**

Kamada provided lists (Tables 68-1 and 68-2) for the systems used for cleaning of equipment used in production of the drug substance and drug product. The equipment are listed in the order that they are used in the API production process.

Kamada provided a table of Systems Used in Cleaning in Place of Drug Substance Equipment. Most of the cleaning systems consisted of (b)(4)-----.

**Reviewer Comments:** Kamada's response is acceptable

**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 soil, the locations of the swab or rinse samples, rationale for the locations tested, and any data resulting from the studies.**

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subject of a 483 item, as the limits were not reflective of process capabilities. Please refer to the EIR for additional details.

- 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.**

Solutions used for the CIP are used once.

**Reviewer Comments:** Kamada's response is acceptable.

- 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.**

Cleaning of pre- and post-viral inactivation process equipment is segregated as follows:

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**Reviewer Comments:** Kamada's response is acceptable. Cleaning with ----- (b)(4) ----- should be effective for viral inactivation.

- f. **Following the CIP of equipment, please explain the timeframe in which SIP must be performed (---- (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.**

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**Reviewer Comments:** Kamada's response is acceptable.

- g. You state that both CIP and SIP are performed manually. Please explain what aspects of the CIP and SIP are performed manually.**

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**Reviewer Comments:** Kamada's response is acceptable.

- 69. 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.**

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**Reviewer Comments:** Kamada's response is acceptable. Kamada believes that the equipment will not be adversely impacted by NaOH. At this point, I have no evidence to the contrary.

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

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**Reviewer Comments:** Kamada's response is acceptable

**71. For the manual cleaning of equipment:**

- a. Aside from ----- (b)(4) -----, please indicate what testing is performed after manual cleaning to assure that the equipment is clean (--- (b)(4) ---).  
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**Please provide a detailed summary of the qualification of the manual cleaning process.**

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**Reviewer Comments:** Kamada's response is acceptable.

- b. Please provide the dirty hold time and the clean hold time for manually cleaned equipment along with data to support those hold times.**

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**Reviewer Comments:** Kamada's response is acceptable.

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**Reviewer Comments:** Kamada's response is acceptable.

**72. Please provide detailed summaries of any sanitization effectiveness studies that were performed.**

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**Reviewer Comments:** Kamada's response is acceptable.

**73. 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.**

A summary of the qualifications performed on cleaning solutions used during routine cleaning of the facility is provided in the answer to Question No. 72.

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**Reviewer Comments:** Kamada's response is acceptable.

### Vial Washing:

**74. 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.**

Kamada provided the acceptance criteria for the allowable levels of -(b)(4)-  
----- residuals, sodium residuals, particle residuals, vial bioburden, and  
endotoxin residuals.

**Reviewer Comments:** Kamada's response is acceptable.

### Media Simulations:

**75. 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.

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**Reviewer Comments:** Kamada's response is acceptable.

- 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.

**Manufacturing Dates for Clinical and Conformance Lots:**

Study	Manufacturing
Lot No.	Date

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**Reviewer Comments:** Kamada's response is acceptable.

**76. 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.

Kamada-API comparability and conformance lots were produced from -----(b)(4)----- derived from either Source or Recovered plasma collected by -----(b)(4)----- Kamada provided a table that lists for the comparability and conformance lots, the -----(b)(4)----- lots used to manufacture the related drug substance.

**Reviewer Comments:** Kamada's response is acceptable

**77. 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.**

Certificates of Analysis of the -----(b)(4)----- lots used for the production of the comparability and conformance lots (refer to Table 76-1) are attached in Attachment 77-1.

**Reviewer Comments:** Kamada's response is acceptable.

- b. For the COA for lot number -----(b)(4)----, the test results for -----(b)(4)----- 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 and lots manufactured during product comparability study (recovered plasma vs. source plasma).**

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**Reviewer Comments:** Kamada's response is acceptable.

- c. Please indicate if any other test result information is routinely provided from -(b)(4)- to Kamada for these lots other than the COAs.**

There is no other test result information routinely provided with each -----(b)(4)----- lot other than the COAs.

**Reviewer Comments:** Kamada's response is acceptable.

**78. 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)-----.**

The -----(b)(4)----- obtained from -(b)(4)- for the manufacturing of Kamada-API is an intermediate product of the registered production process of -(b)(4)-----.

Nevertheless, Kamada contacted -(b)(4)- to receive the information requested. -(b)(4)- confirmed that they are preparing the answers but cannot meet the deadline set by the Agency due to the holidays.

-(b)(4)- may prefer to submit some of the information directly to the Agency. We will contact the FDA to follow up how it should be arranged.

**Reviewer Comments:** This issue was addressed by the firm in their May 4, 2010 response (see reviewer's comment below)

**March 11, 2010 Amendment (#16):**

In response to discussions during the pre-approval inspection concerning changes to the manufacturing process, Kamada submitted an amendment dated March 11, 2010 (amendment #16). The amendment had four items. Two of those items are relevant to my review. Specifically, the amendment contains a -----(b)(4)-----.

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**Reviewer Comments:** Kamada's response is acceptable.

**May 4, 2010 Amendment (#21) (response to December 9, 2009 IR question 78):**

**Question 78: 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) - -----.**

Kamada reports that in Chapter 3.2.S.2.3, the Control of Materials section was updated. Table S.2.3-1 and Table S.2.3-2 were added to provide the limits for the operational parameters and the quality attributes for the manufacturing of ---- (b)(4) ----. The limits are as follows below.

Quality Attributes Limits for -----(b)(4)----- Process:

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**Reviewer Comments:** Kamada's response is acceptable.

**June 2, 2010 Amendment (#26) in Response to May 19, 2010 FAX:**

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**Reviewer Comments:** The Chairperson and RPM of this file have requested that Kamada withdraw their request for ---(b)(4)---, and resubmit it after approval when data from a ---(b)(4)--- full scale lot is available.

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**Reviewer Comments:** Kamada's response is acceptable.

- 3) In Appendix 1 of TR-Rep-VL-07704-PV/A2 entitled *Summary of the Alpha-1 Antitrypsin (AAT) Uniformity-of-Filling Validation*, you indicate that the results for the ----- (b)(4) ----- were greater than the difference specified for tests performed on duplicate samples. A decision was made to repeat the protein assay for this lot to determine with the differences in the test results represented real differences between samples as opposed to assay variability. Please indicate what your criteria are for repeat testing during validation studies. Further, please explain why there was assay variability in the first set of test results (which were atypical), whereas, there was less assay variability in the second set of test results (which were expected).

The criteria for repeat testing during validation are the following:

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**Reviewer Comments:** The test results did meet acceptance criteria, and that was never an issue. This is part of a larger issue regarding the handling of unexpected or potential OOS results (SOP reviewed, but no OOS results have actually occurred yet). The review committee has been in discussions with Kamada regarding OOS results, which was resolved in recent weeks with Kamada's refinement of their OOS SOP and ----- (b)(4) ----- . Kamada's response is acceptable.

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**Reviewer Comments:** Kamada's response is acceptable.

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- 6) Throughout the submission, there are a number of references to the process parameters for sterile filtration. However, not all of the process parameters are consistent. For example, in one instance the maximum sterile filtration pressure is -(b)(4)-, whereas in another instance this process parameter is listed as -(b)(4)-. Please provide limits for pressure, flow rate, and time based on your filter validation studies and the process validation studies.

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

**Reviewer Comments:** Kamada's response is acceptable.

**7) Please provide maximum limits for different categories of defects that will be used in the 100% visual inspection process that are based on historical data generated from lots that have been already manufactured.**

The maximum control limits of the different categories of defects for the 100% visual inspection process are listed in the table below, based on the severity of the defect and the data of (b)(4) lots manufactured in 2007-2010. Kamada divided the different categories into four classes:

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**Reviewer Comments:** As revealed during the inspection, Kamada had already identifying, removing, and counting the numbers of defects. However, they did not have limits until now. Kamada's response is acceptable

- 8) **For the Comparability Protocol provided in Section 3.2.R.2, please provide the following information:**
- a) **Any operational parameters to be used for the ----(b)(4)--- process.**
  - b) **Elaboration on the cleaning studies that will be performed on the ---(b)(4)-- and submitted with the follow-up supplement.**
  - c) **A description of the specific types of testing that will be performed during the validation study (the proposal contains phrases such as "Test results for in-process quality attributes..." without referencing the specific tests).**
  - d) **The reporting category you intend to use for the supplement to be submitted to CBER that contains data generated from the executed Comparability Protocol.**

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

**Reviewer Comments:** The acceptance criteria for cleaning validation are acceptable. The product office reviewer may evaluate the characterization testing to be performed. Kamada's response is acceptable.

- 9) **Regarding the "package integrity test," or the container closure integrity test, performed on your product.**
- a) **Please describe:**
    - i) **Positive controls used in the test (including hole diameter).**
    - ii) **Differential pressure(s) exerted on the vials during immersion used to simulate processing or distribution conditions.**
    - iii) **Limit of detection that the method can detect for -(b)(4)- that was found in the containers.**
  - b) **Please elaborate on how the -(b)(4)-, as you have implemented it, correlates to microbial ingress.**
  - c) **Lastly, please define a critical leak rate that is appropriate for your container closure system and provide sensitivity data demonstrating that your method can achieve this level of detection.**

The package integrity test procedure was revised since the BLA submission, based on conclusions of its final validation.

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

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**Reviewer Comments:** Container closure integrity is an issue that we are increasingly focused on. At that point, the -(b)(4)- diameter wire between the stopper and vial is within the range that we consider acceptable. Kamada's response is acceptable.