



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

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**To:** BLA STN 125325\0 File

**From:** Maria L. Virata-Theimer, Ph.D., LPD/DH/OBRR, HFM-345

**Through:** Dorothy E. Scott, M.D., Chief, LPD/DH/OBRR, HFM-345  
Mei-ying W. Yu, Ph.D., LPD/DH/OBRR, HFM-345

**CC:** Cherie Ward-Peralta RPM, DBA/OBRR, HFM-380

**Applicant:** Kamada Ltd., -----(b)(4)----, Israel

**Product:** Alpha-1-Proteinase Inhibitor (Human)  
Proposed Trade name: Apikam™

**Subject:** Midcycle CMC Review: Original BLA – Sterility, Pyrogen, Endotoxin, General Safety Testing

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**Recommendation**

An information request will be sent to the firm (see Letter-Ready Comments).

**Background Summary**

FDA CBER received on 1-JUN-09 this original Biologics License Application (BLA) submission (dated 29-MAY-09) from Kamada Ltd. for Alpha-1-Proteinase Inhibitor (Human) with the proposed trade name, “Apikam™,” (Kamada-API or AAT). Kamada-API is indicated for chronic augmentation and maintenance therapy of individuals with congenital deficiency of alpha-1-proteinase inhibitor and clinical evidence of emphysema.

Ewa Marszal, Ph.D., of LPD/DH/OBRR, HFM-345 is the chair of this BLA submission. My CMC review is limited only to sterility, pyrogen, endotoxin, and General Safety testing.

**Supplement Review Summary**

**Sterility, Pyrogen, Endotoxin, and General Safety Testing**

**A. Documents pertaining to these tests that were submitted and reviewed – see Appendix**

**B. Analytical Procedures and Method Validations**

The Kamada-API drug product (DP) is a sterile liquid solution for intravenous administration, containing 2% Alpha-1-Proteinase Inhibitor prepared from -----(b)(4)------. The -(b)(4)- are derived from either US Source or recovered plasma and are supplied by -----(b)(4)------. Kamada stated that the analytical methods to test the drug substance (DS) have been validated according to the ICH Q2B Guidelines. In addition, methods for the critical in-process controls have been validated (Section 3.2.S.4.3, page 6 of 78). The composition of the DS and

DP is very similar. The only difference between them is that in formulation of the DP, the DS is ---(b)(4)---

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**Reviewer’s Comments (General):**

*(1) I noticed that Kamada uses the term “validation” interchangeably with “qualification” and “verification” in several documents, so the distinction between “method qualification or verification” and “method validation” is lost. The original documents were written in Hebrew, so the English translated versions are at best only approximate representations of the original contents.*

*(2) All of the method SOPs for the sections I reviewed were missing. The method validation SOPs and reports that were submitted were disorganized and confusing to read. The method validation results were not presented in a way that one could easily conclude that the expected validation parameters were adequately tested.*

**1. Sterility Testing**

**Analytical Procedure:** Kamada uses a membrane filtration method for sterility testing based on the -(b)(4)-  
----- and the -----(b)(4)----- To perform this test, they use the  
------(b)(4)-----.

**Reviewer’s Comments:** *(1) CBER prefers the use of the membrane filtration method, where possible. Kamada stated that they are following the -(b)(4)-, but we could not confirm this because they did not provide the method SOP mentioned in the submission, SOP N-1420 version 9, Performance of Sterility Test. We also do not know what sample volumes were used for testing.*

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*(3) From the lists of DS and DP specifications that Kamada submitted, it appears that they only test for sterility at the final container stage (see Table S.4.1-1, Section 3.2.S.4.1 and Table P.5.1-1, Section 3.2.P.5.1). 21 CFR 610.12 requires that both the bulk and final container materials are tested.*

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**Reviewer's Comments:** FDA does not require a full validation of the sterility test method. In fact, Kamada did not incubate for the full 14 days of incubation as outlined in 21 CFR 610.12. Therefore they did not do the observation and sampling on days 3, 4, 5, 7, 8 and 14.

2. **Pyrogen Testing**

**Analytical Procedure:** Kamada stated that an approved contract laboratory performs the rabbit pyrogenicity test of their DP samples according to ----- (b)(4) -----  
----- . In Table 2.3-30, the contract laboratory is listed as ----- (b)(4) -----  
-----, whose responsibility is to perform pyrogen testing for batch release and stability testing.

**Reviewer's Comments:** (1) The rabbit pyrogen test described in ---- (b)(4) ---- is similar to 21CFR610.13(b).  
(2) Kamada did not submit ----- (b)(4) ----- method SOP for the rabbit pyrogen test, therefore we do not know what sample volumes they use for testing.

**Method Validation:** No formal method validation study for the rabbit pyrogen test was submitted. However, Kamada provided the following tabulated data: ----- (b)(4) -----  
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**Reviewer's Comments:** A full method validation study is not required by the FDA, however, verification or demonstration of suitability under actual conditions of use must be provided.

3. **Bacterial Endotoxin Testing**

**Analytical Procedures:** Kamada reported that they use two endotoxin test methods for lot release testing: the - (b)(4) - and the ----- (b)(4) ----- methods. ----- (b)(4) -----  
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----- (b)(4) -----  
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**Reviewer's Comments:** (1) Kamada did not provide the method SOP that was mentioned in the submission, SOP N-1260 – Determination of Bacterial Endotoxin Using -(b)(4)- Method (I could not tell whether this was for the ------(b)(4)----- method).

(2) It was not clear which method will be used the primary method for lot release testing. To me, it seemed like the -----(b)(4)----- method was the primary one, while the -(b)(4)- method was the alternate method. However, their specification did not mention anything about the -----(b)(4)----- method, which made it more confusing.

(3) We consulted Dr. William McCormick of DPQ/OVRR, HFM-407, an FDA expert on endotoxin testing (see attached email dated 17-NOV-09 in Data Appendix). He stated that companies use multiple -(b)(4)- test configurations with the same license all the time. However, they usually do not present (nor does FDA advocate) the use of alternate reagent configurations for testing the same manufacturing stage, especially not for lot release where full validation is required. Both methods are used to test -(b)(4)- and DP. One method configuration should be selected, developed and validated. Regarding the dispute resolution Kamada proposed, Dr. McCormick has concerns whether there is something insufficient about the validation study or that there is an inconsistency in the sample being tested. These concerns are not to be addressed or refereed through the use of an alternate method.

(4) Dr. McCormick also said that the specifications should be method-specific. He agreed that the current specification does not reflect the capability of performing the assay as per the -----(b)(4)----- configuration. He also said that Kamada's current specification and justification are not typical.

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(2) Kamada only submitted documents that validated their -(b)(4)- test method in terms of inhibition or enhancement testing. Like that for the -(b)(4)- method, they did not provide any evidence of user validation of -(b)(4)- testing using the -(b)(4)- method (see similar comments above).

#### 4. **General Safety Testing**

**Analytical Procedure:** Kamada stated that their General Safety Test was performed according to 21 CFR 610.11. Mice and guinea pigs are observed and weighed 7 days after intraperitoneal injection of the test material. A safety test is satisfactory if all animals meet the requirements described in 21 CFR 610.11 (Part 6.4 General Safety Test, Section 3.2.P.5.2 Analytical Procedures (DP)). In Table 2.3-30, -----(b)(4)----- is listed as the contract laboratory that performs the General Safety Test for batch release.

**Reviewer's Comments:** Kamada did not provide -----(b)(4)----- method SOP for performing the General Safety Test, therefore we do not know what sample volumes they used.

**Method Validation:** No formal method validation was provided. However, Kamada provided the conformance lot data taken from -(b)(4)- DP lots made from recovered plasma and -(b)(4)- DP lots made from Source Plasma; all met the requirements for passing the General Safety Test (see Table P.5.4-2, Section 3.2.P.5.4 Batch Analyses).

#### **LETTER-READY COMMENTS**

1. You have two bacterial endotoxin methods listed for release testing of -----(b)(4)----- and drug product samples. Please select only one endotoxin method to develop for release testing of both and provide a full validation of this method according to recommendations in the 1987 FDA Guideline on *Validation of the -----(b)(4)----- Test as an End-Product of Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices*, which should include the following:
  - (a) qualification of each analyst to conduct the test according to the SOP
  - (b) assessment of variability in the testing laboratory by using the lab equipment (no samples are run at this point)
  - (c) demonstration of ability to confirm labeled sensitivity of the -(b)(4)- reagent
  - (d) confirmation of the -(b)(4)- reagent sensitivity or linearity on each new lot of -(b)(4)- reagent prior to use
2. For bacterial endotoxin testing, please also provide the information requested below:
  - a) Depending on which endotoxin method you choose for lot release testing, please provide the English translation of the SOP for performing this method.
  - b) Please specify which reference endotoxin standard you are using.
  - c) Please specify in the method SOP the sample volumes you use for testing.
  - d) Please cite the source(s) of your -----(b)(4)----- reagents in your method SOP and validation SOP.
  - e) Please provide a Certificate of Quality from the -(b)(4)- reagent supplier that indicates the specific RSE/CSE correlation of each -(b)(4)- reagent lot.
  - f) Depending on which endotoxin method you choose for lot release testing, please revise your bacterial endotoxin specification accordingly such that it is method-specific.
3. For sterility testing, only the final container (drug product) is tested. 21 CFR 610.12 requires that both the bulk and the final container should be tested. Please provide the following information:
  - a) Please refer to the requirements in 21 CFR 610.12 and modify your method SOP for sterility testing accordingly. Please submit the revised version (English translation).
  - b) Please specify in the method SOP the sample volumes you will use for testing the bulk and the final container.
  - c) Please set the sterility specification for the bulk.
  - d) Please provide the evidence that verifies or demonstrates the suitability of the revised method under actual conditions of use (e.g., 14 days of observation).
4. For pyrogen testing, please provide the following information:

- a) the method SOP for performing rabbit pyrogen testing.
  - b) the sample volume used for testing.
  - c) the evidence that verifies or demonstrates the suitability of the method under actual conditions of use.
5. Please provide the method SOP for performing the General Safety Test. Please specify the sample volumes that are being used for testing.

## **APPENDIX**

### **Supporting documents submitted that were reviewed:**

#### **Sterility Testing:**

1. TR-N-1016-06: Validation of Sterility Determination (version 6, translation approved 31-MAR-09)
2. Rep-VL-07073-AM: Validation of AAT Sterility Test Procedure (N-1016)(version 1, effective 10-JUL-07)

#### **Bacterial Endotoxin Testing:**

1. TR-N-2011-04: Validation of -(b)(4)- Test (version 4, translation approved 8-APR-09)
2. TR-N-2011-05: Validation of -(b)(4)- Test (version 5, effective 1-JUL-07, translation approved 8-APR-09) –  
-(b)(4)- *method*
3. TR-N-1P-0001-48-01: Validation of Testing Endotoxin Concentration in -----(b)(4)----- Method by the  
----- (b)(4)----- (version 1, translation approved 20-APR-09)
4. Rep-VL-07076-AM: Validation of the --(b)(4)-- Method for Measuring Bacterial Endotoxins in -----(b)(4)----  
----- (version 1, effective 27-JAN-08)
5. (Protocol) Addendum Rep-VL-07076-AM/A1: Validation of the -(b)(4)- Method for Measuring Bacterial  
Endotoxins in -----(b)(4)----- (version 1, effective 1-JUL-07)
6. Addendum Rep-VL-07076-AM/A1: Validation of the -(b)(4)- Method for Measuring Bacterial Endotoxins in  
----- (b)(4)----- (version 1, effective 27-JAN-08)
7. Rep-VL-0307-AM/9: Validation of the -(b)(4)- Method for Measuring Bacterial Endotoxins in AAT Drug  
Product Samples (version 1, effective 15-APR-08)
8. Rep-VL-100041-AM: Validation of the -----(b)(4)----- Method for Measuring Bacterial Endotoxins in  
----- (b)(4)----- (version 2, effective 8-APR-09)
9. Rep-VL-100025-AM: Validation of the -----(b)(4)----- Method for Measuring Bacterial Endotoxins in  
AAT Drug Product (version 3, effective 8-APR-09)

#### **General Overviews/Summaries:**

1. Section 3.2.S.4.1 Specifications (DS)
2. Section 3.2.S.4.2 Analytical Procedures (DS)
3. Section 3.2.S.4.3 Validation of Analytical Procedures (DS)
4. Section 3.2.S.4.4 Batch Analyses (DS)
5. Section 3.2.S.4.5 Justification of Specifications (DS)
6. Section 3.2.P.5.1 Specifications (DP)
7. Section 3.2.P.5.2 Analytical Procedures (DP)
8. Section 3.2.P.5.3 Validation of Analytical Procedures (DP)
9. Section 3.2.P.5.4 Batch Analyses (DP)
10. Section 3.2.P.5.6 Justification of Specifications (DP)