

Ross: ask them to send in revised draft labeling that takes into account the new class labeling for IV A1-PI products like what ... sent to -(b)(4)- and CSLB, following the model of recently approved Prolastin C. (Kelly did it for Ross. You can ask Kelly for wording).

Clinical Issues:

1. Cherie, could you please include as a first item Ross' request, which is above?
2. Please include in the label a table of AEs on both per infusion and per subject basis for AEs that began during or within 24 hours of an infusion, irrespective of causality opinion.
3. From review of medical records, please submit additional pre-augmentation therapy serum AAT levels for the following subjects whom you identified as having either MZ genotype or phenotype in your response to item 3 from our fax IR dated 31 July 2009:

Table 1: Subjects with MZ Phenotype or Genotypes and Their Corresponding AI-PI levels

Subject #	Treatment Group	A1-PI Levels baseline (microM)	Genotype	Phenotype
------(b)(6)-----	Kamada-API	9.24	ZZ	MZ
------(b)(6)-----	Kamada-API	9.98	MZ	PLoweliZ
------(b)(6)-----	Kamada-API	7.5	ZZ	MZ
------(b)(6)-----	Prolastin	<4 ¹	ZZ	MZ
------(b)(6)-----	Kamada-API	6.51	MZ	MaltonMZ

¹ The AI-PI level was reported in the dataset as <20mg/dL.

4. Please conduct a randomized BAL study to evaluate various ELF analytes (including antigenic and functional A1-PI, neutrophil count, total and free neutrophil elastase (NE), and A1-PI:NE complexes) in an adequate number of subjects to observe significant changes from pre-augmentation therapy baseline in subjects receiving (a) Kamada A1-PI and (b) another U.S.-licensed A1-PI product dosed to steady-state. Please submit a protocol to the IND with a cross-reference letter as an amendment to the BLA at this time. Please include this study in your letter of post marketing commitments and be sure to provide estimated milestones for submission of a final protocol, start of the trial, completion of enrollment, completion of the study, and submission of the final study report to the BLA with a letter of cross reference to the IND. The data from the BAL study submitted with your BLA are insufficient

because (a) satisfactory BAL samples were available pre- and post- augmentation therapy for only 2 Prolastin subjects and (b) a technical error in BAL sample processing led to the inability to assess functional A1-PI in ELF in all samples. FDA considers this to be a key BAL study analyte.

5. Please submit to the IND and cross-reference the BLA with an amendment for a clinical protocol to evaluate the immunogenicity and to further evaluate the viral safety of your product following multiple repeat exposures over a period of at least 6 months of regular weekly administration. Please include this study in your letter of post marketing commitments and be sure to provide estimated milestones for submission of a final protocol, start of the trial, completion of enrollment, completion of the study, and submission of the final study report to the BLA with a letter of cross reference to the IND. The protocol should include provision for measuring inhibitory antibodies in any subjects who have treatment-emergent positive antibody samples. Viral safety should be assessed by baseline and follow-up (in subjects testing negative at baseline) measurements *by both antibody and PCR* for parvovirus B19, HIV, HBV, HCV, and hepatitis A. The following testing schedule is recommended if each subject receives the same lot of product throughout the study. If the same subject receives more than one lot, 3 and 6 month testing following the end of the 6 month period of dosing should be performed.

Viral Markers and Testing Frequency for a 6 Month Dosing Study

Virus	Baseline	3-month	6-month	3 & 6 months* post-final administration
HIV-I & II	Serology & NAT	Serology & NAT	Serology & NAT	Serology & NAT
HCV	Serology & NAT	Serology & NAT	Serology & NAT	Serology & NAT
HBV	Serology (& NAT)	Serology (& NAT)	Serology (& NAT)	Serology (& NAT)
B19**	Serology & NAT	NAT	NAT	NAT
HAV**	Serology & NAT	NAT	NAT	NAT

* To establish the viral safety of the doses given at the end of the trial

** To be performed only if the subjects are negative at the baseline

6. Please submit to the IND as soon as possible a protocol and plan to conduct and report the results of a stage 1 study that examines the proposed dose plus a dose at least 2-fold higher using one or more clinically meaningful endpoints, such as pulmonary exacerbations of COPD, high resolution CT lung density, mortality, and/or serial pulmonary function testing. The objective of the study is to estimate the

magnitude of the difference in efficacy between the currently recommend dose and the higher dose. The study should ideally be initiated prior to licensure but may be completed during phase IV. Please include this study in your letter of post marketing commitments and be sure to provide estimated milestones for submission of a final protocol, start of the trial, completion of enrollment, completion of the study, and submission of the final study report to the BLA with a letter of cross reference to the IND. **[Sponsor should also be sent the same language regarding the 2 stage clinically meaningful endpoint PMC program that has been sent to Talecris for Prolastin C, to Baxter for Aralast NP, and to CSL Berhring for Zemaira.]**

7. Please modify your Adverse Event (AE) databases for study -(b)(4)-API-001 and package insert to reflect the headache for which subject -(b)(6)- too acetaminophen (see Note to file No. 01). FDA considers this to be a treatment-emergent AE notwithstanding the fact that the subject experienced headaches prior to the start of the study.
8. Please submit the addendum to clinical study API-001 containing complete viral safety follow-up data from the 3 and 6 month follow-up visits. Your study report for API-001 states that the original submission contained viral f/u data [primarily] through the 4-week post-therapy f/u and “any available data” from 3 and 6 month f/u visits. You state in the study report that you plan a 2nd database lock for this study after complete virology results are available, which will result in an addendum to the study report. This conflicts with statements you have made in the cover letter to Amendment 5 dated 15 October 2009, in which you state that you do not plan to submit a 120 day safety update “since no additional safety data has been collected with intravenously administered Kamada-API since the data cutoff for the Integrated Summary of Safety (Section 2.7.4).” The cover letter to Amendment 5 also states “Complete safety and efficacy data from Studies API-001 and API-002 were submitted in the BLA, and no additional subjects have been dosed or followed-up for safety.” Please correct these misleading and erroneous statements.
9. Please explain the “Listing of Subjects receiving test drug(s) investigational” (Section 5.3.5.1.3, Appendix 16.1.6). Lot assignment appears to be inconsistent with the study protocol. Some patients appear to receive exclusively Prolastin. Some patients are stated to be on Prolastin; however, the number of lot assigned indicates that Kamada-API was used.

Pharmacovigilance:

10. Clinical studies have shown non-inferiority to Prolastin. The product appears to be safe and well-tolerated, although very few patients were evaluated in clinical trials.

You should develop and implement a post-licensure pharmacovigilance plan, per the ICH E2E Pharmacovigilance Planning guidance, to monitor long-term safety with the use of Kamada. The major components of a pharmacovigilance plan for Kamada should include routine pharmacovigilance (i.e., compliance with applicable post-

market reporting requirements under FDA regulations) and possibly additional post-market actions to address any potential adverse events that may be identified. This may include a patient registry to evaluate adverse events such as headache, allergic reaction and disease transmission or any other unexpected side effects, particularly serious ones that may emerge through systematic monitoring of larger numbers of treated patients.

11. Continue routine post-marketing as outlined in Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (<http://fda.gov/CDER/guidance/63590CC.htm>).

Pharm/Tox:

12. Please provide signature of pathologist responsible for the pathology report presented in Appendix A, study report KAM/031/RIT, titled “Repeated Intravenous (IV) Toxicity in Rabbits”.
13. Please confirm the calculations in page 19 of 24 of Toxicology Written Summary regarding the dose of TnBP in animal studies. The TnBP dose of -----(b)(4)----- the maximal daily exposure of --(b)(4)--- TnBP from the 60 mg/kg dose in the clinic. Your narrative refers to a 5-fold margin. Similar discrepancy follows the calculation of the exposure after the repeated dose. Please clarify.
14. Please cross-reference the publication used to derive the LD₅₀ value for the IV administration of TnBP as being 733 fold higher than the daily exposure in the clinic (Toxicology Written Summary, page 19 of 24).

Viral Safety:

15. In your submission, plasma testing for manufacturing of Kamada-APITM includes -(b)(4)- tested in -----(b)(4)-----
Please provide validation data for such in-process NAT procedures. Within the submission, please be sure to include the following:
 - a. The sensitivity of -(b)(4)- NAT for screening -(b)(4)- and the threshold level of -(b)(4)-- to exclude those positive plasma donations from getting into the -----(b)(4)-----.
 - b. A copy of the SOP for -(b)(4)- NAT describing sample preparation, sample input volume, sequences and map locations of the primers and probes used, and cycling conditions.
 - c. -(b)(4)- analysis of all -----(b)(4)----- and probes to demonstrate that all -(b)(4)- genotypes can be efficiently detected.
 - d. The yields of -----(b)(4)----- donations since the implementation of NAT assays

for -(b)(4)- per year basis? Please identify the genotype(s) if known.

- e. The sensitivity of -(b)(4)- NAT ----- (b)(4)----- -- and the threshold level of --- (b)(4)-- set, if any.
- f. A copy of the SOP describing the management procedures for those positive donations (i.e, beyond the threshold level) of Source Plasma and recovered plasma to be excluded from manufacturing.

Alternatively, -(b)(4)- may want to submit the data as separate supplements for all their products because of proprietary information.

- 16. You have provided the data of robustness studies for PPV. Please provide data to support that the viral clearance by nanofiltration is robust for clearance of other enveloped and non-enveloped viruses under the worst-case conditions.
- 17. Please provide justification for not including both ----- (b)(4)----- as critical parameters in your study for the robustness of viral clearance for PPV at the step of nanofiltration.
- 18. The higher value (Log_{10}) of the duplicate runs is selected for the claim of the viral log_{10} reduction at the steps of nanofiltration and S/D treatment. The calculation will potentially overestimate the viral inactivation effect of the treatment. Please recalculate the values of viral log_{10} reduction and claim them accordingly.

Bioburden, pyrogen, general safety:

- 19. You have two bacterial endotoxin methods listed for release testing ---- (b)(4)--- ----- 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)--
 - d. confirmation of the ---- (b)(4)---- sensitivity or linearity on each new lot of -(b)(4)- ----- prior to use
- 20. 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)--- supplier that indicates the specific --(b)(4)-- correlation of each ---(b)(4)--- 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.
21. 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: 21. For pyrogen testing, please provide the evidence that verifies or demonstrates the suitability of the method under actual conditions of use.
- 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).
22. 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.
23. Please provide the method SOP for performing the General Safety Test. Please specify the sample volumes are being used for testing.

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

32. Please provide an SOP for calibration and stability monitoring for the in house reference standard. Since product potency assessed using RHS#1 is 3% higher compared with potency assessed with the WHO standard, a correction factor should be applied. Please establish a correction factor and corrected potency values for lots whose potency was established using RHS#1 reference standard.
33. Please provide copies of contractual agreements with laboratories involved in raw material, product in-process intermediate and final container testing. Please provide an SOP describing your audit policy.
34. Please provide an SOP describing your raw material supplier qualification program.
35. Please provide a list of raw materials used in the Kamada-API purification process and indicate the quality of each material and testing that is performed.
36. Please provide a table with all process control parameters (not only critical) and all quality attributes. Please note that all process parameter ranges should have two-sided limits. In the table, please include time of each operation.
37. Please provide a table similar to Table S.2.5-55 containing operating parameters for the manufacture of the drug substance and drug product for the clinical lots, lots manufactured during product comparability study (recovered plasma vs. source plasma) and for the conformance lots. For the clinical lots, please provide observed parameter ranges, for the comparability and conformance lots, please provide individual results. Also, please provide a table with all in-process product quality attributes observed for the lots mentioned above with product quality attributes ranges for the clinical lots and individual results for the comparability and conformance lots.
38. -----(b)(4)-----

39. We note that ----(b)(4)--- is not listed as a critical process parameter in the -----(b)(4)---- step. Please comment.
40. -----(b)(4)-----

41. For nanofiltration, it appears that ----(b)(4)---- is used as a critical control parameter and not -----(b)(4)----- . Please note that -----(b)(4)----- is one of the parameters that should be maintained in small scale validation studies and full scale manufacture (PDA Technical Report No. 41 "Virus Filtration"). Thus, please

establish a range for ----(b)(4)----- consistent with small scale virus validation data.

42. -----(b)(4)-----

43. -----(b)(4)-----

44. Operational limit for endotoxin of -----(b)(4)-----, which is measured at -(b)(4)- of the final target volume, appears inconsistent with the limit of -----(b)(4)---- in the final container. Please tighten the limit or justify.

45. Please provide equipment flow diagram with indication of sampling points and all tests performed at each sampling point.

46. Please clarify whether single product --(b)(4)-- that is proposed in this submission was validated in the full scale manufacture. Please note that --(b)(4)-- should be validated in the full scale and the --(b)(4)-- lots should be placed on stability.

47. Please clarify what amount of -----(b)(4)----- was used in the pilot scale. Section 3.2S.2.5 p.166 and Section 2.3.S.2.3 p. 17 appear to provide conflicting information, -(b)(4)- of the full scale and -----(b)(4)-----, respectively.

48. Please provide a list of all pilot and full scale lots manufactured thus far and the year of their manufacture. Please include lots, manufacture of which was not completed. If such lots exist, please provide the reason for stopping the manufacturing process.

49. Please provide a list of deviations observed during the manufacture of -(b)(4)- comparability lots and conformance lots. Also, please provide summaries of the investigations.

Sterilization/Sanitization:

50. 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.
51. 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.
52. 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.
53. 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.

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

55. 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.

56. 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.

57. -----(b)(4)-----

58. 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:

59. 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):

60. 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.

61. 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.

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

63. 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 (e.g. -----(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. In table A.1-36 (p68/94) (cleaning validation acceptance criteria), you state that the acceptance criteria for rinse water -(b)(4)- is -(b)(4)-; and in table A.1-37 (cleaning validation following facility upgrade) you state that the acceptance criteria for rinse water -(b)(4)- is -(b)(4)-. Please explain this discrepancy.

- 64. Please provide detailed summaries of any sanitization effectiveness studies that were performed.
- 65. 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:

- 66. 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:

- 67. 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)-----:

- 68. 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.

69. 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.
- Please provide COAs for the other -----(b)(4)----- lots that may have been used to manufacturing your conformance lots.
 - 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).
 - Please indicate if any other test result information is routinely provided from -(b)(4)- to Kamada for these lots other than the COAs.
70. 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)-----.