

**From:** [Marszal, Ewa](#)  
**To:** ["Ruth Wolfson"](#)  
**Cc:** [\(b\)\(4\)](#); [Ward- Peralta, Cherie](#); ["Dudu Nakar"](#); ["Shabtai Bauer"](#); [Scott, Dorothy](#)  
**Subject:** RE: some FU questions in view of our discussions  
**Date:** Monday, March 22, 2010 6:13:32 PM

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Dear Ruthy,

Please perform the study as you proposed with the following modification: please perform the total of 4 mock runs under the same conditions as proposed for virus spiked runs.

We agree with performing the study at the higher protein concentration, [\(b\)\(4\)](#) (please apply maximum protein load). Also, we agree to performing the study for PPV only.

In addition, please make sure to have bench controls in order to assess virus bench stability during nanofiltration runs.

With viral reduction results, please provide information on the time of filtration, inlet pressure, and flow rate in a graphical format. Please demonstrate that these parameters are consistent with those observed in the full scale manufacture. Please provide analogous graphs for the conformance lots. A specification for the rate of filtration for the full scale manufacturing will be required. I am consulting on whether differential pressure specification needs to be established in the future or whether flow rate specification can fulfill this requirement.

Also, please respond to the following request:

1. For [\(b\)\(4\)](#) NAT testing, two NAT methods (i.e., [\(b\)\(4\)](#) method for Source Plasma (SP) and [\(b\)\(4\)](#) method for both SP and recovered plasma (RP)) are used for [\(b\)\(4\)](#) while one method (i.e., [\(b\)\(4\)](#)) is used for testing [\(b\)\(4\)](#) s. [\(b\)\(4\)](#) needs to respond to IR item 25 a-c and e (dated Dec 09, 2009) for the use of their own method, and to IR item 25, d and f, for both methods. Since in-process [\(b\)\(4\)](#) NAT testing has been applied to [\(b\)\(4\)](#) pools destined for all plasma derivatives manufactured by [\(b\)\(4\)](#) r should provide validation data and relevant SOPs in BLA supplements as a CBE for all their products.
2. [\(b\)\(4\)](#) should submit the following information as an amendment to their master file: [\(b\)\(4\)](#) analysis data for [\(b\)\(4\)](#) NAT primers and probes with known [\(b\)\(4\)](#) isolates, especially genotype III isolates, should be submitted to ensure that all three human [\(b\)\(4\)](#) genotypes can be detected by [\(b\)\(4\)](#) NAT procedure.
3. In your submission, plasma testing for manufacturing of Kamada-API also includes [\(b\)\(4\)](#) [\(b\)\(4\)](#) tested in [\(b\)\(4\)](#) Are two [\(b\)\(4\)](#) NAT methods, i.e., [\(b\)\(4\)](#) method for SP and [\(b\)\(4\)](#) method for both SP and RP, for screening [\(b\)\(4\)](#), while only one method, i.e., [\(b\)\(4\)](#) method, for [\(b\)\(4\)](#) ? If so, please provide several information request items listed below:
  - a. For either method, the sensitivity of [\(b\)\(4\)](#) NAT and the threshold level of [\(b\)\(4\)](#) [\(b\)\(4\)](#) to exclude those positive plasma donations from getting into the [\(b\)\(4\)](#) [\(b\)\(4\)](#)
  - b. For either method, 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. For either method, [\(b\)\(4\)](#) analysis of [\(b\)\(4\)](#)- specific primers and probes to demonstrate that all [\(b\)\(4\)](#) genotypes can be efficiently detected.
  - d. For [\(b\)\(4\)](#) method, the sensitivity of [\(b\)\(4\)](#) NAT for [\(b\)\(4\)](#) and the threshold level of [\(b\)\(4\)](#) set.
  - e. A copy of the SOP describing the management procedures for those positive donations

(i.e, beyond the threshold level) of SP and RP to be excluded from manufacturing by (b)(4). Since (b)(4) NAT has been applied to (b)(4) destined for all plasma derivatives similar to (b)(4) NAT and B19V NAT, (b)(4) should provide the information in BLA supplements as a CBE for all their products. For (b)(4), proprietary information, especially for responding items b and c above, can be provided by authorizing Kamada to reference their IND for donor screening of (b)(4) by (b)(4) NAT.

4. (b)(4) for Kamada-API are also tested for HBsAg, HIV1&2-Ab, HCV-Ab by serological methods and HCV RNA and HIV RNA by NAT methods. Please provide the following information:
  - a. Brief summary of method description, test sensitivity, and other validation studies for each of the serological methods. Please also provide copies of the SOPs.
  - b. Are HCV RNA and HIV RNA in (b)(4) derived from both SP and RP tested by (b)(4) licensed (b)(4) NAT procedures for donor screening of HCV RNA and HIV RNA? If so, what is the assay sensitivity and the maximum limits set for each in (b)(4)?

Please provide a response to items 1-4 within a month. Also, please let us know how soon the report from additional viral validation studies described below will be available.

Best regards,

Ewa

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**From:** Ruth Wolfson [mailto:RuthW@kamada.com]  
**Sent:** Saturday, March 20, 2010 3:53 PM  
**To:** Marszal, Ewa  
**Cc:** (b)(4) Ward- Peralta, Cherie; Dudu Nakar; Shabtai Bauer  
**Subject:** RE: some FU questions in view of our discussions

Hi Ewa,

Since we did not get any request/additional comment regarding the NF viral validation we assume FDA accept our approach of worst case and we will cancel the slot (b)(4) was holding for us (for April 12) unless we get from you differently on Monday (March 22<sup>nd</sup>). This is due to the fact that we have to notify (b)(4) by Tuesday what is the status.

Thank you for your understanding,  
Ruthy

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**From:** Marszal, Ewa [mailto:Ewa.Marszal@fda.hhs.gov]  
**Sent:** Saturday, February 27, 2010 3:08 AM  
**To:** Ruth Wolfson  
**Cc:** (b)(4) Ward- Peralta, Cherie; Dudu Nakar  
**Subject:** RE: some FU questions in view of our discussions

Hi Ruthy,  
Unfortunately, I cannot communicate to you an unofficial reviewer's response, which needs to be approved by the management. I forwarded your email and will try to get an official response as quickly as possible.  
Ewa

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**From:** Ruth Wolfson [mailto:RuthW@kamada.com]  
**Sent:** Friday, February 26, 2010 9:51 AM  
**To:** Marszal, Ewa  
**Cc:** (b)(4) Ward- Peralta, Cherie; Dudu Nakar  
**Subject:** RE: some FU questions in view of our discussions

Hi Ewa,  
Any news for us from the viral safety specialist?  
I am asking now since we need to reserve a time slot for the study at (b)(4) if the study need to be performed, essentially if it is a prerequisite for the BLA approval  
Ruthy

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**From:** Marszal, Ewa [Ewa.Marszal@fda.hhs.gov]  
**Sent:** Tuesday, February 23, 2010 6:57 PM  
**To:** Ruth Wolfson; Dudu Nakar  
**Cc:** (b)(4) Ward- Peralta, Cherie  
**Subject:** RE: some FU questions in view of our discussions

Dear Ruthy,

Thank you very much for this information. I am forwarding it to our viral safety specialist. We will get back to you soon regarding viral safety validation.

Ewa

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**From:** Ruth Wolfson [mailto:RuthW@kamada.com]  
**Sent:** Tuesday, February 23, 2010 11:45 AM  
**To:** Marszal, Ewa; Dudu Nakar  
**Cc:** (b)(4)  
**Subject:** some FU questions in view of our discussions

Dear Ewa,

In view of the discussions during the inspections with respect to the viral robustness study for the Nanofiltration (NF) step of Kamada-API process and the possibility that the Agency may request additional study to evaluate the (b)(4)

(b)(4)

(b)(4)

We will appreciate your advice in your earliest convenience so that we can make the required preparations for the worst scenario....in which we have to perform the study.

Kind regards,  
Ruthy