From:	Wood, Lorraine
To:	Ammons, Stanley
Subject:	Information Request for BLA 125612: Human Fibrinogen
Date:	Thursday, November 10, 2016 6:18:00 PM
Attachments:	image001.png image002.jpg image003.jpg image004.jpg image005.jpg image006.jpg
Importance:	High

Dear Mr. Ammons,

We are reviewing for your submission for BLA 125612 and we request the following information to continue our review:

1. For Section 3.2.S.2.3 *Control of Materials*, please clarify if human plasma used for the manufacturing of Human Fibrinogen is US-sourced recovered plasma, Source Plasma, or a combination of these two types of plasma.

2. Please summarize all the viral tests performed on donors, mini-pools, and the manufacturing plasma pools.

3. Regarding the method validation of b) (4) for Human Immunodeficiency Virus (HIV), the document provided in this submission is for (b) (4) (i.e., Document No. *MV/2012/06/EP/*(b) (4)). Please provide the correct document for the method validation of b) (4) for HIV.

4. (b) (4) are critical parameters for the solvent/detergent (S/D) treatment. Please include these (b) (4) parameters in the In-Process Control at the step of S/D treatment.

5. Please provide information on all of the raw materials and reagents of non-biological origin, and biological origin, other than human plasma, which are used in the manufacture of Human Fibrinogen.

6. The starting material for the production of Human Fibrinogen is a (b) (4) Step (b) (4) (i.e., (b) (4)) in the manufacturing process of (b) (4).

   a) Please provide detailed information on this step, and describe how to generate the starting material for the production of Human Fibrinogen.

   b) Reuse of the (b) (4) has been validated as part of the process validation of (b) (4), and Octapharma used the same data to justify the b) (4) at this step in the manufacturing of Human Fibrinogen. To

support this justification, please provide additional information on the reuse of the same (b) (4) in the Human Fibrinogen process (e.g., results from commercial scale (b) (4)).

7. Please provide the results from commercial scale (b) (4) for the reuse of b) (4) at the step of the b) (4) in the manufacture of Human Fibrinogen.

8. Please provide information on the b) (4) integrity test used for the Pegasus SV4 nanofilter.

9. Please revise the limit of Water in the release specification of Human Fibrinogen drug product from b) (4) .

10. Please provide a *Certificate of Analysis* for the reference standard used for the determination of fibrinogen in the (b) (4) assay.

11. For the manufacture of Human Fibrinogen, the proposed expiry period for (b) (4) However, the stability data to support the expiry periods are from (b) (4) . To be accurate, please revise the expiry period for (b) (4)

12. Please provide the updated stability data on the batches of Human Fibrinogen in stability studies *#14P012* and *14P013*.

13. On Page 13 of 23 in Section 2.3 *Drug Substance*, the results of b) (4) Please justify these discrepancies.

14. On Page 97 of 125 in the Process Performance Qualification report *#089PPQR14007.106_US*, the results of the impurity b) (4) in (b) (4) of the conformance batches (b) (4) failed to meet the acceptance criterion (b) (4)). Please provide an evaluation on the deviations.

15. On Page 114 of 125 in the Process Performance Qualification report *#089PPQR14007.106_US*, the results of the impurity b) (4) in the final container of all (b) (4) conformance batches failed to meet the acceptance criterion ((b) (4)). Please provide an evaluation of the impact of the

deviations on the quality and safety of the final drug product of Human Fibrinogen.

16. On Table 4 in Section 3.2.P.5.5 *Impurities Report* No. *020STD34x312/00*, the levels of (b) (4) in either the clinical batches or the conformance batches of Human Fibrinogen drug product were b) (4) , whereas on Page 14 in the same report, you state that the test results of b) (4) in these batches were b) (4) . Please clarify this discrepancy.

Please contact me with any questions.

Thank you

Lorraine

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