



Our Reference: BLA 125668/o

Octapharma Pharmazeutika Produktionsges.m.b.H.

Attention: Mr. Stanley Ammons

August 10, 2018

Sent by email

Dear Mr. Ammons:

We are reviewing your December 28, 2017, biologics license application (BLA), for Immune Globulin Subcutaneous (Human). We determined that the following information is necessary to continue our review:

1. For lot numbers:
 - a. Please specify which letter stands for which plant in eCTD section 3.2.S.2.4.3 (response to Question 11 of FDA's IR dated May 31, 2018).
 - b. Why is (b) (4) lot (b) (4) (lot number starts with letter "(b) (4)") different from the rest of the PPQ (b) (4) lots (lot numbers start with letter "(b) (4)")?
2. Regarding the table (Manufacturing process control parameters and acceptance limits) on page 20 of 25, eCTD section 3.2.S.2.2:
 - a. Please confirm the provided information from Step (b) (4) to Step (b) (4) for Cutaquig is (b) (4) to what is currently approved for manufacturing US licensed Octagam 5% and 10% at the OPG facility.
 - b. "(b) (4)" is listed as one of the process parameters for Step (b) (4) and Step (b) (4). "Duration of sterile filtration" is listed for Step (b) (4). Please include the results of these parameters for the PPQ runs into your process validation report o89PPQR15387.103/03/US.
3. For Table 1 in eCTD section 3.2.S.2.2.1 (response to Question 6 of FDA's IR dated May 31, 2018), please remove "See MOP" and provide the executed process control parameters in conformance batches and clinical batches.
4. Regarding the table on page 2 of 25, eCTD section 3.2.S.2.2:
 - a. Please confirm that the allowed amounts from "Plasma pool size" to "Number of (b) (4) batches pooled for further processing" are (b) (4) to what is currently approved for manufacturing US licensed Octagam 5% and 10% at the OPG facility.

- b. The minimum plasma pool size is (b) (4) . However, the amount of plasma used for (b) (4) during PPQ runs was (b) (4) with the acceptance criterion of (b) (4) . Please explain.
 - c. To support the requested “up to (b) (4) ”, please provide the “amount of bulk for further processing” you have challenged in the PPQ runs.
 5. Regarding your response to Question 7b of FDA’s IR dated May 31, 2018:
 - a. Please confirm the process and holding times from Step (b) (4) to Step (b) (4) for Cutaquig is (b) (4) to what is currently approved for manufacturing US licensed Octagam 5% and 10% at the OPG facility.
 - b. You referred “(b) (4) to end of pre-v.i. bulk” as “Step (b) (4) to Step (b) (4) ”. Do you mean “Step (b) (4) to Step (b) (4) ”?
 - c. You referred “Post-v.i. bulk to end formulation” as “Step (b) (4) to Step (b) (4) ”. Do you mean “S/D treatment to end formulation”? If yes, please provide the breakdown for the process and holding times of (b) (4) for STEP (b) (4) to STEP (b) (4) ”.
 - d. Please use the process and holding times validated during the clinical and PPQ runs and change “Approximate duration” to “Validated duration”.
 6. In Table 3, eCTD section 3.2.S.2.2.3:
 - a. Please include the filters used from Step (b) (4) to Step (b) (4) in the Cutaquig manufacturing process, how many of each filter are allowed to be used per batch, how are they configured (parallel, sequential) if more than one filter, and whether they are changed out.
 - b. Please confirm the provided information on filter usage from Step (b) (4) to Step (b) (4) for Cutaquig is (b) (4) to what is currently approved for manufacturing US licensed Octagam 5% and 10% at the OPG facility.
 - c. For filters used at Step (b) (4) :
 - i. According to eCTD section 3.2.S.2.2, (b) (4) are used, which is in conflict with what are indicated in the table: (b) (4) . Please explain.
 - ii. If more than one filter is used, how do you determine the number of filters to be used for each kind of filters?
 - iii. What are the differences between (b) (4) and (b) (4) ? Please indicate which filter was used during PPQ runs.

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Thank you

- d. The allowable number of filter usage is (b) (4) at Step (b) (4). Please explain why they are also allowed to be (b) (4) during the batch.
- e. For filters used at Step (b) (4):
 - i. According to eCTD section 3.2.S.2.2, (b) (4) filter with a (b) (4) is used at Step (b) (4), which is in conflict with what you provided: (b) (4). Please explain.
 - ii. What are the differences for the filters of (b) (4)? Please indicate which filters were used during PPQ runs.
- f. What is the difference between the filters (b) (4) at Step (b) (4)? Please indicate which filter was used during PPQ runs.
7. Since the final product has a concentration of 16.5%, please (b) (4) the lower IgG Content specification from (b) (4).
8. In the Process Performance Qualification Report on page 107, the Polysorbate 80 concentration for all (b) (4) conformance lots was (b) (4). Please (b) (4) the lower limit of the Polysorbate 80 specification from (b) (4).
9. Please submit the OOS investigation 7485.
10. Please provide a table of the mixing speeds for each step and conformance lot in the process validation

The review of this submission is on-going and issues may be added, expanded upon, or modified.

Please submit your response to this information request as an amendment to this file by August 27, 2018, referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is December 29, 2018.

Please send an email message acknowledging receipt of this request.

If you have any questions, please contact me.

Sincerely,

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Thank you

Edward Thompson
Regulatory Project Manager
FDA/CBER/OBRR/RPMS

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