



Our Reference: BLA 125668/o

Octapharma Pharmazeutika Produktionsges.m.b.H.

Attention: Mr. Stanley Ammons

May 31, 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:

Lot Release Protocol

1. We recommend the following modifications to the Lot Release protocol (LRP):
 - a. On page 1 of 5, please remove (b) (4) plasma from the lot release protocol since all clinical and conformance lots were manufactured with (b) (4) Plasma only. Once you have comparability data for (b) (4) Plasma products, you may submit a Prior Approval Supplement requesting to add (b) (4) plasma to your manufacturing process.
 - b. Please add a separate test which is specific for IgG Content.
 - c. Please include (b) (4) for lot release testing to determine the degree of opalescence since the submitted SOP (13oSOP115/04) for appearance does not include determination of opalescence. The visual method described in the (b) (4) would be acceptable.
 - d. On page 3 of 5 for Sterility: Please change the specification of sterility test from Sterile to No Growth.

Please submit your response to this LRP information request as an amendment to this file by June 11, 2018, referencing the date of this request.

Chemistry, Manufacturing, and Controls (CMC)

2. Since Cutaquig was first approved in other markets, please identify the number of lots manufactured, the number of lots rejected, the number of lots withdrawn, a list of deviations, and available stability data.
3. Please provide the FDA submission tracking number (STN) under which the following study reports were submitted for Octagam: downscale virus validation study reports 020STD50x.137, 020STD84x.85x.150 and 020STD84x.85x.151.

4. Please provide the STN number under which the prion validation study report FR-SP1511 was submitted for Octagam 5%.
5. Please provide study report 020STD81x.US.392/00, which should include (1) biochemical characterization and investigation of (b) (4) activity in the final Cutaquig container of Cutaquig downscale batches; (2) comparison between final container data of Cutaquig downscale batches and Cutaquig technical batches manufactured at (b) (4).
6. Please provide a table containing Cutaquig manufacturing process control parameters and acceptance limits as an amendment to eCTD section 3.2.S.2.2 Description of Manufacturing Process and Process Controls. Please also supply a side-by-side comparison of the process control parameters between clinical lots and Cutaquig.
7. Please amend the following two tables in the eCTD section 3.2.S.2.2 Description of Manufacturing Process and Process Controls.
 - a. Review your master batch records and provide a minimum and maximum range for your times and mixing speeds based upon your clinical and conformance batch data.
 - b. A table indicating maximum and minimum batch sizes as well as maximum and minimum process and holding times.
8. Page 17/43 of 20STD81x.US.387/01 Development Report: Drug Product Formulation (b) (4):
 - a. A black bar blocks part of Figure 3. Please provide a clear version.
 - b. Please provide detailed information about the change control CC48915 (adjustments made in the analytical procedure regarding the target concentration of Polysorbate 80 was changed to (b) (4) for the conformance batches).
9. For Page 11 of 18 in eCTD section 3.2.S.2.2 Description of Manufacturing Process and Process Controls, please provide information on the pore size of the (b) (4) filter, and if (b) (4) are involved and how these are performed.
10. Regarding the (b) (4) specification for the in-process control samples:
 - a. Please justify why the (b) (4) specification limit for sample (b) (4) is set at “(b) (4).” At the similar manufacturing step (Step 13 Formulation and bulk filtration) for Octagam, the (b) (4) specification limit is “(b) (4).”

- b. With regards to Table 3 (page 29) in the Comparability Study Report, Step (b) (4) notes a change in the (b) (4) upper limit from (b) (4) , and this should also be valid for Octagam. Please provide the STN where this change was approved for Octagam.
11. Please explain how the batch numbers are named throughout Cutaquig's manufacturing process. If already provided, please indicate its location in the eCTD.
12. Prescribing Information, section 11 Description:
- a. Please justify your claim of "...even lower amounts of (b) (4)." The (b) (4) content test is not included in your Lot Release Protocol.
 - b. The sum of IgG subclasses is more than 100%, please correct. Please take a conservative approach when rounding the IgG subclass percentages.
 - c. Paragraph 4 where it states, "that are capable of (b) (4) of microbes and toxins," please remove toxins since there is no data to support this.
13. In the Process Validation Report 089PPQR15387.103/03/US,
- a. Page 11/126, you state that the PPQ covers minimum and maximum amount of starting material. Please indicate which lot was manufactured with minimum starting material and the volume of that starting material. Likewise, for the maximum amount of starting material please also indicate the lot number and its starting volume.
 - b. Please provide the following investigation reports as well as CAPA: deviations 50374, 50382, 50479 and 53138.
 - c. Page 24/126, you state that target amount of (b) (4) is (b) (4) plasma. However, according to the ratio of (b) (4) plasma, (b) (4) should be used instead of (b) (4) . Please explain.
 - d. Please provide detailed information on the change controls indicated in Table 73, page 122/126.
14. Regarding report "Production Scale Validation 089VRE15086.103 (b) (4) : Revalidation after (b) (4) ," please provide the following information:
- a. Process Validation Report 089VRE15029.103, "Lifecycle Validation (b) (4) : Revalidation of (b) (4)

(b) (4) Covering (b) (4)
Removal Efficiency for Q1/2015”

- b. Please provide a table of the (b) (4) raw data for Figure 4.
 - c. What was the disposition of the final lots which contained the validation batches (b) (4)? Please also provide a description of any deviations in the manufacture of these lots.
 - d. Please explain why the revalidation for (b) (4) was performed at production scale and the revalidation for (b) (4) was performed at downscale.
15. Regarding report “Downscale 089VRE15406.103, Revalidation after (b) (4) Breakthrough Study,” please provide the following information:
- e. Please provide the report: Process Validation Report 089VRE15353.103 “Lifecycle Validation (b) (4) : Revalidation of (b) (4) Breakthrough Study (Downscale) and (b) (4) Removal Efficiency for Q3/2015”
 - f. Has (b) (4) batch (b) (4) been used in manufacturing previously? If so, for how many cycles?
 - g. In Figure 4 of Report 089VRE15406.103, it is difficult to make out individual batch numbers. Please provide a table of the (b) (4) raw data for Figure 4. Batch manufactured near (b) (4) appears to have a (b) (4) breakthrough. Please provide a description of the incident. Please also explain the two out-of-limit results for batches manufactured between (b) (4) .
16. Regarding “020STD81x.US.369/01: Impurity Profile (b) (4) - Conformance Batches OPG 2016,” please explain the variability of the (b) (4) content in Cutaquig batches in Table 4. I.e., the content of the (b) (4) conformance batch is (b) (4) times the first, and the (b) (4) conformance batch is almost (b) (4) times the first.
17. At which (b) (4) cycle was the (b) (4) used for the manufacture of each of the conformance batches?
18. Regarding the mixing validations, please explain how the (b) (4) stirring speed ((b) (4)) was qualified. For example, to avoid foaming. Please provide the stirring speeds for the mixing report 089PQR155221.103/US.

- a. Please state why samples were not taken for batch (b) (4), as PS80 should have been added and could have been measured.
19. For Step (b) (4) in the batch record, please provide a validation for maximum stirring time for (b) (4) maltose.
20. Please provide the executed batch records for Steps (b) (4) for all the conformance lots.
21. Please provide a table containing a list of filters which have direct contact with product solutions 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. Please include this table in eCTD section 3.2.S.2.2 Description of Manufacturing Process and Process Controls.
22. Regarding removal of osmolality testing in final container, please submit data to demonstrate IPC sample (b) (4) and final container results are comparable for the conformance lots. Following (b) (4), polysorbate 80 is added, and the concentration is adjusted with maltose (b) (4).
23. Please identify the submission where (b) (4) was approved to replace the (b) (4) assay for Octagam 5% and 10%.
24. Please submit the endotoxin validation study for IPC sample (b) (4).
25. In your December 11, 2013, response to the addition of (b) (4) testing, you noted you did not believe adding (b) (4) as a lot release test was necessary but would test for (b) (4) following any manufacturing changes to Cutaquig. Please test (b) (4) consecutive lots to determine a baseline value for (b) (4).
26. For the analytical method validation report for Determination of (b) (4), there is a discrepancy in data table 6.3.4.1.1. When calculated, the average of the (b) (4) does not agree with the average of (b) (4). Please explain.
27. Regarding visual inspection,
 - a. Please clarify what is meant by a “small amount of particulate matter” which is part of the description for visual inspection in the stability and conformance reports.
 - b. For the stability and comparability report, please replace “conform” with the actual results (data) for both clinical and conformance lots.
 - c. The lot release protocol and final specifications do not include the mention of particulate matter. Please remove the mention of particulate matter

from the current stability and comparability reports, and all future stability studies.

28. Regarding the comparability study report

- a. In Table 16, it is noted that the sample (b) (4) concentrations for all batches tested are within the acceptance criterion. There is one lot manufactured at OPG which is unusually elevated compared to the others, including the clinical lots. Please explain.
- b. Please explain how the (b) (4) acceptance criterion was determined.
- c. In Table 38, the (b) (4) present in the final containers for the conformance lots are (b) (4) as much as in the clinical lots. Please explain.

29. For the (b) (4) specification, please set individual specifications for each impurity. Please explain how the (b) (4) for the (b) (4) was determined.

30. Regarding the stability studies,

- a. Please identify the “FDA stat software” used in the analysis of the stability data, including the version.
- b. Please note stability data should not be analyzed as a pool if the slopes of the lines are not comparable. Please identify all test parameters and lots affected where the data was manually pooled to generate a common linear regression line.
- c. For Figure 13 in Study FFH 1332, please explain the (b) (4) Measles Ab titer starting at month 18.
- d. Regarding the final bulk lots (b) (4), please clarify if any of this material was manufactured into final product, (b) (4), and placed on stability.
- e. Please identify under what circumstances the final bulk would be (b) (4).
- f. Please explain the differences between appearance and visual inspection including differences in the methods. Please submit 013MPS81x/07/US.CA which is a footnote in the stability tables in Study 16P001.
- g. Please submit the SOP and validation for visual inspection. There is only a method for Appearance included in the submission.

- h. Please clarify how “slightly opalescent” is determined.
 - i. With regard to Stability Study FFH 1332, please explain the sudden (b) (4) of maltose concentration at 25°C during storage.
 - j. Please include (b) (4) as a testing parameter to determine degree of opalescence since the SOP (13oSOP115/04) submitted for appearance does not contain information regarding determination of opalescence.
 - k. Please add separate testing which is specific for IgG Content.
31. Please submit one 48 mL vial from each conformance lot for (b) (4) and other testing. Please ship the samples to the following address:

FDA/CBER/OTAT
Attn: Dr. Dorothy Scott/Nancy Eller
Building 52/72, Room 4124
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Telephone: (301) 928-2993/ (240) 402-8193

Please notify Dr. Dorothy Scott (dorothy.scott@fda.hhs.gov) and Ms. Nancy Eller (nancy.eller@fda.hhs.gov) when the samples are being shipped, and please include the tracking number in the email.

Please submit your response to this CMC information request as an amendment to this file by June 18, 2018, referencing the date of this request.

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

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