

From: Rana, Pratibha
Sent: Wednesday, April 25, 2012 4:34 PM
To: Rangetiner, Barbara; Ammons, Stanley
Subject: STN 125416/0 Information Request (4-25-2012)
Our Reference: STN 125416/0

Octapharma USA, Inc.
Attention: Stanley Ammons

Dear Mr. Ammons:

We are reviewing your December 22, 2011 biologics license application (BLA) for Pooled Plasma, Solvent Detergent Treated (Human). We are providing the following comments and request for additional information to continue our review:
BLA 125416: Chemistry, Manufacturing and Controls and Establishment Information Request

1. Please provide a detailed list of other products that share the same manufacturing areas/rooms with OctaplasLG[®] (US) at both OPG and OAB sites. Octapharma provided a list of products that share the same general area with OctaplasLG[®] (US) manufacturing, but not specific rooms shared during each step of the manufacturing process.
2. Please provide a detailed list of product contact equipment, including single-use and reusable, dedicated and shared for manufacturing of OctaplasLG[®]. For each piece of shared equipment, please list all products that share that piece of equipment with OctaplasLG[®] (US) at both OPG and OAB sites.
3. Please provide the following regarding automatic cleaning and sanitization for stainless steel vessels:
 - a. Rationale for the selected cleaning procedures which addresses their effectiveness for the residual products to be removed.
 - b. Validation report, including SOP number, describing the cleaning validation procedures for removal of product residues and cleaning agents. The report should identify the sampling and analytical methods used and address their sensitivities and specificities, and revalidation intervals.
 - c. Specify sterile hold time for cleaned equipment and intervals when CIP/SIP needs to be performed again.
 - d. Please justify why TOC, bioburden and endotoxin are not tested during cleaning procedures to monitor their effectiveness.
4. Regarding manual cleaning:
 - a. Please justify the omission of surface swab sampling and testing for bioburden or endotoxin after cleaning. Please reference the relevant SOP on how monitoring is performed and the acceptance parameters.

- b. Please explain why different detergents (----- (b)(4) ----- at OPG and ----- (b)(4) ----- at OAB) are used at different sites for manual cleaning of minor equipment.

5. The submission does not contain information regarding if any (b)(4) or chromatography units are used for the manufacturing of the product. Please provide a description of the equipment, the dates for IQ/OQ/PQ, and validation report.

6. Please provide the following for the C-18 --(b)(4)-- column:
 - a. The construction of the column including materials and specifications
 - b. Validation studies that support the adequacy of cleaning and regeneration procedures
 - c. Justification for the omission of conductivity, TOC and bioburden tests
 - d. Quantitative assessment of --(b)(4)-- with adequately justified acceptance criteria
 - e. Sterile hold/storage time and re-qualification interval with supportive data to justify the set times
 - f. Cleaning procedures and frequency of replacement for accessory parts, such as gaskets and flow plates
 - g. ----- (b)(4) -----.
 - h. Criteria for switching between control of column loading procedure by ----- (b)(4) ----- or validation of their interchangeability
 - i. Operational temperature
 - j. Elution conditions and criteria for peak collection
 - k. Representative elution profile

7. Please provide the following for prion removal LG chromatography column:
 - a. Specification of the -(b)(4)- column and the ----- (b)(4) ----- column, including construction materials and dimensions.
 - b. Cleaning validation and routine cleaning for the column. Please include dirty hold and clean hold time and studies performed to support these times.
 - c. Qualification of the column
 - d. Justification for the omission of ----- (b)(4) ----- tests
 - e. Quantitative assessment of --(b)(4)-- with adequately justified acceptance criteria
 - f. Cleaning procedures and frequency of replacement for accessory parts, such as gaskets and flow plates and supportive data to justify the frequency
 - g. Explanation for why two different procedures are used during ----- (b)(4) ----- -- at OPG site in Vienna ----- (b)(4) ----- and at OAB site in Stockholm (----- (b)(4) -----).
 - h. Operational temperature
 - i. Elution conditions and criteria for peak collection
 - j. Representative elution profile

8. Please indicate where in the submission the specification and validation of the filters used in the following steps in the manufacturing process can be found or if not

included in the submission, please provide a description of the filtration processes as well as specifications and validation data for filters used in production:

- a. 1 µm membrane filters used after pooling of the thawed plasma and before S/D treatment in Step 2 of the manufacturing process for removal of cells, cell fragments and aggregates.
- b. -----(b)(4)----- filters used to clear up the aqueous phase after S/D treatment in Step 3 of the manufacturing process.
- c. The 0.45 µm and 0.2 µm filters used in the final sterile filtration step.

9. Regarding filling machines:

- a. Please provide a description of the filling machines used at both sites as well as its qualification, summaries of the test results, and summaries of any deviations (if deviations occurred, a summary of the investigation and resolution)
- b. Please provide changeover procedures, and provide study data to support the adequacy of the procedures.

10. Regarding Container closure:

- a. Please clarify if --(b)(4)-- of plasma bags (-----
----- (b)(4) -----)
used for OctaplasLG[®] (US) have been previously submitted to FDA and reviewed as part of other submissions. Please provide the STN and approval date if they have been. If not, please provide studies to support the suitability of using these bags for OctaplasLG[®].
- b. Please clarify if --(b)(4)- bags are qualified and used -----(b)(4)----- facilities.
- c. Please clarify if --(b)(4)- types have been used in your CCIT and stability study.
- d. Please explain why -----(b)(4)----- for CCIT long term stability study were not conducted under pressure.

11. Information and data submitted to the BLA in support of analytical characterization and pharmaceutical development were restricted to conformance lot manufacture in support of process validation for OctaplasLG[®]. In order to provide complete information, please submit the following additional information and data:

- a. Batch analysis and additional analytical characterization (as applicable) of key development lots. Please include lots manufactured in support of your predecessor product, Octaplas[®] and those manufactured in support of OctaplasLG[®].
- b. Key additional lots should include pre-clinical and clinical lots and may also include applicable engineering lots.
- c. The BLA cites the following OctaplasLG[®] development/ engineering lots for which analytical data do not appear to have been submitted: (i) (b)(4) development lots manufactured in 2007 and (ii) -----(b)(4)-----
----- (b)(4) ----- . Please clarify the purpose of these cited lots and submit summary data from their manufacture and characterization.

- d. For each key development lot, please present the following information in tabular format: (i) Lot number, (ii) Date of Manufacture, (iii) Batch size, (iv) Plasma type, (v) Purpose
 - e. Please explain any differences in the manufacture and release of lots used in pivotal clinical trials with that intended for commercial distribution.
 - f. Study report 020STD952.074 submitted in support of pharmaceutical development made reference to, "Process Mapping and Harmonization (MAP)," implemented according -----(b)(4)----- guidelines and associated study reports, which purportedly documented the identification of critical quality attributes, critical process parameters and the evaluation of their established limits. Please submit the relevant, supportive documents. Please provide in tabular format: (1) a list of product quality attributes, their designated criticality, associated limits, justification of limits, action taken when limits are exceeded and (2) a list of process parameters, their designated criticality, associated limits, justification of limits, action taken when limits are exceeded.
12. The BLA does not contain adequate information to provide a high degree of assurance for proper sourcing and control of plasma starting material. Therefore please provide the following additional information.
- a. For each supplier of Source Plasma or recovered plasma
 - A list of blood establishments under each supplier's administration
 - b. For each blood establishment
 - Name and address
 - License number
 - Responsible head
 - Inspection history
 - Epidemiological data on blood transmissible infections
 - c. Regarding adventitious agents testing of plasma
 - -----(b)(4)-----
 - A list of laboratories' names, addresses, license numbers and inspection histories
 - A list of test kits including name of test kit, manufacturer and regulatory status e.g., licensed, cleared, under IND
 - d. For each manufacturer of recovered plasma
 - A Short Supply Agreement detailing conditions for plasma collection, freezing, storage and shipment to Octapharma
13. The BLA did not provide information regarding sourcing and control of raw materials, reagents or excipients used in the manufacture OctaplasLG[®]. Therefore, please provide the following additional information:
- a. A list of all raw materials, reagents and excipients used in the manufacture of OctaplasLG[®], including chemicals and reagents used in the preparation of processing buffers and column regeneration/ cleaning solutions
 - b. For each raw material, reagent or excipient, the name and address of each supplier and the quality standard to which each is controlled

- c. Materials or reagents guaranteed by a supplier with a Certificate of Analysis (CoA) and materials or reagents manufactured and/or controlled, in-house
 - d. For each material guaranteed with a CoA, a representative CoA
 - e. For each material manufactured and/or tested in-house, the official material specification document
14. Please provide the following additional information to the process narrative so that a complete and accurate assessment can be conducted of the intended commercial manufacturing procedure and supportive information.
- a. For each manufacturing step: location of operation (e.g. room number), major equipment used and procedures used to transfer material between manufacturing steps; please identify critical manufacturing steps.
 - b. For each mixing or collection vessel: equipment identifier, material of construction and vessel volume.
 - c. For each filter: material number, supplier, materials of construction and filtration area
 - d. Additional process controls and acceptance criteria, as follows:

(b)(4)

[(b)(4)]

15. Please provide additional clarification regarding the relationship between -----
----- (b)(4) -----
-----.

16. Please provide information on batch numbering.

17. Please provide composition and storage requirements for all buffers used to support manufacture.

18. Please implement a process during the freezing step of the final product for making an indent marker in each filled plasma bag as an indicator of proper frozen storage, transport, distribution and consignee use.

19. During conformance lot manufacture, lots ----- (b)(4) -----
----- to comply with the in-process limit for ----- (b)(4) -----

-----; thereby, invalidating these lots as conformance lots. Please repeat this component of process validation.

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

Please submit your response to this information request as an amendment to this file May 24, 2012 referencing the date of this request

The action due date for this file is October 22, 2012.

If you have any questions, please contact me.

Sincerely,

Pratibha Rana
Pratibha Rana, M.S.
Regulatory Project Manager

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