



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation Research
Office of Blood Research and Review

To: STN 125416/0 and Pratibha Rana
From: Nancy Kirschbaum, PhD, Chemist, OBRR/DH/LH
Applicant: Octapharma
Product: Octaplas™, Pooled Plasma (Human), Solvent/Detergent Treated
Subject: Action review of Original BLA
Through: Tim Lee, PhD, Acting Chief, OBRR/DH/LH
Review Committee: Michael Brony, Harold Boxenbaum, Christine Drabick, Mitchell Frost, Jie He, Anthony Lorenzo, Jerald Mullersman, Michael Nguyen, Mikhail Ovanesov, Ze Peng, Renee Rees, M. Keith Wyatt

Basis for Approval

The Chemistry, Manufacturing and Controls information and data submitted to Biologics License Application (BLA) 125416/0 are adequate to ensure commercial product quality and stability. The summary basis for BLA approval is documented in the separate, "Summary Basis for Regulatory Action."

Introduction

Octapharma Pharmazeutika Produktionsges.m.b.H (Octapharma) has submitted an original biologics license application (BLA) for Pooled Plasma (Human), Solvent Detergent Treated for transfusion. The product is a frozen, sterile, pyrogen-free, solvent/detergent treated (1% tri-n-butyl phosphate/1% octoxynol), pooled human plasma product filled in 200 mL doses into 300 mL polyvinyl chloride (PVC) plasma bags. It is manufactured from 630 to 1,520 single donor units of either Source Plasma or recovered plasma from the same ABO blood group. The original BLA refers to the product as OctaplasLG; however, the proprietary name of the US marketed product will be Octaplas™.

Background

OctaplasLG/Octaplas™, Pooled Plasma (Human), Solvent Detergent Treated was developed for US market under IND 13956. Octaplas™/OctaplasLG is a modified version of Octaplas®, marketed in Europe since 1992. The rationale for product development was to provide a standardized, cell-free human plasma for transfusion with improved viral safety compared to Fresh Frozen Plasma (FFP). Improved viral safety regarding enveloped viruses has been achieved through incorporation into the manufacturing process of a solvent/detergent (S/D) treatment step validated to inactivate relevant enveloped viruses, while preserving the activity of relevant plasma proteins. A significant amount of clinical and manufacturing experience exists for its predecessor, Octaplas®. The manufacturing process for Octaplas® incorporates an S/D treatment time of 4 – 4.5 hours. Octaplas™/OctaplasLG manufacture has incorporated two changes to the process for Octaplas®: (1) reduction of S/D treatment time to 1 – 1.5 hr. and (2) addition of an affinity column designed to remove prion protein infectivity, the causative agent in Creutzfeldt Jakob Disease (CJD) and variant CJD (vCJD). First approved in 2009, OctaplasLG/Octaplas™ is currently approved in Australia, United Kingdom, Belgium, Finland, Ireland, Luxembourg, The Netherlands, Sweden, Portugal, Switzerland and Germany.

Review Milestones

Task	Date
Received	23 December 2011
First committee meeting	13 January 2012
Filing meeting	06 February 2012
Filing date	21 February 2012
Mid-cycle	23 May 2012
Pre-approval inspection	24 July – 08 Aug 2012
BPAC	20 September 2012
Major Amendment Designation	19 October 2012
Action Due	21 January 2013

Drug Substance

Description and Characterization

Description

Product description and composition may be found in Drug Product modules.

Characterization

Analytical Characterization During Development

Analytical characterization data submitted in the BLA focused on comparability of conformance lots for Octaplas™ to its predecessor, Octaplas® and FFP. The majority of analytical characterization data were presented in **Study Report 020STD952.072/00**: Biochemical Characterization of OctaplasLG Validation Batches Manufactured from US Plasma [16 December 2011] submitted under Appendix II, **module 3.2.P.2**. **Module 3.2.S.3** presented data taken from **Study Report 020STD952.072/00**. These same data were also used in support of process validation in **module 3.2.P.3.5**. Table 1 lists comparative data.

[(b)(4)]

One (1) page determined to be not releasable (b)(4)

[(b)(4)]

-----~~(b)(4)~~-----

Methods of Manufacture and Packaging and Process Controls

Description of the Manufacturing Process and its Control

The manufacturing process for Octaplas and its control are described for drug product under **module 3.2.P.3.**

Support for the Manufacturing Process and Established Process Controls

Raw Materials [Module 3.2.S.2.3]

Materials of Animal or Human Origin

Human Plasma Starting Material

The following statement regarding sourcing and control of plasma used in manufacture of Octaplas™ represented the entire content of **module 3.2.S.2.3.**

“The starting material, human plasma, used in the manufacture of OctaplasLG is obtained from U.S. based plasmapheresis centers and community blood banks. All donations used by Octapharma comply with the requirements of 21 CFR 640.30 and 21 CFR 640.60. OctaplasLG will be manufactured from either Source or recovered plasma.”

In response to an information request, complete information about control and supply of plasma for further manufacture was submitted in amendment 3. The quality agreement submitted indicated that recovered plasma for further manufacture was restricted to that placed in (b)(4) freezer within (b)(4) of blood draw. Upon further consideration, OBRR required Octapharma to use only FFP as starting material i.e., separated from cellular components and placed in a (b)(4) freezer within (b)(4) of blood draw.

Regulatory guidance: According to GFI: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture...[May 1999]: (1) Short Supply Agreements are only between the licensed manufacturer of the final product and the facility which recovers the plasma (not a broker), (2) shipment of products in short supply require oversight by the licensed

final manufacturer, who reports periodically to FDA regarding production specifications and suppliers of the short supply material.

Materials and Reagents of Non-animal/ Non-human origin

The batch formula in **module 3.2.P.3.2** listed the following information regarding materials used in the production of Octaplas™.

[(b)(4)]

Control of Raw Materials and Reagents

Compendial Materials – Certificates of Analysis

According to information in **module 3.2.P.3.2**, the majority of raw materials or reagents are controlled to compendial specification. Octapharma stated that quality and compliance of compendial raw materials are either guaranteed by the supplier or tested in-house. In response to an information request, the in-house specification and representative Certificate of Analysis for each raw material were provided in amendment 3.

Non-compendial Materials – In-house specification document and in-house testing

----- (b)(4) -----

Process Development and Validation

Information and data to support development and validation of the commercial process were provided under respective drug product modules.

Drug Substance Container Closure and Stability

Information and data addressing container closure system and product stability were provided under respective drug product modules.

Drug Product

Product Attributes and Pharmaceutical Development

Product Description and Composition [Module 3.2.P.2.1]

Description

Octaplas™ is a frozen, sterile, pyrogen-free, solvent/detergent treated (1% tri-n-butyl phosphate/ 1% octoxynol), pooled human plasma product filled in 200 mL doses into 300 mL PVC plasma bags. It is manufactured from 630 to 1,520 single donor units of either Source Plasma or recovered plasma from the same ABO blood group.

Composition

Table 3: Product Composition

Ingredient	Amt. per 200 mL bag	Function	Standard
Human plasma containing expected spectrum of plasma proteins	9.0 – 14.0 g	Active	--(b)(4)--
Na-citrate·2H ₂ O	0.88 – 1.48 g	Anticoagulant	USP; Ph. Eur.
NaH ₂ PO ₄ ·2H ₂ O	0.06 – 0.24 g	Buffer	USP/NF; Ph. Eur.
Glycine	0.80 – 1.20 g	Osmolality regulator	USP/NF; Ph. Eur.

It was noted that solvent/detergent treated plasma contains a reduced content of lipids and lipoproteins as a result of exposure to solvent/detergent reagents and subsequent oil extraction.

Formulation Development [Module 3.2.P.2.2]

The BLA made reference to **study report 020STD952.074**. Na-citrate is not added to the final formulation. It is present as anticoagulant during blood/ plasma collection. Its concentration in the final product is ---(b)(4)----- . NaH₂PO₄·2H₂O is added as a buffer. The ---(b)(4)---- concentration ranges from –(b)(4)----- depending on initial concentration in plasma source material. Glycine is added to adjust osmolality and ranges from ---(b)(4)-----

Excipients and Their Control [Module 3.2.P.4]

Table 4: Excipients

Excipient	Supplier	Quality Control
Na-citrate·2H ₂ O	---(b)(4)----- -----	-----(b)(4)-----
NaH ₂ PO ₄ ·2H ₂ O	--(b)(4)-----	-----(b)(4)-----
Glycine	---(b)(4)-----	-----(b)(4)-----

Impurities [Module 3.2.P.5.5]

[(b)(4)]

[(b)(4)]

Summary report PBL/R22/138/1/01110: Toxicological Studies on Prion Binding Resin

(b)(4) test and maximum tolerated dose/estimated maximum dose study in (b)(4) rats were performed with ----(b)(4)----- ligand. Other potential resin leachables i.e., from the ---(b)(4)----- resin were not investigated. The decision to investigate potential toxicity of the ligand and not other leachates was based on estimated total leachate weight of ----(b)(4)----- and a statement that such resins (“adsorbents”) are widely used in plasma protein purification and are known to be stable under chromatographic operational and (b)(4) conditions. The -----(b)(4)----- is widely used in biopharmaceutical purification processes under the trade name, ---(b)(4)---- In response to an information request, Octapharma submitted in amendment 9, updated **Study report: ---(b)(4)-----, Safety, Leachables and Extractables**, which was considered adequate to address safety of potential leachables and extractables impurities, which may be derived from the ---(b)(4)-----

Drug Product Release Specification

The drug product final release specification was the subject of discussion throughout BLA review. In response to information requests, Octapharma proposed the release specification listed in Table 6, which was considered acceptable.

Table 6: Release Specification [Module 3.2.P.3.5.1]

Specification No. 013FPS952/05/US		
Test	Method	Acceptance Criteria
<i>Characters</i>		
Visual Control	---(b)(4)----	Clear to slightly opalescent and free of solid or gelatinous particles
<i>Identity</i>		
---(b)(4)-----	----(b)(4)----- ----- -----	----- ----- -----
---(b)(4)-----	---(b)(4)----	---(b)(4)----
<i>Tests</i>		
(b)(4)	---(b)(4)---	--(b)(4)---
(b)(4)	---(b)(4)---	----(b)(4)----
Protein	----(b)(4)----	45-70 mg/mL
(b)(4)	---(b)(4)---	(b)(4)
(b)(4)	---(b)(4)----	(b)(4)
(b)(4)-----	---(b)(4)---	(b)(4)
(b)(4)	---(b)(4)----	---(b)(4)---
--(b)(4)--	---(b)(4)---	---(b)(4)---
--(b)(4)--	---(b)(4)---	---(b)(4)--
--(b)(4)---	---(b)(4)---	---(b)(4)---
Sterility	--(b)(4)---	Sterile
Pyrogens	CFR §610.13	Free of pyrogens
<i>Assays</i>		
Factor II	----(b)(4)----	---(b)(4)---
Factor V	---(b)(4)---	---(b)(4)---
Factor VII	---(b)(4)---	---(b)(4)---
Factor VIII	---(b)(4)---	--(b)(4)--
Factor X	---(b)(4)---	---(b)(4)---
Factor XI	---(b)(4)----	---(b)(4)---

Specification No. 013FPS952/05/US		
Test	Method	Acceptance Criteria
<i>Characters</i>		
Protein C	---(b)(4)---	--(b)(4)--
Protein S	---(b)(4)---	≥0.4 IU/mL
Plasmin inhibitor (α ₂ -antiplasmin)	---(b)(4)---	≥0.4 IU/mL
ADAMTS13	(b)(4)	---(b)(4)---
----- <i>(b)(4)</i> -----		
----- <i>(b)(4)</i> -----		---- <i>(b)(4)</i> ----
<i>(b)(4)</i>		---- <i>(b)(4)</i> ----
<i>Additional Tests</i>		
--- <i>(b)(4)</i> ---	-- <i>(b)(4)</i> --	--- <i>(b)(4)</i> ---
-- <i>(b)(4)</i> ---	--- <i>(b)(4)</i> --	--- <i>(b)(4)</i> ---
TnBP	-- <i>(b)(4)</i> ---	<2 µg/mL
Octoxynol	--- <i>(b)(4)</i> ---	<5 µg/mL
Fibrinogen	-- <i>(b)(4)</i> --	--- <i>(b)(4)</i> ---
<i>(b)(4)</i>	--- <i>(b)(4)</i> --	-- <i>(b)(4)</i> --
<i>(b)(4)</i>	--- <i>(b)(4)</i> ---	--- <i>(b)(4)</i> ---
<i>(b)(4)</i>	--- <i>(b)(4)</i> ---	--- <i>(b)(4)</i> --

Justification of Release Specification [Module 3.2.P.5.6]

The release specification was justified by compliance to -----*(b)(4)*-----, addressed safety with respect to levels of Protein S and Plasmin Inhibitor and reflected manufacturing capability. Octapharma requested an exemption from the General Safety Test. Their justification included an inability to properly perform the test due to the intrinsic irritant nature of plasma and adequate control of extraneous toxic contaminants through performance of the ---*(b)(4)*-----
Exemption from the General Safety Test will be granted. Regarding impurities specification, justification and supportive data were provided under **module 3.2.P.5.5**. Justification for safety parameters: anti-HAV antibody, anti-B19 antibody and anti-HEV antibody was provided in study report **020STD003.932 and 952/00: Pathogen Safety Evaluation** submitted to **module 3.2.A.2.4.5**. Acceptance limits for antibody levels were derived from ----*(b)(4)*-----
----- for HAV, ---*(b)(4)*----- for B19V or ----*(b)(4)*-----
- to HEV.

Methods of Manufacture and Packaging and Process Controls

Manufacturers

Octaplas™ will be manufactured at two facilities:

1. Octapharma AB
Elersvägen 40
S-112 75 Stockholm
Sweden
2. Octapharma Pharmazeutika Produktionsges.m.b.H
Oberlaaer Strasse 235
A-1100 Vienna
Austria

Testing Facilities

<u>Operation</u>	<u>Name and address</u>
--- <i>(b)(4)</i> -----	----- <i>(b)(4)</i> ----- ----- -----

Four (4) pages determined to be not releasable (b)(4)

Conformance lot manufacture in support of process validation was summarized in **study report 080VRE11366.105** submitted to **module 3.2.P.3.5** and **study report 020STD952.072** submitted to **module 3.2.P.2**.

The process validation exercise covered both conformance lot manufacture and manufacturing process transfer from OPG Vienna to OAB Stockholm. Indicated lots (Table 9) were manufactured with ---(b)(4)----- . Lots from recovered plasma or Source Plasma were manufactured from A, B or O blood groups.

A risk assessment of potential impact of manufacturing operations on product quality was performed indicating the relevant quality control tests to be -----(b)(4)-----
----(b)(4)----- for discrete phases of manufacture were defined and validated. Table 9 lists conformance lot information derived from **module 3.2.P.3.5** and **study report 080VRE11366.105**

[(b)(4)]

Process validation approach

Study report 020STD952.072 indicated a process validation approach based on a stated objective for each manufacturing step, step description and operational controls and documentation of results from conformance lot manufacture with reference to pre-determined acceptance criteria for operational parameters and quality control testing. Data derived from monitoring conformance lot manufacture were provided in the study report and are reproduced in Tables 10-13. A closer analysis of critical -----(b)(4)----- as a function of processing was provided in **study report 020STD952.074** and reproduced here as Figure 2.

Ten (10) pages determined to be not releasable (b)(4)

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.

Response review: DMPQ

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)----- --- (b)(4)----- at OAB) are used at different sites for manual cleaning of minor equipment.

Response review: DMPQ

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.

Response review: DMPQ

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)-----
---(b)(4)----- Please justify the high acceptance limit of ---(b)(4)-----
 - h. Criteria for switching between control of column loading procedure by ---(b)(4)----- ---(b)(4)----- or validation of their interchangeability
 - i. Operational temperature
 - j. Elution conditions and criteria for peak collection
 - k. Representative elution profile

Response review: Items a-c reviewed by DMPQ.

Item d: Octapharma explained there ----(b)(4)----- which corresponds to the (b)(4) specified limit.

Items e-f reviewed by DMPQ.

Item g: Octapharma agreed to revise the IPC ---(b)(4)-----
----- (b)(4)-----

Item h: The range for ----(b)(4)----- at both OPG and OAB. -----(b)(4)-----
----- (b)(4)----- is set to protect equipment.

Item i. -----(b)(4)-----

Item j: -----(b)(4)-----

Item k: Elution profiles for conformance lots were provided.

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)----- OPG site in Vienna -----(b)(4)----- (b)(4) and at OAB site in Stockholm (----(b)(4)----- (b)(4)----
 - h. Operational temperature
 - i. Elution conditions and criteria for peak collection
 - j. Representative elution profile

Response review: Items a-c reviewed by DMPQ.

Item d: ---(b)(4)----- are controlled at material receipt. This is ---(b)(4)-----column.

Item e: See item 6d.

Items f-g: reviewed by DMPQ

Item h: -----(b)(4)-----

Item i: -----(b)(4)-----

----- (b)(4)-----

Item k: Elution profiles for conformance lots were provided.

The response was adequate.

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)----- 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

Response review: DMPQ.

9. Regarding filling machines:

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

Response review: DMPQ.

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)----- have been used in your CCIT and stability study.
- d. Please explain why ---(b)(4)----- tests for CCIT long term stability study were not conducted under pressure.

Response review: DMPQ.

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) ---(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.

Response review:

Items a-e: Octapharma provided a discussion and tabulation of development lots. ---(b)(4)--- ---
(b)(4)----- occurred between 2007 and 2011: ----(b)(4)-----

Biochemical characterization data from lots supporting phases (b)(4) (including “technical” lots cited in item 11c) were provided in relevant study reports. Table 14 listed information about each key development lot in accordance with item 11d. The following lots were placed on stability.

[(b)(4)]

Octapharma stated that the manufacturing procedure used to produce clinical lots used for study LAS-203 was identical to the intended commercial process; however, extensive biochemical characterization of clinical lots had not been performed.

------(b)(4)-----

Validation Report 080RPQ08231.105 [2008]

This was the validation for ---(b)(4)----- Lots ---(b)(4)-----
(b)(4)----- were manufactured and extensively characterized. Stability data for (b)(4)
months' storage were derived from these lots. Octapharma cited the following quality indicators
used for in-process monitoring:

------(b)(4)-----

Each manufacturing step was addressed with a step objective, risk assessment and quality evaluation. Rationale and justification were provided for each cited process parameter or quality

One (1) page determined to be not releasable (b)(4)

[(b)(4)]

---(b)(4)-----

----- (b)(4) -----

---(b)(4)-----
----- (b)(4) -----

The response was adequate.

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.

For each supplier of Source Plasma or recovered plasma

- A list of blood establishments under each supplier's administration

For each blood establishment

- Name and address
- License number
- Responsible head
- Inspection history
- Epidemiological data on blood transmissible infections

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

For each manufacturer of recovered plasma

- A Short Supply Agreement detailing conditions for plasma collection, freezing, storage and shipment to Octapharma

Response review: The information requested in items a-c was provided in tabular format. In response to item 12d, Octapharma submitted current templates for Quality Assurance Agreements (QAA) covering US Source Plasma or recovered plasma suppliers or shippers.

Quality Assurance Agreement Between Octapharma AG, Seidenstrasse 2, 8853 Lachen Switzerland and Plasma Supplier (Name of blood bank, address)

Regulatory requirements refer to relevant EC directives, recommendations, monographs and guidelines; national requirements and PIC/S guidelines. There is adequate coverage of operations, logistics and concerns pertaining to: communication and records; donor selection and

deferral; plasma testing; deviations; look-back notification and post-donation information; plasma production, labeling and storage and quality assurance. Section 7.1 defines two types of plasma: (1) FFP -- ...processing including freezing process occurs within (b)(4) of donation and (2) Rec24 – processing including freezing process occurs within 24 hr. of donation. Either product may be obtained from whole blood donations or automated apheresis. Section 7.3 further indicate requirement to cool whole blood units to (b)(4) if plasma is not separated and frozen within (b)(4) QAA information indicated that the worst case scenario for starting plasma would be a product separated and placed in a ---(b)(4)----- after donation. Plasma temperature must remain at (b)(4) for the duration of storage. Plasma must be received by Octapharma within (b)(4) (b)(4) of processing/freezing.

The response was adequate.

12. 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

Response review: The information requested in items a-c was provided in tabular format. Representative CoA's or in-house quality standard specifications were provided. For administrative purposes, this information may be submitted to **module 3.2.S.2.3** instead in the cover letter response submitted to **module 1.2**.

The response was adequate.

13. 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)]

One (1) page determined to be not releasable (b)(4)

----(b)(4)-----

The response was adequate.

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

Response review: ---(b)(4)----- during plasma thawing and pooling.

The response was adequate.

15. Please provide information on batch numbering.

Response review: The requested information was provided in **module 1.2** cover letter. For administrative purposes, the batch numbering scheme should be submitted to **module 3.2.P.3.3**.

The response was adequate.

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

Response review: The requested information was provided in **module 1.2** cover letter. For administrative purposes, composition and storage requirements for process buffers should be submitted to **module 3.2.P.3.3**.

The response was adequate.

17. 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.

Response review: Octapharma does not want to implement a freezer indent marker for the following reasons:

- a. the marker must withstand exposure to dry ice
 - b. not feasible to activate each individual marker
 - c. additional validation
 - d. potential for product recall, customer complaints, product replacement
 - e. inappropriate use of indent marker information after product leaves Octapharma's control
- Octapharma contends that its "validated" cold chain management is sufficient and that Octapharma is not responsible for product once it leaves Octapharma's control.

The response was adequate.

18. During conformance lot manufacture, lots ----(b)(4) ----- failed to comply with the in-process limit for bulk ---(b)(4)-----; thereby, invalidating these lots as conformance lots. Please repeat this component of process validation.

Response review: The response indicated that only ---(b)(4)--- data would be provided for (b)(4) additional lots manufactured at OAB. During a teleconference with Octapharma to discuss the pending pre-approval inspection, FDA communicated to Octapharma its requirement for the manufacture and characterization of--(b)(4)- additional conformance lots at OAB under a full process validation protocol. Octapharma acknowledged FDA's requirement and has manufactured conformance lots ----(b)(4)-----, which met pre-determined validation acceptance criteria.

The response was adequate.

Amendment 4

A multi-discipline information request was conveyed to Octapharma on 07 June 2012. Octapharma submitted amendment 4 in response, on 22 June 2012. Contained herein, is the section from the product review office.

1. The OctaplasLG manufacturing process is controlled by ----(b)(4)----- (b)(4)----- Please establish in-process control limits for critical process parameters based on evaluation of data from manufacturing experience. Please describe the action taken should in-process limits be exceeded.

Response review: Octapharma contended that in-process control limits have not been implemented because there is ----(b)(4)----- performed during manufacture. Follow-up with Octapharma to establish licensed in-process control limits was conducted during the pre-approval inspection. ----(b)(4)----- (b)(4)----- were submitted to amendment 18.

2. There was no toxicological or leachables/extractables assessment of the ---(b)(4)----- (b)(4)----- support for the (b)(4) ligand column. Please provide the requested information and data.

Response review: A report on leachables and extractables was provided. The report was compiled on 14 June 2012 by ----(b)(4)----- (b)(4)----- from publically available information. Although, the report presented some data on extractables and potential leachables, there was no explanation of the data as they related to potential toxicity if leached into the product. Additional information was submitted to amendment 9 upon request.

3. Column lifetime validation for the C-18 column chromatography step was inadequate.
 - a. Please provide the following information and data that were lacking from study 020VAP950/930-SPE01:
----- (b)(4) -----

 - b. Please provide results from commercial scale column lifetime validation or provide a validation protocol for concurrent validation that may be performed as a post-marketing commitment.

Response review: The requested information was provided with the exception of --(b)(4)---- (b)(4)-----, which was not performed. Adequate correlation between small and commercial scale process parameters was provided in study report, 020STD952.123/00: ---(b)(4)---- validation of

the C-18 chromatography in OctaplasLG[®] production process as used for column validation studies. Complete data from monitoring -----(b)(4)----- were provided in Table 3. Commercial scale monitoring of process parameters and quality attributes was provided.

The response was adequate.

4. There is no established control for ---(b)(4)--- impurity during commercial manufacture. Please comment.

Response review: Inadequate removal of -(b)(4)- impurity level would be reflected in an out-of-specification result for TnBP.

The response was adequate.

5. Study report 080VRE11366.105 indicated that bag -(b)(4)-was controlled through ---(b)(4)--- - --(b)(4)----- . Please establish a final product fill --- (b)(4)----- limit that applies to each filled bag, independently.

Response review: ----(b)(4)-----

The response was adequate.

6. Please establish an in-process control for HEV NAT in manufacturing plasma pools.

Response review: The planned implementation date is 01 November, 2012 since the -(b)(4)---- - ----(b)(4)-----

The response was adequate. This will be captured as a post-marketing commitment.

7. Please revise your release and shelf-life specification for the listed parameters, to reflect manufacturing capability.

Parameter	Current	Recommended
Protein S	---(b)(4)---	---(b)(4)---
α_2 -antiplasmin (A2PI)	---(b)(4)---	---(b)(4)---
Coagulation Factors V, VIII	---(b)(4)---	---(b)(4)---
Coagulation Factor XI	---(b)(4)---	---(b)(4)---
Fibrinogen	---(b)(4)---	---(b)(4)---

Response review: Octapharma accepted FDA's proposal for ---(b)(4)----- --(b)(4)----- initially rejected FDA's proposal for the ---(b)(4)----- -----

An acceptable final release specification was submitted to amendment 11.

8. Regarding final product stability:
 - a. Although lots from study 08P010 were manufactured from non-US plasma, stability data may be supportive if extrapolation is adequately justified. Please indicate whether or not the manufacturing process and container closure system for study 08P010 lots are identical to that intended for US commercial distribution.
 - b. Similarly, data from studies 09P020, 10P026, 09P030, 10P027 may be applicable if manufactured by a process comparable to that intended for commercial distribution.

Therefore, please clarify any differences between the intended commercial process and that used to manufacture lots submitted to the four cited studies.

- c. Please submit 6 month long-term stability data from studies 11P018 and 11P029.

Response review: Octapharma indicated that lots entered into stability studies: 08P010, 09P020, 10P026, 09P030 and 10P027 were manufactured by the process intended for US market. Study 08P010 presented (b)(4) month data from monitoring ---(b)(4)--- conformance lots. Six month stability data were submitted for study 11P018. Three month stability data were submitted for study 11P029; six month stability data will be available by 31 August 2012.

[(b)(4)]

- 9. Regarding the analytical procedure for ---(b)(4)-- performed at the Stockholm facility:

- -----(b)(4)-----

Response review: Octapharma committed to conduct the requested re-validation by 31 August 2012. Acceptable re-validation data were submitted to amendment 18.

The response was adequate.

Amendment 5

----- (b)(4) -----

----- (b)(4) -----

 -----(b)(4)-----

 -----(b)(4)-----

Amendment 7

Amendment 7, received 10 July 2012, contained the request for proprietary name review.

Response review: Octapharma submitted a complete application for proprietary name review containing information as instructed in, "GFI: Contents of a Complete Submission for the Evaluation of Proprietary Names." Two names: (1) Octaplas or (2) (b)(4) were proposed for consideration. An evaluation of each name for medication error potential or promotional consideration was conducted in the context of the intended use of the product, Pooled Plasma (Human), Solvent/Detergent Treated.

The proposed proprietary name, "Octaplas™," was deemed acceptable.

Amendment 8

Amendment 8, received 10 July 2012, contained test method instructions and validations for (b)(4) (b)(4) 130SOP065 and 130SOP165.

Amendment 9

Amendment 9, received 16 July 2012, contained responses to an information request sent 27 June 2012.

1. Upon further review and in consideration of the intended use of OctaplasLG as an alternative to FFP for all its clinical indications, FDA requests that Octapharma revise the final product release specification as indicated in the following table.

Parameter	Rationale for Revision	Recommended Limit	Conformance Lot Range
Protein S	(b)(4) ---	(b)(4)	(b)(4)
α_2 -antiplasmin (A2PI)	(b)(4) --	(b)(4)	(b)(4)
Factors V	(b)(4)	(b)(4)	(b)(4)
Factor XI	(b)(4)	(b)(4)	(b)(4)
Fibrinogen	(b)(4)	(b)(4)	(b)(4)
Factor II (Prothrombin)	(b)(4) ----	(b)(4)	(b)(4)
Factor X	(b)(4) ----	(b)(4)	(b)(4)
Factor VII	(b)(4) -----	(b)(4)	(b)(4)
ADAMTS13	(b)(4)	(b)(4)	(b)(4)

Response review: An acceptable final release specification was submitted to amendment 11 and is reflected in Table 6 (above)

2. Regarding (b)(4) report titled, “(b)(4) Safety, Leachables and Extractables:
- although the report presented some data on extractables and potential leachables, there was no explanation of the data as they related to potential toxicity if leached into the product
 - line listings in appendix 1 are illegible
- Please provide a meaningful discussion of the safety of the (b)(4)

Response review: Octapharma provided: (1) updated Study report: (b)(4) Safety, Leachables and Extractables and (2) a re-worked presentation in tabular format of the originally submitted information. Extractables study conducted in (b)(4) Extractables study with (b)(4) Toxicity information on chemical derivatives indicated acceptable safety margin for conditions of resin use.

The response was adequate.

Amendment 11

Amendment 11, received 13 August 2012, contained shipping validation reports describing studies performed during shipments from Vienna, Austria to (b)(4) Adequacy was assessed by Jie He, OCBQ, DMPQ.

Amendment 11 also contained test methods for (b)(4) Factor V, Factor VII, Factor VIII, Factor XI, Plasmin inhibitor, Protein C and Protein S updated for implementation of (b)(4) paradigm for final container biochemistry testing. Method validation for Factor VII test was submitted. Validation of remaining biochemistry tests will be provided, as they become available. Adequacy was assessed by Mikhail Ovanesov, OBRR, DH.

Revised final product specification 013FPS952/04/US was provided.

Response review: The specification was acceptable.

- Editorial changes to the header were requested as follows:
 - Name: Pooled Plasma (Human), Solvent/Detergent Treatment
 - Description: solvent/detergent treated pooled human plasma
- Proper citations for tests: (b)(4) Factor V, ADAMTS13 were requested.

The response was adequate. (b)(4)

An initial lot release protocol was submitted in amendment 11, which was revised to acceptable status in collaboration with FDA/OCBQ and Octapharma.

Amendment 13

Amendment 13, received 14 August 2012, contained draft container labels.

Response review: The following changes, which should be implemented for the immediate primary container label for all ABO blood groups, were communicated to Octapharma in an IR dated, 21 August 2012.

- The proper name for octaplas™ is Pooled Plasma (Human), Solvent/Detergent Treated
- The font point size, background and contrast for proprietary name, octaplas™ must be similarly prominent to the proper name, “Pooled Plasma (Human), Solvent/Detergent Treated.” Practically, this means enlarging the font size of the proper name and you may consider toning down the color contrast between proprietary and proper name

- iii. Please replace the statement, "octaplas may be stored for (b)(4) months at $\leq -18^{\circ}\text{C}$ (-0.4°F)," with, "Store at $\leq -18^{\circ}\text{C}$ (-0.4°F)," or "octaplas must be stored at $\leq -18^{\circ}\text{C}$ (-0.4°F)."
- iv. Please add the address of either OAB or OPG, as applicable, to the section in the lower left hand side that states, "Manufactured by: Octapharma."

Amendment 15

Amendment 15, received 23 August 2012, contained container labels revised according to requested modifications.

Response review: Further recommendations for the container label:

Regarding paragraph 1 below product name beginning with "200 mL contains..."

- a. Please remove the hyphen from between dihydrogen and phosphate i.e., "dihydrogen-phosphate" should read, "dihydrogen phosphate."
- b. At the end of the list of ingredients, please add the sentence (moved from paragraph 2), "This product contains no preservative."

Regarding paragraph 2 below the product name

- c. Please rewrite the paragraph to read as follows:
"Store at $\leq -18^{\circ}\text{C}$ (-0.4°F) protected from light. Thawed product should be used immediately and must not be refrozen. Do not use product that is cloudy or has deposits. Unused product must be discarded."

Amendment 18

Amendment 18, received 31 August 2012 contained documents related to manufacturing controls, which were revised to comply with FDA communicated requirements.

- 1. -----(b)(4)-----

- 2. Master batch records were revised to comply with several requirements communicated during the pre-approval inspections.
- 3. 150MAP952/03, Process mapping and Harmonization (MAP) was revised to comply with certain requirements communicated during the pre-approval inspections.

and

- 4. Six month stability data for study 11P029 (OAB) and nine month data for study 11P018 (OPG), which were reviewed by Ze Peng, OBRR, DH.
- 5. Re-validation of the (b)(4) assay, which was reviewed by Mikhail Ovanesov, OBRR, DH.

Response review: The following revisions to 150MOP952/03/US and 150MAP952/03 were requested:

- Update to specify an in-process control limit of ----(b)(4)----- --(b)(4)-----, as documented in the master batch record
- Removal of FFP from list of auxiliary materials. It should be noted that subsequent to this request, OBRR imposed the requirement to use FFP as the starting material.

Amendment 19

Amendment 19 was received on 10 September 2012 and contained process validation report, OC12-0273 describing results from manufacture of conformance lots, ----(b)(4)----- (b)(4)----- . Although, one major deviation occurred during ----(b)(4)-----, all other in-process controls and final container testing results met specification. Process validation is

considered acceptable. Of note, are -----(b)(4)----- monitored during conformance lots manufacture.

[(b)(4)]

The response was adequate.

Amendment 20

Amendment 20 was received on 11 September 2012 and contained the revised method for the fibrinogen test, which was reviewed by Mikhail Ovanesov, OBRR, DH.

Amendment 21

Amendment 21 was received on 17 September 2012 and contained:

- Response to information request from 15 August 2012
- Revised Prescribing Information (label)
- Revised Lot Release Protocol in response to information request from 10 September 2012

Question 1: Upon concurrence of an acceptable Lot Release Protocol, please submit to CBER Product Release Branch, lot release protocol for Lots ----(b)(4)-----
------(b)(4)-----.

Response review: Lot release protocols for the (b)(4) conformance lots were submitted to the amendment. Upon concurrence of the finalized version, Octapharma was requested to deliver the protocols through courier e.g., FedEx, UPS, revised lot release protocols to:

Attn: Sample Custodian (HFM-672)
Center for Biologics Evaluation and Research
Nicholson Lane Research Center (NLRC)
5516 Nicholson Lane, Building B, Room 113
Kensington, MD 20895

Question 2: Regarding final release specification 013FPS952/04/US:

- i. Please revise the header information as follows:
 - Name: Pooled Plasma (Human), Solvent/Detergent Treated
 - Description: Solvent/detergent treated pooled human plasma
- ii. Please provide a complete citation for the following tests: --(b)(4)-----
(b)(4)-----, Factor V, ADAMTS 13
- iii. Please add the General Safety Test. Please be advised that you may request an exemption from the General Safety Test pursuant to 21 CFR 610.11(g)(2).

Response review: Requested editorial revisions were made; **specification 013FPS952/05/US** was submitted to **module 3.2.P.5.1**. Octapharma requested an exemption from the General Safety Test. Their justification included an inability to properly perform the test due to intrinsic irritant nature of plasma and adequate control of extraneous toxic contaminants through performance of the (b)(4) test. Exemption from the General Safety Test will be granted.

The response was adequate.

Question 3: Please update document 150MAP952/03, Process Mapping and Harmonization (MAP) and 150MOP952/03/US, Method of Preparation Octaplas/USA to specify an in-process control limit of (b)(4), as documented in your master batch record.

Response review: Octapharma explained that the (b)(4) listed in the master batch record were warning limits. Octapharma revised 150MAP952/03, to specify validated (b)(4) (b)(4) Updated 150MAP952/04 and master batch record for OAB were submitted to the BLA.

Follow-up was required to harmonize (b)(4), Octapharma agreed in an e-mail communication sent 04 October 2012, to up date batch records and 150MOP952, accordingly. Updated documents were submitted in amendment 27.

Question 4: Please remove the citation for fresh frozen plasma (FFP) from the list of auxiliary materials under Batch Formula in 150MOP952/03/USA, since your starting plasma may derive from either Source Plasma or 24 hr. recovered plasma.

Response review: Octapharma made the requested revisions.

The response was adequate. Note: Octapharma was asked by OBRR to restrict source material quality to FFP (i.e., placed in a freezer within (b)(4).); therefore, Octapharma may choose to list FFP as the starting material.

Question 5: Regarding draft labeling text of the Full Prescribing Information (FPI):

- i. Please remove from Table 1 in section 11, rows representing log reduction factors from immune neutralization of non-enveloped viruses and global reduction factors. You may make a statement pertaining to risk reduction strategy with immune neutralization
- ii. Please change the proprietary name from OctaplasLG to Octaplas.

Please be advised that review of the product labeling is ongoing.

Response review: A revised FPI was submitted in pdf format. Further review and suggested revisions should be made on a word version.

Review is ongoing and will be documented directly on the FPI.

(b)(4)

(b)(4)

-----**(b)(4)**-----

Question 7: Please commit to implementation of HEV NAT in order to limit the viral load in the manufacturing pool. The implemented HEV RNA NAT must be validated to have a limit of detection of 2.5 log₁₀ copies/mL or less and the acceptance criterion for in-process testing must be a negative result.

Response review: The test will be implemented on 01 November 2012, validated to have a -----
-----**(b)(4)**-----
--

The response was adequate.

-----**(b)(4)**-----

-----**(b)(4)**-----

---**(b)(4)**-----

-----**(b)(4)**-----

-----**(b)(4)**-----

---**(b)(4)**-----

Amendment 23

Amendment 23 was received on 24 September 2012 and contained revised container labels and method validation for ADAMTS13 assay, which was reviewed by Mikhail Ovanesov, OBRR, DH.

Response review: Requested revisions to container labels were made.

The response was adequate.

Amendment 24

Amendment 24 was received on 26 September 2012 and contained 483 responses and lot release protocol.

Response review: Adequacy of 483 responses was reviewed and documented in the Establishment Inspection Report (EIR). Octapharma's responses to FDA Form 483 observations including planned implementation of corrective and preventive action were considered adequate. The lot release protocol was considered acceptable.

The response was adequate.

Amendment 26

-----**(b)(4)**-----

Amendment 31

Amendment 31 was received on 31 October 2012 and contained: (1) SOPs and reports revised in response to Forms 483 from OPG or OAB pre-approval inspections that were updated in amendment 32, (2) Container Closure Integrity Study Report and (3) Method and validation report for testing HEV in the plasma manufacturing pool.

Response review for items (1) and (2) was performed by Jie He, DMPQ. Response review for item (3) was performed by Ze Peng, DH.