



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: OctaplasLG[®], Solvent/Detergent Treated Plasma for Transfusion
Subject: Mid-cycle review of Original BLA
Through: Tim Lee, PhD, Acting Chief, OBRR/DH/LH
CC: Review Committee Members: Michael Brony, Christine Drabick, Mitchell Frost, Jie He, Anthony Lorenzo, Jerald Mullersman, Mikhail Ovanesov, Ze Peng, Renee Rees, M. Keith Wyatt

Submission Summary and Related Background Information

OctaplasLG[®] was developed under IND 13956, submitted on 18 February 2009. OctaplasLG[®] is approved in several European countries and Australia; its first approval was in Germany, in January 2009. The original product, Octaplas[®] was developed in the late 1980's and has been marketed in Europe since 1992.

Review History

Task	Date	Comment
Received	23 December 2011	
First committee meeting	13 January 2012	
Filing meeting	06 February 2012	Suitable for filing
Filing date	21 February 2012	Suitable for filing
IR#1	27 March 2012	Teleconference with DMPQ
Amendment 1	06 April 2012	Response to IR #1
IR#2	25 April 2012	CMC IR from DMPQ and DH
Amendment 2	15 May 2012	Response to IR#2, Q1 and Q2
Mid-cycle	23 May 2012	Mid-cycle meeting
Amendment 3	24 May 2012	Response to IR #2
IR#3	05 June 2012	Multi-discipline
Amendment 4		
PAI	24 July – 05 Aug 2012	Tentative, two facilities
Lot Release Protocol		
Labeling Review		
Action Due	22 October 2012	

Drug Substance

Description and Characterization

Description

Product description and composition may be found under Drug Product section.

Characterization

Analytical Characterization During Development

Analytical characterization data submitted in the BLA focused on comparability of conformance lots for the new product OctaplasLG[®] with historical data from 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 OctaplasLG[®] and its control are described for drug product under **module 3.2.P.3.**

Support of 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 raw materials used in production of Octaplas LG[®] represents 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.”

Reviewer comment: The BLA contains inadequate documentation of plasma source material control. Octapharma will be asked to provide adequate documentation of source material control.

Additional Reviewer note: 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 OctaplasLG[®].

[(b)(4)]

[(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.

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

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

Reviewer comment: Sourcing and control of materials or reagents of non-animal/ non-human origin was not addressed in module 3.2.S.2.3, including chemicals or reagents used for preparation of processing buffers or column regeneration/ cleaning solutions. Octapharma failed to provide the name and address of each raw material supplier, identify those raw materials guaranteed by a supplier [i.e. accepted on the basis of a supplier's Certificate of Analysis (CoA)] vs. those tested in-house (i.e. released against an in-house material specification). Octapharma will be asked to provide adequate documentation of raw materials control.

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 LG[®] is a 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

and deep frozen. It is manufactured from 630 to 1,520 single donor units of plasma from the same ABO blood group.

Composition

Table 3: Product Composition

Ingredient	Amt. per 200 ml bag	Function	Standard
Human plasma protein controlled for certain coagulation factors and anticoagulants, containing normal distribution 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 makes reference to [study report 020STD952.074](#) and provides additional information under **module 3.2.P.1.2**, Excipients. 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) (b)(4)- NaH₂PO₄·2H₂O is added as a buffer. The ---(b)(4)--- concentrate ranges from (b)(4)-- -- (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	Manufacturer	Quality Control
Na-citrate·2H ₂ O	<i>not provided</i>	----- (b)(4) ----- -----
NaH ₂ PO ₄ ·2H ₂ O	<i>not provided</i>	----- (b)(4) ----- -----
Glycine	<i>not provided</i>	----- (b)(4) ----- -----

Reviewer comment: Names and addresses of excipient suppliers and representative CoA's were not provided. Octapharma will be asked to provide this information.

Definition and Justification of Critical, Key and Non-critical Quality Attributes [Module 3.2.P.2.2]

The BLA makes reference to [study report 020STD952.074](#) and [study report 020STD952.072](#) also used to support product characterization and process validation. [Study report 020STD952.074](#) references [document 150MAP952/00](#), "Process Mapping and Harmonization (MAP): OctaplasLG® from plasma thawing final container," and [study report 020STD952.055](#), "OctaplasLG® robustness studies," which purportedly document the identification of critical quality attributes and evaluation of their established limits. These documents were not submitted to the BLA.

Reviewer comment: Octapharma will be asked to provide a tabular listing of quality attributes for OctaplasLG®. Information should focus on attributes as they relate to performance of the drug product for its intended use.

Reviewer note: The pharmaceutical development summary claimed superiority over Vitex's PLAS+SD with regard to final product content of Protein S; yet, the final specification was set at (b)(4)--- than the average content exhibited by Vitex's product.

Impurities [Module 3.2.P.5.5]

[(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 -----(b)(4)-----
- -(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.

*Reviewer comment: There was no direct support for safety of the -----(b)(4)-----
(b)(4)----- ligand resin or ---(b)(4)----- of the C18 resin. The C18 resin; however, has been used in the manufacture of Octaplas®, which has been on the European market for over 20 years. Regarding safety of the ---(b)(4)-----
Octapharma claimed its common use in plasma protein purification processes. Octapharma will be asked to provide a risk assessment for (b)(4) ligand matrix safety based on direct toxicity evaluation of extractables/ leachables (see M. Keith Wyatt review memo). There is no established control for (b)(4)--- impurity during commercial manufacture.*

Drug Product Release Specification

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

Specification No. 013FPS952/03/US		
Quality: ---(b)(4)---		
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)-----	---(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 V	---(b)(4)-----	≥0.5 IU/ml
Factor VIII	---(b)(4)-----	≥0.5 IU/ml
Factor XI	---(b)(4)-----	≥0.5 IU/ml
Protein C	---(b)(4)-----	---(b)(4)-----
Protein S	---(b)(4)-----	---(b)(4)-----
Plasmin inhibitor (α_2 -antiplasmin)	---(b)(4)-----	---(b)(4)-----
---(b)(4)---		
---(b)(4)-----		---(b)(4)-----
---(b)(4)---		---(b)(4)-----
<i>Additional Tests</i>		
---(b)(4)---	---(b)(4)-----	---(b)(4)-----
---(b)(4)---	---(b)(4)-----	---(b)(4)-----
TnBP	---(b)(4)-----	<2 µg/ml
Octoxynol	---(b)(4)-----	<5 µg/ml
Fibrinogen	---(b)(4)-----	---(b)(4)-----
---(b)(4)---	---(b)(4)-----	---(b)(4)-----
---(b)(4)---	---(b)(4)-----	---(b)(4)-----
---(b)(4)---	---(b)(4)-----	---(b)(4)-----
<i>Filling volume</i>		
Filling volume		---(b)(4)-----
<i>Storage and Expiry</i>		
"Period of validity from the date of manufacturing"		(b)(4) months when stored at ≤-18°C, protected from light*

*Stability data didn't support proposed shelf life (see Ze Peng review memo)

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

Justification for quality parameters was based solely on a statement of compliance to (b)(4) -----
 (b)(4)----- 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 B19 or ---(b)(4)----- - ---(b)(4)----- to HEV.

Reviewer comment: Revision of the proposed release specification should be considered. The following parameters will be evaluated and revisions discussed with Octapharma.

Parameter	Current	Proposed
----(b)(4)-----	----(b)(4)-----	------(b)(4)----- -----
Protein S	-----(b)(4)-----	------(b)(4)----- -----
α_2 -antiplasmin (A2PI)	-----(b)(4)-----	------(b)(4)----- -----
ADAMTS 13 (see Table 1, above)	-----(b)(4)----	------(b)(4)----- ----- -----
Factors V, VIII, XI	---(b)(4)-----	------(b)(4)----- ----- -----
Fibrinogen	-----(b)(4)-----	------(b)(4)----- -----

¹ Refer to tables 13a and 13b for results of conformance lot release test

Methods of Manufacture and Packaging and Process Controls

Manufacturers

OctaplasLG[®] will be manufactured in either of 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

[(b)(4)]

Batch Formula [Module 3.2.P.3.2]

Table 7: Batch Formula

Five (5) pages determined to be not releasable (b)(4)

[(b)(4)]

Reviewer comment: Batch analysis/characterization of development lots was not provided.

Definition and Justification of Critical Process Steps and Critical Process Parameters

Study report 020STD952.074 indicated that Octapharma has implemented a process mapping and harmonization process according to Octapharma's Risk Management Policy based on (b)(4) - --(b)(4)-----Study report 020STD952.074 references document 150MAP952/00, "Process mapping and Harmonization (MAP): OctaplasLG® from plasma thawing final container," and study report 020STD952..055, OctaplasLG® robustness studies," which purportedly document the identification of critical process parameters and evaluation of their established limits..

Module 3.2.P.3.4 made reference to the fact that in-process parameters, associated ranges, analytical methods and validation data were contained in other modules. Process control parameters, their acceptance criteria and data from conformance lot manufacture were presented in process validation study report 080VRE11366.105 submitted to **module 3.2.P.3.5**. *Of concern, the narrative in module 3.2.P.3.4 stated that -----(b)(4)-----*

----- (b)(4)----- **Section 3.2.P.3.4.3** reproduced results from **module 3.2.P.3.5**, which presented in-process quality control testing of conformance lots (please see reproduced data under "Conformance Lot in-process testing"). Critical process steps identified in Process Evaluation/ Validation **module 3.2.P.3.5** comprised, "plasma pooling to final container." Critical process parameters were never specifically identified and justified.

Reviewer Comment: Critical process control parameters were addressed in process validation study report 080VRE11366.105; however, no formal designation of criticality and justification of acceptance criteria were provided. According to ICH M4Q, information in modules 3.2.S.2.4 or 3.2.P.3.4 should contain at minimum: tests and acceptance criteria with justification, including experimental data performed at critical steps identified in modules 3.2.S.2.2 or 3.2.P.3.3, to ensure that the process is controlled. According to ICH Q8, manufacturing process control depends on identification, characterization and control of critical process parameters to ensure the product is of desired quality. According to draft GFI: Process Validation Considerations for Biological Drug Substances and Biological Drug Products [May 1999], in-process control limits for operating parameters or quality control testing of process intermediates are established in order to confirm process consistency. This quality principle directly contrasts Octapharma's stated intent to -----(b)(4)-----

Conformance Lot Manufacture [Module 3.2.P.3.5]

Process Validation Summary

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. Certain lots were stated as being manufactured with ---(b)(4)-----. Lots from recovered plasma or Source Plasma were manufactured from A, B or O blood groups.

According to study report 080VRE11366.105, document 150MAP952, Process Mapping and Harmonization purportedly lists critical process parameters and document 150SOP007-a5, annex

to process validation corporate procedure, purportedly lists critical quality attributes. A risk assessment of potential impact of manufacturing operations on product quality was performed indicating that relevant quality control tests would be implemented --- (b)(4) -----
--- (b)(4) ----- . Moreover, --- (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**

Table 9: Conformance Lots

[(b)(4)]

Reviewer note: There is a slight difference in conformance lot numbering between module 3.2.P.3.5 and study report 020STD952.072. --- (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)

[(b)(4)]

Column Lifetime Validation

Validation study report 020VAP950/930-SPE01 was submitted to **module 3.2.P.5.5** to support claimed column lifetime of ---(b)(4)----- (Reviewer note: The manufacturing narrative in **module 3.2.P.3.3** claimed ---(b)(4)-----; the narrative in **module 3.2.P.3.5** claimed ---(b)(4)-----). Column validation supports (b)(4)-----
----- (b)(4)-----

Reviewer Note: The recommendation to provide column lifetime validation originated from, --
(b)(4)-----
(b)(4)-- Section B.4.d states that limits should be prospectively set on the number of times a purification component (e.g., a chromatography column) can be reused and that such limits should be based on actual data obtained by monitoring the component's performance over time.

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

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

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

Shipping Validation

OctaplasLG[®] final product (plasma bags) will be shipped frozen from either OAB, Stockholm Sweden or OPG, Vienna, Austria to the US for commercial distribution. Shipping validation **study report 080RPQ11417.000** was submitted to module 3.2.P.3.5 to support shipment duration of up to --- (b)(4) -----

Study Report 080RPQ11417.000

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

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

Reviewer comment: Shipping validation could be better supported with the following additional information

- *Names of qualified shipping vendors*
- *Results from monitoring real shipments from each manufacturing site to distribution centers or consignees in the US*

Discussion with DMPQ, however, indicated precedent for accepting as adequate, simulated shipping validation. Furthermore, implementation of the “freezer bar” or other indent indicator during product freezing may obviate the need for further shipping validation since occurrence of a freeze-thaw event would be directly captured.

Analytical Procedures and their Validation including Establishment and Maintenance of Reference Standards [Modules 3.2.S 4.2; 3.2.S.4.3, 3.2.P 5.2; 3.2.P.5.3, 3.2.S.5, 3.2.P.6, 3.2.A.3]

Detailed review of analytical procedures, their validation and reference standards is documented in review memo from Mikhail Ovanesov. Analytical procedures used for in-process control were submitted to **module 3.2.P.3.4.**

Drug Product Container Closure and Stability

Container Closure Description and Control [Module 3.2.P.7]

Description

OctaplasLG[®] is packaged and stored in primary container closure, sterile polyvinyl chloride (PVC) 300 ml plasma bags controlled according to (b)(4)--. quality standard (see **module 3.2.P.3.3**, manufacturing procedure **150MOP952/02/US**, section 1.2. Auxiliary Materials). Subsequent to final fill into plasma bags, the product is vacuum sealed in--- (b)(4)----- over-wrap.

Control

Table 14: Container Closure

Component	Size	Material	Quality Standard	Supplier	--(b)(4)--
Bag	300 ml	PVC	---(b)(4)----- ----- ----- -----	---(b)(4)----- ----- ----- ----- -----	---(b)(4)--- ----- ----- -----
Bag	300 ml	PVC	---(b)(4)----- ----- ----- -----	---(b)(4)----- ----- ----- -----	---
Over-wrap	<i>not specified</i>	---(b)(4)--- ----- -----	<i>not specified</i>	<i>not provided</i>	<i>not provided</i>

--(b)(4)----- 013AMVPBC/10 for plasma bag receipt from --(b)(4)-----
013AMVPBF/02 for plasma bag receipt from --(b)(4)---- were provided in **module 3.2.P.7.**

Reviewer comment: No information was provided about sourcing and control of the (b)(4)----- (b)(4)---- secondary container closure system. According to DMPQ, quality and control of secondary packaging is an inspection issue.

Container Closure Development and Qualification [Module 3.2.P.2.4]

Integrity testing of the primary container closure (PVC plasma bags) was reported in [study reports: OC10-0346](#): --(b)(4)----- Test for Container/Closure Integrity of bags used for OctaplasLG (for OAB) and [000SSR992.04P003.01/INT](#): Stability Study Report, Container and Closure Integrity Testing: Human Plasma S/D treated, Primary Packing Systems, (b)(4) months' data (for OPG).

--(b)(4)---

(b)(4)

Reviewer note: Review of information on container closure is the primary responsibility of DMPQ (SOPP 8401.4); however, the product office may support the review effort.

Stability [Module 3.2.P.8]

Review of stability information is documented in review memo from Ze Peng.

Labeling

Draft text and reproductions of immediate container labels were provided in **module 1.14.1** for product manufactured at OPG (NDC 68209-952) or OAB (NDC 67467-952). (*Reviewer note: assessment by personnel from OBRR/DBA/BPB of compliance with requirements in 21 CFR 606.121 may be requested.*)

Regional Information

3.2.R.1 Batch Records

Master Batch Records (English translation) for method number 952-TM-101 at OAB or document 060HBE952/00/USA at OPG were provided. Executed batch record for lot ----(b)(4)----- from OAB and ----(b)(4)----- from OPG were also provided. Batch record review will be conducted and documented separately in connection to the manufacturing facility pre-approval inspection.

Communication with Octapharma

IND 13956 Information Request

An information request to the file of IND 13956 containing eight CMC items was conveyed to Octapharma on 07 May 2009. Octapharma responded in August 2009, informing FDA that responses to items 1,3,4,6,7, and 8 would be contained in the BLA.

1. Please specify the composition of the starting material (plasma) used for the manufacture of octaplasLG™.

Review finding: The composition of starting material was stated as either complying with 21 CFR 640.30 or 21 CFR 640.60. The proportions of each type of plasma comprising one 390 kg lot remain undefined.

3. When available, please use FDA cleared antibody detection kits to measure the levels of antibodies for HAV, HEV and B19. Also, please provide justification for the selected antibody limits for anti-HAV (≥ 1 IU/mL), anti-B19 ---(b)(4)----- and anti-HEV (≥ 0.2 IU/mL) in the octaplasLG™ product.

Review finding: Justification of specification for selected antibody limits was provided in study report 020STD003.932 and 952/00: Pathogen Safety Evaluation submitted to **module 3.2.A.2.4.5**. Anti-HAV is assayed using a ----(b)(4)-----
----- (b)(4)----- Anti-B19V is assayed using ----(b)(4)----- . The most recent validation was performed with the ----(b)(4)----- kit. The test for anti-HEV was --- (b)(4)-----
(b)(4) as this is a newly described pathogen.

4. Please provide validation data for the parvovirus B19 NAT assay, including its ability to detect major genotypes of this virus. Please also provide data --- (b)(4)----- used for the detection of this virus, and the --- (b)(4)----- used to ensure that the --- (b)(4)----- in your manufacturing pools does not exceed the (b)(4) limit.

Review finding: Validation of the B19V NAT test was provided in document 501VAL220/01.rep: Calibration of the Parvovirus B19 --- (b)(4)----- and Re-validation of the Quantitative and Qualitative Parvovirus B19 (b)(4) Method using --- (b)(4)-----
System, submitted to module 3.2.P.3.4.4.

6. Please revise the acceptance criteria for the levels of Protein S and Plasmin inhibitor according to the values obtained from product lots through your manufacturing experiences.

Review finding: Acceptance criteria were not revised.

7. Please provide the complete data on the study of (b)(4) leachates for the prion protein removal step ((b)(4) resin) including theoretical calculation of (b)(4)-related impurities in the final drug product. In addition, please provide a complete list of leachates related to the (b)(4) resin.

Review finding: Two summary reports were submitted: (1) Summary Report of Toxicological Studies on (b)(4) Resin Leachates -----(b)(4)----- [module 4.2.3.2] and (2) "Leachate Analysis Results for Samples Supplied as part of Sample Analysis Proposal dated August 2011. These reports only addressed the ligand and not the ---(b)(4)-----

8. Please note that real-time stability data are needed to establish the product's shelf life.

Review finding: Stability data were submitted to module 3.2.P.8.

- Additional studies were also requested to demonstrate robustness of critical process parameters for the solvent/detergent treatment step.

Review finding: Robustness studies were submitted to module 3.2.A.2. Study report 020STD952.074 submitted in support of pharmaceutical development also made reference to, "Process Mapping and Harmonization (MAP)," which purportedly documented critical process parameters and the evaluation of their established limits.

Information Request #2 (IR #1 was sent by DMPQ on 27 March 2012)

An information request containing the following items from DMPQ and the product office was conveyed to Octapharma on 25 April 2012.

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)----- (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)-----
---(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
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)-----
(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
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:
 - 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.
10. Regarding Container closure:
 - a. Please clarify if (b)(4)----- of plasma bags (----- (b)(4)----- --
----- (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.
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) lots ----- (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 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
 - For each raw material, reagent or excipient, the name and address of each supplier and the quality standard to which each is controlled
 - Materials or reagents guaranteed by a supplier with a Certificate of Analysis (CoA) and materials or reagents manufactured and/or controlled, in-house
 - For each material guaranteed with a CoA, a representative CoA
 - 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.
- 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
 - For each mixing or collection vessel: equipment identifier, material of construction and vessel volume
 - For each filter: material number, supplier, materials of construction and filtration area
 - 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)----- 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.

Information Request #3

A multi-discipline information request will be conveyed to Octapharma at mid-cycle. Contained herein, is the section from the product review office.

CMC/Product

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.

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.
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
4. There is no established control for ---(b)(4)---- impurity during commercial manufacture. Please comment.
5. Study report 080VRE11366.105 indicated that bag (b)(4)-- was controlled through ---(b)(4)--- ---
----- (b)(4)----- . Please establish a final product
---(b)(4)----- limit that applies to each filled bag, independently.
6. Please establish an in-process control for HEV NAT in manufacturing plasma pools.
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)---

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. Please submit 6 month long tem stability data from studies 10P027 and 11P029.
9. Regarding the analytical procedure for (b)(4) performed at the Stockholm facility:

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

