

Stability Studies

The stability data indicate that no critical trends are detected during the observed long-term storage period. The data support the shelf-life of Octaplas US, which is 24 months when stored at -18°C (-0.4°F). Within this period, this product may be stored at 2 – 4°C (35.6 – 39.2°F) for up to 24 hours or 20 – 25°C (68 – 77°F) for up to 3 hours after thawing.

Evaluation of Safety regarding Adventitious Agents

The production processes are performed according to GMP regulations, and controlled and monitored by specified process control parameters. The production processes have been validated for the reduction of microbes and viruses.

Residual microbes are reduced by in-process filtration steps and removed by the validated 0.2 µm sterile filtration step. Afterwards, aseptic filling is performed and the product is frozen. The final release testing includes testing for Sterility and Pyrogens.

Ligand chromatography or -----(b)(4)----- resin column in the manufacturing process is designed to remove potential pathogenic prion protein (or PrP^{Sc}) contamination. However, the validation studies are considered to be insufficient, and PrP^{Sc} removal capacity by (b)(4) column has not been established although there are no confirmed reports of variant Creutzfeldt-Jakob Disease (vCJD) prion transmission through plasma or derivatives thereof to date.

Single-donor plasma units are used for the manufacture of Octaplas US, and each unit is routinely tested for the absence of hepatitis B surface antigen (HBsAg), and antibodies against Human Immunodeficiency Virus -1/2 (HIV-1/2), and Hepatitis C Virus (HCV) at U.S. licensed blood or plasma collection centers.

Concerning the enveloped virus reduction capacity of the manufacturing procedure, there is one dedicated viral inactivation step, i.e. S/D treatment, which has been validated in -----(b)(4)----- for its capacity to inactivate viruses. Virus inactivation by S/D treatment was tested at least twice independently using HIV-1, Bovine Viral Diarrhea Virus (BVDV – a model virus for HCV), Pseudorabies Virus (PRV – a model virus for large, enveloped, DNA-containing viruses), and Sindbis Virus (SBV). Immune neutralization based on specified antibody levels and virus load contributes to the safety towards non-enveloped viruses such as Hepatitis A Virus (HAV), Coxsackievirus type B6 (COX-B6), and Poliovirus type 1 (POL-1). In addition, OctaplasLG and its predecessor product, Octaplas have been marketed widely outside the U.S. since 2009 and 1989, respectively, without significant viral safety concerns. The claimed virus reduction factors in the package insert for the following enveloped viruses are acceptable and summarized in the table below.

Virus reduction factor (log₁₀) during the manufacturing procedure of Octaplas US

Manufacturing step	Virus reduction factor (log ₁₀)			
	HIV	PRV	SBV	BVDV
S/D treatment	≥ 6.18	≥ 5.03	≥ 5.31	≥ 5.12

HIV-1: Human Immunodeficiency Virus-1; PRV: Pseudorabies Virus; SBV: Sindbis Virus; BVDV: bovine viral diarrhea virus

In order to reduce the risk of Hepatitis E Virus (HEV) transmission through for Octaplas US, Octapharma will control the level of antibody against HEV in the final product to be not less than 0.2 IU/mL. Moreover, on 1 November 2012, the applicant committed to testing and controlling HEV RNA level in the manufacturing pool using a validated nucleic acid test (NAT) based on the PCR methodology. The manufacturing pool must have a negative result in a test for human HEV RNA by an NAT PCR assay with a sensitivity of $\leq 2.5 \log_{10}$ IU/mL.

Background

Octaplas, produced by Octapharma PPGmbH (OPG), Vienna, Austria, is an S/D treated pooled human plasma-for-infusion product that is prepared from single-donor units of fresh frozen plasma (FFP) pooled according to their specific blood groups (A, B, O, or AB). This product has been widely used outside the U.S. since it was firstly licensed in Germany in 1989.

In this BLA, Octapharma presented a next generation product named OctaplasLG, for which a ligand chromatography column has been included in the downstream of the manufacturing process. This column was designed to selectively bind to PrP^{Sc}. In addition, Octapharma also reduced the S/D treatment time from -(b)(4)- to 1 - 1.5 hours to improve the recovery of activities of plasma proteins, in particularly those of plasmin inhibitor and Protein S. All other features of the original S/D treated plasma have been maintained.

OctaplasLG (i.e., Octaplas US, for the clarity of this review only), intended for the US market is presented as a frozen product manufactured from U.S. recovered or Source Plasma in Octapharma's facilities at Vienna (OPG), Austria, and Stockholm (OAB), Sweden.

Summary of Review

Flow chart of the manufacture process of Octaplas US final product

1. Plasma, frozen
2. Pooling, fast thawing
3. virus inactivation by S/D treatment
4. Oil treatment
5. C-18 chromatography
6. Addition of glycine

7. Ligand chromatography intended for prion protein removal
8. Sterile filtration
9. Aseptic filling, sealing of bags, labeling, and vacuum sealing
10. Fast freezing
11. Visual inspection and storage

Please note that human plasma is defined as drug substance for Octaplas US in this submission.

Stability (Sections 3.2.S.7 and 3.2.P.8)

The stability data provided in this submission are only for the final product. No stability study is performed on the drug substance which is human plasma.

1. Lots tested

Lot No.	Plasma source	Blood group	Manufacturing site	Status	Study No.
---(b)(4)---	non-US Recovered	A	OPG	-----	08P010
---(b)(4)---		O		----- (b)(4) -----	
---(b)(4)---		A		----- (b)(4) -----	
---(b)(4)---	US Recovered	A		----- (b)(4) -----	09P020
---(b)(4)---		O		18 months at -18(b)(4)	
---(b)(4)---		A		18 months at -18(b)(4)	
---(b)(4)---	US Source	A		12 months at -18(b)(4)	10P026
---(b)(4)---		O		6 months at -18(b)(4)	
---(b)(4)---		A		3 months at -18(b)(4)	
---(b)(4)---	US Recovered	A		0 months at -18(b)(4)	11P018
---(b)(4)---		B		0 months at -18(b)(4)	
---(b)(4)---		O		0 months at -18(b)(4)	
---(b)(4)---	US Source	B		0 months at -18(b)(4)	
---(b)(4)---		A		0 months at -18(b)(4)	
---(b)(4)---		O		0 months at -18(b)(4)	
---(b)(4)---	US Recovered	O	OAB	12 months at -18(b)(4)	09P030
---(b)(4)---		O		12 months at -18(b)(4)	
---(b)(4)---		O		12 months at -18(b)(4)	
---(b)(4)---	US Source	O		3 months at -18(b)(4)	10P027
---(b)(4)---		B		3 months at -18(b)(4)	
---(b)(4)---	US Recovered	A		0 months at -18(b)(4)	11P029
---(b)(4)---		B		0 months at -18(b)(4)	
---(b)(4)---		B		0 months at -18(b)(4)	
---(b)(4)---	US Source	A		0 months at -18(b)(4)	
---(b)(4)---		A		0 months at -18(b)(4)	
---(b)(4)---		O		0 months at -18(b)(4)	

*: The lots are also used for stability after thawing.

FDA comment: The lots from Stability Study No. 08P010 were produced from non-US sourced plasma and the stability data may be used to support this BLA. However, we need to confirm with Octapharma that the manufacturing process and container closure system for the lots in Study 08P010 are identical to those for U.S. distribution.

This comment was communicated to Octapharma in an IR on 7 June 2012.

Octapharma's response and FDA comment: In amendment # 125416/0.4 dated 22 June 2012, Octapharma confirmed that both the manufacturing process and container closure system are identical for the lots in Study No.08P010 and U.S. commercial distribution. Thus, the stability data from Study No. 08P010 may be used to support the shelf life of Octaplas US intended for the US market.

2. Comparison of the manufacturing process of OctaplasLG for the non-US market and intended US market (i.e., Octaplas US)

Process step	Non-US marketed OctaplasLG	Intended US marketed Octaplas US
Pooling, Fast thawing	----- (b)(4) ----- ----- ----- (b)(4) ----- -----	----- (b)(4) ----- ----- ----- (b)(4) ----- -----
Addition of glycine	--- (b)(4) ---	----- (b)(4) -----
Prion removal by ligand chromatogra phy	----- (b)(4) -----	----- (b)(4) -----

FDA comment: In general, the manufacturing process is quite similar for the non-US marketed OctaplasLG and intended US marketed Octaplas US. However, the acceptance criterion of ----- (b)(4) ----- in the manufacture of OctaplasLG for non-US market and intended US market. To be sure if these two manufacturing processes are comparable, we sent this comment to Octapharma on 7 June 2012.

Octapharma's response and FDA further comment: In amendment # 125416/0.4 dated 22 June 2012, Octapharma confirmed that the manufacturing process is identical for both non-US marketed OctaplasLG and intended US marketed Octaplas US. They explained that the acceptance criterion for ----- (b)(4) ----- . Therefore, this response is acceptable.

3. Parameter used

Based on the specification 013MPS952/05/US, the following parameters are used in the stability studies:

Parameter	Specification	Test method
Visual control	The thawed plasma is clear to slightly opalescent and free of	(b)(4)

Parameter	Specification	Test method
	solid or gelatinous particles.	
(b)(4)	(b)(4)	(b)(4)
----- (b)(4) -----	---- (b)(4) ----	----- (b)(4) -----
----- (b)(4) -----	---- (b)(4) ----	----- (b)(4) -----
Factor V	---- (b)(4) ----	(b)(4)
Factor VIII	---- (b)(4) ----	----- (b)(4) -----
Factor XI	---- (b)(4) ----	----- (b)(4) -----
Protein C	---- (b)(4) ----	----- (b)(4) -----
Protein S	---- (b)(4) ----	----- (b)(4) -----
Alpha ₂ -antiplasmin	---- (b)(4) ----	----- (b)(4) -----
Fibrinogen	---- (b)(4) ----	(b)(4)
Partial thromboplastin time (aPTT)	---- (b)(4) ----	----- (b)(4) -----
----- (b)(4) -----	---- (b)(4) ----	----- (b)(4) -----
----- (b)(4) -----	---- (b)(4) ----	----- (b)(4) -----
--- (b)(4) ---	----- (b)(4) -----	---- (b)(4) ----
Sterility	Sterile	---- (b)(4) ----
Pyrogens	Free of pyrogens	CFR 610.13
----- (b)(4) -----	---- (b)(4) ----	---- (b)(4) ----
----- (b)(4) -----	---- (b)(4) ----	---- (b)(4) ----

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

Octapharma did the following revisions regarding the stability program since 23 December 2008:

Date	Revision	Stability study No.
23 December 2008	Introduction of the testing of protein C, Protein S, and alpha ₂ -antiplasmin activity	08P010
2 November 2009	Introduction of the testing of Hepatitis E virus antibody	08P010
12 May 2010	Change the wording: from ----- (b)(4) ----- ----- for HAV antibody; from ----- (b)(4) ----- ----- for HEV antibody	08P010
13 December 2011	Revision of the specification for Parvovirus B19 antibody	09P020, 11P018, 11P029

The current parameters and limits used in the stability program is the same as those used for release specification (i.e., specification No. 013FPS952/03/US). In addition, Octapharma ----- (b)(4) -----
----- in the stability program. This is for additional information only.

FDA comment: The changes introduced in the stability program include -----
-- (b)(4) ----- and the minor wording edits, and should not diminish its capacity to monitor the quality, safety, and efficacy of the final product. Therefore, these changes appear to be acceptable.

4. Test schedule

1) For the manufacturing site, OPG, the stability testing plan is listed as follows:

Long-term stability for Octaplas US final product stored at -18 -(b)(4)-

Parameter	Storage time (months)									
	0	3	6	9	12	18	24	(b)(4)	(b)(4)	(b)(4)
Visual control	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
(b)(4)	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
---(b)(4)---	x		x		x		x	(b)(4)	(b)(4)	(b)(4)
----(b)(4)----	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
----- (b)(4) -----	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
Sterility	x						x	(b)(4)	(b)(4)	(b)(4)
Pyrogens	x						x	(b)(4)	(b)(4)	(b)(4)
Factor V	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
Factor VIII	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
Factor XI	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
Protein C	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
Protein S	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
Alpha ₂ -antiplasmin	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
Fibrinogen	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
---(b)(4)---	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
----- (b)(4) -----	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
----- (b)(4) -----	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
----- (b)(4) -----	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)
----- (b)(4) -----	x	x	x	x	x	x	x	(b)(4)	(b)(4)	(b)(4)

X: Tested

2) ----- (b)(4) -----
-----:

(b)(4)

(b)(4)

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

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

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

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3) Stability after thawing

Storage temperature	Storage time (hours)						
	0	2	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
2 (b)(4)	x	x	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
20 ~ 25°C	x	x	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

X: Tested

FDA comment: Octapharma did not provide the stability data on accelerated condition for the product manufactured at both manufacturing sites. Instead, they provide the stability data on the Octaplas US final product manufactured by OAB under referenced temperature excursion conditions. Considering that the final product is derived from pooled human plasma and the manufacturing processes do not differ between the two facilities, in general I agree with the updated version of the stability program provided by Octapharma.

5. Stability Results

- 1) The manufacturing process is different between Octaplas, the previous version of the product distributed in Europe and Octaplas US intended for the US market. Therefore, the stability data derived from Octaplas cannot be used to waive the stability studies for Octaplas US. The Octaplas stability studies include a long-term stability study No. SSR/OCTAPLAS-07 and stability after thawing studies, named as “Stability of S/D treated plasma during ---(b)(4)--- after thawing, report date: 2004” and “Thawing of Octaplas using the -----(b)(4)----- system”.
- 2) Octapharma cancelled four ongoing stability studies on Octaplas US, because of the modification of the manufacturing process but they did not give any details on the modification they referred to. The cancelled stability studies include Study Nos. 09P020, 10P026, 09P030, and 10P027. To compare the stability of Octaplas US manufactured from different sites (OPG and OAB), the limited data from Study Nos. 09P020 and 09P030 are graphed as follows:

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

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

As the data shown above, there are no significant statistical differences although the stability trends of -----(b)(4)----- are slightly different for Octaplas US manufactured in OPG and OAB. Again, Octapharma needs to demonstrate the comparability of the respective manufacturing process of the lots from Study Nos. 09P020, 10P026, 09P030, and 10P027 to the one intended for US licensure.

- 3) Octapharma provided ---(b)(4)--- long-term stability data on non-US marketed OctaplasLG manufactured from non-US human plasma (with reference to

stability study No. 08P010). The final container is 300-mL sterile plasticized polyvinyl chloride blood bag. Octapharma did not confirm if it is the same as those requested for the U.S. commercial distribution. The available test results of non-US marketed OctaplasLG are within the acceptance criteria. There are no deviations for up to -----(b)(4)-----

- 4) With reference to Study Nos. 11P018 and 11P029, there are no long-term stability data for the conformance lots provided in the BLA.
- 5) For stability after thawing, Octapharma provided the data on three Octaplas US lots from each manufacturing site. The results are summarized as follows:
 - For storage at ---(b)(4)---, the test results from all coagulation factors and protease inhibitors met the acceptance criteria for up to -(b)(4)-.
 - For storage at 20 – 25°C, the test results of all coagulation factors and protease inhibitors met the acceptance criteria for up to -----
----- (b)(4) -----
-----;

(b)(4)

- There are no significant differences regarding the stability of Octaplas US batches manufactured either from different plasma sources (i.e., US recovered or Source Plasma) or at different sites (i.e., OPG or OAB). In addition, there are no significant differences for the stability of Octaplas US lots stored in plasma bags from the referenced --(b)(4)-- i.e., -----(b)(4)-----

- 6) Proposed shelf-life for Octaplas US final product:
 - Octapharma proposed a shelf-life of (b)(4) months for Octaplas US final product when stored at $\leq -18^{\circ}\text{C}$ and protected from light.
 - The thawed Octaplas US can be stored at either ----- (b)(4) -----
20 – 25°C ----- (b)(4) -----

FDA comment: With regard to the referenced conformance lots manufactured at either OPG or OAB sites, Octapharma did not provide any data on long-term or accelerated stability studies, which include Study Nos. 11P018 and 11P029.

Therefore, they should provide the available stability data for the lots in these two studies.

In addition, the data from other stability studies in this submission can be used for supporting the shelf-life of Octaplas US intended for the U.S. market, provided that the lots in those stability studies and the conformance lots introduced in the original BLA are comparable in terms of the starting materials and the respective manufacturing process.

These concerns were communicated to Octapharma on 7 June 2012. They responded in the amendments on 22 June 2012 (amendment # 125416/0.4) and 31 August 2012 (amendment # 125416/0.18), respectively.

Octapharma's responses are summarized as follows:

- The lots of stability study No. 08P010 were manufactured by a manufacturing process identical to that intended for the U.S. commercial distribution. The container closure system, i.e., 300-mL plasma bag manufactured by -----
--(b)(4)----- is also identical to the submitted primary packaging material.
- Octaplas US lots used in stability study Nos. 09P020, 10P026, 09P030, and 10P027 were manufactured using a manufacturing process identical to that intended for the U.S. commercial distribution.
- Octapharma submitted 6-month long-term stability data from study Nos. 11P018 and 11P029. The data on some of critical parameters are listed as follows:

(b)(4)

FDA comment: The responses provided by Octapharma appear to be satisfactory based on the following reasons:

- Octapharma confirmed that the manufacturing process and final container for the lots used in study No. 08P010 are identical to those intended for the U.S. commercial distribution. Thus, the only difference for the lots in study No. 08P010 and study Nos. 11P018 and 11P029 is the starting material in the manufacturing process. The lots used in study No. 08P010 are produced from non-US recovered plasma, which might be the worst case scenario when compared with the lots produced from the US sourced plasma. Therefore, the long-term stability data from study No. 08P010 might be used to support the establishment of 24-month shelf-life of Octaplas US intended for the US market.
- Based on confirmation from Octapharma, the stability data on lots in stability study Nos. 09P020, 10P026, 09P030, and 10P027 might be used to support the shelf life of Octaplas US intended for the U.S. market.
- Although the available stability data for the (b)(4) conformance lots are very limited at this time, there are no significant changes in the trend of potency when comparing the data from the 3-month or 6-month time-points to those from the initial (0) time-point. The ----(b)(4)---- are slightly lower when comparing the lots manufactured using recovered plasma with the ones manufactured using Source Plasma. However, all the data met the acceptance criteria. The same is the true for (b)(4). There are no significant differences for the potencies of the lots manufactured at the OPG and OAB sites. Together with the long-term stability data from Study No. 08P010 (produced from non-US recovered plasma), they support the establishment of a 24-month shelf-life of Octaplas US when stored at $\leq -18^{\circ}\text{C}$ and protected from light.

Adventitious Agents Safety Evaluation (3.2.A.2)

1. Viral safety

The safety of Octaplas US towards enveloped viruses is based on the S/D treatment, whereas the safety towards non-enveloped viruses is contributed by immune neutralization and control of virus titer by NAT testing of --(b)(4)--. All viral clearance studies were performed with the intermediate or final product collected from routine production of non-US marketed Octaplas at OPG, and these data are used for supporting the manufacture of Octaplas US at both the OPG and OAB sites.

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

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

----- (b)(4) -----
-----.
- S/D treatment step: S/D treatment in the manufacturing process is performed using 1.0% Triton X-100 (w/w) and 1.0% tri(n-butyl)phosphate (TNBP) (w/w) at $30 \pm 1^\circ\text{C}$ for 60 ~ 90 minutes. In the ---(b)(4)--- study, Octapharma used

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

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

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(b)(4)

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

FDA comment: -----
----- (b)(4) -----
The same is true for the samples collected before and after S/D treatment.

These data support that the --(b)(4)-- study (Study No. 020STD952.024/00) may closely represent the S/D treatment step in the full-scale manufacturing process of Octaplas US.

2) Viral clearance

- Virus screening

Octaplas US is manufactured from human plasma collected in U.S. licensed plasma donation centers. All plasma donations are tested for viral markers in compliance with U.S. regulation.

- Immune neutralization

Pooling of a large number of plasma units is considered as an immune neutralization step mainly against non-enveloped viruses such as HAV, HEV, and human parvovirus B19 (B19V) during the manufacturing of Octaplas US. However, the immune neutralization capacity is dependent on both the specific IgG antibody level and the initial virus load in the manufacturing plasma pool. For this reason, Octapharma introduces the following safety measures:

- a: Virus load is controlled at the -----(b)(4)----- using NAT. All plasma units are tested -----(b)(4)----- for HIV-1, Hepatitis B Virus (HBV), HCV, HAV, and B19V, respectively. A cut-of value for B19V DNA based on quantitative NAT has been implemented -----(b)(4)----- which is acceptable based on the FDA comments during the review of IND for Octaplas US.
- b: Antibody determination in the specification of Octaplas US final product. The level of antibody against HAV, HEV, and B19V is not less than 1 IU/mL, 0.2 IU/mL, and 11 IU/mL, respectively.

The potential capacity of immune neutralization against specified non-enveloped viruses to contribute to viral safety was investigated. Therefore, Octapharma provided the following virus clearance studies on non-enveloped viruses: HAV (*Octaplas and Uniplas: impact of the anti-HAV IgG titer on neutralization of HAV*), COX-B6 (*Complete immune neutralization of COX-B6 by pooled plasma: evaluation of the plasma volume effects*), and POL-1 (*Complete immune neutralization of POL-1 by pooled plasma: re-evaluation of the plasma volume effects*) with regard to immune neutralization.

FDA comment: The Pooling step is identical in the manufacture of non-US marketed Octaplas and Octaplas US except for the sources of human plasma, i.e., the non-US sourced human plasma for non-US marketed Octaplas and the

US sourced human plasma for Octaplas US. The above virus clearance data derived from non-US marketed Octaplas may be used for supporting the viral clearance of the manufacturing process of Octaplas US provided that they demonstrate the comparability between these two sourced human plasma.

Also, Dr. Mahmood Farshid, provided the following comment with regard to the immune neutralization:

It is misleading to include the likely clearance by neutralization as a part of viral clearance table. Therefore, this information should be removed from the viral clearance table, but they could mention it as a part of their risk reduction strategies.

This comment was sent to Octapharma on 15 August 2012 and they responded in amendment # 125416/0.21 dated 17 September 2012.

Octapharma's response and FDA comment: Octapharma agreed with the FDA comment regarding immune neutralization, and withdrew the information on immune neutralization from the viral clearance table. Therefore, their response is acceptable.

In addition, per the request from FDA during the review of IND for Octaplas US, the B19V assay has been validated (with reference to 3.2.P.3.4) and it appears to be satisfactory. This assay can detect B19V -----(b)(4)-----.

- HEV

The immune neutralization capacity for HEV is dependent on both the specific IgG antibody level and the initial HEV load in the manufacturing plasma pool. Octapharma cannot perform any HEV load control in the manufacturing process of Octaplas US, because a laboratory model was not available, and any validation studies on HEV have not been done yet. In order to reduce the risk for HEV in the manufacturing process, they are exploring to maintain the minimal level of antibody against HEV in the Octaplas US final product, which is set to be ≥ 0.2 IU/mL.

Actually, the antibody against HEV level is ---(b)(4)--- in the Octaplas US final product based on their manufacturing experiences. Octapharma stated that the manufacturing process can lead to relatively high safety margin if the immune neutralization capacity of the antibody against HEV is equivalent as the case demonstrated for HAV.

FDA comment: It is known that the presence of antibody against HEV may reduce the risk of HEV transmission. However, the risk assessment for mitigation of HEV transmission by immune neutralization provided in BLA is not adequate. We consulted with Dr. Farshid regarding the risk of HEV

associated with the manufacture of Octaplas US. Dr. Farshid provided the following comment (*in italics*) that was communicated to Octapharma on 7 June 2012.

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

Octapharma responded in amendment # 125416/0.21 dated 22 June 2012. Their response is listed as follows:

Octapharma's response: Introduction of HEV PCR testing for OctaplasLG manufacturing pools will start on 1 November 2012. -----
----- (b)(4) -----
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FDA comment: Considering the safety record of OctaplasLG and Octaplas outside the U.S. and -----
--(b)(4)-----, we agree with Octapharma's schedule for monitoring and controlling HEV level in the manufacture of Octaplas US.

Because of a major amendment submitted in October 2012, the action due date was extended to 21 January 2013, and Octapharma submitted the test method and final validation report for HEV PCR testing in manufacturing pool in amendment # 125416/0.31 dated 31 October 2012. In report #501VAL008/00, Octapharma validated the -----
-----(b)(4)------. They demonstrated that the sensitivity (95% limit of detection) of this assay is -(b)(4)-, which is below what FDA recommended the assay sensitivity of 2.5 log₁₀ IU/mL. They also demonstrated the robustness of this assay. These data support Octapharma's ability to detect the level of HEV RNA in the manufacturing pool using this validated assay in the manufacture of Octaplas US. The test result of HEV RNA in the pool must be negative using this validated assay with a sensitivity of ≤ 2.5 log₁₀ IU/mL (with reference to the amendments # 125416/0.21 dated 17 September 2012 and 125416/0.35 dated 3 December 2012).

- S/D treatment

As supported by the data provided in the virus clearance studies, a virus reduction factor of at least --(b)(4)-- is achieved within --(b)(4)-- of S/D treatment for HIV, PRV, and SBV. The respective inactivation capacity for each virus is mostly achieved in the ----- (b)(4) ----- of the 1 – 1.5 hours of S/D treatment. Thus, a reduction of the S/D treatment time (i.e., 1 – 1.5 hours) may have no significant impact on the safety profile of Octaplas US regarding enveloped viruses. Moreover, Octapharma did robustness studies for the following viruses examining the critical process parameters for S/D treatment.

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- Based on the above studies, The virus clearance data are summarized as follows:

The virus reduction rates (log₁₀) for inactivation/elimination of various viruses achieved by the manufacturing procedure of Octaplas US

Virus	Immune neutralization [log₁₀]	S/D treatment [log₁₀]	Total reduction factor [log₁₀]
HIV-1	N/A	≥ 6.18	≥ 6.18
PRV	N/A	≥ 5.03	≥ 5.03
SBV	N/A	≥ 5.31	≥ 5.31
BVDV	N/A	≥ 5.12	≥ 5.12
WNV	N/A	≥ 5.63	≥ 5.63
VACV	N/A	≥ 5.00	≥ 5.00
HSV-1	≥ 11.1 (Pool)	N/A	≥ 11.1 (Pool)
HAV	≥ 10.0 (Pool)	N/A	≥ 10.0 (Pool)
COX-B6	≥ 8.6 (Pool)	N/A	≥ 8.6 (Pool)
POL-1	≥ 10.9 (Pool)	N/A	≥ 10.9 (Pool)

N/A: not applicable

FDA comment: The intermediates from the full-scale manufacturing of non-US marketed Octaplas were used in the various virus clearance studies. Because the intermediate prior to S/D treatment is comparable between non-US marketed Octaplas and Octaplas US, the virus clearance data for non-US marketed Octaplas may be applied for Octaplas US. However, the viral clearance studies performed to support S/D treatment in the manufacturing process of Octaplas US are inadequate because Octapharma did not provide the information on any -----(b)(4)----- validation for the referenced viruses in the BLA. Moreover, they did not address the experimental determination of LOD in the introduced (b)(4) assay for each referenced enveloped virus. In order to complete the validation of (b)(4) assay they need to demonstrate experimentally that each of the referenced enveloped viruses would be detected at the theoretical limit of detection in a ----(b)(4)---. This IR (*in italics*) was sent to Octapharma on 19 June 2012.

With regard to -----(b)(4)----- used for the determination of viral clearance, please provide the validation data generated experimentally that the virus would be detected at the theoretical limit of detection in a ----(b)(4)----- for all of the referenced enveloped viruses.

Octapharma responded in amendment # 125416/0.5 dated 3 July 2012. Their response is listed as follows:

More than (b)(4) million bags of non-US marketed Octaplas have been transfused to more than (b)(4) million patients over the last 20 years outside the U.S. market. Octaplas US has the same clinical safety and efficacy profile when comparing with non-US marketed Octaplas, except for the increased safety margin in terms of prion disease transmission.

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

-(b)(4)

2. Prion safety

1.0 μm cell filtration before S/D treatment contributes to the overall prion safety, provided that the prion infectivity in plasma is fully or partially cell-bound, whereas ligand chromatography or -(b)(4)- resin column is designed to provide pathogenic prion protein (or PrP^{Sc}) removal capacity.

Studies on prion removal should be done in accordance with relevant guidelines for virus clearance. Therefore, Octapharma performed ---(b)(4)--- studies which were as close as possible to the full-scale manufacturing process, and used the data from these studies to support the evaluation on PrP^{Sc} safety in the full-scale manufacturing process of Octaplas US.

- 1) ---(b)(4)--- validation of the (b)(4) resin column: A -----(b)(4)----- of the (b)(4) resin column used in the manufacturing process of Octaplas US was validated by -----(b)(4)----- for Octapharma. The -----

---(b)(4)-----
-----, More important, the test results indicated that the activities of all coagulation factors and protease inhibitors at ---(b)(4)--- are comparable to those from full scale after the (b)(4) resin column. Thus, these data support this model used for the subsequent PrP^{Sc} removal validation studies.
- 2) Validation studies on potential PrP^{Sc} removal by the (b)(4) resin column at ---- (b)(4)-: PrP^{Sc} for all the validation studies was derived from brains of clinically ill hamsters (hamster-adapted scrapie 263K).

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Taken together, the validation studies are considered to be insufficient and the PrP^{Sc} removal capacity by the (b)(4) column is still uncertain although there are no confirmed reports of vCJD prion transmission through plasma or derivatives thereof to date.

Internal discussion on the PrP^{Sc} removal step introduced in the manufacturing process of Octaplas US

On 10 July 2012, Drs. Basil Golding, Mahmood Farshid, Tim Lee, Dorothy Scott, Nancy Kirschbaum, and Ze Peng from DH and Dr. David Asher from DETTD had an internal discussion on the PrP^{Sc} removal step introduced in the manufacturing process of Octaplas US. Based on the data provided in this BLA, we considered that the validation data to support PrP^{Sc} removal provided in the BLA to be incomplete and insufficient. Therefore, we suggested that they not be allowed to claim prion removal in the label although this step may have a limited capacity for PrP^{Sc} removal.

Octapharma agreed with these comments, and these recommendations have been reflected in the updated Package Insert (with reference to amendment # 125416/0.35 dated 3 December 2012).

Recommendation

Product stability and the measures taken by Octapharma to control adventitious agents in the manufacture of Octaplas US are acceptable. Octaplas US manufacturing process includes one virus inactivation step – S/D treatment to clear enveloped viruses. Moreover, the same product Octaplas LG and its predecessor Octaplas have been marketed outside the U.S. since 2009 and 1989, respectively, without safety concerns. Therefore, I recommend approval of the BLA with ----- (b)(4) -----:

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

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