



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Mid-Cycle Review

To: File (BLA 125416/0), Nancy Kirschbaum & Pratibha Rana
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Through: Timothy Lee, Ph.D., Acting Chief, LH/DH/OBRR
Sponsor: Octapharma
Product: Solvent/Detergent Treated Plasma for Transfusion [OctaplasLG®]
Subject: Mid-cycle review of Characterization, Control of Critical Steps, Method Validation and Impurities sections in BLA under STN 125416/0

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1. Executive Summary

OctaplasLG is a solvent/detergent (S/D) treated blood group-specific plasma-for-transfusion product, which was developed as an alternative to single-donor fresh frozen plasma (FFP) in order to increase the safety of plasma for transfusion by minimizing the risk of virus transmission. OctaplasLG is prepared from 630 to 1,520 single-donor units of the same blood group. During the manufacturing process, whole cells and cell fragments/debris are removed by 1.0 µm size exclusion filtration. Subsequently, the plasma pool is treated with a combination of the solvent [1% Tri(n-butyl) phosphate (TNBP)] and detergent (1% Octoxynol-9) to inactivate any enveloped viruses. These S/D reagents are later removed by oil and solid phase extraction, respectively. After 0.2 µm sterile filtration, OctaplasLG is filled into 200-mL bags and rapidly deep-frozen.

Review summary: Octapharma has developed reasonable lot release tests and identified critical steps and intermediates.

Comments:

1. Lot release specifications for the levels of some of the coagulation factors and inhibitors are not strict enough, and do not represent the manufacturing capability and experience of the process. Available lot characterization data indicate that stricter lot release specifications should be implemented.
2. In addition, I have two technical notes on the -----(b)(4)-----
 (b)(4)----- in Stockholm. -----(b)(4)-----

2. Characterization

Elucidation of Structure and Other Characteristics

Composition

3.2.S.3.1.1 Composition

Names of Ingredients	Per 200 ml Bag	Function	Standard
Human plasma protein	9.0-14.0 g	Active ingredient	internal
Sodium citrate dihydrate	0.88 - 1.48 g	Anticoagulant	Ph.Eur., USP
Sodium dihydrogen-phosphate dihydrate	0.06 - 0.24 g	Buffer component	Ph.Eur., USP/NF
Glycine	0.80 - 1.20 g	Osmolality regulator	Ph.Eur., USP/NF

Physicochemical Characterization

- the total protein concentration is 45-70 mg/mL
- the protein distribution is within the range of normal human plasma
- the coagulation activity values are close to the corresponding values of normal human plasma
- the specifications for Factor (F) V, FVIII, FXI are set at ---(b)(4)---, while those for Protein C, Protein S and α_2 -antiplasmin are set at ---(b)(4)-----, respectively.
- no antimicrobial substance or preservative is added
- viral safety is improved through S/D treatment and immune neutralization (based on control in the titers of specific antibodies and virus load)
- potential removal of pathogenic prion proteins (PrP^{sc}) by affinity ligand chromatography
- free of blood cells and cell fragments

Quality Control Parameters

For detailed results of the quality control parameters in OctaplasLG batches, see Table 1.

As can be seen in Table 1, specifications for ---(b)(4)-----
----- (b)(4)-----

Table 1 Quality control parameters in OctaplasLG conformance batches¹

[(b)(4)]

Additional Comparison Data

Quality of OctaplasLG manufactured from US and European plasma was compared with the data presented for the predecessor product manufactured without the prion removal step and reduction of S/D treatment time from 4-4.5 hours to 1-1.5 hours., i.e., comparison between Octaplas and single-donor FFP lots (for detailed results see Table 2 or Study Report 020STD 952.072/00, A. Heger, December 2011). In OctaplasLG batches, ---(b)(4)-----
---(b)(4)-----

[(b)(4)]

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

[(b)(4)]

4. Methods

In the course of the implementation of the manufacturing process of S/D-treated plasma products at Octapharma Stockholm (OAB) the corresponding validated analytical methods have been compared between QC OPG (Vienna) and QC OAB.

The majority of the methods are well-developed and in use by Octapharma for control of other US- and/or EU-licensed plasma-derived products such as Factor VIII and Factor IX concentrates. Proper suitability controls were developed by Octapharma to ensure the validity of the methods.

With the exception of ---(b)(4)----- (see below), QC OPG and QC OAB utilize similar methodology and equipment. Activities of coagulation factors and inhibitors are determined with commercially available kits ---(b)(4)-----
----(b)(4)-----

Table 1a below summarizes methods used for testing of in-process samples, which are referred by Octapharma as “method of preparation (MOP)” tests. Table 1b summarizes Product Specification methods.

(b)(4)

Table 1b: Test parameters requested by final product specification

Parameter	Sample	
Visual Control ⁵⁾	FC	(b)(4)
(b)(4)	FC	
	FC	
Total Protein	FC	
(b)(4)	FC	
	FC	
Sterility ¹⁾	FC	
Pyrogens ⁸⁾	FC	

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

[(b)(4)]

Reviewer notes:

1. Specification ---(b)(4)----- may need to be corrected to reflect the limitations of the method of detection in Stockholm. Currently, ---(b)(4)-----
(b)(4)-----
2. Stockholm facility uses ---(b)(4)----- concentrations to bring ---(b)(4)----- values ---(b)(4)----- This is not acceptable as ---(b)(4)-----
(b)(4)----- may affect the sensitivity of the assay. For example, validation report 138VAL719 FC 9xx /00 demonstrates that the ---(b)(4)-- values for positive control were ---
--(b)(4)-----

Example of ---(b)(4)----- variation (see 138VAL719 FC 9xx /00, page 13):

[(b)(4)]

5. Impurities

Evaluated Lots

The impurity profile was assessed using the (b)(4) OctaplasLG process validation batches:

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

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

List of Impurities and Sources

Product-related impurities:

- ---(b)(4)----- are present in recovered and Source Plasma
- --(b)(4)-- is present in recovered and Source Plasma as an anticoagulant
- ---(b)(4)----- is present in recovered plasma as an anticoagulant

Process-related impurities:

- Sodium dihydrogen-phosphate dihydrate is added to the OctaplasLG plasma pool as a buffer to protect the plasma proteins from ---(b)(4)-----
- S/D reagents [Octoxynol and TNBP (tri-n-butyl phosphate)] are added after the removal of residual cells, cell fragments and cell debris, to inactivate enveloped viruses
- Castor oil is added subsequently to virus inactivation, to remove TNBP from plasma (i.e., oil extraction)
- Potential leachables of the C18 chromatographic resin (solid phase extraction on the C18 resin is used to remove Octoxynol from plasma after virus inactivation)
- Potential leachables of the ---(b)(4)----- resin (affinity ligand chromatography is used to remove potentially present prion proteins)
- Glycine is added before sterile filtration and filling, to adjust osmolality

Results

Product-related impurities

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

[(b)(4)]

Conclusions & Recommendation

The impurity profile has been determined for (b)(4) OctaplasLG process validation batches at the QC department using routine finished product release testing. The impurity profile of octaplasLG was reproducible and the data demonstrate that the validation batches are well within the specified limits.

I recommend sending the following information request to Octapharma:

6. Letter-ready comments

1. Please increase the specification limits for Factor V, Factor VIII, Factor XI, Protein C and Protein S to reflect the currently available batch testing data.
2. For proteins with low activity, Protein S and plasmin inhibitor, please report results of lot release testing to 2 decimal places.
3. Regarding the (b)(4) test performed at the Stockholm facility:

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

Please submit your responses to FDA by 29 June 2012.