

Final CMC Review - RiaSTAP

MEMORANDUM Recommendation to Waive Pre-Approval Inspection

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Through: Timothy Lee, Ph.D. , Acting Lab Chief,
OBRR/DH/LH
To: The file of STN 125317/0 and Vasantha Kumar,
OBRR/DBA/RPMB
Company: CSL Behring GmbH U.S.
Product: Fibrinogen Concentrate (Human) [RiaSTAP™]
Subject: Final CMC review of the original submission

Summary

CSL Behring has submitted an original BLA STN 125317 for Fibrinogen Concentrate (Human) [RiaSTAP™]. The product has been given orphan drug status. The product is already approved for use in some other countries. The trade names outside the United States, Haemocomplettan® HS and Haemocomplettan® P, the product code designation B13023, and Human Fibrinogen Concentrate, Pasteurized (HFCP) are used throughout the submission interchangeably. However, HFCP for use in the US is made from US licensed human plasma and contains US licensed human albumin as a stabilizer.

Fibrinogen (Factor I) is a soluble plasma glycoprotein dimer which consists of three pairs of polypeptide chains ($A\alpha$, $B\beta$, and γ). Fibrinogen is a physiological substrate of three enzymes: thrombin, Factor XIII, and plasmin. During the coagulation process, the fibrinogen molecule forms fibrin, which is cross-linked to provide tensile strength for the primary hemostatic platelet plug.

HFCP is a sterile, preservative-free, lyophilized fibrinogen concentrate in a single-use 100 ml vial. The amount of HFCP is approximately 1 g of fibrinogen with the actual potency for each lot indicated on the vial label and carton. HFCP is reconstituted with 50 mL Sterile Water for Injection (~20 mg/mL) and is administered intravenously. Each vial contains 900 to 1300 mg fibrinogen, 400 to 700 mg human albumin, 375 to 660 mg L-arginine hydrochloride, 200 to 350 mg sodium chloride and 50 to 100 mg sodium citrate. Sodium hydroxide and hydrochloric acid may be added to adjust the pH.

HFCP is indicated for the treatment of congenital fibrinogen deficiency. The recommended initial dose is 70 mg per kg body weight with subsequent doses depending on target and measured fibrinogen levels. The infusion rate should not exceed 5 mL per minute (100 mg/minute).

Discipline Review

A CMC review was performed.

Other members of the committee and their areas of review are:

Faith Barash: Epidemiology

La Nissa Brown: Pharm/Tox

Christine Drabick: Bimo
Roman Drews: CMC (Adventitious agents' safety evaluation)
Lori Austen Hansberry: Epidemiology Consultant Reviewer
Nisha Jain: Clinical
Vasanth Kumar: Regulatory Project Manager
Don Lebel: CMC Consultant Reviewer (Batch production records)
Timothy Lee: CMC Consultant Reviewer
Iftekar Mahmood: pK data
Loan Nguyen: Labeling
Rebecca Olin: CMC (Facilities and equipment)
Ze Peng: CMC (Analytical methods)
Lisa Stockbridge: Labeling Consultant Reviewer
Boris Zaslavsky: Biostatistics
Craig Zinderman: Epidemiology

2.3.S.1 GENERAL INFORMATION

Due to the minimal storage time of the pure active ingredient solution, the information provided under section 3.2.S (drug substance) refers to the final bulk solution containing the active ingredient in stabilized form. The drug product name is "Fibrinogen Concentrate (Human)", also referred to as HFCP. Haemocomplettan ®P/HS/dual is CSL Behring's fibrinogen concentrate for therapeutic use and has been marketed for many years in several European countries and other regions of the world. The drug substance production processes of both HFCP and Haemocomplettan ®P are equivalent except for the albumin stabilizer used to formulate the bulk solution. Haemocomplettan ®P is stabilized with Human Albumin -----(b)(4)-----
-----, Since this albumin is not registered in the US, CSL Behring utilizes a US licensed -(b)(4)- human albumin, -(b)(4) -, as the stabilizer in HFCP. CSL Behring also produces -----(b)(4)-----, which is used as an intermediate fibrinogen product for further manufacturing use.

2.3.S.2 MANUFACTURE

2.3.S.2-1Manufacturers

CSL Behring GmbH in Marburg, Germany (US License No. 1765) is responsible for the manufacture of the drug substance/final bulk solution (including in-process control testing).

The manufacturer responsible for the starting material, cryoprecipitate, is CSL Behring - (b)(4)- (US license No. -(b)(4)-) in -----(b)(4)-----.

The human albumin excipient comes from CSL Behring -(b)(4)- in -----(b)(4)-----.

The NAT/PCR screening of plasma minipools is carried out by -----(b)(4)-----
----- in ---- -----(b)(4)-----.

The testing of fractionation pools is as follows:

----- (b)(4) ----- is responsible for the PCR testing of the fractionation pool for HAV and B19V. CSL Behring ----- (b)(4) ----- is responsible for the PCR testing of the fractionation pool for HBV, HIV, and HCV. ----- (b)(4) -----, serves as a back-up laboratory for the NAT/PCR testing of fractionation pools.

[illegible]

The drug substance contains human fibrinogen (Factor I) as the active ingredient. It is a soluble plasma glycoprotein with a molecular weight of approximately 340 kD that circulates in plasma as a precursor of fibrin. The native molecule is a homo-dimer, in which both subunits consist of three different polypeptide chains ($\text{A}\alpha$, $\text{B}\beta$, and γ). All three polypeptide chains of the subunits, as well as the dimer, are linked with disulfide bonds.

In order to identify protein impurities in intermediates throughout the entire production process and to evaluate the capacity of the HFCP process to consistently remove these impurities, (b)(4)- full-scale investigations were performed.

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

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

----- (b)(4)

----- (b)(4)

2.3.S.4 CONTROL OF DRUG SUBSTANCE

The drug substance of HFCP is obtained after --(b)(4) --, final adjustment and sterilizing filtration of the bulk solution. No formal release specifications are established for the drug substance; however, the in-process control requirements during manufacture of the bulk solution are equivalent to release specifications of the drug substance. All test procedures are validated.

The -----(b)(4)----- are measured at the bulk solution stage, prior to sterilizing filtration (bulk solution, “Fibrinogen active ingredient solution,” process step 2.6.3.1 of production procedure P-681).

Sterility is tested at the final bulk solution just prior to the filling process, as part of the filling and packaging procedure F-681.

2.3.S.5 REFERENCE STANDARDS OR MATERIALS

Not applicable.

2.3.S.6 CONTAINER CLOSURE SYSTEM

The drug substance of HFCEP, final bulk solution, is obtained after (b)(4)--, final adjustment and sterilizing filtration of the bulk solution. The final bulk is stored in ----- (b)(4)-----.

2.3.S.7 STABILITY

2.3.S.7-1 Stability Summary and Conclusions

The final bulk solution is stored in -----(b)(4)----- for a maximum period of -----
(b)(4)----- to allow transport to the filling and lyophilization area.

The holding time and temperature were validated in down-scale concurrent to routine production in validation study PV-681-002-02 (details in section 3.2.S.7.3-1 of Module 3).

The holding time of the drug substance/final bulk was also assessed during full-scale validation studies (reports in section 3.2.S.2.5 of Module 3).

2.3.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Product description and composition

HFCEP is a purified concentrate of fibrinogen (coagulation factor I). It is derived from human plasma and presented as a white powder for dissolution and infusion. After

reconstitution with sterile water for injection, it is slowly infused intravenously. It is supplied in a one gram dosage form (1 g of human fibrinogen) and does not contain any preservatives. After reconstitution with 50 mL sterile water for injection, the solution contains approximately 20 mg per mL. The quantitative composition of the final product is given in the following table:

Component	Compendial standard	Function	Amount in 1 g dosage
Human fibrinogen	Ph. Eur.	Active ingredient	900-1300 mg
Human albumin	US licensed 1	Stabilizer	400-700 mg
L-arginine hydrochloride	USP	Stabilizer	375-660 mg
Sodium chloride	USP	Electrolyte	200-350 mg
Sodium citrate	USP	Electrolyte/-(b)(4)-	50-100 mg
---(b)(4)-----	-(b)(4)-	-(b)(4)-	-(b)(4)-

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

Reconstitution diluent

Sterile water for injection is not supplied with the drug product.

Type of containers and closures

The HFCEP container closure system consists of an infusion glass vial and a rubber stopper sealed with a ---(b)(4)-----.

Single-dose, --(b)(4)-- infusion vials with a nominal size of 100 mL are used for the HFCEP drug product. The containers are made of -(b)(4)- glass and are suitable for most pharmaceutical preparations in accordance with Chapter <660> “Containers—Glass” of the current United States Pharmacopeia (USP).

The glass vials are sealed with a gray ---(b)(4)---- rubber stopper. The stopper meets type I requirements of the European Pharmacopoeia and the comparable requirements of Chapter <381> “Elastomeric closures for injection” of the current USP. The stopper is free from latex.

The vial and stopper combination is sealed with a red or light blue aluminum crimp cap with a punched hole and -----(b)(4)-----.

2.3.P.2 PHARMACEUTICAL DEVELOPMENT

2.3.P.2-1 Components of the Drug Product

2.3.P.2-1.1 Drug Substance

The active ingredient present in HFCEP is fibrinogen. The active ingredient is isolated and purified from cryoprecipitate in a continuous manufacturing process. -----

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

2.3.P.2-1.2 Excipients

Excipients in HFCP:

Excipient	Function	Target concentration
Human albumin (---(b)(4)---)	Stabilizing agent	-(b)(4)-
L-arginine hydrochloride	Solubilizing and Stabilizing agent	-(b)(4)-
Sodium chloride	Electrolyte	-(b)(4)-
Tri-sodium citrate dihydrate	Electrolyte — --(b)(4)--	-(b)(4)-
Sodium hydroxide	pH adjustment	-(b)(4)-

With the exception of human albumin, all excipients are supplied by major chemical manufacturers (---(b)(4)-). ---(b)(4)--- is produced by CSL Behring ---(b)(4)---, and is licensed in the US.

Since Haemocomplettan ® P was commercially introduced in 1985, the compatibility of the active ingredient and excipients has been demonstrated over 23 years of continuous manufacture.

2.3.P.2-2 Drug Product

2.3.P.2-2.1 Formulation Development

The formulation of lyophilized human fibrinogen was developed in the early 1980s and was based on three major target product characteristics or attributes:

- Sufficient stability
- Good solubility
- Dosage form(s) to achieve a nearly normal fibrinogen plasma level following administration

All ingredients are well known physiological compounds used in numerous manufacturing processes for CSL Behring's other plasma products. They were carefully selected to ensure the compatibility, performance and stability of the lyophilized product. Fibrinogen concentrate in a 1 g dosage form was considered appropriate to obtain adequate fibrinogen plasma levels following administration.

2.3.P.2-2.2 Overages

Not applicable.

2.3.P.2-2.3 Physicochemical and Biological Properties

HFCP is a lyophilized concentrate. After reconstitution with 50 mL sterile water for injection a colorless, clear to slightly opalescent solution is obtained. In the following tables, the physicochemical and biological properties of the final product HFCP are summarized.

Physicochemical Properties

Parameter	Specification (according to Quality control procedure Q-681)
Fibrinogen	---(b)(4)---
Albumin	---(b)(4)---
Appearance	---(b)(4)---

Parameter	Specification (according to Quality control procedure Q-681)
	----- ----- -----
Dissolution time	---(b)(4)-----
---(b)(4)---	---(b)(4)-----
pH value	---(b)(4)-
Protein	---(b)(4)-----
Residual moisture	---(b)(4)-----
Sodium chloride	---(b)(4)-----
Sodium citrate	---(b)(4)-----
L-arginine hydrochloride	---(b)(4)-----
---(b)(4)---	---(b)(4)-----
---(b)(4)----- protein	---(b)(4)-----
---(b)(4)----- protein	---(b)(4)-----

Biological Properties

Parameter	Specification (according to quality control procedure Q-681)
Sterility	According to CFR/USP
Pyrogens	According to CFR/USP
Abnormal toxicity	According to CFR/USP

2.3.P.2-3 Manufacturing Process Development

CLB Behring and its predecessors have been producing human fibrinogen concentrate since 1956. Fibrinogen concentrate for therapeutic use in humans with congenital or acquired fibrinogen deficiency was previously known under the trade names “Human Fibrinogen Konzentrat” and “Human Fibrinogen Behringwerke Konzentrat”. The product was renamed Haemocomplettan ® P 1g/2/ in 1985, coinciding with significant improvements in purity and safety, particularly with regard to the implementation of a pasteurization step. The basic manufacturing process has remained unchanged from this time, with the exception of increases in production scale or necessary updates to GMP and pharmaceutical industry technology standards. The manufacturing process of HFCEP is identical to the manufacturing process of Haemocomplettan ® P, except for the albumin solution used as stabilizer.

The manufacturing process of HFCEP is identical to the manufacturing process of Haemocomplettan ® P. Haemocomplettan ® P is stabilized with Human Albumin -(b)(4)-Behring, manufactured by CSL Behring GmbH in Marburg Germany. Since this albumin is not registered in the US, CSL Behring utilizes a US licensed -(b)(4)- human albumin as the stabilizer in HFCEP, produced by CSL Behring -(b)(4)- in -(b)(4)- ----- (---(b)(4)- ---).

safety were key factors in the selection of primary packaging materials. The principal attributes of the system are consistency in physical characteristics and chemical composition.

Special emphasis has been given to the protection of the lyophilized product against moisture, -(b)(4)- and --(b)(4) --- contamination. Container closure integrity has been validated through -(b)(4)- testing and ---(b)(4)--- testing and found satisfactory.

The container closure system is compatible with the lyophilized product and has been shown not to interact physically or chemically with the lyophilized powder as demonstrated by stability studies utilizing worst-case conditions.

Routine quality control measures are used to ensure the consistent quality of the packaging components and include:

- Supplier audits
- Inspection program for incoming packaging components and materials
- Receipt of certificates of analysis from the vendor and performance of appropriate identification tests

2.3.P.2-5 Microbiological Attributes

Special emphasis is given to the following aspects to minimize microbiological contamination of HFCP through:

- Trained and qualified personnel
- Appropriately designed and constructed production premises and equipment
- Microbiological monitoring of the environment
- Microbiological monitoring of the bulk product
- Sterile filtration of the bulk product
- Validated microbiological efficacy of the sterilization and depyrogenation cycles for primary packaging materials
- Proven integrity of the container closure system
- Routine process simulations by media fill trials
- Sterility and pyrogen testing on a lot-by-lot basis

2.3.P.2-6 Compatibility

No compatibility studies have been performed with HFCP.

2.3.P.3 MANUFACTURE

2.3.P.3-1 Manufacturer(s)

CSL Behring GmbH in Marburg, Germany, is responsible for the manufacture of the lyophilized product and final batch release of HFCP.

Contract laboratories involved in final batch release testing include:

1. CSL Behring -(b)(4)- in ----(b)(4)----- – -----(b)(4)-----
2. -----(b)(4)----- – -----(b)(4)-----
3. -----(b)(4)----- – -----(b)(4)-----

Routinely the sterility test of the drug product is performed in the sterility testing laboratory of CSL Behring in Marburg. The sterility laboratory of -----(b)(4)----- is used only as a back-up lab. These contract labs are also used for testing of US-licensed Vivaglobin ® and Humate-P ®. All other testing is performed by the Quality Control Department of CSL Behring GmbH.

2.3.P.3-2 Batch Formula

HFCP is manufactured in batches of ----(b)(4)-----, corresponding to a final bulk volume of --(b)(4)-- -- (each -(b)(4)- of final bulk solution results in -(b)(4)- of HFCP 1 g final lyophilized product).

2.3.P.3-3 Description of Manufacturing Process and Process Controls

The manufacturing process of the drug product is divided into two main steps:

- Filling into containers and lyophilization
- Packaging

Manufacture according to filling and packaging procedure F-681

Filling into final containers and lyophilization

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

Packaging

The dried substance vials are labeled and boxed.

Release

HFCP is tested in accordance with quality control procedure Q-681.

In-process controls

----- (b)(4) -----, a sample is taken for a sterility test [Requirement: specification according to Code of Federal Regulation (CFR)/United States Pharmacopeia (USP)].

2.3.P.3-4 Controls of Critical Steps and Intermediates

Control of critical steps

Critical process steps for the manufacture of HFCP drug product were identified in risk assessments. Based on these assessments, the production process was validated. A summary of the critical PCPs is presented in the table below:

Critical PCPs for the production process of HFCP drug product

Production procedure	Description of the critical process steps	Process control parameter	Target value of the PCP
F-681	Filling, lyophilization and packaging	---(b)(4)---	---(b)(4)----- -----
		---(b)(4)----- -----	---(b)(4)-----
		---(b)(4)-----	---(b)(4)---
		---(b)(4)-----	---(b)(4)----- -----
		---(b)(4)----- -----	--- (b)(4)----- -----

The lyophilization process was assessed as critical for the manufacture of the drug product. The validation of the lyophilization clearly demonstrates that this process is well

under control. -----(b)(4)----- testing of every lyophilized and sealed glass vial, as well as final batch release testing contributes to the control of the drug product for every batch.

Quality and control of intermediates

Sterility testing is performed routinely at the ----(b)(4)----- filling process as defined in filling and packaging procedure F-681. The testing is performed by the inoculation method according to CFR/USP requirements. The analytical procedure is # Q-01-002 and the procedure validation report is # MVR-25-001-Q660-01.

Lot release parameters/testing

Lot Release Parameter	Specified Range
Fibrinogen	--(b)(4)-----
Albumin	--(b)(4)-----
Practicability and ---(b)(4)---- properties	--(b)(4)-
Dissolution time	--(b)(4)- -
---(b)(4)----	--(b)(4)-----
pH value	--(b)(4) -
Protein	--(b)(4)-----
Residual moisture	--(b)(4)-
Sodium chloride	--(b)(4)-----
Sodium citrate	--(b)(4)-----
L-arginine hydrochloride	--(b)(4)-----
---(b)(4)----	--(b)(4)-----
---(b)(4)----- protein	--(b)(4)-----
---(b)(4)----- protein	--(b)(4)-----
Sterility	Pass
Pyrogens (rabbit)	Pass
General Safety Test	Pass

Intermediate holding times and stability studies

HFCP drug product is manufactured from the final bulk solution in a continuous manufacturing process such that an intermediate stage is not defined. However, due to a batch-mode production flow, the following brief holding times for intermediate fractions are required for the filling and packaging procedure:

- Holding time of the ---(b)(4)----- for -----(b)(4)-----
- Time between -----(b)(4)-----

The holding times of these intermediate --(b)(4)- were assessed during full scale validation studies. The holding times during the studies corresponded to the routine conditions or were exceeded in order to investigate worst case conditions.

2.3.P.3-5 Process Validation and/or Evaluation

2.3.P.3-5.1 Process validation approach

From the historical experience of routine manufacture of HFCP and the results of formal studies, the criticality of operating parameters was evaluated and summarized in a risk assessment report that reflected the available information about the drug product process steps and their function, in addition to the process control parameters (PCPs) and their effect on the corresponding product quality attributes (PQAs).

Based on the risk assessment, the entire drug product production process was validated at full-scale with manufacturing batches that were produced with PCPs set to the target values. All critical PCPs and IPCs were evaluated.

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

--

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

In addition to the study reports listed in section 2.3.S.3-5.1 (see Table 11 above), the company lists several more:

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

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

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

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

2.3.P.3-5.2 Process validation overview

Process validation studies of Human Fibrinogen Concentrate Pasteurized (HFCP) are comprised of the risk assessment for the production process of the drug product (with particular emphasis on the identification and control of critical steps), full-scale validation studies, investigation studies and process simulation studies.

Full-scale process validation studies were conducted by manufacturing consecutive batches under routine conditions at full-scale as specified in the respective production procedures. These validation studies were performed to validate the effect of individual processing steps and holding times on particular process quality attributes (PQAs).

These studies used target values for all process steps; however, holding and filling

[illegible]

Full-scale process validation studies were conducted specifically -----(b)(4)--
----- (PV-680-

The current lyophilization validation studies performed with Haemocomplettan® P 1 g (according to P-680 and F-680) are also considered as being representative of HFCEP (according to P-681 and F-681). The lyophilizers -----(b)(4)----- are installed in the filling and lyophilization area of BLDG -(b)(4)- and have been validated for Haemocomplettan® P 1 g / HFCEP (PV-660-002-01). Lyophilizers ----(b)(4)----- are also deemed suitable for the manufacture of Haemocomplettan® P 1 g / HFCEP based on the results of lyophilization validation study PV-680-004-01. In 2007, CSL Behring conducted a full-scale process validation study by manufacturing three consecutive batches of lyophilized HFCEP. The results obtained (report PV-681-003-02) are comparable to those from earlier lyophilization validation studies.

Full-scale investigation studies were conducted in parallel with routine production to evaluate the bioburden and endotoxin levels -----(b)(4)----- (IR-681-004-02). These studies were also conducted to identify the major potential impurities -----(b)(4)-----

----- (IR-680-003-01, IR-682-005-01).

Aseptic processing conditions were validated by simulation using media fill studies, performed under the same production conditions as the drug product, but dispensing sterile -----(b)(4)----- medium that had confirmed microbial growth promoting properties (MF-681-001-01).

2.3.P.3-5.3 Overall summary and conclusion

All pre-defined acceptance criteria from the various process validation studies were met, and the company concludes that the HFCP manufacturing process is successfully validated.

2.3.P.4 CONTROL OF EXCIPIENTS

Specifications

Human albumin, L-arginine hydrochloride, sodium chloride, and sodium citrate act as excipients in HFCP. They all comply with requirements of the USP. With the exception of human albumin (from CSL Behring -----(b)(4)-----) all excipients are supplied by major chemical manufacturers (----(b)(4)----).

Analytical Procedures

A certificate of analysis with results of tests complying with the relevant monographs is provided with each delivery. In-house testing is performed to confirm identity. The microbiological quality (bioburden, exclusion of -----(b)(4)-----) is confirmed by CSL Behring GmbH internal testing at regular intervals. Only lots of substances tested in accordance with the specifications and released by the QC Department can be used in further manufacture. All analytical procedures have been validated. The specifications of the excipient testing comply with the requirements of the US Pharmacopeia and Code of Federal Regulations.

Excipients of Human or Animal Origin

HFCP contains human albumin. No excipients of animal origin are used in HFCP.

2.3.P.5 CONTROL OF DRUG PRODUCT

2.3.P.5-1 Specification

HFCP final product is tested according to quality control procedure Q-681.

2.3.P.5-2 & 3 Analytical Procedures & Validations

The analytical procedures from quality control procedure Q-681 are listed in Table 14 with the corresponding validation report numbers. (Dr. Ze Peng is performing the CMC review of the analytical procedures.)

2.3.P.5-4 Batch Analyses

2.3.P.5-4.1 Comment on certificates of analysis

Certificates of analysis for the HFCP conformance lots are provided in section 3.2.P.5.4-2 of Module 3.

2.3.P.5-5 Characterization of Impurities

CSL Behring conducted studies to investigate the impurity profile of the manufacturing process, to evaluate the capacity to consistently remove these impurities as well as to compare the impurity profiles of the production process using filters from different vendors.

Specific proteins (e.g. -----(b)(4)-----
-----) and non-proteins (----- (b)(4)-----

-----) were analyzed throughout the production process. In addition, protein distribution was determined with -----(b)(4)----- and -----(b)(4)----- and individual proteins were identified by -----(b)(4)----- analysis (---(b)(4)---).

The results of these studies indicate that both protein and non-protein impurities are consistently eliminated or reduced throughout the process, resulting in an acceptable and reproducible impurity profile. No difference in the impurity profile was observed between lots manufactured using filters from different vendors. The manufacturer concludes that the production process is therefore capable of reliably and reproducibly purifying fibrinogen and removing impurities.

2.3.P.5-6 Justification of Specifications

HFCE lyophilized product is tested according to quality control procedure Q-681. A justification for the specifications listed in Q-681 is provided in the table below. The testing and specifications comply with the current USP and CFR wherever possible. Other references such as the European Pharmacopoeia (Ph. Eur.) have been utilized when an equivalent specification does not exist in the USP/CFR.

Justifications for the specifications of HFCE drug product

Parameter	Analytical procedure	Specification	Justification
Sterility	Q-25-001	From CFR/USP	According to CFR/USP
Practicability and ---(b)(4)---- properties	Q-04-003	---(b)(4)----- : max - (b)(4)- Appearance : Almost colorless and clear to slightly opalescent solution; -- (b)(4) - ----- ----- -----	---(b)(4)----- : manufacturer specification. Appearance : according to Ph. Eur.
---(b)(4)----- protein	Q-04-010	---(b)(4)-----	Part of identity testing according to 21 CFR Section 610.14
Albumin	Q-04-031	---(b)(4)-----	Range reflects process and assay variability and was based on historical data.
---(b)(4)----- protein	Q-04-040	---(b)(4)-----	Part of identity testing according to 21 CFR Section 610.14
Protein	Q-16-002	---(b)(4)-----	Range reflects process and assay variability and was based on historical data.

Parameter	Analytical procedure	Specification	Justification
Fibrinogen	Q-16-003	--- (b)(4)-----	Assay according to PH. Eur. Range reflects process and assay variability
Sodium chloride	Q-16-018	---(b)(4)-----	Range reflects process and assay variability and was based on historical data.
pH	Q-16-380	---(b)(4)--	Physiological pH
---(b)(4)-----	Q-16-023	---(b)(4)-----	Assay according to PH. Eur. Upper limit reflects process and assay variability and was based on historical data.
---(b)(4)-----	Q-16-033	---(b)(4)-----	Range reflects process and assay variability and was based on historical data.
Sodium citrate	Q-16-048	---(b)(4)-----	Range reflects process and assay variability and was based on historical data.
L-Arginine hydrochloride	Q-16-087	---(b)(4)-----	Range reflects process and assay variability and was based on historical data.
Residual moisture	Q-16-345	---(b)(4)-----	Assay method according to ---(b)(4)----- Range reflects process and assay variability and was based on historical data
Pyrogens	Q-21-001	From CFR/USP	According to CFR/USP
Abnormal toxicity	Q-21-101	From CFR/USP	According to CFR/USP

2.3.P.6 REFERENCE STANDARDS OR MATERIALS

No reference standard is available for the determination of fibrinogen functional activity. For the measurement of the fibrinogen concentration and functional activity of the HFCEP drug product, the testing procedure according to analytical method Q-16-003 is used (“--

---(b)(4)----- determination of the clottable protein” according to -(b)(4)--. This method utilizes -----(b)(4)-----

2.3.P.7 CONTAINER CLOSURE SYSTEM

Refer to section 2.3.P.2-4 above.

2.3.P.8 STABILITY

CSL is proposing a shelf life of -(b)(4)- months at +2 to +25 oC for HFCEP.

The HFCEP conformance lots manufactured in November 2006, February 2007 and April 2007 are being assessed in a stability study to demonstrate compliance with the final lyophilized drug product specifications and to identify any trends indicative of a potential change to the quality attributes over a

-(b)(4)-month storage period. Results of testing after storage at +5 oC \pm 3 oC and +25 oC \pm 2 oC/-(b)(4)- relative humidity (RH) are currently available at the 18 month time point for 2 lots, and at the 12 month time point for 1 lot. A study of the three lots stored at -(b)(4)- \pm 2 oC/-(b)(4)- RH for six months has also been completed. As a result of a CBER information request, statistical trend analysis has been submitted for the data on total fibrinogen and on --(b)(4)--.

The following table lists the storage conditions and testing intervals:

Type	Storage conditions	Storage period	Sampling intervals
Long term storage	+5 \pm 3 OC	-(b)(4)- months	0,3,6,9,12*, 18*, 24, ---(b)(4)-----
New long-term storage condition	+25 oC \pm 2 oC / --(b)(4)-- RH	-(b)(4)- months	0,3,6,9,12* 18*, 24, ---(b)(4)-----
Accelerated storage	-(b)(4)- oC \pm 2 oC / --(b)(4)-- RH	6 months	0, 1, 3 and 6* months
Stability after reconstitution	+5 \pm 3 OC and +25 oC \pm 2 oC / --(b)(4)--RH	-(b)(4)- months	0*, ---(b)(4)-----

*currently tested sampling point

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

Stability study test parameters include -----(b)(4)-----

Detailed results are provided. Data covering 18 months (lots -----(b)(4)-----) and 12 months (lot -(b)(4)-) are available for the long-term conditions (at +5 oC and +25 oC) and 6 months data are available for the testing of all three lots stored at accelerated conditions (-(b)(4)- oC). All three lots were tested for stability after reconstitution (up to 24 hours) at the initial time point.

All stability lots met the biochemical and physical quality requirements of all tested parameters at all time points and under all storage conditions.

A statistical analysis to estimate the shelf life was performed according to ICH guideline Q1E comparing two-sided 95% confidence intervals for the mean values against the specifications. The appropriate analysis-of-covariance model was selected by backward elimination using a type-one error probability of 25%. All measured values of the variables analyzed in the report were within specification at all temperatures. The two-sided 95% confidence intervals stayed within specification during the current observation period of 18 months (first two lots) and 12 months (third lot) at storage temperatures of +5 oC and +25 oC / -(b)(4)- RH. The two-sided confidence intervals also stayed within specification when extrapolating to a storage period of -(b)(4)- months. The ICH guideline Q1E, however, only allows for extrapolating up to 30 months (real time plus 12 months) for storage at room temperature.

Significant changes were observed in the following cases ($p=0.01$ or less):

Change

Variable Storage conditions Lot per year p -value

Fibrinogen (mg/mL) +5oC All combined -1.048 0.0007

+25 oC / -(b)(4)- RH All combined -0.897 0.0034

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

-area 1 (% fibrinogen aggregates) +40 oC / -(b)(4)- RH All combined +5.105 0.0019

-area 2 (% monomers) +40 oC / -(b)(4)- RH All combined -5.152 0.0021

Graphs are shown for fibrinogen with extrapolated lines out to -(b)(4)- months, which indicate that the level is not likely to fall below the specified limit.

The company concludes, with respect to the variables analyzed in this report, that the data support a tentative shelf life of at least 30 months for HFCEP when stored at +25 oC / -(b)(4)- RH and this shelf life has to be confirmed (and may be extended) by real time data when the stability study is completed.

The company maintains that the stability of HFCEP is further supported by data from previous stability studies on its related product, Haemocomplettan P ®, which confirm a shelf-life of -(b)(4)- months at a storage temperature of -(b)(4)-. However, the Haemocomplettan P ® used in those studies was made at -(b)(4)- of the batch scale of HFCEP (RiaSTAP™), and the source of the albumin used as an excipient was different. Also, stability at +25 oC was not studied for Haemocomplettan P ®.

Stability of Excipients

In response to CBER's September 5, 2008 information request regarding any available stability data for the excipients used in HFCEP, the company has provided stability data for three lots of human albumin,

--(b)(4)--- produced by CSLB -----(b)(4)-----, as follows:

Lot Number Volume Temperature Duration

----(b)(4)----- -(b)(4)- mL -(b)(4)- oC -(b)(4)- months

----(b)(4)----- -(b)(4)- mL -(b)(4)- oC -(b)(4)- months

----(b)(4)----- -(b)(4)- mL -(b)(4)- oC -(b)(4)- months

The specified shelf life is -(b)(4)- months. All results for all three lots complied with the final product specifications. Statistical analysis revealed a significant increasing trend in --(b)(4)-- over time for two of the lots (----(b)(4)----- and ----(b)(4)-----), but all the values were well under the specified limit of -(b)(4)- µg/L. For lot ----(b)(4)-----, there was a statistically significant decreasing trend for -(b)(4)-, but the lowest value was still well

above the lower limit. All the results were comparable with values from previous follow-up stability studies.

Other excipients are not tested for stability by CSL Behring.

Information Request after Mid-cycle

The company was asked to acknowledge that the dating period will be 30 months unless more stability data was available, and to change their conformance lot protocols accordingly. Their response included those changes, as well as appropriate changes in labeling.

Conformance Lot Testing at CBER

Conformance lots (Numbers -----(b)(4)-----) were tested at CBER for residual moisture, pH, solubility, appearance, sterility and LAL by members of the Division of Product Quality. All results were within specifications.

CMC Summary and Conclusions

This submission is approvable from a CMC perspective. The manufacturing process has been adequately validated and is well controlled. Essentially the same product has been marketed in a number of other countries since 1986 without incidences of viral seroconversions. Therefore, CBER reviewers have accepted a single viral inactivation step as adequate. This product will be in the lot release program for protocol review only, due to the rarity of congenital fibrinogen deficiency and the resulting small number of product lots being produced. The expiration dating for the product will initially be set to 30 months at 2-25 oC, and reconstituted product should be used within 24 hours.