BLA Recommendations - RiaSTAP

MEMORANDUM

To:	File BL STN 125317/0
From:	Rebecca Olin, OCBQ/DMPQ/MRB2
Through:	Chiang Syin, PhD, Chief, CBER/OCBQ/DMPQ/MRB2
Subject:	CSL Behring (License #1765) BLA : For the use of Human Fibrinogen Concentrate, Pasteurized, Riastap, in the treatment of congenital fibrinogen deficiency.

Action Due: January 16, 2009

Action Recommended

Recommend approval

Product

Human Fibrinogen Concentrate, Pasteurized

Summary

CSL Behring submitted this BLA in support of the manufacture of Human Fibrinogen Concentrate, Pasteurized (HFCP) for the treatment of congenital fibrinogen deficiency at the Marburg, Germany location. This BLA was granted Fast Track Status with a 6-month review timeframe because of HFCP's potential to treat a life-threatening condition. This facility has been inspection several times in the last two years with the most recent inspections in March/April 2008 (routine biennial) and May/June 2008 (PAI for ---------(b)(4)----------). The biennial and PAI inspections were classified as VAI. With this inspection history an inspection waiver was requested and approved. Review of this BLA did not show any significant issues that would prevent approval and I recommend this file be approved.

Review Narrative

Human Fibrinogen Concentrate, Pasteurized (HFCP) is a purified concentrate of fibrinogen (coagulation factor I) and indicated for the treatment of congenital fibrinogen deficiency.

HFCP is a lyophilized product in a 1 gram dosage form without preservative. The container closure is a single use glass infusion vial with rubber stopper and crimp cap. The lyophilized white powder is reconstituted with sterile water and slowly infused intravenously.

Drug substance and final bulk solution will be manufactured at CSL Behring GmbH located in Marburg Germany (License #1765). Pre-treatment of equipment is conducted at the Main Work site. Manufacture of the ----------(b)(4)---------- are conducted at the ---(b)(4)---- complex in Marburg.

-----(b)(4)------ will be manufactured at CSL Behring -(b)(4)- located in --(b)(4)--, US (License #-(b)(4)-).

Human albumin excipient will be manufactured at CSL Behring -(b)(4)- in ---(b)(4)---- (License #-(b)(4)-).

Manufacturing Process Overview

- Cryoprecipitate from source plasma is supplied by CSL Behring in ----(b)(4)----- (US license #-(b)(4)-)
- Dissolution, adsorption to Al(OH) 3: Cryoprecipitate is dissolved in a buffer solution containing ----------(b)(4)----------. Contaminating proteins are eliminated by adsorption to $Al(OH)_3$.
- First glycine precipitation:
- Glycine precipitate dissolution, adsorption to $Al(OH)_3$:
- Pasteurization:
- Second glycine precipitation:
- Dissolution, -(b)(4)-
- -(b)(4)- filtration
- --(b)(4)- and final adjustment

- Sterilizing filtration
- Filling, Lyophilization and Packaging

Site Description

The facilities used for the manufacture and testing of HFCP are included in the table below:

[----------(b)(4) ----------]

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

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

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

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

Process Validation

Full scale process validation studies were conducted by manufacturing -(b)(4)- full scale fibrinogen lots which were used in -(b)(4)- consecutive HFCP lots and -(b)(4)- consecutive --(b)(4)-- lots. These lots were manufactured under routine conditions at full-scale 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 times were validated at full-scale under worst case conditions.

Three consecutive batches of lyophilized product were manufactured in support of the lyophilization process using lyophilizers ----------(b)(4)----------.

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

Media Fills

Aseptic processing conditions were validated by simulation using sterile nutrient medium and were performed under the same production conditions as the drug product.

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

Drug Product : -(b)(4)- media fill runs were conducted to validate the aseptic processing on filling and stoppering machine -(b)(4)- and lyophilizers ----------(b)(4)---------- located in Building -(b)(4)-. Routine and non-routine interventions were included in the studies and were identified in the final report.

The number of units per run ranged from ----(b)(4)----. Media was incubated for at least -(b)(4)- days at -(b)(4)-°C followed by -(b)(4)- days at -(b)(4)-°C. After incubation, visual exam showed no contaminated units. Growth promotion studies were conducted successfully using indicator microorganisms per USP as well as local isolates.

Container Closure

Drug Substance : The drug substance of HFCP, final bulk solution, is obtained after --(b)(4)--, final adjustment and sterilizing filtration of the bulk solution. The final bulk solution is stored in ----------(b)(4)---------- and can be stored up to --(b)(4)- at --(b)(4)--. Holding/storage times and container closure integrity of the final bulk vessels have been validated using -(b)(4)---------- to verify the tanks ability to maintain sterility for up to -(b)(4)-.

Holding times were determined via media fill studies.

Drug Product : Single-dose 100 ml infusion vials made of ------(b)(4)------- glass along with gray ---(b)(4)---- rubber stoppers and an ---(b)(4)-- crimp cap with a punched hole and ----------(b)(4)----------.

Container closure integrity was validated using ---(b)(4)--- and ----------(b)(4)----------. Vials were ----------(b)(4)---------- and a -(b)(4)- applied to create a ------(b)(4)-------- in the vials. ----------(b)(4)----------, the -(b)(4)- test samples of HFCP 1g were checked and no -(b)(4)- was noted in the sample vials. For the ----------(b)(4)---------- containers were filled with ------(b)(4)------, sealed and crimped according to routine processing procedures. Samples of these vials were -----(b)(4)---------- for -(b)(4)-. The samples were incubated for -(b)(4)- and visual inspection showed no turbidity or sediment.

Bioburden/Endotoxin

Bioburden and endotoxin are measured as in-process controls (IPC) at the -------(b)(4)------ ----------. Three consecutive production lots were evaluated for bioburden and endotoxin from process step ----------(b)(4)----------. Samples for bioburden were taken at the following process steps:

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

Endotoxin samples are taken also at the above steps in addition to the following steps:

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

Bioburden results show that an initial bioburden of 33-95 CFU/ml at the -----(b)(4)------ ---------- step decreased to 0 CFU/ml at the -(b)(4)- sampling step and maintained this level to final testing.

Endotoxin results were below the specification of -(b)(4)-/ml for all sample points for all lots manufactured.

Packaging and Labeling

Packaging and labeling occurs in Building -(b)(4)-, a -(b)(4)-story building. The labeling and packaing area on the -(b)(4)- floor is currently licensed for the production of Humate P ® and Vivaglobin ®. This area was inspected during the PAI of May/June 2008.

Lyophilization

There are -(b)(4)- lyophilizers that will be used for HFCP production, ----------(b)(4)----------. They are located in Building -(b)(4)-. The validation of the lyophilization process was conducted using both HFCP and Haemocomplettan P lots. The composition of Haemocomplettan P is essentially identical to HFCP and they are also identical with respect to ----------(b)(4)----------. Validation data from both products were included in support of the use of lyophilizers ---------(b)(4)----------
----------. Residual moisture data for the Haemocomplettan P validation lots and the three full scale HFCP lots were within the release specification of -(b)(4)-.

Equipment

----------(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)-----

Six (6) Pages Determined to be Not Releasable: (b)(4)

Utilities

Building -(b)(4)-

Purified Water : The PW system is currently licensed for the manufacture of Humate-P ® and was covered during the GMP inspection in March/April 2008. PW is used as feed water to generate WFI by distillation and pure steam. This system was originally validated in February 1998 and the most recent re-qualification was conducted in November 2003. Monitoring data from January to March 2008 was included in the submission. There were no significant deficiencies.

WFI : The WFI system is currently licensed for the manufacture of Humate-P ® and was covered during the GMP inspection in March/April 2008. PW is used as feed water for the generation of WFI. The generation system consists of -(b)(4)- distillation units ----------(b)(4)---------- distillation units consist of ----(b)(4)----- that produce WFI by a --------(b)(4)---------- process. WFI is stored in ---------(b)(4)---------- that supplies -(b)(4)- WFI storage tanks. Each of the -(b)(4)- sub-storage tanks supplies a WFI -(b)(4)- in Building -(b)(4)-. For the production of HFCP, WFI loops ----------(b)(4)---------- are relevant. WFI is used in Building -(b)(4)- as ------(b)(4)------- water and for ----------(b)(4)---------- ----------.

The -(b)(4)- WFI ----(b)(4)----- and the ----------(b)(4)---------- are supplied with Purified Water. The -(b)(4)- produce hot (-(b)(4)-). The --(b)(4)--- is a multi-effect still which delivers nominally ------(b)(4)--------. The -(b)(4)------- WFI -(b)(4)- is a ---(b)(4)---- with delivers nominally -------(b)(4)------- of WFI.

WFI from the -(b)(4)- is supplied to the main WFI distribution system consisting of a storage tank and pump. Water from the main system supplies --(b)(4)--.

The quality of the water is continuously monitored using a conductivity meter installed on each loop return. Each storage tank and distribution loop has ----------(b)(4)---------- to allow for an -(b)(4)- procedure for system sanitization. All low points in the system including points of use have steam traps available to ensure the removal of air and condensate during the -(b)(4)-procedure.

The initial validation of the WFI system and ---(b)(4)--- was conducted in October 2005. (b)(4)---------- was originally validated in January 1998.

Trend reports for the WFI system for the period of January 1, 2008 to March 31, 2008 were provided. Monitoring data for bioburden, endotoxins, TOC and conductivity were all within acceptance criteria.

HVAC : There are -(b)(4)- HVAC units that supply the -(b)(4)- floors of Building -(b)(4)-. ----------(b)(4)---------- ----------

----------(b)(4)---------- feed it ----------(b)(4)----------. HVAC systems -------(b)(4)-------- service the ----(b)(4)---------- manufacturing areas on the -(b)(4)- floor which are classified -(b)(4)- (rooms -------(b)(4)--------) and -(b)(4)- (rooms -----(b)(4)-----). -(b)(4)- services the -(b)(4)- floor areas relevant to HFCP production.

Qualification of HVAC system -(b)(4)- was initially conducted from January to April 1998. -(b)(4)- services the cleaning room, gowning rooms, storage areas and material air lock on the -(b)(4)- floor. The pre-treatment area on the -(b)(4)- floor of -(b)(4)- is monitored for surface bioburden and airborne particulates. Data summaries for environmental monitoring of the -(b)(4)- floor show bioburden, airborne particulates and airborne viable particulates were within specification for the January to March monitoring period.

Qualification of HVAC system -(b)(4)- was initially conducted from January to May 1998. -(b)(4)- supplies the ----------(b)(4)---------- ---------- and other manufacturing and support areas on the -(b)(4)- floor. Rooms in this area are classified as --(b)(4)--.

Qualification of HVAC system -(b)(4)- was initially conducted from January to May 1998. -(b)(4)- supplies the ----------(b)(4)---------- areas on the -(b)(4)- floor. Rooms in this area are classified as ----(b)(4)---.

Data summaries for environmental monitoring of the third floor show bioburden, airborne particulates and airborne viable particulates were within specification for the January to March monitoring period.

Building -(b)(4)-

Purified Water (PW) : is generated by reverse osmosis (RO) on the -(b)(4)- floor in Building -(b)(4)- and supplied to the storage and distribution system in Building -(b)(4)-. PW is used as feed water for WFI and pure steam generation. The WFI system is currently licensed for the manufacture of Humate-P ® and was covered during the PAI of May/June 2008. There were no 483 observations regarding this system.

WFI : WFI is generated by -(b)(4)- separate multistage ----------(b)(4)----------. During production of WFI, conductivity and temperature are monitored continuously at each plant. In the event these parameters are not within specification, the WFI is dumped to drain. WFI is circulated at a temperature range of ---(b)(4)---. The WFI system is currently licensed for the manufacture of Humate-P ® and was covered during the PAI of May/June 2008. There were no 483 observations regarding this system.

HVAC : There are -(b)(4)- HVAC units that provide conditioned air to the -(b)(4)- floors of Building ----------(b)(4)---------- ---------- HVAC -(b)(4)- services the classified filling area. -(b)(4)- services the material and personnel air looks for the filling and production support areas on the -(b)(4)- floor relevant for ----------(b)(4)----------. -(b)(4)- services the personnel air locks in the uncontrolled areas. Classification of manufacturing areas are ----------(b)(4)----------.

HVAC -(b)(4)- which services the classified filling area was originally validated from Jan - Feb 1998. This HVAC system was reviewed during the PAI inspection in May/June 2008. Review of the monitoring report for the filling area from January 1 to March 31, 2008 indicates the system is under control. For airborne particle counts, 4 samples failed of -(b)(4)- samples. For airborne viable particles there were 17 failures of -(b)(4)- samples; two of the failures were in -(b)(4)- areas. Surface sampling for bioburden had 1

failure out of -(b)(4)- samples. The two failures in the -(b)(4)- area were in Room -(b)(4)-; a men's gowning airlock. An investigation was conducted and the conclusion was that it was seen as a temporary hygiene deficit and no corrective action was taken. This airlock services Filling Room -(b)(4)- for filling lines -(b)(4)----------. There is no information provided on what the isolates were or the timing of the failures in relation to each other. However, since there were only two excursions and no 483 item from either 2008 inspection indicated a problem with the HVAC system or controlled areas air quality, it was most likely an isolated incident.

Cleaning Validation

Building -(b)(4)-

Major equipment cleaned in Building -(b)(4)- include -(b)(4)- final bulk vessels in which sterile bulk solution is stored prior to sterile filtration, filling and lyophilization. Since these tanks are dedicated to HFCP production and have not been evaluated during the last two inspections, the cleaning validation of these tanks is reviewed in this section. Three consecutive cleaning validation runs were conducted. The tanks were disassembled according to SOP. Cleaning was conducted by a -(b)(4)- cleaning procedure for the tank. The tank body is cleaned in the -(b)(4)---------- and the parts are cleaned by the ----------(b)(4)----------.

The cleaning procedure for both the -(b)(4)- and ----(b)(4)---- consists of the following steps:

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

Used tanks were washed after exceeding the -(b)(4)- dirty equipment hold time (DEHT). Sampling was performed on predefined product contact worst case location such as areas difficult to clean (----------(b)(4)----------), and all large areas.

Final rinse samples were taken from the sampling valve of the ----(b)(4)----- and ------(b)(4)- ---------- and tested for ---------(b)(4)---------- and ----(b)(4)----. Swab samples were taken at the ----------(b)(4)---------- and tested for --(b)(4)-- ----------. Data summaries show all acceptance criteria were met.

Building -(b)(4)-

Equipment that was not reviewed during the last two inspections of CSL Behring will be reviewed in this section. Equipment includes:

- ------(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)----------

Building -(b)(4)-

The filling equipment (----------(b)(4)----------) is cleaned manually. -----(b)(4)----- are for single use only. The other filling equipment is ----------(b)(4)---------- and the final bulk vessels are dedicated to HFCP. The final bulk vessels are cleaned in ----------(b)(4)----------.

Manual cleaning of filling equipment consists of the following:

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

-(b)(4)- cleaning of the filling machines consists of the following:

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

----(b)(4)--- cleaning of vials consists of ----------(b)(4)---------- and -------(b)(4)---------- at a temperature -(b)(4)-.

Depyrogenation conducted on the -(b)(4)- floor of building -(b)(4)- is limited to the depyrogenation of the vials under conditions ensuring an endotoxins reduction of -(b)(4)-.

Filling Line -(b)(4)- was covered during the PAI inspection of May/June 2008.

History

Review Initiated: August 11, 2008
Review Completed: December 22, 2008
Telecon Date(s): None

Resources for You

- **Approval History, Letters, Reviews and Related Documents - RiaSTap (/7993/20170723144441/https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm094010.htm)** [ARCHIVED]

More in Fractionated Plasma Products (/7993/20170723144441/https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/default.htm)