

Memo - Inspection Waiver, January 5, 2011 - Corifact

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
Division of Manufacturing and Product Quality

WAIVER MEMORANDUM

Date: January 5, 2011

From: Martha O'Lone, Reviewer, OCBQ/DMPQ/MRB1

To: Administrative Files for: STN 125385/0

Subject: Recommendation to waive pre-license inspection

Sponsor: CSL Behring GmbH, U.S. License # 1765

Product: Factor XIII Concentrate (Human) STN 125385/0

Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/MRB1

cc: Ze Peng, Chairperson, OBRR/DH/LH
Nanette Cangunun, Regulatory Project Manager, OBRR/DBA

Concurrent Clearance Routing

John A. Eltermann, Jr., R.Ph., M.S.	Date	CONCUR
Director, Division of Manufacturing and Product Quality		
Office of Compliance and Biologics Quality		
Center for Biologics Evaluation and Research		DO NOT
CONCUR		

Basil Golding, MD
Director, Division of Hematology, HFM-345
Office of Blood Research and Review
Center for Biologics Evaluation and Research
CONCUR

Date

CONCUR

DO NOT

Summary:

This memorandum recommends that a pre-license inspection be waived for CSL Behring GmbH in Marburg, Germany. CSL is requesting approval for manufacture of Factor XIII Concentrate (Human) in their currently licensed multiproduct facility using equipment and processes that have been approved for other US licensed products sourced from US donor plasma such as Fibrinogen Active Substance (Human) and Riastap (Fibrinogen Concentrate).

Concurrence for this recommendation is requested.

Brief History:

CSL has submitted a BLA in accordance with the draft guidance document "Cooperative Manufacturing Arrangements for Licensed Biologics" for the manufacture of Factor XIII Concentrate (Human) for the routine prophylactic treatment of congenital FXIII deficiency.

In 2004, ZLB Behring, then known as Aventis Behring, was acquired by CSL Limited, an Australian firm specializing in the development, manufacture, and marketing of biologically based healthcare products. In April 2007, ZLB Behring changed its name to CSL Behring and the license number was changed from 1708 to 1765 for currently licensed products. CSL Limited includes: CSL Bioplasma, CSL Biotherapies and CSL Behring. CSL Behring is headquartered in King of Prussia, PA with manufacturing facilities in Kankakee, IL, Bern, Switzerland, and Marburg, Germany.

US Licensed products manufactured at CSL Behring, Marburg include Humate-P® [Antihemophilic Factor (Human), STN 103960], Vivagloblin® [Immune Globulin Subcutaneous (Human), STN 125115], and RiaSTAP® [Fibrinogen Concentrate, (Human), STN 125317], Fibrinogen Active Substance (Human), For Further Manufacturing Use, STN 125356, and Thrombin Active Substance (Human), For Further Manufacturing Use, STN 125357.

CSL Behring GmbH also provides the following contract manufacturing services for products sold on the US market: Afluria®, influenza vaccine, contract filler and contract packaging for Carimune® and Rhophylac®.

Facility and Manufacturing Information:

Currently CSL's approved operations for their Marburg site encompass (b)(4) buildings at (b)(4) complexes:

- Marburg (main facility), -----(b)(4)-----;
- -----(b)(4)-----.

----- (b)(4) ----- are licensed to manufacture multiple US licensed products. CSL will fill and lyophilize Factor FXIII in Building (b)(4) in the ----(b)(4)--- facility and use Building (b)(4) for labeling and packaging. These production areas are currently licensed for multiple US products such as Fibrinogen 2G and RiaSTAP®.

Basis for the Waiver:

This waiver is based on criteria outlined in CBER SOPP 8410 "Determining When Pre-License / Pre-Approval Inspections are Necessary." As stated in the aforementioned SOPP, it is CBER's policy that a pre-license or pre-approval inspection will generally be necessary for an application if any of the following criteria **in bold** are met:

The manufacturer does not hold an active US license, or in the case of a contract manufacturer, is not approved for use in the manufacturing a licensed product.
CSL holds U.S. License #1765.

FDA has not inspected the establishment in the last 2 years.

Review of the FACTS database indicates that Team Biologics conducted a GMP inspection in March 2010 which was classified as VAI. The previous GMP inspection completed in March 2008 was classified as VAI. The previous GMP inspection completed in Oct 2005 was classified as VAI as well. A pre-license inspection for C1 Esterase Inhibitor (STN 125287) conducted by DMPQ/Product Office team in May/June 2008, was classified as VAI, but the application has not been approved to date.

The previous inspection revealed significant GMP deficiencies in areas related to the processes in the supplement (similar processes) or systemic problems, such as QC/QA oversight.

The March 2010 Inspection performed by Team Biologics was a Level I inspection which was rated VAI. At the close of the inspection, a FORM FDA 483 was issued for the following GMP deficiencies: inadequate results for Out of Specification (OOS) testing for licensed release potency and -(b)(4)- testing for Factor VIII Activity, inadequate investigation for malfunction of the needle lifter of the filling machine used for final Humate-P vials; investigations and corrective actions into multi-use Pasteurization Vessels -(b)(4)- and -(b)(4)- filters both of which failed ----- (b)(4) -----; inadequate hold time validation study was noted for 1 of 4 product buffers and a lack of Quality Unit oversight of the media fill simulations. The inspection further noted deficiencies in: growth promotion studies for media used in the Microbiology and Sterility Laboratories; cleaning validation data could not be provided for the entire life cycle of Berinert and Vivaglobin ----- (b)(4) -----; deficiencies in the CSL's CAPA initiated response to repeated deviations

of particles in Humate vials and inadequate cleaning validation for the (b)(4) stacking tanks and attachment parts used for manufacture of RiaSTAP®.

The previous Team Biologics inspection completed in May 2008 was a Level II inspection which covered Quality Systems, Production System, and the Laboratory System, as well as limited coverage extended to Facilities and Equipment System and Materials System (Source Plasma receipt). The deficiencies noted on the 483 included: retesting conducted for assays that were not within specification; six final drug product lots were released after exceeding the final product visual inspection limit of (b)(4) for particulates, identification of particulates were consistent with -----
------(b)(4)-----
-----, and Adverse Event Reporting did not have criteria for examining retain samples.

The previous inspection (Sept/Oct 2005) resulted in the issuance of a 483, listing six observations for the following deficiencies: deviation investigations did not include investigating all causes of contamination; Quality Investigations did not include determining the root causes of all environmental monitoring excursions; -----
-(b)(4)----- on Humate-P active ingredient; -----
------(b)(4)-----; lack of established alert and action limits during Humate-P production; and lack of validation of non-U.S. suppliers of -----(b)(4)-----.

A pre-license inspection (May/June 2008) performed by DMPQ/Product Office team resulted in the issuance of a FORM FDA-483, listing the following deficiencies: deviations associated with laboratory analysis errors, OOS, and repeat testing; no interim examination of media fills were performed; no validation for -----

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

-----.

The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.

The manufacture of Factor XIII Concentrate (Human) shares manufacturing similarities with currently US licensed products.

The manufacturing process is sufficiently different (new production methods), specialized equipment or facilities) from that of other approved products produced by the establishment.

The manufacturing processes and equipment for Factor XIII Concentrate (Human) are

considered equivalent or identical to those used for current US licensed products, Humate-P®, RiaSTAP®, Vivaglobin®, Fibrinogen Active Substance (Human), For Further Manufacturing Use, and Thrombin Active Substance (Human), For Further Manufacturing Use.

Waiver Recommendation:

Based on the information provided in the Biologics License Applications and previous inspection reports supporting the overall compliance status, and that performing an inspection of CSL would not provide any additional public health benefit, the review committee recommends waiving the pre-license inspection for the CSL Marburg facility.

CAPT Martha O'Lone, RN, CMC Reviewer, DMPQ_____

Ze Peng, Chairperson, OBRR/DH/LH _____