

DEPARTMENT OF HEALTH & HUMAN SERVICES



Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: Administrative File: Submission Tracking Number (STN) -
BL 125287, C1 Esterase Inhibitor (Human)
CSL Behring GmbH
Lic. # 1765, BLA

From: David Doleski, Biologist, CBER/OCBQ/DMPQ/MRB2, HFM-676

Through: Chiang Syin, Ph.D., Chief, CBER/OCBQ/DMPQ/MRB2

Subject: **Recommend Complete Response Letter:** This is BLA for C1 Esterase Inhibitor (Human).

Action Due Date: December 6, 2008

Recommendation:

Based on the information provided, I recommend a Complete Response letter based only on outstanding inspection issues. All review issues are acceptable.

Review Details:

This submission was provided in CTD format in paper form. The product may be referred to as: C1 Esterase Inhibitor, C1-INH, Berinert P, or Berinert.

The drug substance and drug product for Berinert P is manufactured by CSL Behring GmbH, located in Marburg, Germany at the following address:

CSL Behring GmbH
Emil-von-Behring-Straße 76
35041 Marburg
Germany

A pre-approval inspection was conducted of this firm from May 26 to June 3, 2008. The CBER inspection team consisted of myself, Felice D'Agnillo, and Marion Michaelis. Please see the EIR for more details.

Buildings:

Building -b(4)-:

- ---b(4)----- of Human Plasma
- --b(4)----- of C1 esterase inhibitor -b(4)- DEAE Sephadex (--b(4)---)

- Storage of Plasma and ----b(4)-----

Building -b(4)-

- Further processing until manufacture of the final bulk solution Filling and Lyophilization of the Final Product

Building -b(4)-

- Packaging and Labeling of the Final Product

Additionally CSL Behring purchases services from other companies. The relevant companies and the respective services are listed below:

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*Routinely the sterility test of the drug substance is done in the sterility laboratory of CSL Behring, Marburg. Sterility. ----b(4)----- is only back-up.

Contract Testing Laboratories:

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Physicochemical properties of the drug substance

Physical Form/Appearance: Colorless and clear solution

Composition:

Active ingredient: C1 esterase inhibitor 50 - -b(4)- U/mL

Excipients: Sodium chloride, Sodium citrate, Glycine

Protein Content: Total protein 5 - 8 mg/mL

Summary of the Production Process

For details of the production process (e.g. buffer composition, ranges, temperatures etc.), please refer to the referenced production procedures (3.23.2.2-4.1 - 4.3).

- **Separation of -----b(4)-----**

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

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

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The manufacturing of the product containing the active ingredient C1 esterase inhibitor started in the 1970s for the European market. Over time, improvements were introduced to the process to improve quality and meet relevant standards. The firm claims that the production process is well known, well established, robust, reliable and consistently and reproducibly delivers a drug product that meets its defined quality attributes.

The latest improvements were made in order to enhance production efficiency. The production steps -----b(4)----- have been automated. The production step -----b(4)----- became redundant after introduction of the ---b(4)----- system and was consequently omitted. Moreover, an optional -----b(4)----- was introduced by combining --b(4)-----.

Thus, the improved process could be run at ----b(4)----- . It is intended to exclusively use the ----b(4)----- for future supply of the US market.

The entire production process has been validated at full-scale with a minimum of three consecutive production batches that were produced with process control parameters to be used in commercial production. Full-scale validation also included the validation of -----b(4)-----pasteurization, final bulk ----b(4)-----, and final bulk sterility / final bulk container closure integrity.

The validation studies conducted are as follows:

Risk analysis:

- Basic ---b(4)-----, Study Number RA-6 I7-003-01,
- Berinert P drug substance production process, Study Number RA-617-001-03

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Full-scale process validation:

- Process validation, Study Number PV-617-004-02
- -----b(4)----- Number PV-6 I7-008-01

- ---b(4)----- prior to pasteurization, Study Number PV-617-009-01
- Final bulk ----b(4)----, Study Number PV-6 I7-005-01

Process simulation:

- Final bulk sterility (final bulk container closure integrity), Study Number MF-617-001-01

Validation Studies (in more detail)

Study: Validation of ----b(4)----- Filter Media for Sterile Filtration of Berinert P (CEI145) (Phase -b(4)-), Study Number SF-617-001-01

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

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

A suspension of -----b(4)----- containing -----b(4)-----
----- of effective filtration was used for the validation study.

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

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

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

Since the objectives of this study were met it is concluded that the sterilizing grade filter elements are validated for sterile filtration of Berinert P.

Study: Process Validation of the Bulk Production Process for Berinert P according to the Production Procedures P-QOOC, P-400C1, and P-617-03V1, Study Number PV-617-004-02

The objective of this full-scale process validation study was to demonstrate and verify that the production process comprising all steps and intermediates from starting material --b(4)----- plasma) through drug substance (final bulk) constantly and reproducibly delivers a product meeting its predefined product quality attributes.

Samples were taken and investigated from three consecutive production batches -b(4)- batch size and three consecutive production batches --b(4)-- batch size. All process control parameters were performed at target routine conditions and are therefore representative for the current production process. The analysis of all samples included all product quality attributes at -b(4)- different steps of the manufacturing process and comprised routine and additional validation in-process controls. At the ---b(4)----- plasma stage, the ---b(4)----- acceptance criteria was ---b(4)----- . At the QAE-Sephadex A-50 -b(4)-- stage, the --b(4)-- acceptance criteria was ---b(4)----- .

At the C1-INH solution after ----b(4)----- step, the --b(4)----- action limit is ---b(4)----- . At the final bulk stage, the --b(4)---- limit is --b(4)----- and the sterility testing is performed according to the requirements in the biologics regulations. All of these test results were passing. The firm also listed approximately -b(4)- process control parameters. All data were within the specified ranges.

Lots Manufactured/Batch Analyses:

The following lots were manufactured during Full Scale Process Validation

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

The following conformance lots were provided:

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

Certificates of Analysis were provided for all six lots. All lots passed specifications for dissolution time, pH, residual moisture, potency, and sterility.

Media Fills

Study: Process Simulation Testing by Media Fill of the Aseptic Process Steps in the Production of Berinert, Study Number MF-617-001-01

Sterile ----b(4)----- was sterile filtered into final bulk containers to simulate the Berinert production process from sterile filtration through aseptic filling. The simulations were performed under the following conditions:

- -----b(4)-----
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- Sterile -----b(4)----- into final bulk containers
- Exceed holding of media-filled final bulk containers -b(4)- hours) to simulate product storage between sterile filtration and aseptic filling.
- Sampling and incubation -----b(4)-----.

Acceptance Criteria:

- Samples must be sterile after incubation.
- The medium must demonstrate microbial growth promoting properties at the end of incubation.

Three consecutive media fill runs were performed and met the acceptance criterion.

Further, during the routine review period of July 2006 to June 2007 a total number of b(4) individual process simulation runs were conducted in the aseptic production area of Building -b(4)- The media fill runs ranged between -----b(4)----- units (total: --b(4)-- units). The following results were obtained:

Acceptance criteria met:

- -b(4)-runs, 0 contaminated unit of a total number of ---b(4)--- units
- -b(4)- runs, each 1 contaminated unit of --b(4)----- units (alert limit reached)

Action limit reached (acceptance criteria failed):

- -b(4)- runs, 2 contaminated units of -b(4)- and 1 contaminated unit of -b(4)- units.

¹ During the inspection, there were issues discovered regarding the --b(4)----- of media, the timing of visual examination, and the timeliness of reporting deviations associated with media fills.

Final Bulk Holding Time

The final bulk holding time was validated in ---b(4)----- experiments. It could be demonstrated that the product stability was well beyond the intended holding conditions. Therefore, a holding time of -b(4)- hours at -b(4)- is considered validated.

Final Bulk Sterility

The sterility of the final bulk was demonstrated by full-scale process simulation using an suitable nutrient medium contained in final bulk containers. Since the sterility requirements were met, it could be concluded that a holding time of the sterile filtration set-up of b(4)days after sterilization and a final bulk holding time of b(4) hours after sterile filtration are validated.

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

Study: Process Validation PV-617-005-01: Validation of the ---b(4)-----of the Berinert P Final Bulk, dated January, 2005

The --b(4)----- of the Berinert P final bulk was validated during production of -b(4)- consecutive conformance lots with -b(4)-- batch size. In this validation study, the extended maximum holding time for the final bulk before filling of b(4) hours (PV-617-002-01) was also considered.

All release specifications for the Berinert P final product were met. A statistical evaluation of the results revealed no statistically significant in --b(4)-----of the parameters C1-INH activity, protein concentration and NaCl concentration for samples collected at the beginning, in the middle and at the end of the filling process. Therefore, it is validated that the --b(4)----- of the Berinert P final bulk is maintained throughout the filling process.

Container Closure System

Glass Vials

Injection vials with a nominal size of 17 mL are used for Berinert P drug product. The containers are made of colorless, molded glass. The glass containers for Berinert P meet the requirements for type b(4)glass that are suitable for all preparations including products for parenteral administration in accordance with section <661> USP.

Stopper

A ---b(4)----- rubber stopper developed for pharmaceutical closure applications is used for Berinert P. The formulation of the stopper does not contain latex and represents a 100% --b(4)----- compound. "Ready-to-sterilize" stoppers are supplied to the pharmaceutical manufacturer and, can directly be used for sterilization and subsequent drying without the need of any further pre-treatment.

Container Closure Integrity Testing

Study: Container Closure Integrity --b(4)-- (CCIS-617-01) dated August 24, 2006

Container closure integrity testing of Berinert was performed with a vial/stopper/cap combination. The 17mL injection vials were filled with Berinert, sealed with rubber stoppers and secured with crimp caps. A total of b(4) test samples were -----b(4)-----

----- Therefore, the selected container closure system is capable of maintaining container closure integrity.

b(4)

b(4)

_____ $b(4)$ _____

The objectives of the study were as follows:

- Provision of documented evidence that lyophilization cycle -b(4) leads to uniform product quality of Berinert.
- Demonstration that drug product key quality attributes are within specified ranges.
- Demonstration of homogeneity of these quality attributes throughout the entire lyophilizer chamber.
- Verification that an appropriate ----b(4)----- product in the lyophilizer has no negative impact on product quality.

Three validation runs were conducted for commercial-scale Berinert P batches -----b(4)-----

----- During these runs sampling and testing of final product vials was performed for -b(4)- vials for each quality attribute.

Samples were taken from -b(4)- positions per shelf and tested for key product quality attributes (residual moisture, C1 esterase inhibitor activity, and solubility (dissolution time and appearance of reconstituted solution)).

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Residual moisture, activity, and solubility of the drug product were considered as key product quality attributes.

- Residual moisture: -b(4)-
- CI esterase inhibitor activity: --b(4)--
- Solubility: a) Dissolution time---b(4)-----, and b) Appearance of reconstituted solution: Colorless and clear solution

The process control parameters (time, temperature, and pressure) were met during each step of the freeze-drying process for each validation run.³

- **Residual Moisture:** All results met the acceptance criterion --b(4)--- and ranged from --b(4)---
- **C1 Esterase Inhibitor Activity:** All results met the acceptance criterion --b(4)---- ----) and ranged from ---b(4)-----.
- **Solubility:** All results met the acceptance criterion ----b(4)----- since all samples were ----b(4)----- . The appearance of all reconstituted drug product samples met the acceptance criterion.

Individual data demonstrate homogeneity for the key product quality attributes.

Since the objectives of this process validation study were met, the firms concluded that lyophilization cycle -b(4)- constantly and reproducibly delivers a product that meets its product quality attributes.

³*During the inspection, we discovered that there had been an earlier validation study that did not meet acceptance criteria. Please see the EIR for more details.*

Vial Washing:

Study: Qualification, Operational Qualification, Vial Washer --b(4)-- - and - Certificate of Qualification, Requalification, Vial Washer --b(4)--

The firm provided validation reports for the vial washing machine (-b(4)-) in building -b(4)-.

Verification of effectiveness of the cleaning process was accomplished by evaluating the -----b(4)-----

- For the -----b(4)----- vials of every tested vial size are used.
- For --b(4)-----, all criteria were met for all sizes of -----b(4)-----

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HVAC and Environmental Monitoring:

The firm provided qualification reports and routine environmental monitoring for the buildings used to manufacturing this product. The data appears adequate.

Cleaning:

The firm provided qualification reports for the different cleaning processes utilized for equipment used in the production of this product.

For containers and small equipment, a washing machine in Building -b(4)- is used. -b(4)- consecutive runs were performed to cover all possible loading patterns that would be used in the washing machine. ---b(4)----- were analyzed for ----b(4)----- for the equipment after cleaning. For --b(4)--, the --b(4)-- was performed. The results appear adequate.⁴

⁴ During inspection, there were issues discovered with ---b(4)----- limits as well as cleaning validation studies that were incomplete or not passing.

The firm has an extensive CIP system for cleaning vessels in the facility. Validation reports were provided in the submission for individual equipment. For example, the firm provided *Cleaning Validation of ----b(4)----- in the ----b(4)----- Area*. Three runs were performed using the CIP process. Acceptance criteria were met for -----b(4)----- . The firm also provided cleaning validation reports for the columns. For example, the firm provided a report entitled *Cleaning Validation of ---b(4)----- Chromotography System -b(4)- in the ----b(4)----- Area*. Three runs were performed utilizing the maximum holding time prior to cleaning. Initially, the samples did not meet acceptance criteria. The cleaning was modified, and three runs were successful for -----b(4)-----

Steam Sterilization:

The firm provided numerous qualification reports for the steam sterilizer.⁵ In particular, the firm provided *Certificate of Qualification, Performance Qualification, Autoclave -b(4)-*. This involves a --b(4)----- Autoclave. The firm performed three runs for each load pattern, using thermocouples and biological indicators. The results were that the biological indicators were inactivated and the temperature data met the predefined limits.

⁵ During the inspection, sterilization was covered. The firm was cited for sterilization issues.

Transfer, Shipping and Storage Conditions:

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

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