FOOD AND DRUG ADMINISTRATION

Center For Biologics Evaluation and Research

Memorandum

FROM: Tigist Kassa, Ph.D., LBVB/DBCD/OBRR/CBER

THROUGH: Abdu Alayash, Ph.D., Chief, LBVB/DBCD/OBRR/CBER

TO: Felice D`Agnillo, Chair, LBVB/DBCD/OBRR/CBER

Nannette Cagungun, Regulatory Project Manager

SUBJECT: Review of the Chemistry, Manufacturing, and Control section: Characterization of Drug Substance 3.2.S.3, Control of Drug Substance 3.2.S.4, Control of Drug Product (Characterization of Impurities 3.2.P.5.5 and Justification of Specification 3.2.P.5.6). Original Biologics License Application submission (BL 125606/0) by CSL Behring (CSLB).

The submission BL 125606/0 was received 06-30-2016, and was given DCC login ID 636359

RECOMMENDATIONS: There are no problematic issues identified from my review perspective that would preclude final approval of this product. However, please relay the following information requests to the sponsor:

IR questions:

1. Please submit the study that established the acceptance criteria for Berinert manufacturing process, Study# IR-617-001-01.

   ***The sponsor's response**: Study IR-617-001-01 is provided (Attachment Q1).*

   ***Reviewer's comment**: The response is acceptable.*

2. *Please provide the investigational study IR-688-002-02 on impurity analysis of CSL830 1500 IU.*

   ***The sponsor's response**: IR-688-002-02 on impurity analysis of CSL830 1500 IU is provided (Attachment Q2).*

   ***Reviewer's comment**: The response is acceptable.*

3. *Please provide a summary of the* (b) (4) *data that characterized the protein impurities in the typical* (b) (4) *obtained for CSL830 1500 IU, and also a justification for how these results are applicable to CSL830 2000/3000 IU final product.*

The sponsor's response: *A summary of the* (b) (4) *data is included in report IR-688-002-02. This report contains a list of the characterized proteins via* (b) (4) *analysis as well as* (b) (4) *. These results are applicable for CSL830 2000/ 3000 as well due to the fact that these (2000 IU and 3000 IU) are two* (b) (4) *filling sizes for CSL830. The* (b) (4) *of CSL830 1500 and 2000/ 3000 are* (b) (4)

Reviewer's comment*: The data provided is reviewed and the response is acceptable.*

4. *Please provide SOPs for* (b) (4) *, and quantitative protein determination in the* (b) (4)

The sponsor's response: *The testing instructions (SOPs) for* (b) (4) *are provided in the dossier. Please refer to section 3.2.P.5.2. The testing instruction for* (b) (4) *determination of* (b) (4) *and quantitative protein determination in the* (b) (4) *are provided (Attachment Q4a-b).*

Reviewer's comment: *The response is acceptable.*

5. *In Study# IS-617-015, you indicated that* (b) (4) *could not be determined due to difficulties with the test kit. Please provide further explanation for why the method did not work. Additionally, please justify how the expectation ranges defined within the previous study would be valid for CSL830 2000/3000 IU final product.*

The sponsor's response: *The* (b) (4) *could not be determined because the positive control doesn`t provide a plausible result and therefore the results of the samples for* (b) (4) *in study IS-617-015 are not credible. However, in study IS-617-015 additional* (b) (4) *were investigated. The expectation ranges for these impurities are also valid for CSL830 2000/ 3000 due to the fact that the* (b) (4) *. CSL830 1500 and CSL830 2000/ 3000* (b) (4) *and therefore, CSL830 2000/ 3000 contains* (b) (4)

Reviewer's comment: The response is acceptable.

SUMMARY:

This memorandum summarizes my review of the characterization of drug substance, control of drug substance and reference standard information submitted in support of C1 Esterase Inhibitor subcutaneous (Human) with proposed proprietary name HAEGARDA. It is a (b) (4) HAEGARDA (b) (4) produced by CSL Behring in Marburg, Germany. HAEGARDA is manufactured from (b) (4) plasma. Manufacturing of HAEGARDA uses manufacturing steps, equipment, and methods that are (b) (4) . The manufacturing steps are essentially (b) (4) specifically, from the (b) (4) . It will be marketed as a single-use vial available in two sizes: 2000 International Units (IU) with 4mL water for injection and 3000 International Units (IU) with 6mL water for injection. Each size contains 500 IU/ml C1-esterase inhibitor after reconstitution. Collected data in support of the drug substance characterization and control suggests that the manufacturing process can yield C1 Esterase Inhibitor subcutaneous (Human) with an acceptable purity profile. The manufacturing details, process validation, and product characterization provided here suggest that HAEGARDA manufacturing is well controlled. Biochemical analysis data shows that product characteristics (e.g. purity) are (b) (4) final drug product, reference materials, excipients, specifications and release method validations are acceptable and can ensure the safety, quality, and consistency of the product.

BACKGROUND

CSL Behring (CSLB) submitted an original Biologics License Application (BLA) to seek U.S. licensure for a human plasma-derived C1-Esterase Inhibitor concentrate intended for twice weekly self-administration by subcutaneous (SC) injection for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescents. Type I and II HAE are autosomal dominant inherited disorders that are associated with a deficiency in C1-Esterase Inhibitor. In Type I HAE (common form genotype), impaired synthesis of a normal and functionally active C1-INH molecule occurs. In Type II HAE (variant form genotype), normal levels of a functionally impaired C1-INH molecule are synthesized, but the normal form of C1-INH is considerably reduced in the circulation. The prevalence of Type I and II HAE is estimated to be in the order of 1:50,000, with approximately 85% of subjects having Type I HAE. Treatment for Type I and II HAE can be subdivided into acute treatment of attacks and prophylaxis. The treatment of choice in the event of an HAE attack is the rapid replacement of the functionally missing plasma protein. C1 Esterase Inhibitor Concentrate is exclusively produced from human plasma obtained from FDA approved US plasma collection establishments. The manufacturing process of the (b) (4) C1-Esterase Inhibitor Concentrate (human) starts with the (b) (4)

(b) (4)

REVIEW SUMMARY

CHARACTERIZATION OF DRUG SUBSTANCE (Sections 3.2.S.1 and 3.2.S.3)

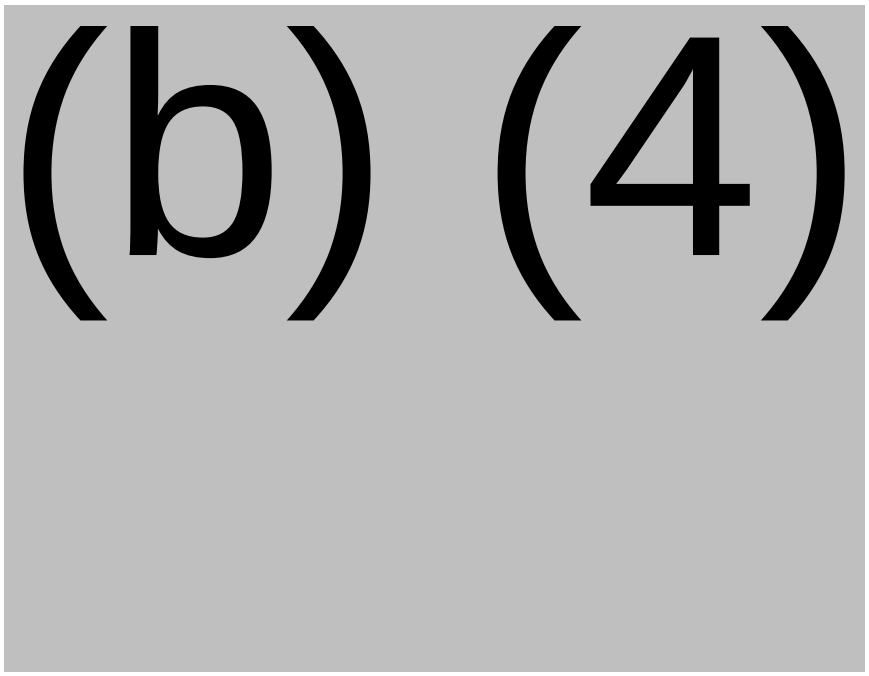
3.2.S.1 GENERAL INFORMATION (DS)

3.2.S.1.1 Nomenclature

(b) (4)

3.2.S.1.2 Structure

(b) (4)



3.2.S.1.3 General Properties

Physicochemical properties of the drug product

Physical Form / Appearance: colorless clear to slightly opalescent solution

Composition: a) Active ingredient: C1 Esterase Inhibitor (b) (4)

b) Excipients: Sodium chloride, Sodium citrate, Glycine (b) (4)

Protein Content: Total protein (b) (4)

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

3.2.S.3.1 Elucidation of Structure and Other Characteristics

Biochemical Properties of (b) (4)

(b) (4)

3.2. S.3.2 IMPURITIES(b) (4)

The sponsor provided relevant information concerning the impurity profile of (b) (4) production process and the report also summarizes the quantification data of (b) (4)

(b) (4)

(b) (4)

1 Page determined to be not relesable: (b)(4)

(b) (4)

Sodium chloride, sodium citrate (b) (4) are excipients and are not considered as impurities as they are added to perform a specific function in the final product. (b) (4)

(b) (4)

(b) (4)

5 Pages determined to be not relesable: (b)(4)

(b) (4)

(b) (4)

3.2.S.4. CONTROL OF DRUG SUBSTANCE

3.2.S.4.1. Specifications

(b) (4) serve as specification for (b) (4) . A description of the specifications used for the release of (b) (4) and justification is provided.

3.2.S.2.4-2 Control of Critical steps: In-process Controls

(b) (4)

(b) (4)

2 Pages determined to be not relesable: (b)(4)

(b) (4)

.

3.2.S.4.5 Justification of Specification

CSLB provided justification of the (b) (4) control tests carried out on the (b) (4) solution in the table below. These (b) (4) tests serve as specification for the (b) (4) .

(b) (4)

Reviewer's Comment*: Specifications and justifications are acceptable.*

1 Page determined to be not relesable: (b)(4)

(b) (4)

(b) (4)

Reviewer's comment*: These parts of validation studies are acceptable.*

Testing presence or absence of human and animal protein (b) (4) :

(b) (4)

(b) (4)

Reviewer's comment: This part of validation studies is acceptable.

Test Methods and Validation of (b) (4) **Determination of Protein**

CSLB provided Master-SOP for analytical determinations. (b) (4) was used for the quantitative determination of protein concentration in finished products (b) (4). The validation report summarized the testing results from executing both SOP and demonstrating the assay for determination of protein concentration is satisfactory with respect to (b) (4).

(b) (4)

***Reviewer's comment**: This part of validation studies is acceptable.*

Test methods and Validation of (b) (4) **method on the** (b) (4)

CSLB provided Master-SOP for analytical determination of (b) (4) . The test method is (b) (4)

(b) (4)

Reviewer's comment: This part of validation studies is acceptable.

Test methods and validation of (b) (4) **determination of** (b) (4) **-method**

The analytical method is the determination of (b) (4)

1 Page determined to be not relesable: (b)(4)

(b) (4)

Reviewer's comment: This part of validation studies is acceptable

Test methods and validation of (b) (4) **determination of** (b) (4) **-method**

The objective is to show that the test method is applicable for the (b) (4)

(b) (4)

[redacted]

<u>Reviewer's comment</u>: This part of validation studies is acceptable.

3.2. P.5.5 Impurity characteristics

Relevant product-related impurities of HAEGARDA have been assessed including plasma proteins and small molecules. Process-related impurities that have been assessed for (b) (4) . See section 3.2.S.3.2 (b) (4) for details. During storage of the drug product, the entry of impurities and contaminants is prevented by suitable primary packaging material. In addition to long-term stability testing, (b) (4) testing was applied to demonstrate that the container closure system protects the sterile product from microbial contamination.

Reviewer's comment: *I found that CSLB's impurity investigations were complete and their findings were acceptable.*

3.2. P.5.6 Justification of Specification(s) for the lyophilized product

The final product specifications meet the requirements and summarized in the table below:

Justification of Specification(s)

Product Quality Attribute	Specification	Justification
Practicability and organoleptic properties: - Dissolution time - Appearance	- Dissolution time: (b) (4) - Colorless , clear to slightly opalescent solution	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Residual moisture	(b) (4)	(b) (4)

Protein	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Sodium chloride	(b) (4)	(b) (4)
Sodium citrate	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Purity	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Sterility	Specification CFR/USP	Acc. to CFR/USP
Pyrogens	Specification CFR/USP	Acc. to CFR/USP

Reviewer's comment: This part of validation studies is acceptable.

3.2.P.6 Reference Standards or Materials

As an in-house standard for (b) (4) testing a (b) (4) is used that has been calibrated against the valid (b) (4) is determined using the (b) (4) test kit, which is supplied by (b) (4) . The test kit is commercially available.

***Reviewer's comment**: List of reference standards and materials with corresponding testing methods are acceptable.*