FOOD AND DRUG ADMINISTRATION

Center For Biologics Evaluation and Research

Memorandum

FROM: Yiping Jia, 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

The file (BL 125606/0)

SUBJECT: Review of the Chemistry, Manufacturing, and Control sections for the original Biologics License Application submission (BL 125606/0) submitted by CSL Behring (CSLB).

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

RECOMMENDATIONS:

This memorandum summarizes the review of CMC sections including drug substance and drug product manufacture, control of materials, critical steps and intermediates, batch formulation and analysis, analytical procedures and validation reports submitted in support of C1 esterase inhibitor subcutaneous (Human) with proposed proprietary name HAEGARDA.

There are no major issues with the review of CMC sections covered in this memo at this stage of review cycle. Further reviews may be needed to follow up with the responses to IR questions 1 and 6.

OVERVIEW:

CSL Behring (CSLB) submitted an original Biologics License Application (BLA) for a human plasma-derived C1-esterase inhibitor concentrate, HAEGARDA (company code: CSL830), intended for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients. HAEGARDA is a human plasma-derived C1-esterase inhibitor concentrate (b) (4) for subcutaneous administration as a (b) (4) The manufacturing process of the CSL830 human C1-esterase-inhibitor (C1-INH) concentrate for subcutaneous administration use is based on the well-established C1-INH (Berinert) process and is (b) (4)

(b) (4) CSL830 batches of 2000IU and 3000IU vial sizes (CSLB internal production code (b) (4) indicating (b) (4) have been established to accommodate the presentation sizes relevant for the intended new indication routine prophylaxis to prevent HAE attacks in adolescent and adult patients by subcutaneous self-administration. Both presentations are produced (b) (4) . The production process for the C1-INH presentations (CSL830) (b) (4) , 2000IU/ 3000IU (b) (4) batch: (b) (4) . In summary, (b) (4) Certain steps within the (b) (4) are specific for C1-INH product for subcutaneous administration, from the (b) (4) 2000 International Units (IU) with 4mL water for injection and 3000 International Units (IU) with 6mL water for injection each containing 500 IU/ml C1-esterase inhibitor after reconstitution.

REVIEW SUMMARY AND COMMENTS

3.2.S.2.1 Manufacturer(s)

Manufacturer

C1 Esterase Inhibitor Concentrate (human) is manufactured by CSL Behring GmbH, located at the pharmaceutical production and research areas in Marburg, Germany. The address of the manufacturing site is:

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

Testing Laboratories

In-process controls during (b) (4) production and testing of the (b) (4) is carried out at:

CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

3.2.S.2.2 manufacturing process summary

- (b) (4)

(b) (4)

(b) (4)

The following critical process steps in the manufacture of C1 Esterase Inhibitor Concentrate (human) were identified by a risk analysis approach:

- (b) (4)
)

During the manufacturing process of the (b) (4)

Reprocessing and Rework

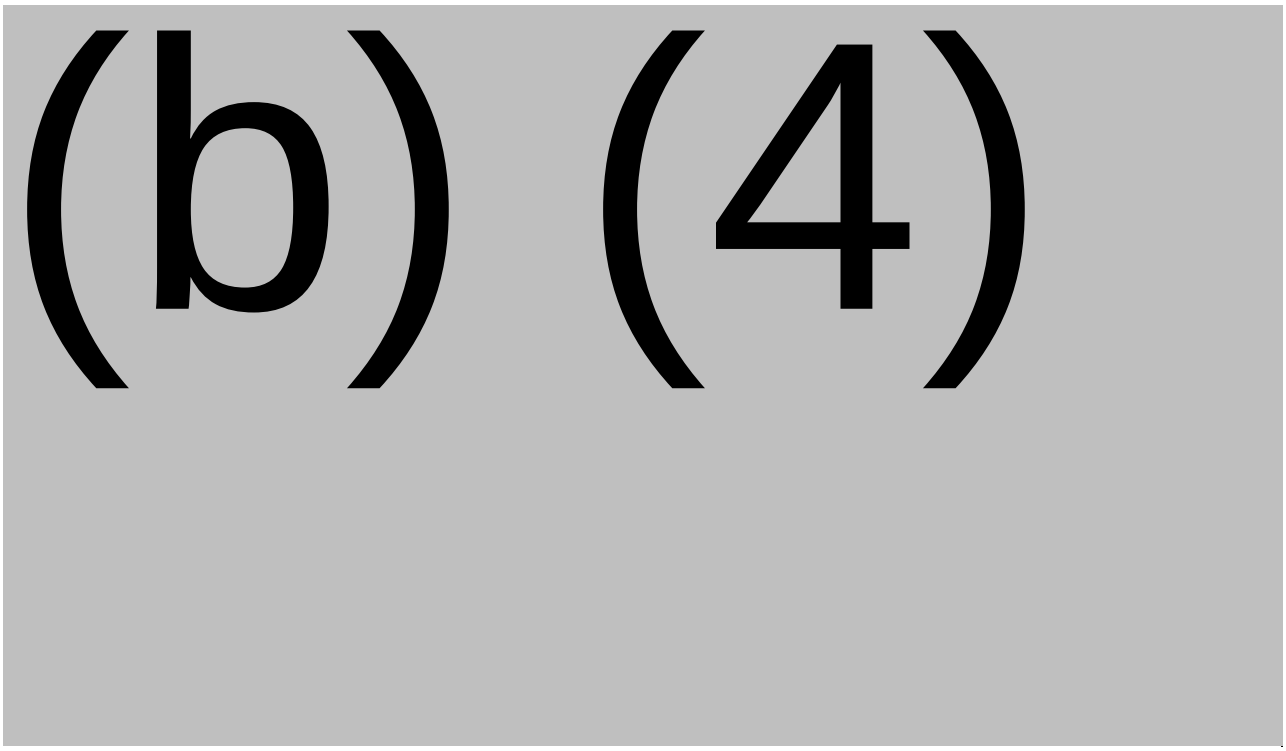
Reprocessing (i.e. unplanned repetition of a step that is part of the licensed manufacturing process) may be performed in line with the current versions of ICH Q7, EU GMP Guide, the EMA "Reflection paper on a proposed solution for dealing with minor deviations from the detail described in the Marketing Authorization for human and veterinary Medicinal Products" and revised Annex 16 coming in operation on April 15, 2016. As part of the deviation investigation a quality risk assessment will be performed that needs to support the conclusion that the deviation does not have an adverse effect on the quality, safety or efficacy of the product. This includes the compliance with active substance and finished product specifications as described in the marketing authorization. Any reprocessing will be documented in accordance with GMP and assessed by the Qualified Person as part of the batch certification process. It will also be communicated to the Center of Biologics Evaluation and Research (CBER) according to the US legal requirements (usually prior approval submission to cover a one-time batch release).

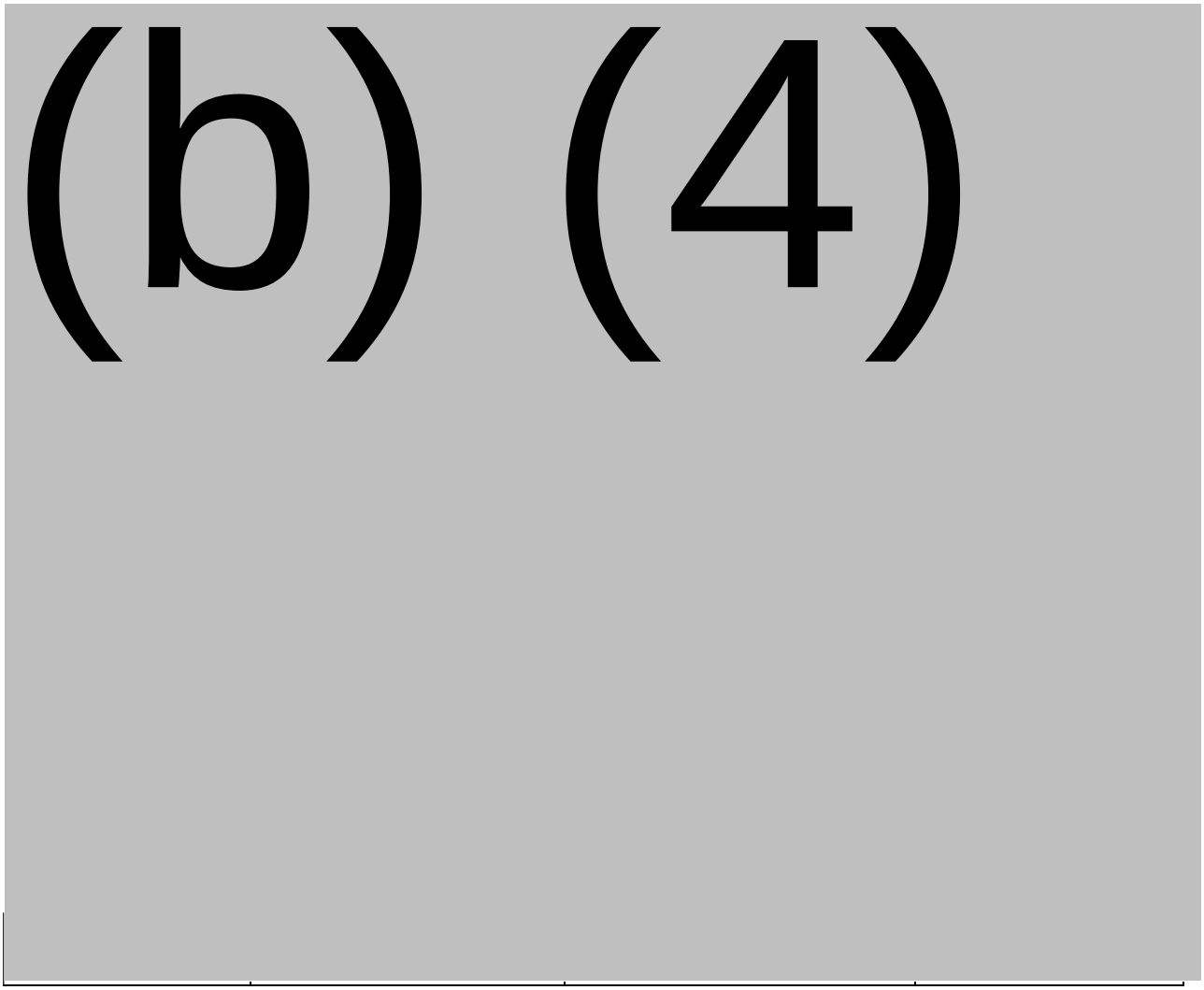
Rework (i.e. subjecting a product to one or more processing steps that are different from the licensed manufacturing process) is only performed after prior approval of FDA.

3.2.S.2.3 Starting Material (Human Plasma)

C1 Esterase Inhibitor Concentrate is exclusively produced from human plasma obtained from FDA approved US plasma collection establishments.

3.2.S.2.4 Controls of Critical Steps and Intermediates





In-process controls are routinely performed to control the product quality attributes at different stages during manufacture. In-process control tests for C1 Esterase Inhibitor Concentrate (human) are not restricted to the manufacturing steps where (b) (4) are defined, but are conducted from the (b) (4) stage of the manufacture of the (b) (4) . The tests include parameters for (b) (4) . The corresponding method validations were provided.

The stability of (b) (4) was validated in (b) (4) experiments and the (b) (4) holding time of the (b) (4) was covered during full scale validation of the filling process. The holding times and storage conditions met the requirements of the current production procedure. The stability of (b) (4) is therefore considered validated. The following holding times were validated and established for routine production:

- (b) (4)

- (b) (4)

3.2.P.3.2 Batch Formula

Starting from the (b) (4), which is defined as the (b) (4) solution, C1 Esterase Inhibitor Concentrate (human) is manufactured in batches of (b) (4)

3.2.P.3.3 Manufacturing Process and Controls

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

- Filling into the final containers

The (b) (4) depyrogenated (b) (4) injection vials for 2000 IU and (b) (4) injections vials for 3000 IU.

- Lyophilization and sealing

After filling, sterilized and dried stoppers are partially seated onto the vials and the product is lyophilized. Subsequently, the vials are (b) (4) in the lyophilizer. (b) (4)

- Final processing

An (b) (4) cap is crimped around the bottle neck and stopper of the closed containers. Every filled container is tested for the presence of (b) (4) and subjected to visual inspection prior to labeling and packaging.

(b) (4)

3.2.P.4. Control of Excipients

The excipients contained in the drug product comply with the current compendial standards including glycine, sodium chloride, (b) (4) . No excipient is from human or animal origin.

A certificate of analysis is provided with each delivery, confirming results of tests in compliance with the relevant monographs. In-house testing is performed to confirm identity and microbiological quality. Full specification testing is performed at CSLB performed (b) (4) . The identity of the incoming materials is verified in QC laboratories after receipt at CSL Behring GmbH for each batch. In addition, the microbiological quality (bioburden, exclusion of (b) (4) is tested in (b) (4) . Only lots of substances tested in accordance with the specifications and released by Quality department can be used.

3.2.P.5. Control of drug product

3.2.P.5.1. Specifications 2000 IU/ 3000 IU

Specifications included **PRACTICABILITY AND ORGANOLEPTIC EXAMINATION (**colourless, clear to slightly ophalescent solution**),**
(b) (4)
RESIDUAL MOISTURE (b) (4)
PROTEIN ((b) (4)
(b) (4)
SODIUM CHLORIDE ((b) (4)
SODIUM CITRATE ((b) (4)
PURITY (b) (4)
(b) (4)

STERILITY (Specification according to CFR/USP**),**
PYROGENS (Specification according to CFR/USP**),**
(b) (4)

Reviewer's comment: Please relay the following information request question to the sponsor for additional information regarding final product specifications.

"Please clarify whether endotoxin and (b) (4) testing were included in the final specifications for HAEGARDA products, and the rationales if these assays are not used for final product testing."

3.2.P.5.2. Analytical Procedures

Analytical procedures for the control of the drug product including analytical method No. analytical procedure are as follows.

Q-04-003 Practicability and Organoleptic Test (Determination of dissolution time and appearance)
Q-04-314 (b) (4)
Q-10-121 (b) (4)
Q-16-004 (b) (4)
Q-16-048 (b) (4)
Q-16-204 (b) (4)
Q-16-334 (b) (4)
Q-16-345 (b) (4)
Q-16-380 (b) (4)
Q-16-399 (b) (4)
Q-21-001 (b) (4)
Q-25-002 (b) (4)

3.2.P.5.3. Validation of analytical procedures

Q-04-003 Practicability and organoleptic properties;

-Dissolution time: (b) (4)
-Colorless, clear to slightly opalescent solution

Specification was set according to manufacturing experience

Reviewer's comment: This method was established based on manufacturing experiences. Additional data may be requested to support the validation of this method as follows.

"For the analytical method Q-04-003 Practicability and organoleptic properties, the specification was determined based on manufacturing experiences, please provide summary of historical data from product manufacturing include any deviations or out-of-specification results and investigation reports if there were any."

Q-04-314 (b) (4) ; MVR-04-314-Q-617U

The method validation report for molecular identity by (b) (4) appeared to be the same report based on validation protocol No. MVP-04-314-Q-617U-01 submitted and reviewed previously for Berinert® P original BLA STN 125287/0.

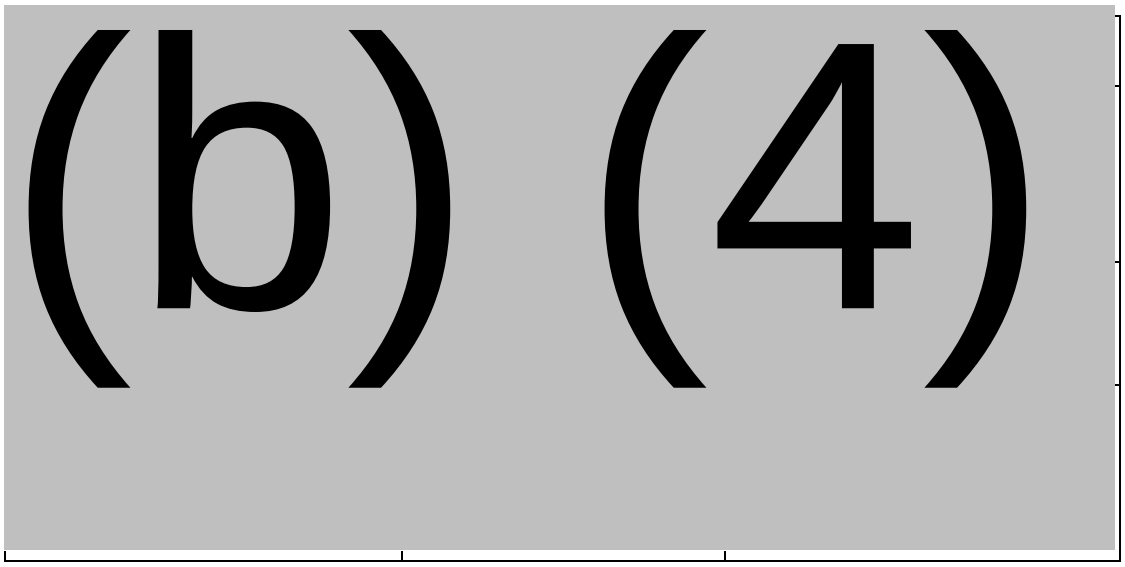
Reviewer's comment: This method validation was previously reviewed and approved previously for Berinert® P original BLA STN 125287/0. But additional information is needed for recent re-validations or protocol changes if any. The following IR question could be sent to the sponsor for additional information.

"For Q-04-314 (b) (4) , the method validation report appeared to be the same report based on validation protocol No. MVP-04-314-Q0617U-01 for Berinert® products. Please provide any revalidation studies, and/or summaries of deviations or out-of-specification results and investigation reports if any since the approval of Berinert® products."

Q-10-121 (b) (4); MVR-10-121_10-121I

This method validation report covered products including Berinert®, Berinert® 1500, and the current product C1-Esterase Inhibitor Concentrate (human) 2000 IU/3000 IU.

The test method is based on the (b) (4) . The following parameters were validated and the results were summarized as follows:



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

(b) (4)

Reviewer's comment: Based this method validation report, the method Q-10-121/Q-10-121I met all validation criteria to determine the C1-Esterase Inhibitor activity in test samples manufactured from plasma. This method can be used for release testing of C1-Esterase Inhibitor Concentrate (human) 2000 IU/ 3000 IU as well as for in-process control of their process intermediates. Please send the following information request to the sponsor for additional information.

"For the Q-10-121 (b) (4) assay, the method validation report covered products including Berinert®, Berinert® 1500, and the current product C1-Esterase Inhibitor Concentrate (human) 2000 IU/3000 IU. Please provide summary of historical manufacturing data for Berinert® products including any deviations or out-of-specification results and investigation reports for this assay if any."

Q-16-004 Protein; MVR-16-004-Q688/689

This testing is to (b) (4) proteins in samples by (b) (4)

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

(b) (4)

Reviewer's comment: This method validation report showed that the method Q-16-004 met all validation criteria to determine the protein concentration and therefore in support of its use as release testing of C1-Esterase Inhibitor 1500 IU/ 2000 IU/ 3000 IU. Please relay the following information request to the sponsor for additional information.

"For Q-16-004 Protein assay, please provide summary of historical manufacturing data for Berinert® products using this assay, including any deviations, and/or out-of-specification results if there were any involving this assay."

Q-16-048 Sodium citrate; MVR-16-048

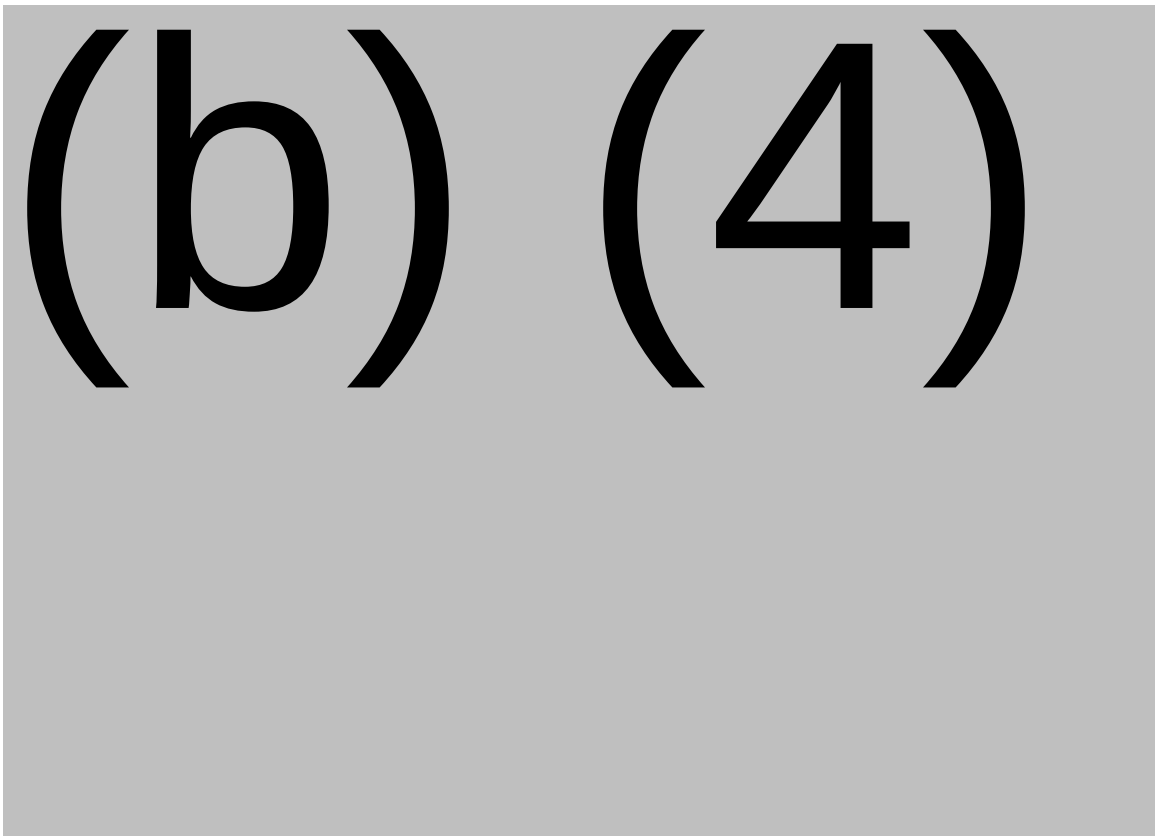
This method validation report is based on previously submitted and reviewed Method validation MVR-16-048-Q617 -01. Method Q-16-048 was validated for determination the Citrate Content in Berinert P and Berinert 1500 (b) (4)

Reviewer's comment: this method validation report appeared to be acceptable.

Q-16-204 (b) (4) ; MVR-16-204-Q617/688/689

This method validation report is based on previously submitted and reviewed Method validation MVR-16-204-Q617-01, with addition of (b) (4) for Berinert 1500, 2000, 3000, and (b) (4) .

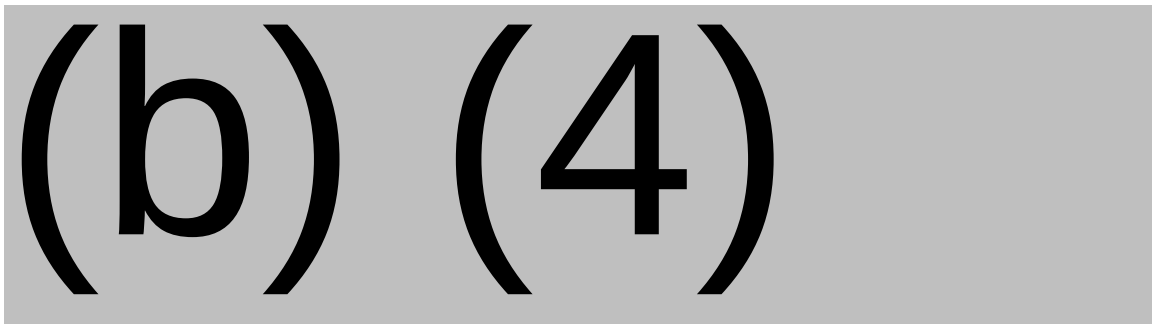
(b) (4)



Reviewer's comment: this method validation report appeared to be acceptable.

Q-16-334 Sodium chloride; MVR-16-334-Q617/688/689

This method validation report is based on previously submitted and reviewed Method validation MVR-16-334-Q617-Q617J-01, with experiments for parameters (b) (4) Berinert 1500/2000/3000.



(b) (4)

Reviewer's comment: this method validation report appeared to be acceptable.

Q-16-345 Residual moisture; MVR-16-345-C1

This method validation report is a verification of compendial procedure to determine residual water in dry substances of C1-Esterase Inhibitor by (b) (4)

(b) (4)

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

(b) (4)

Reviewer's comment: this method validation report appeared to be acceptable.

Q-16-399 Purity; MTR-16-399-01 and MEV-22r

The method for purity measurement is based on the (b) (4)

Reviewer's comment: These method validations appeared to be based on those for Berinert® products. Please relay the following information request to the sponsor for additional information.

"Please clarify whether the submitted method validation reports for Q-16-399 Purity are applicable to the purity measurement of both Berinert® and HAEGARDA products, or submit any additional validation studies for this method if available."

3.2.P.5.4. Batch analyses

Certificates of Analyses are provided for lots from full scale process validation (conformance lots), i.e., (b) (4) for 2000 IU; and (b) (4) for 3000 IU. All lots were tested according to batch release requirements of the relevant Quality Control Procedure and met all specifications.

Information requests:

The following informational requests were sent to the sponsor on 05 January 2017 to facilitate the evaluation of submitted product manufacturing information. The responses to these IR questions were received on 31 January 2017 and summarized as follows.

IR questions:

1. Please clarify the rationale for not including (b) (4) as a final release specification for CSL830 2000/3000 IU.

The sponsor's response: Osmolality as a final release specification is recommended for products intended for i.v. application and thus has not been regarded as a required test for products intended for s.c. application. However, **if the testing for (b) (4) is deemed recommended for products intended for s.c. use, CSLB is prepared to include the test as a final release specification for CSL830 2000/3000 IU.** The respective method and specification are proposed for the release specification Q-689U:

(b) (4) (Q-16-023)

Method: (b) (4)

Requirement: (b) (4)

This reviewer's comment: the response is acceptable. <u>The incoming review committee will need to make the determination for such requirement.</u>

2. For the analytical method Q-04-003 Practicability and organoleptic properties, the specification was determined based on manufacturing experiences. Please provide summary of historical data from product manufacturing include any deviations or out-of-specification results and investigation reports.

The sponsor's response: A data retrieval for the period from October 2009 (since license approval of Berinert in the US) up to date was performed for test code Q-04-003 "Practicability and organoleptic properties" in course of the release testing for Berinert. In the 7 years period (about (b) (4)) under review no out-of-specification results were received.

This reviewer's comment: the response is acceptable.

3. For Q-04-314 (b) (4), the method validation report appeared to be the (b) (4) report based on validation protocol No. MVP-04-314-Q0617U-01 for Berinert® products. Please provide any revalidation studies, and/or summaries of deviations or out-of-specification results and investigation reports if any since the approval of Berinert® products.

The sponsor's response: Data retrieval for the period from October 2009 (since license approval of Berinert in the US) up to date was performed for test code Q-04-314 (b) (4) in course of the release testing for Berinert. In the 7 years period (about (b) (4)s) under review one (1) out of specification result recently occurred. The deviation investigation for this out-of-specification result is still ongoing. The root cause was identified as personnel failure within production of the batch and was not related to the performance of the test method.

This reviewer's comment: the response is acceptable.

4. For the Q-10-121 (b) (4) assay, the method validation report covered products including Berinert, CSL830 1500, and the current product CSL 2000 IU/3000 IU. Please provide summary of historical manufacturing data for Berinert products including any deviations or out-of-specification results and investigation reports for this assay.

The sponsor's response: Data retrieval for the period from October 2009 (since license approval of Berinert in the US) up to date was performed for testcode Q-10-121 (b) (4) assay" in course of the release testing for Berinert. In the 7 years period (about (b) (4)) under review no out-of-specification results were received.

This reviewer's comment: the response is acceptable.

5. For Q-16-004 Protein assay, please provide summary of historical manufacturing data for Berinert® products using this assay, including any deviations, and/or out-of-specification results if there were any involving this assay.

The sponsor's response: Data retrieval for the period from October 2009 (since license approval of Berinert in the US) up to date was performed for testcode Q-16-004 "Protein assay" in course of the release testing for Berinert. In the 7 years period (about (b) (4) under review no out-of-specification results were received.

This reviewer's comment: the response is acceptable.

6. Please clarify whether the submitted method validation reports for Q-16-399 Purity are applicable to the purity measurement of both Berinert® and CSL830 2000/3000 IU, or submit any additional validation studies for this method if available.

The sponsor's response: **An updated method validation MVR-16-399** covering both Berinert and CSL830 2000/3000 IU is available and is provided in section 3.2.P.5.3.-8 (replacing the validation MTR-16-399-01 and Mev-22r, section 3.2.P.5.3.8-9).

This reviewer's comment: the response is acceptable. A more recent method validation MVR-16-399 was submitted for the incoming review committee to review.