DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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From: Felice D'Agnillo, LBVB/DBCD/CBER

Through: Abdu Alayash, Chief, LBVB/DBCD/CBER

To: Nannette Cagungun, Regulatory Project Manager, CBER

Sponsor: CSL Behring
Product: C1 esterase inhibitor subcutaneous (Human) or HAEGARDA
STN#: 125606/0
Subject: Final Review: Validation of Manufacturing Process

RECOMMENDED ACTION

Based on the information provided in the original submission and the responses to the information requests dated January 05, 2017, the process validation studies are approvable from a CMC perspective. However, this recommendation may be subject to revision by the new OTAT CMC review team that inherited this file after the Midcycle meeting.

REVIEW OF SPONSOR RESPONSES TO INFORMATION REQUESTS (January 5, 2017)

Responses to CMC information requests dated January 5, 2017 were received on January 31, 2017. This memo provides a review of the responses related to the process validation information requests. For ease of review, background information from the filed midcycle memo is appended to this final memo.

1. Please provide a side-by-side comparison of all the critical and non-critical process parameters, in-process tests and acceptance criteria, and final release specifications for Berinert, CSLB830 1500 IU, and CSLB830 2000/3000 IU.
   Reviewer Comments: CSLB provided three attachments with the requested information. This response is acceptable.

2. Please provide validation documentation supporting the hold time for the (b) (4) manufactured according to production procedure (b) (4)
   Reviewer Comments: The information is in Report# P(b) (4) . This response is acceptable.

3. Regarding the process parameter (b) (4) , please provide the final report of the(b) (4) study that will be used to support the new (b) (4) for this step.

Reviewer Comments: CSLB's response is not consistent with other information provided in the package. Further review will be needed by the incoming review team in consultation with the previous team.

4. Please provide the following change control documents for review; PR#136281, PR160694, and PR#162637.
   Reviewer Comments: CSLB provided translated summaries of these documents for review. This response is acceptable.

5. Please consider implementing upper and lower limits as well as an alert limit for the process parameter (b) (4) Also, please clarify what actions are taken in the event of nanofilter malfunction or blocking during filtration, and whether these actions are described in relevant SOP(s) for the virus nanofiltration step.
   Reviewer Comments: CSLB will implement an alert limit of (b) (4) to go along with the upper limit of (b) (4) . The alert limit will be added to an updated SOP. CSLB also indicated that in case of malfunction the filtration would be repeated and filter blocking issues would be corrected by using a new filter. Both changes will be included in the new SOP and these events, if they occur, will be tracked as deviations. This updated SOP should be requested and reviewed by the incoming review team.

6. Please provide the following documents for review; FS-617-022 and 900806-1.
   Reviewer Comments: CSLB indicated that the information in the requested documents was summarized in Reports# (b) (4) and PV-617-030-01. This response is acceptable.

7. Please provide the final release testing results for all the CSL830 1500 IU batches used in clinical studies.
   Reviewer Comments: CSLB provided this information.

8. Please provide a plan for how the stability of your product will be monitored post-approval.
   Reviewer Comments: This response was reviewed as part of the Stability review.

9. You proposed a shelf-life for CSL830 2000/3000 IU of 36 months at +30°C/(b) (4) . Please review all submitted labeling documentation to ensure this shelf-life is correctly indicated.
   Reviewer Comments: CSLB has proposed a shelf-life of 36 months at +30 °C (b) (4) However, the labeling documentation indicates that a temperature storage range of 2 - 30 °C. CSLB has not performed stability studies for CSL830 at the 2 °C temperature.

   CSLB will need to provide further clarification. Based on how CSLB responds, the incoming review team may have to inform CSLB that only the +30 °C temperature claim should be included in the labeling. If CSLB wants to include the 2 °C temperature, further stability studies would be required which they possibly can conduct with their proposed post-approval studies.

10. Please provide a list of lots that would be available for FDA release testing. Please indicate whether there are lots identified as potential launch lots for the US market.

    Reviewer Comments: CSLB indicated the following lots are available:

    Lot nos. (b) (4)

    Lot nos. (b) (4)

    Lots (b) (4) are intended as potential launch lots. Additional batches are already included in the actual production plan and will be produced according to plan. Samples of these concurrent batches can be shipped for CBER release testing soon after internal batch release has been conducted. The incoming review team should specify how many samples they wish to receive from each lot.

SUMMARY

CSL Behring has developed CSL830, a human plasma-derived C1-esterase inhibitor (C1-INH) concentrate intended for twice weekly self-administration by subcutaneous injection for the routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients. The manufacturing process for CSL830 (b) (4) manufactured by CSL Behring in Marburg, Germany.

The licensed Berinert product is a purified, pasteurized, lyophilized preparation of human plasma-derived C1 esterase inhibitor derived from U.S. Source Plasma. The manufacturing process steps include (b) (4), filtration, heat, and chromatography steps. Berinert is supplied as a lyophilized powder in single-use glass vials. Berinert is administered by intravenous injection after reconstitution with the appropriate volume of Sterile Water for Injection (USP) (supplied in the package). Berinert is indicated for the treatment of acute attacks in patients with HAE, a disease characterized by low levels of endogenous or functional C1 esterase inhibitor.

CSL830 is a (b) (4) to be administered subcutaneously for prophylaxis against HAE attacks. The manufacturing process for CSL830 (b) (4) CSL830 will be marketed as a single-use vial available in two sizes: 2000 International Units (IU) with 4mL water for injection (USP) and 3000 IU with 6mL water for injection (USP) each containing 500 IU/mL C1-esterase inhibitor after reconstitution. The release specifications for CSL830 (b) (4).
The CMC sections of this application were reviewed by four reviewers and each generated memos that will be filed.

Active Ingredient: C1 esterase inhibitor (derived from U.S. Source Plasma)

Established Name: C1 esterase inhibitor subcutaneous (Human)

Proposed Proprietary Name: HAEGARDA

Dosage Form: Lyophilized powder supplied as 2000 or 3000 IU per vial. To be dissolved in sterile water for injection for final concentration of 500 IU/mL.

Proposed Shelf Life/Storage Conditions: 36 months at 30°C/(b) (4) (8 hours at room temp when reconstituted)

Proposed Indication for Use: Prophylaxis for patients with HAE

Route of Administration: Subcutaneous

Container closure: Supplied in (b) (4) injection vials made of colorless molded Type (b)(glass. Vials are closed with stoppers made of (b) (4) rubber and sealed by (b) (4) caps. The cap is an (b) (4) crimp cap with punched concentric hole and integrated plastic disc made of (b) (4)

Packaging: The finished product comprises one vial of lyophilized powder, and one vial containing the diluent, Water for injection, USP, for reconstitution as well as a needleless medical device (Mix2Vial™) to transfer the diluent into the vial containing the lyophilized powder.

Mechanism of Action: Plasma C1 esterase inhibitor regulates the activation of complement, contact, and fibrinolytic systems. Patients with HAE have low levels of endogenous or functional C1 esterase inhibitor. Replacement therapy with C1 inhibitor is intended to increase plasma levels of C1-esterase activity and restore control over the complement, contact, and fibrinolytic systems.

CHEMISTRY, MANUFACTURING, AND CONTROLS

I. Introduction

CSL830 (Haegarda) is a sterile, pasteurized, lyophilized product of C1 esterase inhibitor. The overall starting material is U.S. Source Plasma collected at FDA-licensed and inspected plasma collection centers from qualified plasma donors. The product package consists of one carton containing a single-use vial of Haegarda and a vial of sterile water for injection, and an additional carton with a Mix2Vial filter transfer set, a disposable syringe, infusion set, and two alcohol swabs.

II. Manufacturers/Facilities

1. CSL Behring GmbH, Emil-von-Behring-Straβe 76, 35041 Marburg, Germany
   Role: (b) (4) product manufacturing and testing
2. (b) (4)
   Role: Pyrogen testing

III. Method of Manufacture and Packaging

1. Starting Materials:

U.S. Source Plasma from FDA-approved and inspected blood centers. All units are tested and found non-reactive to hepatitis B surface antigen, negative for antibodies to human immunodeficiency virus (HIV-1/2), hepatitis C virus (HCV). In addition, plasma (b) (4) are tested by NAT/(b) (4) for genomic material of HCV, HBV, HAV, HIV-1 and parvovirus B19. Manufacturing (b) (4) are tested for hepatitis B surface antigen and anti-HIV1/2. Only manufacturing (b) (4) non-reactive for HCV RNA, HBV DNA, HAV RNA, HIV-1 RNA and (b) (4) of parvovirus B19 are released. Viral reduction steps in the manufacturing process include; pasteurization (10 h at 60 °C), hydrophobic interaction column (b) (4) and nanofiltration.

2. Materials used in processing:

(b) (4), Glycine, (b) (4), NaCl, (b) (4), water for injection in (b) (4).

Note: The specifications for these materials are (b) (4)

3. Other materials (without reference to a monograph)

(b) (4).

4. Overview of Manufacturing Process:

Starting Material (U.S. Source Plasma)

(b)

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

(b) (4)

(b) (4)

Filling into the final containers
Lyophilization and sealing
Final processing

↓
Drug Product (2000 or 3000 IU)

Note: (b) (4)

Critical Process Steps:

(b) (4)

NOTE: For production procedure (b) (4) (clinical trial batches), the manufacturing is unchanged from

(b) (4)

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(b) (4)

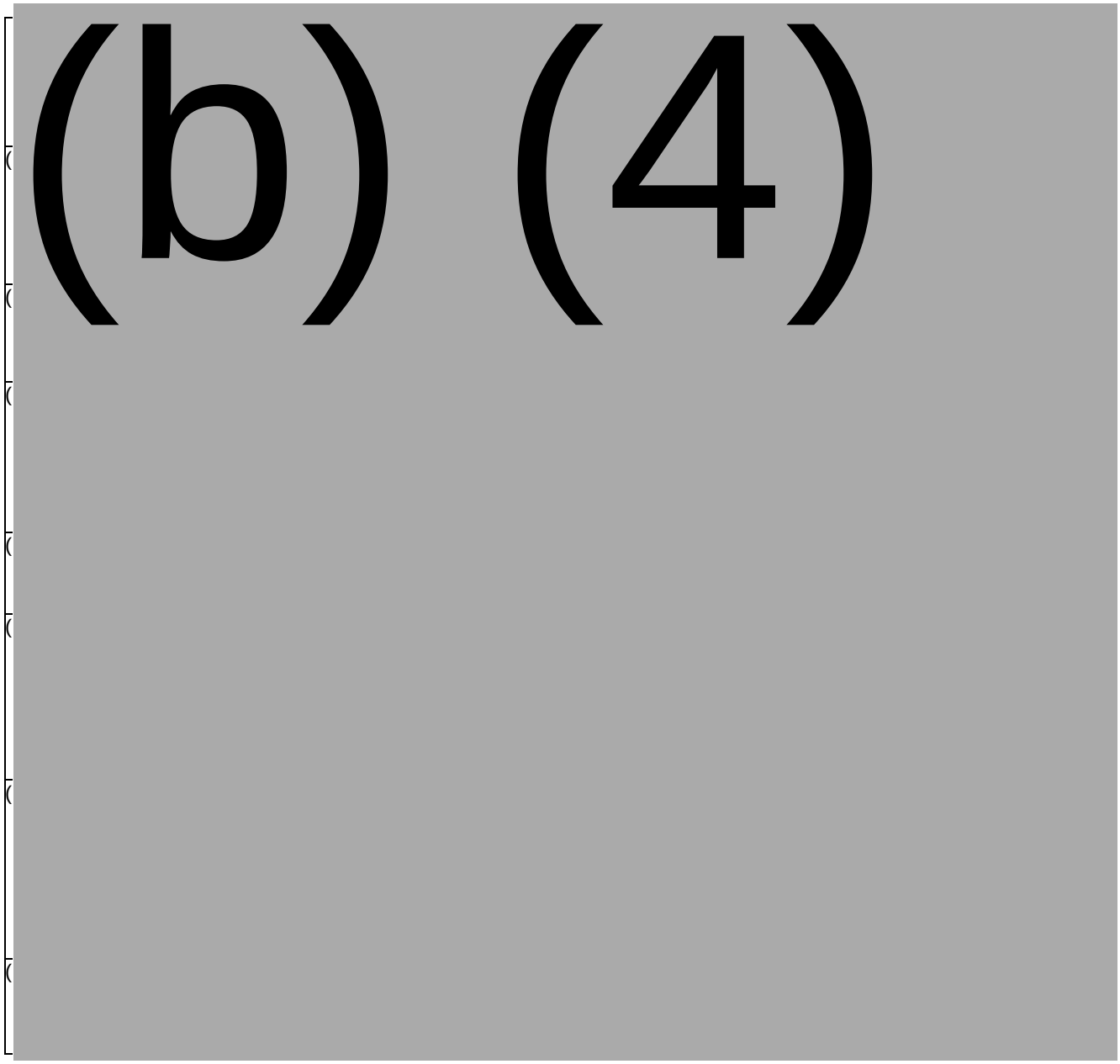
(b) (4)

5. Drug Substance Specifications (b) (4)

(b) (4)

6. Critical Process Parameters

(b) (4)



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

(b) (4)

(b) (4)

7. Final Product Composition:

Constituent	Amount/ vial 2000 IU	Amount/ vial 3000 IU	Function	Compendial Standard
C1 esterase inhibitor Total Protein	2000 IU/mL (b) (4)	3000 IU/mL (b) (4)	Active ingredient -	WHO International Standard -
Glycine (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium chloride	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium citrate	(b) (4)	(b) (4)	(b) (4)	(b) (4)

8. Final Product Release Specifications:

Product Quality Attribute	**Specification** *(acc. to Quality Control procedure* (b) (4)
Practicability and organoleptic properties: - Dissolution time - Appearance	-Dissolution time: (b) (4) -Colorless, clear to slightly opalescent solution
(b) (4)	(b) (4)
Residual moisture	(b) (4)
Protein	(b) (4)
Glycine (b) (4)	(b) (4)
Sodium chloride	(b) (4)
Sodium citrate	(b) (4)
(b) (4)	(b) (4)
Purity	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Sterility	Specification CFR/USP
Pyrogens	Specification CFR/USP

IV. Validation of Manufacturing Process

A. Manufacturing Process Development (Module 3)

Berinert (Approved 2009): 500 IU/10 mL (50 IU/mL), i.v. administration.

CSL830 1500 IU clinical batches: (b) (4)

(b) (4)

CSL830 2000/3000 IU commercial scale: (b) (4)

CSL830: 2000 IU/4 mL, 3000IU/6mL (500 IU/mL).

B. Process Validation Studies for Drug Substance (Module 3)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

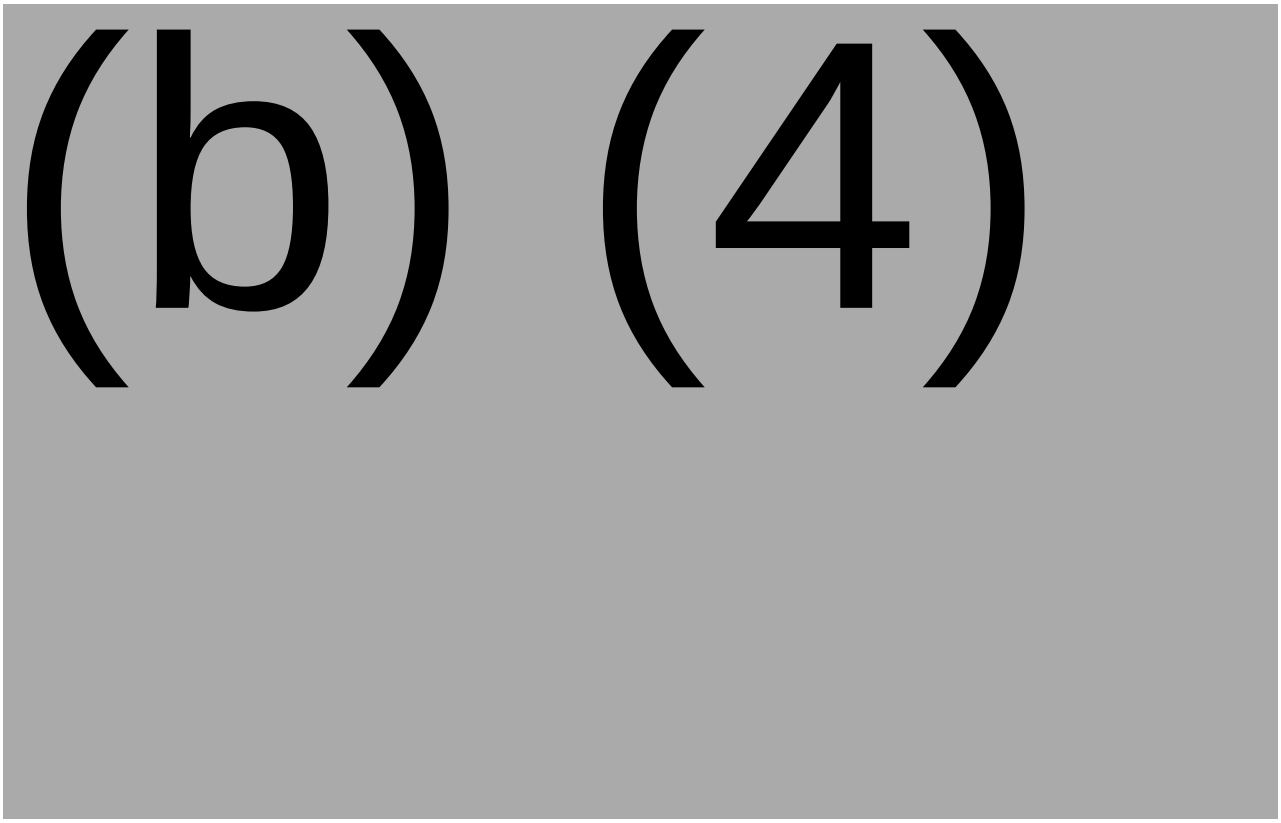
C. Process Validation Studies for Drug Product (Module 3)

Risk Analysis

RA-689-002-01 Risk analysis of the production process of the C1 Esterase Inhibitor concentrate (human) drug product and visual inspection of the (b) (4) product on the (b) (4) floor, (b) (4)

This assessment covers all aseptic and non-aseptic drug product production steps of C1-INH starting from the final bulk through the (b) (4) drug product according to (b) (4) . The following critical process parameters were identified:

(b) (4)

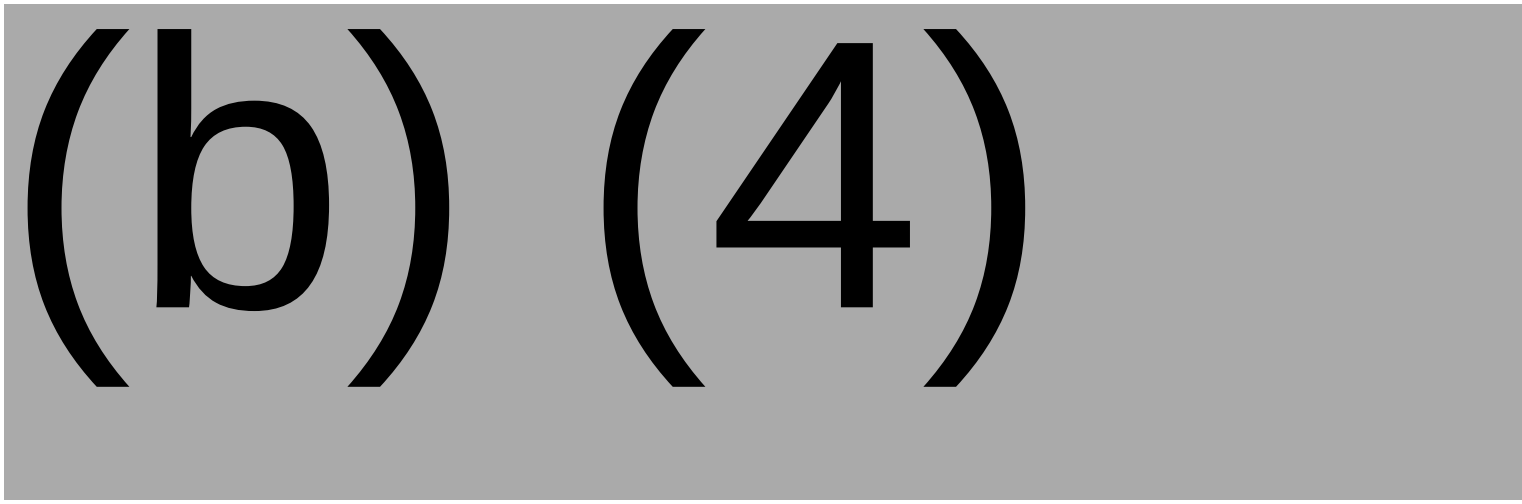


Full Scale Validation

(b) (4) Process validation of the filling process of C1-Esterase Inhibitor Concentrate (human) 2000 IU / 3000 IU / (b) (4) performed in Building (b) (4) floor:

The study was conducted to validate the (b) (4) in the new (b) (4). Process validation included the manufacturing of (b) (4) validation lots of CSLB830 2000IU (b) (4) vial)/3000IU (b) (4) vial) in the filling and lyophilization area in building (b) (4) floor (see below)

Validation Lots:



In this study, CSLB provided supportive data that for all fill sizes; the in-process control parameter for volume in container (filling weight) for all validation lots tested met the predefined acceptance criteria.

Data obtained for C1INH (b) (4), protein content, and NaCL concentration from the start to the end of the filling process supported the homogeneity of the filled product. No differences of the product composition and no impact on the predefined specifications and product quality attributes were observed. Individual visual inspection parameters (e.g. container interior, product alterations, foreign particles, etc.) met the established limits. Furthermore, the (b) (4) test showed that all vials were within the acceptance criterion of max. (b) (4) losses.

(b) (4) Lyophilization validation of C1-Esterase-Inhibitor Concentrate (Human) US 2000 IU (building (b) (4) floor). To be reviewed by DMPQ reviewer.

(b) (4) Lyophilization validation of C1-Esterase-Inhibitor Concentrate (Human) US 3000 IU (building (b) (4) floor). To be reviewed by DMPQ reviewer.

Process simulation

(b) (4) Routine (b) (4) of aseptic processes by media fills in the filling area (b) (4) floor (summary report 2014/15). To be reviewed by DMPQ reviewer.

(b) (4) Routine (b) (4) for aseptic processing steps of (b) (4) containers Filling area (b) (4) To be reviewed by DMPQ reviewer.

D. Viral safety studies

For viral safety studies, CSLB cross-referenced previous validation studies including (b) (4) evaluations that were reviewed and approved for the Berinert (see Report# AASE-617-04-US, DSVR-617-002-01). The following process steps were evaluated for their capacity to remove/inactivate test viruses (shown below in bold):

(b) (4)

(b) (4)

	Manufacturing stages studied / Scale reduction (% of manufacturing scale)			
	Stage 5 / reduction N/A	**Stage 7 / 0.47 %**	**Stage 8 / 0.1 %**	
Virus Studied	**Heat treatment in aqueous solution (pasteurization) (n)[a] [$log_{10} \pm SD$]**	**Hydrophobic interaction chromatography (n)[a] [$log_{10} \pm SD$]**	**20N/15N virus filtration (n)[a] [$log_{10} \pm SD$]**	**Overall Virus Reduction [$log_{10} \pm SD_{cum}$]**
Enveloped Viruses				
HIV	≥ 6.6 (8)	≥ 4.5 (2)	≥ 5.1 (2)	≥ 16.2
BVDV	≥ 9.2 (5)	≥ 4.7 (3)	≥ 5.3 (3)	≥ 19.2
PRV	6.3 ± 0.6 (3)	≥ 6.5 (4)	≥ 7.1 (2)	≥ 19.9
WNV	≥ 7.0 (4)	n.d.	≥ 8.0 (2)	≥ 15.0
Non-enveloped Viruses				
HAV	≥ 6.4 (4)	2.8 ± 0.4 (6)	≥ 5.3 (2)	≥ 14.5
CPV	1.4 ± 0.1 (3)	6.4 ± 0.5 (7)	≥ 7.2 (2)	≥ 15.0
B19V[c]	3.9 ± 0.4 (3)	n.d.	n.d.	N/A

[a] Number of experiments covering production conditions used for evaluation
[b] Report: VER-B19-03
n.d. not determined
N/A not applicable

As noted earlier, the manufacturing changes implemented for CSLB830 2000/3000IU do not impact the (b) (4) or hydrophobic column steps; however, the (b) (4) could be impacted. In the new process (b) (4). The process parameters and product attributes related to this modified step were investigated during process validation studies and compared to the production of CSLB830 1500 IU batches. All acceptance criteria were met in these studies although there is additional information being requested regarding the (b) (4) (see above for details). In pre-BLA discussions,

CSLB agreed to provide sufficient validation data to ensure that previous viral validation studies for the (b) (4) approved with Berinert would be applicable to the (b) (4) approach prior to (b) (4). Based on the process validation results for the (b) (4), CSLB should provide additional justification for a new range for this process parameter. Moreover, it is recommended that these (b) (4).