**DEPARTMENT OF HEALTH AND HUMAN SERVICES** Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Ave
Building 71, G112
Silver Spring, MD 20993-0002

**To:** DATS: 636359

STN BLA 125606/0
C1 Esterase Inhibitor (Human), Subcutaneous

**From**: CDR Donald Ertel, Regulatory Officer, OCBQ / DMPQ / MRB1

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

**CC:** Nannette Cagungun, RPM, OTAT/DRPM/RPMBI
Ewa Marszal, Ph.D., Chair, OTAT/DPPT/PDB
Felice D'Agnillo, Product Office, OBRR/DBCD/LBVB

**Subject:** DMPQ Primary Review for Original Biologics License Application filed per 21 CFR 601.2 for CSL Behring GmbH facility for C1 Esterase Inhibitor (Human), Subcutaneous indicated for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients

**Applicant:** CSL Behring GmbH (License Number #1765)

**Facility** CSL Behring GmbH (CSLB) FEI # 3003098680 - Emil-von-Behring-Strasse 76 D-35041 Marburg Germany

**ADD:** 30 June 2017

## Conclusion and Recommendation

Overall conclusions and recommendation will be made in my Final Amendment Addendum Review Memo.

The following information request is being sent to the Firm to be assessed in my addendum review memo:

1. Reference your response to Question #1 (125606/0.12 received 13 Jan 2017 to Information Request on 21 Dec 2016):

a. Please provide a summary of the microbial testing performed as part of the CV (b) (4) . Please include the sampling method, acceptance criteria, and a summary of the results (and any deviations).
b. CV-689-001-01 (that was provided in the application) for CV of (b) (4) does not include data for microbial testing (bioburden).Was microbial testing performed as part of the CV for the (b) (4) ? If so, please include the sampling method, acceptance criteria, and a summary of the results (and any deviations).

2. Please provide a description of the segregation activities /controls of (b) (4) areas from (b) (4) areas. You may use diagrams or images of rooms and equipment to support your response, as needed.

3. Please provide a summary of the validation (PQ) of the (b) (4) depyrogenation of the (b) (4) Vial. Please ensure to include the following:
   - reference to the equipment used for (b) (4) depyrogenation, and reference to associated equipment qualification documents
   - dates of the validation studies
   - acceptance criteria
   - summary of the results and any deviations

4. Please provide a copy of (b) (4) Test Instruction (b) (4) for review.
5. Please provide, in table format, all steps of the process where (b) (4) is monitored as an in-process test. Please provide the applied limit at that step, and the justification /rationale for the limit.

Additionally, we have requested a written response in amendment, expected 02/28/17, to our follow-up items related to the Design Controls (and related DHF) for the Mix2Vial and Combination Product Requirements.

**Review Memo Format and Table of Contents▪**

I have provided a summary of information provided in the submission that is under DMPQ purview as outlined in SOPP 8401.4: My review included evaluation of parts or the entirety of the following sections:

- 3.2.A.1 Facilities and Equipment
- 3.2.S.1 Manufacture
- 3.2.S.4 Control of Drug Substance
- 3.2.S.6 Container Closure System
- 3.2.S.7 Stability
- 3.2.P.1 Description and Composition of Drug Product
- 3.2.P.2 Pharmaceutical Development
- 3.2.P.3 Manufacture
- 3.2.P.5 Control of Drug Product
- 3.2.P.7 Container Closure

- 3.2.P.8 Stability

In general, my Review Assessment / Comments are provided at the end of review sections in a double lined box. Any information requests (IRs) related to review will be included in these boxes in bolded text. A summary of the firm's response to that IR will immediately follow in italicized text or in a subsequent Amendment Review memo. My assessment of the response will immediately follow in a double lined box.

The table of contents of this review is as follows (major sections numbered, subsections lettered):



## 1. Amendments related to Review

- 125606/0.3 (&4) received 6 Sep 2016 (&13 Sep 2016, CSLB corrected reports) to Information Request on 15 Aug 2016
- 125606/0.11 received 06 Jan 2017 to Information Request on 16 Dec 2016
- 125606/0.12 received 13 Jan 2017 to Information Request on 21 Dec 2016

## 2. Regulatory History

The agency received the BLA in eCTD format on 30 June 2016. I was assigned as a CMC reviewer on 01 July 2016. The application was appropriately filed per 21 CFR 601.2

An Inspection Waiver was submitted and approved for this submission for the CSL Behring facility (approved 19 Sep 2016).

The following DMF were referenced:

- (b) (4) (Rubber Stopper, (b) (4)
- (b) (4) (Glass Type (b) (4) Containers, (b) (4)
- (b) (4) Glass Type (b) (4) Containers, (b) (4)
- (b) (4) (Water for Injection, CSL Behring GmbH)
- (b) (4) (Mix 2 Vial, Medimop Medical Projects, Ltd.)

## 3. Environmental Assessment

CSLB is claiming an exemption from the requirement for preparing an environmental assessment for this BLA for C1 Esterase Inhibitor (Human), Subcutaneous, based upon 21 CFR 25.31(c) which allows a categorical exclusion for an action on an application for marketing approval, for marketing a biologic product for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

CL830 is a human plasma-derived concentrate produced as a highly purified, pasteurized, virus filtered, lyophilized C1-esterase inhibitor concentrate for subcutaneous use. CSL830 is (b) (4) . C1-esterase Inhibitor Concentrate, human is proportionally similar in its active and inactive ingredients to Berinert®.

Review Assessment / Comments: To CSL's knowledge, no extraordinary circumstances exist. I am in agreement with the CE.

## 4. Product Overview

CSLB 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 attacks in adolescent and adult patients.

C1-INH is a plasma-derived concentrate produced as a highly purified, pasteurized, virus filtered, lyophilized C1-INH concentrate for subcutaneous use. It is provided in a single-use vial containing either 2000 or 3000 IU (in (b) (4) vials respectively) of C1-INH following reconstitution to 500 IU/ml with the respective amount of WFI diluent. The product is sterile, free of pyrogens and does not contain preservatives. C1 Esterase Inhibitor Concentrate is supplied with a Mix2Vial™ and a diluent vial for reconstitution containing 4 mL or 6 mL water for injection (USP).

Since 1985, a 500 IU fill size of C1-INH has been produced and marketed by CSLB under the trade name Berinert® (based on a C1-esterase inhibitor (b) (4) in the (b) (4)

Meanwhile, CSLB has a marketing authorization in several countries for the additional strength 1500 IU in a (b) (4) presentation associated with an approximately (b) (4) C1-esterase inhibitor concentration in the final bulk (250 IU/mL). This concentrated (b) (4) is formulated with (b) (4) compared to the 500 IU product. The later reconstitution volume prior to application is approximately the (b) (4) dispensing volume. In this way, the reconstituted product to be administered features the (b) (4) concentration of C1-esterase inhibitor, (b) (4) .

In 2011, CSLB developed a plasma-derived C1-esterase Inhibitor Concentrate, human (b) (4) for subcutaneous administration as a (b) (4) . C1-esterase Inhibitor Concentrate, human is proportionally similar in its active and inactive ingredients to Berinert®. The 2000 IU presentation shall be realized by filling (b) (4) of the approximately (b) (4) . As described above, the pertaining reconstitution volume prior to application is (b) (4) The 3000 IU presentation is realized by filling (b) (4) of the approximately (b) (4) . As described above, the pertaining reconstitution volume prior to application is (b) (4)

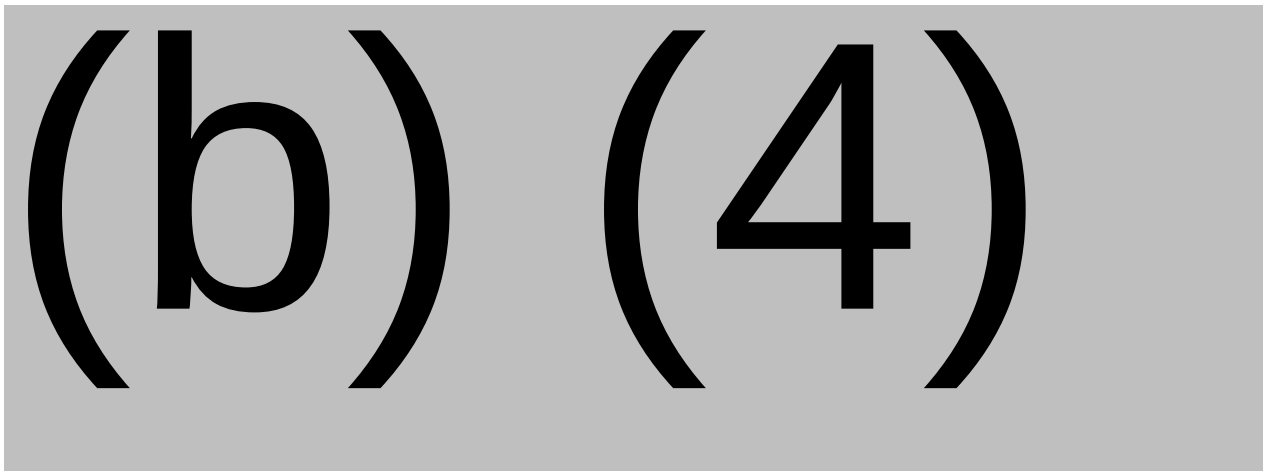
The production process for the C1-INH presentations (CSL830) is (b) (4) Additionally, the filling and lyophilization process has been (b) (4) to account for the (b) (4) volume.

## 5. Process Overview

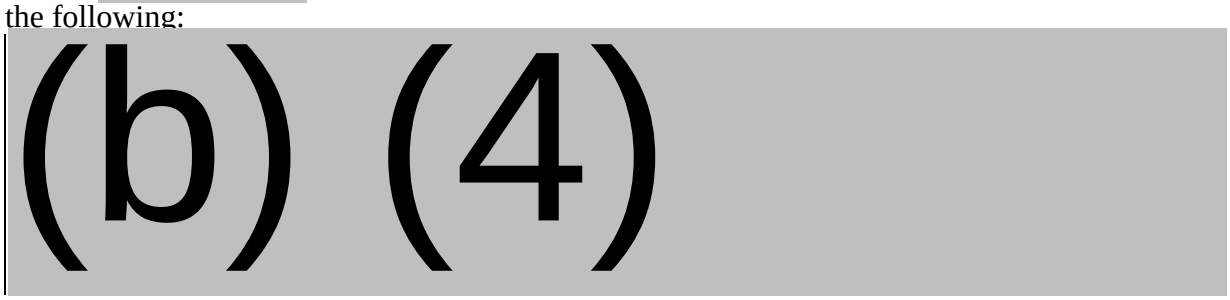
The C1 Esterase Inhibitor (Human), Subcutaneous [Company Code, CSL830] product/process is very similar to the approved Berinert (STN 125287; approved by CBER in October 2009). CSLB outlines the comparison of the process to Berinert as follows:

(b) (4)

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




All the (b) (4) is used for CSL830 as in production of Berinert with the exception of the following:




Lyophilizer (b) (4) is currently licensed for the manufacture of Prothrombin complex concentrate (human), Kcentra (STN BL 125421). (b) (4) is not used for any other US or non-US products. There are no novel configuration or performance features associated with (b) (4) located in Lyophilization (b) (4) Room (b) (4), that is approved for multi-product use including:

- Berinert® P (STN BL 125287)
- Humate-P® (STN BL 103960)
- Corifact™ (STN BL 125385)
- Kcentra (STN BL 125421)
- Idelvion, rIX-FP (STN BL 125582)

Filling Line (b) (4) is currently licensed for the manufacture of the US products listed above. The manufacturing rooms did not change from those used for the manufacture of Berinert®, nor was there a need to modify them for CSL830.

CSLB reports that the (b) (4) vial is already approved for use with their US approved products:

- Humate-P® (STN BL 103960)
- Corifact™ (STN BL 125385)
- Kcentra® (STN BL 125421)

The (b) (4) vial is not approved yet for use with any of their US products.

The stopper (CSL Part #(b) (4) , nominal size (b) (4) ) is used for both the (b) (4) vial sizes, additionally the stopper is used and approved for the following products:

- Afstyla®(STN 125591)
- Idelvion®(STN 125582)
- Corifact™ (STN BL 125385)Kcentra ®(STN BL 125421)

The (b) (4) vial and stopper (b) (4) combination is approved for use by CBER for Corifact™ and Kcentra®

Review Comment/ Assessment: No different or new processes appear evident. (b) (4) virus filtration are(b) (4) batch size only. For Process filtration and (b) (4) .

Because much of the data on the same facilities, and associated utilities, and equipment was approved in STN 125287, the following items appear to be the critical items to be evaluated as part of this review:

(b) ( . (b) (4)

## 6. Overall Manufacturing and Testing Facilities

The facilities involved in the manufacture and testing of CSL830 are listed below along with a short description of their manufacturing responsibilities and an indication if an inspection was performed. The facilities involved in the manufacturing and testing of CSL830 are as follows:

| Manufacturing / testing (b) (4) | Facility | Comments |
|---|---|---|
| (b) (4) Manufacturing (b) (4) ) | CSL Behring GmbH (CSLB)<br>Emil-von-Behring Straße 76<br>35041 Marburg, Germany<br>Final DS Manufacture<br>FEI#3003098680<br>DUNS 326530474 | Propose Inspection Waiver; Facility inspected by DMPQ for PLI for rIX-FP in(b) (4) : VAI and in (b) (4) :VAI |
| (b) (4) | CSLB Marburg | Inspection Waiver approved; Facility inspected by |

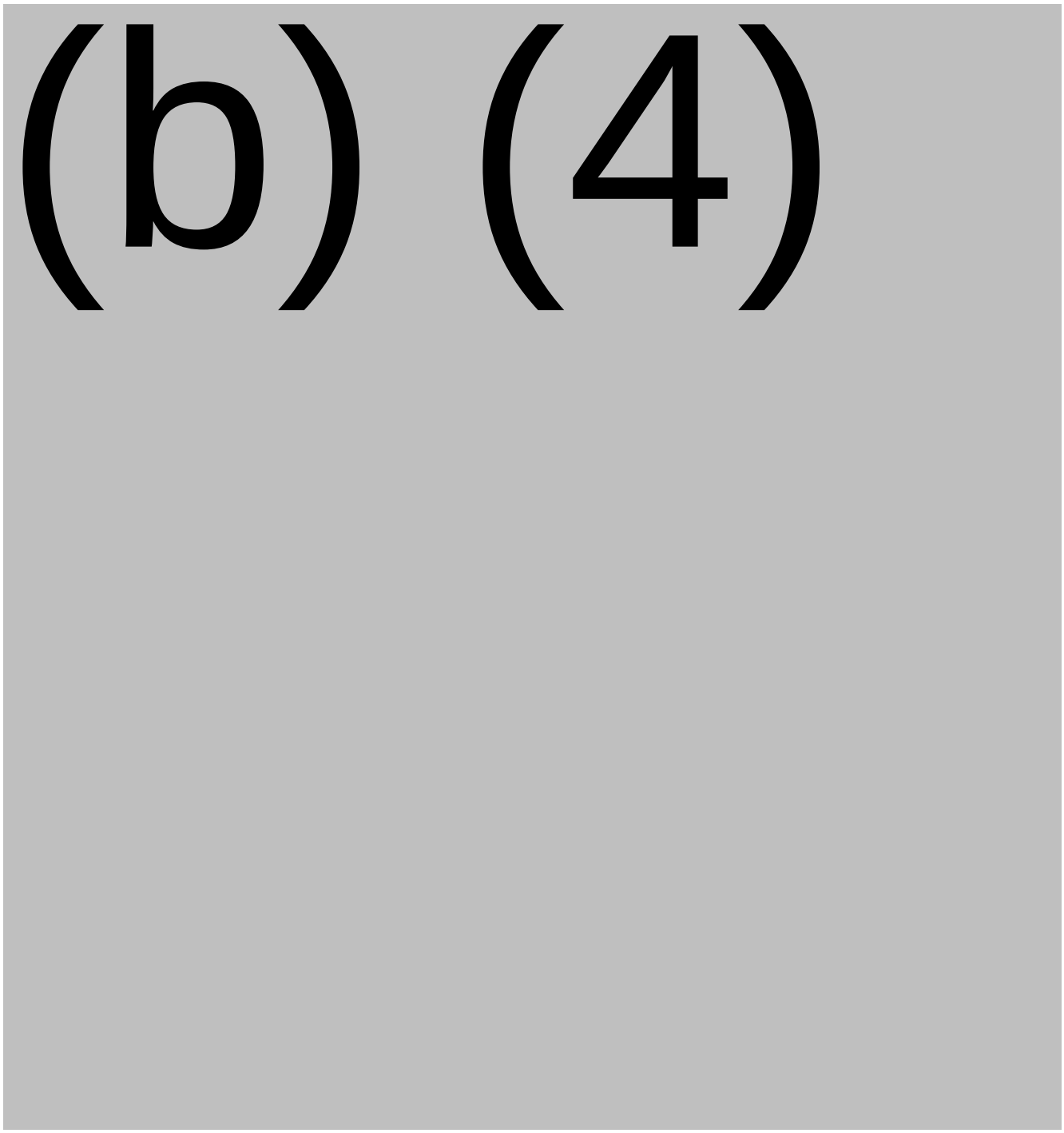
| Manufacturing / testing (b) (4) | Facility | Comments |
|---|---|---|
| (b) (4) | | DMPQ for PLI for rIX-FP in (b) (4) VAI |
| Drug product manufacturing, fill, lyophilization | CSLB Marburg | Inspection Waiver approved; Facility inspected by DMPQ for PLI for rIX-FP in (b) (4) :VAI |
| Labeling/crimping/ packaging | CSLB Marburg | Inspection Waiver approved; Facility inspected by DMPQ for PLI for rIX-FP in (b) (4) :VAI |
| Final release testing of drug product | CSLB Marburg | Inspection Waiver approved; Facility inspected by DMPQ for PLI for rIX-FP in (b) (4) :VAI |
| Pyrogen Testing (DP Release) | (b) (4) | Inspection waiver approved; Last Inspection (b) (4) : NAI |
| Component testing (vials, water quality, environmental monitoring samples, etc.) | CSLB Marburg | No inspection or waiver needed |
| Diluent manufacturing "Sterile Water for injection" | CSLB Marburg (b) (4) | The site is licensed by both the US and German authorities to manufacture and distribute sterile and non-sterile therapeutic goods for human use Inspection Waiver approved; Facility inspected by DMPQ for PLI for rIX-FP in (b) (4) |
| Transfer Device Mix2Vial® | Manufactured by Medimop; Supplied by CSLB Marburg | 510K Cleared device #K031861 No inspection or waiver |
| Stability testing and storage of samples | CSLB Marburg | Inspection Waiver approved; Facility inspected by DMPQ for PLI for rIX-FP in (b) (4) VAI |
| Records or quality assurance functions with no testing | | |
| Storage of drug substance and drug product | | |

## 7. Processing Equipment Overview

The main production equipment used for (b) (4) / Drug Product production of CSL830 is:

(b) (4)

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




As part of the (b) (4) were needed for the (b) (4) for the collection of the virus filtrates in the virus filtration step. Furthermore, virus filter with a (b) (4) . PQ was performed under 900806-01 and reported in PV689-006-01 for:

- (b) (4) Chromatography
- (b) (4) for Virus Filtrate, (b) (4)

- Virus Filtration (b) (4)
- Virus Filtration (b) (4) equivalent to (b) (4)

Review Comment/ Assessment: All the equipment listed is currently licensed for Berinert® with the exception of those denoted with an "*". Some of the equipment is licensed for use with other US products as noted in the tables. CSLB reports performance of IQ/OQ of all equipment. Qualification of the Lyophilizer equipment is covered in a separate section in this memo. PQ of (b) (4) is covered in the overall process validation. (See Process Validation Section of this memo)

## 8. Equipment Cleaning Validation

Review Comment/ Assessment: Product (b) (4) are dedicated to CSL830, and have not been approved for use with Berinert. Lyophilizer (b) (4) manufacture of Berinert. However (b) (4) is approved for used with Prothrombin complex concentrate (human) & Kcentra (STN BL 125421). All other equipment, including (b) (4), is approved for Berinert, and cleaning has been validated. I am focusing my review of cleaning on these "new' equipment.

Per 860606-01 [March 2015 to August 2015, CSLB performed cleaning validation performed for the (b) (4) (reported in CV-689-001-01) and (b) (4) itself (reported in CV-680-002-01). The (b) (4) together with the (b) (4) is dedicated equipment, located in the (b) (4) Berinert production area, used in a (b) (4) step of C1-INH only. After the process step, (b) (4) and Virus-Filtration (per (b) (4)), the filtrate of the Virus- Filtration is collected in (b) (4)

The (b) (4) is cleaned automatically in the (b) (4) area in building (b) (4), CSLB executed (b) (4) validation runs covering the (b) (4) holding time before cleaning were performed using the (b) (4) cleaning procedure according to SOP 531249-12.1.

The (b) (4) is cleaned in the (b) (4) according to SOP 530125- 06, and the disassembled parts are cleaned by the (b) (4) according to SOP 535778-02.

In the submission, CSLB provided a reference to the sampling and analytical methods used in this validation and a description of the cleaning method. Cleaning method included the use of (b) (4).

For the (b) (4), CSLB performed the validation in (b) (4) runs, after the equipment had been used (b) (4)

(b) (4)

- (b) (4)
  .

The specified holding time of (b) (4) was exceeded to ensure that worst case conditions are reflected in this validation study.

For (b) (4) sample was performed as well.

For the (b) (4) was performed (b) (4) .
Sampling sites were chosen with the aim to cover:

- Areas difficult to clean such as (b) (4) .
- All large areas which strongly contribute to the total surface.

# (b) (4)

Residue testing:

All pieces of equipment were visually clean during all validation runs, and the contamination with protein was below the quantitation limit. These results show that protein, the main contaminant in the equipment, is sufficiently removed by the respective cleaning process and no significant carryover from one batch to the next occurs.

Since (b) (4) were used as the only cleaning agents, the removal of the cleaning agent was investigated by (b) (4) . In addition to protein and cleaning agent residues, the (b) (4)

The samples were analyzed for protein with the (b) (4) test according to CSLB's testing instruction Q-16-389. To calculate the actual amount of protein on the sampled surfaces, each measured (b) (4) ,
which has been determined in previous studies. The results of these studies are documented in the reports MV 560156-001 and MV 560156-002.

Concerning final rinse samples, the (b) (4) calculation cannot be performed, because (b) (4) . The exact value for the (b) (4) is not precisely known. Therefore, the quantitation limit of the (b) (4) protein determination method was used as the acceptance criterion for final rinse samples.

Review Assessment/ Comments: CSLB refers to CV-680-002-01 for the cleaning of (b) (4) itself. CSLB states that due to (b) (4) were chosen for sampling representing listed (b) (4) in the protocol. However, CSLB does not list (b) (4) in this protocol. They claim that the (b) (4) listed in SOP 545217-0.1 (referenced in the protocol) belonging to this equipment group are constructed equivalent to the (b) (4) and are cleaned by the same procedure. Therefore, the validation of their cleaning and sanitization process is also covered by this study. Additionally, the protocol covered (b) (4) used for (b) (4) , and CSLB does not mention the (b) (4) studied for protein residual, and I found no evidence of a justification for not validating a CSL830 residual protein.

**Reference your Cleaning Validation:**

1. **Why was microbial testing not performed in the Cleaning Validation studies for (b) (4)**
2. **How is Cleaning Validation Report CV-680-002-01 relevant to the cleaning of (b) (4)**
   a. **What protein residuals were studied in CV-680-002-01 and how are they relevant to the C1-INH protein residuals? Please provide your justification if a worst case (b) (4) is being represented.**

*CSLB Response*

1. *Microbial testing was part of the qualification of the respective (b) (4) and was therefore not performed in scope of the initial validation report CV-680-002-01. However microbial testing was performed during the last (b) (4) . Concerning the (b) (4) , cleaning was shown in respect to study number CV-689-001-01.*
2. *The Cleaning Validation Report CV-680-002-01 applies to the (b) (4) as well. The Initial Validation covered (b) (4) . Due to the protein load and cleanablity, these (b) (4) are used as a worst case scenario, and all other (b) (4) with the same volume and mode of operation are covered by this validation as well.*

Review Assessment/ Comments: CSLB references CV-689-001-01 for microbial testing for (b) (4) Review of that document does not show that microbial testing was performed. CSLB also does not specify the details of microbial testing from the last revalidation of the (b) (4).

**The following information request is being sent to the Firm to be assessed in my addendum review memo:**

**Reference your response to Question #1 (125606/0.12 received 13 Jan 2017 to Information Request on 21 Dec 2016):**

1. **Please provide a summary of the microbial testing performed as part of the CV (b) (4) . Please include the sampling method, acceptance criteria, and a summary of the results (and any deviations).**
2. **CV-689-001-01 for CV of (b) (4) does not include data for microbial testing (b) (4)**

**A. Was microbial testing performed as part of the CV for the (b) (4) ? If so, please include the sampling method, acceptance criteria, and a summary of the results (and any deviations).**

I verified that (b) (4) protein residue was being used as a worst case scenario and (b) (4) are similar in volume and mode of operation, this is not a change from their previous CV approach, no objections noted.

CV for Lyophilizers (b) (4)

The lyophilizers are as follows:

| Internal name | (b) (4) | (b) (4) |
|---|---|---|
| Presentation | 3000IU | 2000IU |
| Building | (b) (4) | |
| Room | (b) (4) | (b) (4) |
| Manufacturer | (b) (4) | (b) (4) |
| Number of shelves | (b) (4) | |
| Total area of shelves | (b) (4) | |

Report 860525-01 summarizes the results obtained during the cleaning validation performed for the (b) (4) . CLSB performs a (b) (4) cleaning procedure with a (b) (4) according to SOP 536721 0.1.

Report 860454-02 summarizes the results obtained during the cleaning validation performed on the (b) (4) . Cleaning is performed according to SOP 536720 2.0 (b) (4) using the (b) (4) system.

All these lyophilizer are located in the clean room area in the filling area of building (b) (4) floor at the Marburg site of CSL Behring. During these cleaning validations, the freeze dryers were (b) (4) , because, according to CSLB, there is no deliberate product contact of the lyophilizer surface in routine production. (b) (4) represents worst case regarding cleaning of lyophilizers in building (b) (4).

CSLB studied the cleaning procedure related to lyophilizer (b) (4)

For both studies, (b) (4) consecutive validation runs were performed. All runs resulted in residue levels within the preset acceptance criterion regarding protein. The product (b) (4) positions also were visually clean after execution of the respective cleaning procedure.

CSLB described the materials and methods used in the cleaning validation studies in the submission.

During execution of the validation predefined points in the lyophilization (b) (4) were (b) (4)

During execution of the cleaning validation runs the following proceeding was followed within every single run:

(b) (4)

mples

12. Data analysis

Sampling was performed on (b) (4) predefined locations, including (b) (4)

The acceptance criteria for this study were predefined in the respective validation protocols according to the Cleaning Validation Procedure, 420020, the Rationale for Cleaning Validation, Methods and Acceptance Criteria and the supporting SOP 550198 (all documents referenced in the submission).

Visual Inspection:

The lyophilizer had to be visually clean (no visible residues on surfaces inside the lyophilizer chamber) according to SOP 530679.

Protein Residue:

As there is no deliberate contact of the surfaces of the freeze dryer with product, the acceptance criterion for carry-over of protein residue from batch to batch mainly used in

cleaning validations is not applicable. Due to this fact the following acceptance criterion had to be applied, the cleaning procedure has to reduce the amount of protein contamination by a factor of at least (b) (4) i.e. the amount of protein on each sampling position after cleaning and sterilization has to be a factor of (b) (4) than the amount of protein applied to the respective sampling position. In case of a protein value reduced by a factor of (b) (4) would be below the quantitation limit, each sample taken after cleaning has to contain protein values below the quantitation limit.

CSLB reported that the surfaces inside the lyophilizer (b) (4) were visually clean after cleaning and sterilization, and the reduction of the (b) (4) contamination was larger than a factor of (b) (4) in all but one case (this was a factor of (b) (4) for one location on (b) (4)). The amount of residual protein after cleaning was below the detection limit on each of the (b) (4) sampling positions (for (b) (4) positions (for (b) (4)).

During the execution of protocol 860525-01, CSLB reported one deviation. In run # 1, the duration of the (b) (4)-cleaning was longer than demanded, caused by a technical malfunction. Due to this untypical boundary condition the related cleaning validation run was invalidated and a repeated run (b) (4) was conducted. The investigation was performed and no impact to validation was reported.

CSLB reports that all acceptance criteria were met with one deviation that did not impact validation. Acceptance criteria appear adequate for stage of processing. No objectionable findings. The relevant Cleaning Validation Reports were referenced in the submission. The cleaning validation appears to provide evidence that CSLB' cleaning procedures allow for the removal of possible contaminants associated with non-routine production events. No objectionable findings.

## 9. Lyophilizer Qualification / Validation

The Lyophilizers are as follows:

| Internal name | (b) (4) | (b) (4) |
|---|---|---|
| Presentation | 3000IU | 2000IU |
| Building | (b) (4) | |
| Room | (b) (4) | (b) (4) |
| Manufacturer | (b) (4) | (b) (4) |
| Number of shelves | (b) (4) | |
| Total area of shelves | (b) (4) | |

With a surface of (b) (4) lyophilizers (b) (4) 1 are installed in adjacent rooms on the (b) (4) floor of building (b) (4)

Afterwards the product specific lyophilization recipe is started. In the (b) (4) process step the (b) (4)

(b) (4)

(b) (4)

The control system is equipped with a (b) (4) and an (b) (4) . The (b) (4) is programmed with the recipes for all products used with the lyophilizer. It controls the shelf

(b) (4)

The lyophilizers' control system also provides a special mode for emergency cases. In case of (b) (4) failure an (b) (4)

IQ/OQ

CSLB reports completion of IQ of lyophilizers (b) (4) per Qualification Reports 822450 and 5235758 respectively. The IQ consisted of the following verifications:

- (b) (4)

CSLB reports completion of OQ of lyophilizers (b) (4) per Qualification Reports 831401 and 5235759 respectively. The OQ consisted of the following verifications:

- (b) (4)

For Shelf Life Distribution Study, CSLB verified that the system provides constant temperatures across (b) (4)

CSLB provided the Sterilization Studies for routine qualifications of both (b) (4). CSLB performed temperature distribution test runs under worst case conditions with calibrated (b) (4)

(b) (4)

Performance Qualification

Starting from the (b) (4) , C1 Esterase Inhibitor Concentrate (human) is manufactured in batches of (b) (4) for 2000 IU and (b) (4) for 3000 IU corresponding to the (b) (4) .

Starting from the lyophilization process established for the 1500 IU presentation, CSLB developed the (b) (4) was developed during several production-scale feasibility runs. The final version of cycle (b) (4) is defined in SOP 537382-0.1.

For fill sizes 2000 IU and 3000 IU, CSLB performed (b) (4) starting from the (b) (4) , established for the 1500 IU fill size. During these feasibility runs the (b) (4) were operated with a load of roughly (b) (4) (either 2000 IU or 3000 IU), or a placebo solution. This volume covered (b) (4) batches according to production procedure (b) (4) . Besides the (b) (4) , the respective (b) (4) was considered as further "worst case" condition. CSLB also examined boundary conditions by a (b) (4) of the freeze-dryer, application of the (b) (4) time and the (b) (4) allowed dispensing volume per vial. In each case, during the entire lyophilization cycle the product temperature and the process parameters were recorded. Based on the entirely satisfying process and product quality data, a (b) (4) lyophilization process (b) (4) (SOP 537382-0.1) was established for (b) (4) production of C1-INH 2000 IU and 3000 IU.

The Shelf temperature control profiles are depicted graphically for (b) (4) as follows:

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

CSLB performed separate lyophilization validation runs to demonstrate the consistency of lyophilization operations for both CSL DP presentations. The batches used for these lyophilization validation studies were manufactured using the (b) (4) as that used for the PPQ batches. The results are summarized in the attached Lyophilization Validation of CSL830 reports:

- (b) (4), Lyophilization validation of C1-Esterase-Inhibitor Concentrate (Human) (b) (4) GT031
- (b) (4), Lyophilization validation of C1-Esterase-Inhibitor Concentrate (Human) US 3000 IU –GT020

(b) (4)

Lyophilization validation runs for C1-cycle (b) (4) were as follows:

(b) (4)

Note: In order to realize the specified loads required during the certain runs and due to logistical reasons, placebo-filled vials were added to the lyophilizer already containing one respective strength CSL830 batch. The placebo solutions comprised all components of CSL830 respective strength other than the active ingredient CSL830

Per (b) (4) (SOP 537382-0.1)

- (b) (4) .

After lyophilization of the product and the placebo solution, as specified, CSLB collected sample vials (total (b) (4) from each occupied (b) (4) of the lyophilizer applying a (b) (4) pattern, in order to verify the homogeneity of the drug product and of the freeze-drying process with regard to relevant quality attributes. This sampling scheme covers the (b) (4) The (b) (4) vials therefore also contained marked product vials at the (b) (4) predefined sampling positions. Per sampling point, three vials were taken as primary samples for investigating important key quality attributes of the final product: Per run and for each sampling location one value for (b) (4) value were analyzed against the pre-defined acceptance criteria (same as PPQ)

The acceptance criteria were as follows:

(b) (4)

CLSB reported results within specification. According to CSLB, differences in the single readings of the analyzed samples could not be linked to the applied boundary conditions including those deemed as "worst case". Potential (b) (4) as well as potential (b) (4) could be ruled out. CSLB reported that all samples for (b) (4) . The consistent (b) (4) properties also confirm a robust freeze-drying process of the respective (b) (4) , causing no detectable hydrophobicity irrespective of the applied boundary production settings. Within all validation runs the specified values for time, temperature and pressure were met during each step of the freeze-drying process, as documented in the associated study protocol with no deviations reported.

Review Assessment/ Comments: CSLB appears to have taken a standard approach to validation of the lyophilization cycles for both strengths. The lyophilization cycle description and validation data describe the minutes or hours for each step of the cycle from loading to unloading.

**CSLB does not state whether how they established the (b) (4) Freezing time (prior to drying); IR sent to the Firm:**

**Please reference 3.2.P.3.3-4 (b) (4) Filling and Packaging Procedure; page 9 of 9; *Storage*, you state that the product can be stored temporarily in the (b) (4) for a (b) (4)**

*CSLB Response*

*Page 9 of the Filling and Packaging Procedure* (b) (4) *contains a typing error. The corrected page 9 reads as follows: "The product can be stored temporarily in the* (b) (4) *for a* (b) (4)

*Both, the* (b) (4) *freezing time have been validated for C1-INH 2000 IU and C1-INH 3000 IU (validation report* (b) (4) *. The Filling and Packaging Procedure* (b) (4) *has been corrected and revised. Additionally, validation report no.* (b) (4) *has been revised, as it contains the same typing error related to the freezing/ storage temperature. Both documents are replaced in Module 3, Section 3.2.P.3.3-4 and 3.2.P.3.5-2.1 respectively.*

Review Assessment / comments: (b) (4) The validation lots were at the production scale lot size. No objectionable findings were noted for the transferring, loading and unloading of vials into lyophilizers. The matrix of (b) (4) strengths in the (b) (4) lyophilizers including the coverage of the (b) (4) lyophilization cycle time across the lyophilization procedure / cycle appears to be comprehensive to demonstrate robustness of the process .The highest overall final (b) (4) volume freeze-dried per study equates to more than the (b) (4) batch size anticipated for routine production of each strength. Lyophilization cycles appear to be consistent across strengths. Shelf temperature control and profiles including (b) (4) and holding times have been established for the recipe and appear to be robust to provide consistent product output. CSLB reports that (b) (4) from each study (2000IU and 3000IU) ranged between (b) (4) respectively. Response to IR and associated error correction appear adequate. No objectionable findings.

**10. Process Validation**

Lyophilizers of (b) (4) (GT031for 2000IU and GT020 for 3000IU) were used and employed with freeze-drying cycle (b) (4). Based on these risk assessments, the entire manufacturing process including lyophilization was validated at full-scale; down scale studies were not conducted. The production process from (b) (4) drug product comprises filling and lyophilization of the (b) (4) in full scale. The prerequisite for homogenous filling of a solution is a constant composition of the ingredients in solution. Therefore, the homogeneity of the (b) (4) during filling was validated in full scale.

Relevant process validation studies which have been executed to validate the modifications to the production process of the (b) (4) drug product are as follows:

(b) (4)

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

(b) (4)

In addition, analytical results for the IPCs from the entire production process starting with the (b) (4) were listed in this report.

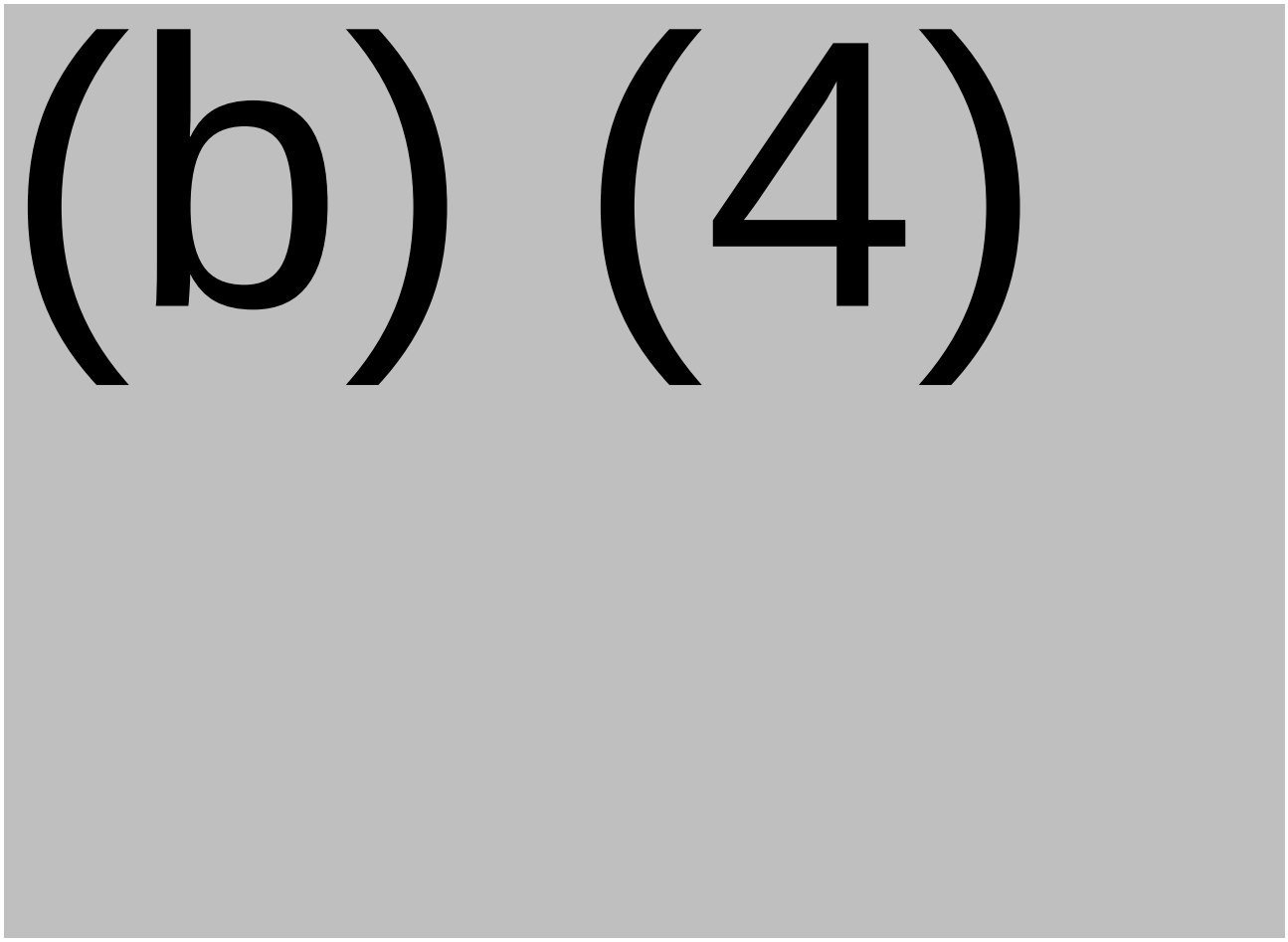
CSLB took acceptance criteria for routine IPCs (IPCa) from the respective production procedures (b) (4) rev 0.1 and SOP. Acceptance criteria for additional IPCs (IPCb) were established by a statistical approach (b) (4) -ranges based on data of (b) (4) lots) and were taken from investigation study no. IR-617-001-01 and IR-617-009-01.

(b) (4)

(b) (4)

(b) (4)

(b) (4)




**b. Filling and Lyophilization Process Validation**

C1-Esterase Inhibitor Concentrate is filled in the filling and lyophilization area in building (b) (4) floor of CSL Behring`s manufacturing site in Marburg. Per (b) (4) & 900808-01,

CSLB validated the filling process in full scale of the (b) (4) C1-INH: a 2000 IU and a 3000 IU presentation introducing (b) (4) final containers for the C1-INH product. This study was conducted to validate the aseptic filling process including the holding times, the (b) (4) homogeneity, and visual inspection according to the filling and packaging procedure (b) (4) conformance lots were (b) (4) container from (b) (4) resulting in (b) (4) final product lots for 2000 IU and (b) (4) final product lots for 3000 IU.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The key equipment is shared with other dosage forms of the same product as well as other products that are filled at CSL Behring´s Marburg manufacturing site:

| Key equipment | Identification/ Inventory number | Location/ room no. |
|---|---|---|
| Filling line | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |
| Filling needle | (b) (4) | |
| Lyophilizer | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |
| Capping machine | (b) (4) | (b) (4) |
| | (b) (4) | (b) (4) |

**Packaging materials according to (b) (4) As follows:**

| Fill size | Container | Closure | Seal |
|---|---|---|---|
| 2000 IU | (b) (4) | (b) (4) | (b) (4) |
| 3000 IU | (b) (4) | (b) (4) | (b) (4) |

**Process control parameters were as follows:**

(b) (4)

The standard operating procedures for filling weight, visual inspection, and (b) (4) test of the filled product containers were as follows:

| Test parameter | Method | SOP# |
|---|---|---|
| Volume in container (filling weight) | (b) (4) | (b) (4) |
| Visual inspection | (b) (4) | (b) (4) |
| (b) (4) test | (b) (4) | (b) (4) |

Samples representing the start, middle and end of the filling process were taken according to

the sampling plan of the sterility samples. In addition, the results of the visual inspection and the (b) (4) test were inspected in this process validation study:

(b) (4)

All acceptance criteria and ranges were predetermined and pre-approved in the process validation protocol 900808-01, the filling and packaging procedure (b) (4), the quality control procedure or in the respective SOPs. The (b) (4) homogeneity primarily is demonstrated by the results of the C1-INH (b) (4), protein, and sodium chloride (table below). The requirements are met, if the results are within the range of (b) (4) of the average value of the (b) (4) tested units. Furthermore the coefficient of variation (Vk) should be equal or less than (b) (4). The samples were taken at the (b) (4) of the filling process. If one unit exceeds the range of (b) (4) of the average and no unit is beyond the range of (b) (4) of the average or if the Vk is greater than (b) (4) additional units have to be tested. These units are again obtained from (b) (4) of the filling process in equal ratios. The requirements are met, if not more than (b) ( unit of the (b) (4) tested units is exceeding the range of (b) (4) of the average value of the (b) (4) units and no unit is beyond the range of (b) (4) of the average value of the (b) (4) units. Furthermore, the coefficient of variation (Vk) should not exceed (b) (4).

(b) (4)

Acceptance criteria for filled containers during the entire filling process as well as drug product after completion of the filling process are defined in standard operating procedures as presented in table below. CSLB states that the details regarding inspection aspects and requirements for visual inspection of drug product containers after capping are documented in the current SOP 565550. CSLB has not changed the their visual inspection criteria or SOP.

(b) (4)

Sealed containers are subjected to a (b) (4) visual inspection for freedom of particles, damages or other defects followed by labeling and packaging in building (b) (4). The finished

drug product containers are stored at (b) (4) until distribution.

The requirements of the Quality Control Procedure must be fulfilled for all drug product lots under study (lot release testing specifications), which included:

- Sterility (Q-25-002); Method: (b) (4) in accordance with 21CFR 610.12 and (b) (4)
- Pyrogens (Q-21-001); Method: Test in rabbits in accordance to 21CFR 610.13 (b) and (b) (4)

CSLB reports that all acceptance criteria were met with no deviations.

| Review Assessment/Comments:<br>CSLB took the similar approach to overall process validation as for similar products and Berinert. No objectionable findings. |
|---|

**c. Media Simulations**

Aseptic processing conditions were validated by simulation using (b) (4) ). Media fills are performed under the (b) (4) as the drug product but, instead of the (b) (4) product, (b) (4) medium that was tested for and confirmed microbial growth promoting properties was used. Routine process simulation runs (media fills) were performed at (b) (4) and at least (b) (4) in (b) (4) on each operating filling line and lyophilizer.

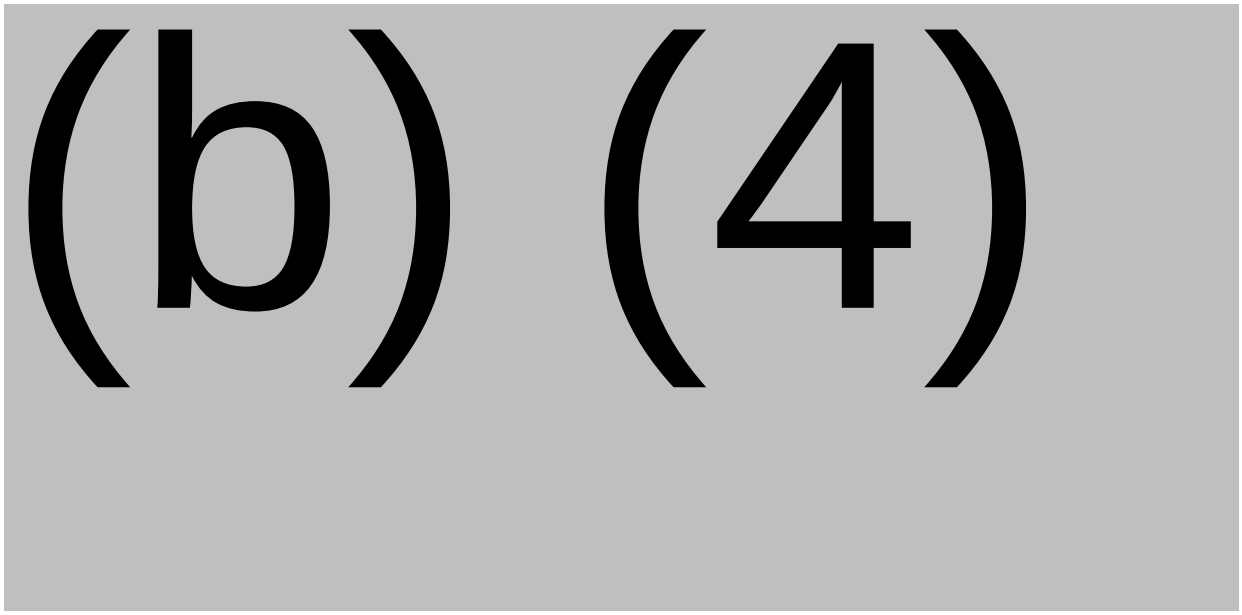
The following summaries were included in the submission:

- (b) (4) : Routine re-validation of aseptic processes by media fills in the filling area (b) (4) floor (summary report 2014/15)
- (b) (4) : Routine re-validation for aseptic processing steps of (b) (4) containers Filling area (b) (4) (2015)

CSLB performed a comprehensive Aseptic Processing Simulation study to include multiple vials, stoppers, (b) (4) , and all Lyophilizers. CSLB determined that the (b) (4) can be stored at (b) (4) Stability data supporting this holding time was generated as part of PPQ. This time period encompasses the total time covering the filling process through to initiation of the lyophilization cycle (next step). The breakdown of hold times within these individual steps is as follows:

- (b) (4)

CSLB conducted (b) (4) media fills to revalidate the aseptic processing of the (b) (4) filling area in building (b) (4) from July 2014 to June 2015. CSLB took a bracketing approach as follows:




The number of evaluated units ranged from (b) (4) units per run. Incubation of media-filled units (b) (4) was performed meeting requirements of (b) (4) . A visual inspection of (b) (4) units regarding microbial growth was performed (b) (4) . Representative samples were taken from the incubated media fill lots and microbiological growth promotion properties were successfully confirmed.

Both the design and the schedule of the execution of the routine media fills in the review period between (b) (4) , including defined interventions, worst case, and challenge conditions were performed in accordance with process simulation project plan #920619-01. The overall strategy for the execution and evaluation of media fill is summarized in CSL Behring's PVP 420015 and standard operating procedures that are defined in the referenced protocols. The media fill program incorporates the contamination risk factors that occur on a production line and accurately assesses the state of process control. Media fills closely simulate aseptic manufacturing operations that incorporate worst case activities and conditions that provide a challenge to aseptic operations.

CLSB defines the following Medial Fills Requirements:

Frequency and number of runs

- Routine re-validation was performed at least (b) (4) and at least (b) (4) per financial year on each operational filling line. Each individual lyophilizer should be covered in media fill runs at least every (b) (4) and at least (b) (4) (time period of re-validation plan). These media fills covered all product presentations filled on the respective filling line.
- A bracketing approach was considered to cover all combinations of primary packaging materials (vial/stopper combinations) processed in the filling area. Vial sizes were chosen according to the PVP 420015, which requires that the smallest and the largest vial to be

(b) (4) in media fill. All further vial sizes can be tested in media fills as appropriate. However, all combinations of primary packaging materials (vial/stopper combinations) running on a filling line have to be (b) (4) by media fill on a (b) (4) basis.

Additionally, the media fill program addresses the following but are not limited to these topics:

Duration of Runs: Duration is determined to incorporate manipulations, interventions, worst case and challenging conditions, as well as appropriate consideration of the duration of the actual aseptic processing operation.

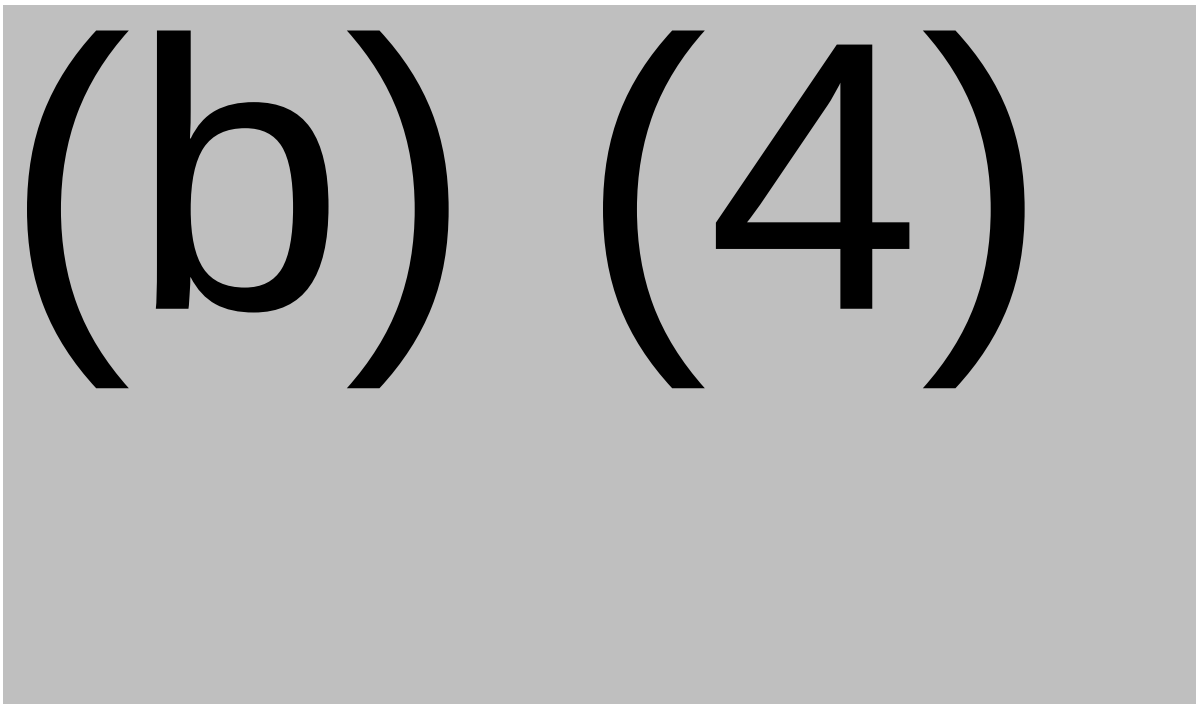
Interventions

- Routine interventions including technical interventions were performed in each media fill as defined in the process simulation project plan no. 920600-01. Routine interventions are summarized as follows:

(b) (4)

- Trending of routine interventions during routine production is performed on a (b) (4) frequency. If applicable the intervention concept has to be adapted regarding number of interventions and new interventions.
- Worst case and challenging conditions were performed as defined in the process simulation project plan no. 920600-01, as follows:

(b) (4)




Size of Runs

- Simulation size was adequate to simulate commercial production conditions and accurately assessed the potential risk for commercial batch contamination.
- For batch sizes of (b) (4) units at least (b) (4) units were filled in each process simulation run. For production batches with less than (b) (4) units or limited equipment capacity (e. g. lyophilizers), at least the maximum production batch size, or the maximum equipment capacity was reflected in media fill runs.

Filling Volume: The fill volume was appropriately chosen to (b) (4) of the vials. The fill volume may vary from (b) (4) of the vial volume. If the medium amount was less than (b) (4) it was ensured that the (b) (4)

Filling Speed: The filling speed was in accordance with routine filling production. (b) (4) speed were simulated as worst case conditions.

Simulation of Lyophilization Processes: During the simulation of the lyophilization process the loading of (b) (4) into lyophilizer, maximal batch loading, evacuation, and (b) (4) lyophilizer (b) (4) and closure process of vials were covered. (b) (4) are used (b) (4) to simulate the lyophilization process. Vials were closed to regular (b) (4) as appropriate for proper product closure. The (b) (4) were replaced by (b) (4).

Medium

- (b) (4)

Personnel

- Each operator assigned to the aseptic filling operation has participated in a successful media fill at least (b) (4) year (organized and tracked by production department (b) (4)). Each shift type (early, late, night) performing filling operations has participated in a successful media fill at least (b) (4) year.
- New filling personnel had been qualified and took part in a successful media fill before they participated in routine filling process.
- The number of personnel involved in media fills corresponded to the routine operations and represented also worst case conditions with more operators attending in media fills than in routine production

Environmental Conditions and Monitoring Program

- Environmental conditions were adequately representative to the routine production conditions.
- The execution of media fills was accompanied by the routine environmental and personnel monitoring program according to appropriate SOPs.

Incubation and Examination of Media-Filled Units

- (b) (4)
- After incubation all media filled units were inspected for contamination. The inspection was only performed by personnel with appropriate education, training, and experience in inspecting media fill units regarding microbiological growth.

Reconciliation

- Filled units were accurately counted and any removed media filled units strictly reconciled and (b) (4) were accounted for. The following acceptance criteria were applied:

(b) (4)

Experienced and trained personnel performed the visual inspection for microbial growth in accordance with standard operating procedures, which are defined in the media fill protocols. Visual inspections were accompanied by QAO oversight. CSLB reported (b) (4) media fills were performed with no units showing microbial growth were found during evaluation. CSLB reported 16 deviations associated with (b) (4) media fills as follows:

(b) (4)

CSLB reports that growth promotion testing of the media fills met the acceptance criterion for all runs.

**Requalification**

CSLB reports that each individual lyophilizer is required to be covered in media fill runs at least (b) (4) and at least (b) (4) financial year (time period of re-validation plan), and the following requalifications requirements (matrix):

(b) (4)

(b) (4)

Review Assessment / Comments: The Aseptic process validation appears adequate, a minimum of (b) (4) run were executed with the inclusion of each presentation across multiple shifts. (b) (4) container media simulation took the similar approach with no issues reported. The media fill runs were carried out with at least the equivalent maximum [target] batch size made on the processing line with at least (b) (4) for production sizes greater than (b) (4) . Environmental monitoring was performed during runs with acceptance criteria meeting acceptable room classification requirements. Relevant documents are referenced in the submission. Media Simulation recommendations in Guidance: Sterile Drug Products Produced by Aseptic Processing- Current Good Manufacturing Practice appears to have been met. Deviations appear minor in nature of risk to validation and appears to be comprehensive with (b) (4) was added into the matrix. I agree with their assessment of no impact to validation. Media fills are performed No objectionable findings noted.

**11. Reprocessing**

CSLB defines reprocessing as an unplanned repetition of a step that is part of their licensed manufacturing process. CSLB states that they would perform reprocessing 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, April 15, 2016. CSLB states that, as part of the deviation investigation, a quality risk assessment will be performed 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 CBER according to the US legal requirements (usually prior approval submission to cover a (b) (4) batch release).

CSLB defines rework as subjecting a product to one or more processing steps that are different from the licensed manufacturing process, and states that they would only perform a rework after prior approval of the competent authority of the respective country.

Review Assessment/ Comments: CSLB reports no validated reprocessing steps. CSLB's approach to reprocessing and rework appears adequate for regulatory compliance. No objectionable findings noted.

**12. Sterilization Filtration**

Review Assessment / comments:

CSLB did not provide any detail on the sterilizing filter and how it was qualified with the new (b) (4) product. **Information Request Sent:**

**1. Please provide a description (including manufacturer, item #, etc.) of the sterilizing filter used.**

**a. Please provide summary of the filter qualification performed associated with the (b) (4)**

*CSLB Response*

*The qualification of the filter has been performed by bacterial challenge tests. The reports SF-688-001-01 (for (b) (4) and SF-688-002-01 (b) (4) were submitted for CSL830 (1500 IU). Since the (b) (4) of CSL830 2000 IU and 3000 IU is identical, the validation data described in the reports are also applicable to the new product presentations. The (b) (4) of CSL830 2000 IU and 3000 IU are achieved during (b) (4)*

Review Assessment / comments: CSLB reports no changes to filter or the filtration procedure. CSLB provided the referenced reports , SF-688-0001-01 and SF-688-002-01. I evaluated the reports. See following summary.

CSLB performed filter validation studies using (b) (4) strength is (b) (4) as 2000IU and 3000IU) due to the (b) (4) protein concentration. CSLB uses a (b) (4) to filter formulated (b) (4) prior to filling. . A sample of formulated (b) (4) was sent to (b) (4) filter manufacturers to evaluate bacterial retention capability of the filter in the presence of product and to determine the product-specific (b) (4) for (b) (4) testing after use.

After determining that the formulated (b) (4) is not bactericidal, a bacterial retention study was performed to determine the microbial retention level of the (b) (4) after being exposed to formulated (b) (4) was suspended in formulated (b) (4). The filtration pressure was challenged by applying (b) (4) temperature. The results demonstrated that the processing conditions used to filter formulated (b) (4) do not alter the ability of the (b) (4) to retain the challenge organism (b) (4) than or equal to (b) (4) . The (b) (4) filter challenge level used during the bacterial retention testing was (b) (4) .

The entire system, excluding the analytical (b) (4) The recommended (b) (4) value for the filter (b) (4) . This is the acceptable range used for the (b) (4) test of this filter.

During regular production at CSL Behring, (b) (4) with a minimum of (b) (4) (both (b) (4) challenged) may be used to filter a batch volume of up to (b) (4) .

Review Assessment / comments: The Validation Studies reports for the (b) (4) filters are nearly (b) (4) in approach and acceptance criteria. All acceptance criteria were met with no deviations. CSLB appears to perform adequate filter validation for formulated (b) (4) filtration. The overall evaluation of chemical compatibility and extractable / leachable studies is deferred to the Product Office Specialists. No objectionable findings noted.

**13. Container Closure**

For the 2000IU presentation, for dispensing (b) (4) , CSLB is using a (b) (4) glass vial. For the 3000IU presentation, for dispensing (b) (4) , CSLB is using a (b) (4) glass vial.

CSLB reports that the (b) (4) (CSL material# (b) (4) ) is already approved for use with their US approved products:

- Humate-P® (STN BL 103960)
- Corifact™ (STN BL 125385)
- Kcentra (STN BL 125421)

The (b) (4) vial is not approved yet for use with any of their US products.

The stopper (CSL Part # (b) (4) , nominal size (b) (4) is used and approved for:

- Afstyla®(STN 125591)
- Idelvion®(STN 125582)
- Corifact™ (STN BL 125385)
- Kcentra (STN BL 125421)

The C1 Esterase Inhibitor Concentrate (human) container closure system consists of an injection Type (b) (4) glass vial and a rubber stopper sealed with a combination crimp cap. The vials

containing the lyophilized drug product and diluent are packed in carton boxes. Each carton box contains one product vial, one diluent vial, and a Mix2Vial® transfer device.

Container closure is as follows:

| Presentation | Container Closure Part | Material Number |
|---|---|---|
| 2000 IU | (b) (4) | |
| 3000 IU | | |

The packaging materials are accompanied by the vendor's documentation which is controlled for each shipment. Quality Control Procedures are established for in-house testing on a regular basis for identity, physical characteristics, chemical and biological properties. The procedures reflect current compendia requirements and the relevant national and international standards (DIN, EN, ISO), as applicable.

Single-dose colorless injection vials with a nominal size of (b) (4) are used for C1 Esterase Inhibitor Concentrate (human) lyophilized drug product. The containers are made of colorless, molded glass. All glass containers for C1 Esterase Inhibitor Concentrate (human) meet the requirements for type (b) (4) glass that are suitable for all preparations including products for parenteral administration in accordance with Section *3.2.1. GLASS CONTAINERS FOR PHARMACEUTICAL USE* of the (b) (4) and with section *CONTAINERS* (b) (4)

The vials are closed with ready-to-sterilize (b) (4) rubber stoppers that comply with Type (b) (4) requirements of (b) (4). and the comparable requirements of chapter (b) (4) "Elastomeric closures for injections" of the current (b) (4). The stopper is not manufactured with natural rubber latex

The stoppers are secured by combination caps consisting of an (b) (4) crimp cap with a concentric hole and an integrated (b) (4) plastic disc. The crimp caps meet international standards for dimensional criteria.

All materials defined as primary packaging material undergo a release testing prior to use. The container/closure system is identical to that used during final production scale development, stability studies and the media fill validations.

CSLB reports no changes to their incoming materials inspection procedures. CSLB performs release on all primary packaging materials. According to CSL SOP, Q-00R, the Inspection of injection vials of tube glass occurs as follows:

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

(b) (4)

Review Assessment/ Comments: CSLB reports no changes to vial and stopper specifications or suppliers. No objectionable findings noted with the control of the (b) (4) vial and the rubber stopper.

**The following information request is being sent to the firm (the response will be evaluated in my addendum review:**

**1. Please provide a summary of the validation (PQ) of the (b) (4) depyrogenation of the (b) (4) Vial. Please ensure to include the following:**
***reference to the equipment used for (b) (4) depyrogenation, and reference to associated equipment qualification documents**
*** Dates of the validation studies**
*** Acceptance criteria,**
*** Summary of the results and any deviations**

**CCIT**

CSLB validated the integrity of the primary packaging components (listed above) through (b) (4) testing (b) (4) supported by (b) (4) testing post crimping.

Container closure integrity testing of the packaging material combination was performed with samples from three media fill lots (from each vial size, (b) (4) , , totaling (b) (4) media fills) with the same packing material combinations to evaluate the integrity of the vial glass body, stopper, vial neck. A total number of (b) (4) samples from each lot were tested with the (b) (4) method using the (b) (4) test system according to testing instruction (b) (4)

With the (b) (4) method, the samples can be non-destructively evaluated. CSL Behring uses the (b) (4) system, detecting leaks using a differential (b) (4) . The test method permits the non-destructive detection of leaks, even not visibly detectable. Leak detection is based on the ability to detect the change in (b) (4) as a result of (b) (4) from the test sample when challenged with (b) (4) conditions for a defined time period.

If the (b) (4) loaded with a sample is not altered, it is considered that the sample is hermetically sealed. On the other hand, if the (b) (4) the container closure system does not seal properly. For each test run, a needle valve in combination with a (b) (4) is used to represent a positive control of a theoretical leak of (b) (4)

Review Assessment/ Comments: Evidence of completed CCIT study is provided, with reference to relevant protocols. CSLB reports no leaks observed in any of the test samples.
**In order to confirm specific acceptance criteria for the (b) (4) method, the following information request is being sent to the firm (to be evaluated in my addendum review):**

| 1. Please provide a copy of (b) (4) Test Instruction (b) (4) for review |
|---|

**14. Drug Product Stability**

CSLB proposes shelf-life of 36 months for Finished product (unopened container) at 30°C (b) (4) (b) (4). Both studies are performed at (b) (4)

The stability studies supporting the proposed shelf life, STR -689-002), started in April 2015, are ongoing and CSLB commits to continue the stability studies.

Review Assessment/ Comments: For final DP container, sterility is tested at $T_0$. (b) (4) test is performed at the final time point (36 months). CSLB reports no sterility OOS to date.

No objectionable findings noted. I defer the review of the Drug substance Stability to the Product Office Specialists.

**15. Medical transfer device**

The only medical transfer device supplied with CL830 is a transfer device used for both transfer of sterile water for injection into the product vial and filtering of the reconstituted product before withdrawal into syringe. For ease of use, the Mix2 Vial device is provided together with an alcohol swab.

Review Assessment/ Comments: The Mix2Vial device is manufactured by Medimop; I confirmed that the device is a 510K cleared since 2003 (K031861). It is the same device used with rIX-FP, recently approved.

**The following Information Request was sent to the Firm:**

**Please provide a summary of your quality oversight, and incoming acceptance criteria of the Mix2Vial device, including a summary of how you comply with the requirements of 21 CFR820 Subpart C- Sec. 820.30, Design controls, and 21 CFR Subpart E- Sec. 820.50, Purchasing controls.**

*CLSBRF Response:*

*The Mix2Vial is manufactured by a qualified supplier who is audited on a regular basis every* (b) (4). *In addition to that a Quality Agreement with the relevant supplier has been established.*

*The incoming inspection of the Mix2Vial device is performed for each lot according to our internal procedure, including* (b) (4) *-sample for visual defects, functional tests to assess the transfer capability, a check of the printed data on the peel paper, and a check of the supplier*

*certificate.* (b) (4) *additional tests as* (b) (4) *, retention capacity of the filter and endotoxin tests are performed.*

*Summary of compliance with requirements of 21 CFR820, Subpart C – Sections 820.30 and 820.50*

*Position statement*

*The Mix2Vial device is a customized filter transfer system of Medimop Medical Products Ltd. It is used for many of the drug products of CSL Behring and is not dedicated to a certain product. It is considered to be a component of a convenience kit and not a combination product; therefore the manufacturer of the device has the responsibility for design control activities according to 21 CFR820.30 and 21 CFR820.50.*

*The Mix2Vial filter transfer device is a legacy product and not a new development for CSL 830 /* (b) (4) *. It is used in the US market since 2005 (for Helixate, Humate-P, Berinert 500 IU, Kcentra, Corifact as well as for the currently licensed products Afstyla and Idelvion.*
*Development history*

*Following a selection procedure the Mix2Vial® filter transfer device of Medimop Medical Products Ltd. in 2003 has been chosen to* (b) (4) *needle-transfer device and a filter spike for withdrawal of the reconstituted drug product. The Mix2Vial® device in the original design of the manufacturer did offer two important features:*

- (b) (4)

*CSL Behring did* (b) (4) *to the Medimop standard presentation:*

- (b) (4)

*Later a so called "*(b) (4) *" has been introduced in addition: a* (b) (4)

*Certification*

*The M2V device (Catalogue No. 900165 (Medimop), SAP No. 68120 (K3), 8890744 (Marburg) has the following certification numbers:*

- *510K registration under # K031861*
- *Medical Device Establishment Licenses No. 69269 (Canada)*
- *CE certification acc. to guidance 93/42/EEC under number "CE-0473".*

Review Assessment/ Comments: We disagree with CSLB that the co-packaged kit is not a combination. Clarity is needed for the referenced Development History.

**The following information request was sent to the Firm.**

1. **Reference your amendment, 125606/0.3 (received 06 Sep 2016), the Agency disagrees with your position statement. We conclude that your convenience kit is a co-packaged combination product, as defined by 21 CFR 3.2(e)(2). In this case, according to 21 CFR 4.4, you must demonstrate that the following provisions of the QS regulation have been satisfied:**

- **Section 820.20: Management responsibility.**
- **Section 820.30: Design controls.**
- **Section 820.50: Purchasing controls.**
- **Section 820.100: Corrective and preventive action**

**This information must be submitted for review in a consolidated section of your BLA. The Agency suggests that you please reference Draft Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (April 2015). (In particular, Section IV. What do I need to know about the CGMP requirements specified in 21 CFR 4.4(b)?)**

2. **For clarification, please identify when the following optimizations / improvements were made to the Mix2Vial presentation:**

- (b) (4)

a. **How did CSLB confirm that these changes did not affect the 510K clearance of the device?**

**On 20 Dec 2016, at the Mid-Cycle meeting (teleconference) with the Firm, our concerns were discussed prior to CSLB responding to the above IR. CSLB agreed that their "convenience kit" is a combination product. In the meeting, and we recommended that they respond as they could to our IR, and suggest a plan for gathering their data for a Device History File (DHF). CSLB agreed, requested that we have a follow-up discussion**

**(via teleconference) to discuss their approach to creating a DHF. Their response to the above IR follows.**

*CSLB Response to #1*

*The following provisions of the QS regulation are considered satisfied:*

***CFR Section 820.20: Management responsibility***

*CSL Behring GmbH has a quality management system in place instituting management responsibilities in compliance with 21 CFR820.20. For reference see the Site Master File table of contents (Attachment 1). In addition, reference can be made to SOP "Quality Management – Tasks and Responsibilities" (No. 41002e / Attachment 2).*

***CFR Section 820.50: Purchasing controls***

*CSLB has a quality management system in place instituting purchasing controls in compliance with 21 CFR820.50. For reference see Site Master File (Attachment 1). CSL Behring GmbH has a supplier qualification system in place that covers quality descriptions (specifications) defining our requirements (Attachment 3) and quality control procedures to verify the requested properties of a purchased product (Attachment 4). Moreover, incoming inspections are performed on every delivery finished by a formal approval of the "Qualified Person".*

***CFR Section 820.100: Corrective and preventive action***

*A Standard Operating Procedure is in place regulating the "Responsibilities of Quality Assurance in the deviation process". Please refer to Section 4.3.4 of the SOP for the "definition of CAPAs" (Attachment 5).*

*The following provision of the QS regulation is considered satisfied and documentation is in-process:*

***CFR Section 820.30: Design controls***

*The Mix2Vial (M2V) system was designed by Medimop Medical Projects Ltd. It enables a vial-to-vial transfer and mixing between two vials for the reconstitution of lyophilized drugs. The reconstituted drug product is available for immediate aspiration into the syringe used for administration. The Mix2Vial system is 510(k) # K031861 cleared by the FDA. In reference to 21 CFR 820.30 Design Controls, CSLB commits providing a M2V Design History File (DHF) focusing on CSLB specific modification and taking into consideration information released by Medimop Medical Projects Ltd.*

*In this submission, CSLB has provided a table outlining the proposed sections of the DHF (**Table 1**).*

*CSLB requests FDA review of this DHF outline and a CSLB/FDA teleconference to be held the week of January 23, 2017 to review the outline, offer advice, and discuss timelines for the finalized document to be submitted for FDA.*

***Table 1: Outline of a Design History File***

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

*CSLB Response to #2*

*Time of introduction of optimization / improvement to the M2V presentation:*
*The bullet points 1, 3, and 4 have been introduced to the supplier's design concept as a customized version of the device immediately at the beginning of the life cycle; the M2V has been introduced to CSL Behring's portfolio with these features.*

*Bullet point No. 2 CSL Behring does not have a specific customized feature* (b) (4) .

(b) (4) *is the introduction of an improved* (b) (4) *improvement' was communicated to the supplier on March 4, 2011 and the* (b) (4) *of the device with the new feature was delivered on July 27, 2011 (Medimop batch* (b) (4)*, CSL Behring SAP-batch 50677). Ad a) Validation / verification / review and approval information about these design changes: Customized features of Mix2Vial 20/20 ZLB Behring/CSL Behring*

- *Target Product Profile (prepared by* (b) (4) *Project Management) Revision date: April 24, 2003-Att. 06*
- *May 02, 2005 internal development release of Mix2Vial 20/20 – 8890744 referring to Functionality Test / User Test* (b) (4) *(2005-05-30)-Att. 07*

*Remark: Further Reports with other coagulation products (functionality, flow rate, user and* (b) (4) *tests) are available (e.g.* (b) (4) .

(b) (4)

- *Announcement of FINAL APPROVAL to manufacturer Medimop: March 04, 2011*
- *First delivery of optimized design on July 27, 2011 (Medimop batch* (b) (4)*, CSL Behring SAP-batch* (b) (4)

*Please refer to the BLA for further information:*

*A study was conducted to demonstrate compatibility of transfer and infusion devices with C1- Esterase Inhibitor products. For details see report 030200188_r in Section 3.2.P.2.6-1 of the BLA.*

*Detailed information about the Mix2VialTM device is available in the US in in the Premarket Notification 510(k) # K031861.*

*A technical drawing of the Mix2VialTM device is provided in Section 3.2.R.2 of the BLA.*

Review Assessment/ Comments: I am in agreement that CSLB has fulfilled the requirements of 820.20, 50, & 100. I confirmed that cited SOPs and policies are relevant to their arguments. CSLB appears to taking the right approach with Design control and including the necessary content in the DHF. CSLB provides evidence that they verified acceptability of original design and incremental changes/ improvements to the device.

**In follow-up meeting with the firm:**

1. I will recommend that CSLB clearly establish their procedure for review of all the records at all stages of development of the DHF (in their case, that this device is appropriate for use with their product), and the reviews are documented and recorded in the DHF itself.
2. Reiterate to CSLB that the records are specific to C1 Esterase Inhibitor (Human), Subcutaneous and M2V combination product, and should be a complete package and closed. (preferably prior to marketing of the product), and the DHF should be readily available for auditing (both internally and externally). Although the Agency has no official format or organization requirements for the DHF, most manufacturers will organize the DHF in a binder and organize the binder chronologically to match a design project plan. Meeting minutes from each design meeting are typically included as an appendix to the DHF, while reviewed and approved documents such as the design plan, design inputs, design outputs, and records of design reviews typically comprise the bulk of the DHF. Manufacturers also typically will conduct an internal auditor of active DHF binders in order to ensure that design projects are following the approved design plans.
3. I will remind them that an important consideration is, since CSLB does not manufacture the M2V constituent, through their Quality Agreement with Medimop, CSLB should establish a well-defined procedure for Medimop to notify CSLB of changes (particularly those involving physical features and materials of construction) to the M2V, prior to making the changes, to allow for CSLB to perform the appropriate design review.
4. Another Quality Agreement point-to-consider would be that CSLB require that Medimop notify them of any proposed amendment(s) to the 510K for the M2V to allow for CSLB to perform the appropriate design review.
5. The Agency considers (b) (4) of the Mix2Vial to be a critical quality attribute of the device. Please provide details on how you verify that (b) (4) of the device is being consistently met.

Review Assessment/ Comments: We held a teleconference with CSLB on Tuesday 02/14/17 to discuss the follow-up items, and the overall approach that CSLB is taking with the DHF. One of the documents (Target Product Profile), which CSLB sent to us in the previous amendment, referenced an occurrence of (b) (4) after

reconstitution associated with an early (2003) design of the Mix2Vial. We have asked that CSLB provide some detail on the issue and resolution. CSLB will be submitting another amendment outlining their response to the follow-up items, as well as the additional design control details related to Humate P, to the submission by 02/28/17. I will do the final evaluation of the response in my addendum review.

**16. Sterile Water for Injection (sWFI)**

sWFI is a preparation used to reconstitute lyophilized products. A formulation development was not necessary since it is plain water. Water for Injection is produced by a (b) (4)

According to CSLB, the Sterile Water for Injection complies with the requirements of the current editions of the USP Monograph "Sterile Water for Injection".

The sterile, endotoxin-free diluent does not contain any preservative or excipient. The appearance of the diluents is clear and colorless. The Sterile Water for Injection consists of water only, there is no drug substance, and there are no excipients except of the water itself.

In the respective carton, the 2000IU CL830 product is supplied with one vial containing 4 mL of sWFI (diluent) and 3000IU CL830 product is supplied with one vial containing 6 mL of sWFI. The data supporting manufacture and control of the sWFI is referenced in (b) (4) .

Review Assessment/ Comments: I reviewed (b) (4) (in Feb 2016 as part of review for rIX-FP, BLA STN 125582/0) for the Sterile Water for Injection, which is co-packaged with the product. (My DMF review dated 18 Feb 2016 is on file with CDER DCC). Christine Harman, DMPQ, reviewed the DMF again in November 2016 in support of STN 103960/5644 and found no objectionable findings. Both 4ml and 6ml fill sizes are validated. I have no objectionable findings, and no further evaluation of the DMF or associated facility is required as this time.

**17. Shipping Validation (Drug Product)**

CSLB performed validation of shipping of drug product from Marburg, Germany via (b) (4) per Transport Validation Plan 5317066-01. The transport system (b) (4) is used in conjunction with (b) (4) for finished products in the temperature range (b) (4)

(b) (4)

(b) (4) validation runs were carried out as according to Validation Plan 5317066-01, in the period from 02/25/14 to 08/15/14. These shipments included the finished product (b) (4) with different quantities, depending on the batch quantities.

The pallets were always (b) (4)

Review Assessment/ Comments: DP Shipping appears complete; temperature graphs appear to coincide with data descriptions. This is an study identical to study 5306842-01 (2013) reviewed by me in submission of two other CSL Behring products. No objectionable findings or further evaluation required.

**18. Inspection Considerations**

*Note: Line items below are hyperlinked to the applicable section of this review memo, as applicable.*

- None