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/RPMB1
Ewa Marszal, Ph.D., Chair, OTAT/DPPT/PDB
Felice D'Agnillo, Product Office, OBRR/DBCD/LBVB

Subject: DMPQ Addendum 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

This is the final DMPQ review memo; No more addendum reviews will follow.

I recommend approval of this submission. At the CSL Behring Marburg facility, the qualification, validation, and control activities as related to facility, equipment, and container closure appear to be adequate for the (b) (4) drug product manufacturing of C1 Esterase Inhibitor, Subcutaneous. From my purview of the original application, there appears to be no evidence that the identity, strength, safety, quality, and purity of the product produced in the facilities would be adversely impacted based on the completed development /qualification data and experience.

A PLI at the CSL Behring Marburg facility was waived on 23 Nov 2016.

Inspection Considerations

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

1. Verify that the DHF for C1 Esterase Inhibitor (Human), Subcutaneous, Haegarda™, is complete and closed.

CBER understands that the recommendation may or may not be taken (based on risk and available resources), and is not requesting documentation to be submitted as evidence of completion.

1. 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

My primary review was completed and approved on 03/03/17. The following information request was sent to the Firm to be assessed in this 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 (b) (4) 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 Q-52-A07 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.

CSLB submitted the following amendments to the submission in response to the above IR:

- 125606/0.15 received 28 Feb 2017
- 125606/0.17 received 28 Feb 2017
- 125606/0.18 received 03 Mar 2017
- 125606/0.21 received 24 Apr 2017
- 125606/0.22 received 11 May 2017

Review Memo Format and Table of Contents▪

For reference, I left the original sections from the Primary Review that were related to the IRs. My original Review Assessment / Comments are provided at the end of review sections in a double lined box with the related Information requests (IRs). The IRs that were pending from the primary review were left in bolded text. A summary of the firm's response to that IR will immediately follow in italicized text. 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):

2. Equipment Cleaning Validation

<Begin original text from Primary Memo>

Review Comment/ Assessment: Product (b) (4) are dedicated to CSL830, and have not been approved for use with Berinert. Lyophilizer (b) (4) have not been used for 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 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 (b) (4) Virus-Filtration (per (b) (4) the filtrate of the Virus- Filtration is collected in (b) (4).

(b) (4) , CSLB executed (b) (4) validation runs covering the maximal holding time before cleaning were performed using the (b) (4) cleaning procedure according to SOP 531249-12.1.

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) The equipment was cleaned by production personnel after holding times:

- (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) .

For the (b) (4) was performed on predefined product contact worst case locations. 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)

(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 endotoxin content in the (b) (4) samples was determined by a (b) (4) The (b) (4) was in all cases below the acceptance limit of (b) (4) which is consistent with WFI quality.

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 (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 (b) (4) 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) determination method was used as the acceptance criterion for (b) (4) samples.

Review Assessment/ Comments: CSLB refers to CV-680-002-01 for the cleaning of (b) (4) itself. CSLB states that due to comparability (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 (b) (4) . 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 Re-validation. 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) used for Haemocomplettan. Due to the protein load and cleanablity, these (b) (4) are used as a worst case scenario, and all other (b) (4) with the (b) (4) 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 revalidation of the (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) was being used as a worst case scenario and (b) (4) are (b) (4) , this is not a change from their previous CV approach, no objections noted.

<End original text from Primary Memo>

CSLB Response to #1

Please find the Cleaning Revalidation Report CV-680-002-01R06 in Attachment 1 of this section. Herein detailed information can be found regarding microbial testing for the (b) (4) as well as the results of the testing.

CSLB provided Report, CV-680-002-01R06 in attachment 1 of their response. The report summarizes the results obtained during the revalidation study performed in April 2016 for the (b) (4) for the production of Haemocomplettan® P. The (b) (4) are

cleaned in the (b) (4) *area building* (b) (4) *floor with* (b) (4) *. The equipment described here is dedicated equipment, used for a* (b) (4) *step only.* (b) (4) *revalidation run was performed for the* (b) (4) *for equipment washer cleaning. Furthermore* (b) (4) *runs were performed to validate new holding times.*

The equipment-(b) (4) *is used to clean* (b) (4) *from various production areas and is located in the* (b) (4) *in building* (b) (4) *in room* (b) (4)

Besides visual inspection, the cleaning procedure was investigated by (b) (4) *and* (b) (4) *samples.* (b) (4) *, and endotoxin levels were investigated in the* (b) (4) *, protein levels were investigated in the* (b) (4) *samples.*

The revalidation (b) (4) *for the* (b) (4) *resulted in* (b) (4) *, protein, and endotoxin residue levels within the preset acceptance criteria. The acceptance criteria for residual cleaning agents concerning conductivity were achieved.*

The revalidation for this cleaning process is representative for the following devices which match in structure and surface, and are cleaned with the same cleaning process:

- (b) (4)

According to change no. (b) (4) *depyrogenation process in the* (b) (4) *. The previously validated holding times of* (b) (4) *Therefore* (b) (4) *were performed to validate new holding times.*

Remaining residual water in containers must be (b) (4) *to a sufficiently* (b) (4) *to prevent accumulation of germs and endotoxins. To confirm that only* (b) (4) *. In order to be able to store the* (b) (4) *for as long as possible prior to sanitization* (b) (4) *), the maximum holding time between cleaning and sanitization was limited to* (b) (4) *).*

The effectiveness of the (b) (4) *drying and sanitization process is to be demonstrated by means of analyzes on the* (b) (4)

sanitization and was performed with (b) (4) *were examined for* (b) (4) .

(b) (4)

All acceptance criteria were met, no deviations reported.

CSLB Response to #2
Microbial testing of the (b) (4) *was not performed in terms of Study* (b) (4) *but in terms of Study IR-MUE-005-01. The goal of this study was to validate the* (b) (4) *is cleaned. During this study* (b) (4) *testing was performed on each material cleaned in the* (b) (4) *These tests apply to all equipment cleaned in the* (b) (4)*. The Cleaning Investigation Report IR-MUE-005-01 is enclosed in Attachment 2.*

CSLB provided the Study IR-MUE-005-01 with their response. The report summarizes the (b) (4) *endotoxin status of equipment which is cleaned in the* (b) (4) *and held more than the maximum clean hold time in the* (b) (4) *in* (b) (4)*. Therefore dedicated and non-dedicated (multi-purpose) equipment was observed. All equipment is cleaned by an* (b) (4) *process.* (b) (4) *of equipment and the* (b) (4) *were* (b) (4) *.*

The (b) (4) *sanitization and holding time the* (b) (4) *of equipment after cleaning and holding time is covered in the study.*

(b) (4) *different loading patterns of maximum load were analyzed. Each pattern includes equipment with product contact but not exclusively. Non-product contact equipment was able to be used if it provides "worst case" conditions to the* (b) (4) *program.*

The collected data shows that the equipment (b) (4) *in the* (b) (4) *is cleaned effectively according to the procedures described in the respective SOP and* (b) (4) *and endotoxin burden occurs during clean hold time.*

(b) (4) *for pharmaceutical use and built as a* (b) (4) *system between room no.* (b) (4) *. All investigations described in this report were conducted concurrently to routine production. The equipment was cleaned by production personnel. Samples from the* (b) (4) *were taken to investigate the* (b) (4) *of the* (b) (4) *for potential contamination by microorganism and endotoxins.*

(b) (4) *investigation runs were executed according to the pre-approved investigation study protocol IS-MUE-014 (Ref. 17). According to SOP 531249-11.0 (Ref. 1) loading patterns no.* (b) (4) *are available.* (b) (4) *are defined in SOP 530124-10.0 (Ref. 2). This study observes* (b) (4) *loading patterns at* (b) (4) *load.* (b) (4) *on* (b) (4) *and* (b) (4) *on* (b) (4) *were conducted.*

To determine the (b) (4) *the* (b) (4) *of the* (b) (4) *was analyzed. To determine the* (b) (4) *of equipment before sanitization /depyrogenation samples of equipment after* (b) (4) *and holding time were taken by* (b) (4) *samples.*

The chosen equipment is representative for all other equipment of comparable surface and area, cleaned by the (b) (4) *program. The investigated cleaning process is validated by cleaning validation protocols:*

- *860267-01 reported as CV-MUE-032-01*
- *860287-01 reported as CV-MUE-041-01*
- *860288-01 reported as CV-MUE-043-01*

After a holding time of (b) (4) *sampling was performed on predefined locations with focus on increased potential of* (b) (4) *and endotoxin burden. Sampling sites and conditions were chosen with the aim to cover:*

- (b) (4)

The chosen equipment is representative for all other equipment of comparable surface and area, cleaned by the same (b) (4) *program. CSLB details the sampling points of all the load patterns in the study.*

Loading patterns (b) (4) *and for* (b) (4) *were cleaned with* (b) (4) *endotoxins. Load pattern were described in the study report.*

In accordance with SOP 531249-11.0, loading patterns (b) (4) *were cleaned by program* (b) (4) *was precleaned according to SOP 536390-1.0. Cleaning include* (b) (4) *cleaning and* (b) (4) *(described in study).*

CSLB defines holdings times for routine use according to SOP 520177-8.0. Due to the study objective the defined holding times were exceeded as a worst-case consideration.

(b) (4)

Acceptance criteria in the Cleaning Validation Procedure Doc. No. 420020, the Rationale for Cleaning Validation, Methods and Acceptance Criteria and the supporting SOP 550198 were as follows:

(b) (4)

Every part of cleaned equipment was found visually clean before sampling. The predefined clean hold time for every part of equipment was exceeded.

No (b) (4) *occurred at any sample of all* (b) (4) *investigation runs including* (b) (4) *samples.*

The highest endotoxin concentration of (b) (4) *which is within the analytical target was found for a* (b) (4) *sample of a* (b) (4) *cleaned in* (b) (4) *. All other samples were determined less than* (b) (4) *. No deviations were reported.*

CSLB Response to #3

(b) (4) *are clearly defined. Virus inactivation* (b) (4) *consists of* (b) (4) *process steps: A pasteurization step performed in building* (b) (4) *and a* (b) (4) *virus filtration* (b) (4) *performed in Building* (b) (4) *.*

The facility is (b) (4) *. Material, personnel, and product flows are defined preventing cross contamination.*

Additionally the following measures apply.

- (b) (4)

- (b) (4)

Pasteurization is an automated and validated process and is re-qualified (b) (4) *The implementation of the virus filtration step takes place towards the* (b) (4) *. By means of this the process steps after virus filtration can be performed in better functionally closed systems.*

In-process controls and (b) (4) *integrity tests ensure the validated status of the steps. Related flow diagrams showing the segregation of* (b) (4) *area can be found in Sections:*

- *3.2.A.1.4-1.1.5, Environmental Classification Plan,* (b) (4) *Floor, Building* (b) (4) *and*
- *3.2.A.l.4-1.1.13, Product Flow Plan,* (b) (4) *Floor, Building* (b) (4)

Review Assessment/ Comments: CSLB provided evidence of completed cleaning validations, with acceptable limits. CSLB provided an overview the pre and post viral inactivation segregation controls that include (b) (4) controls appear adequate.

The following information request was sent to the Firm:
In your amendment received 02/28/17: Reference your Attachment 1, CV-680-002-01R06, page 2 of 11- please provide your scientific rationale for why (b) (4) **products represent the worst case scenario for cleaning.**

CSLB Response:

(b) (4) *with a volume of* (b) (4) *are used for the production of several CSL Behring products, e.g. Factor I and C1-Esterase Inhibitor (C1-INH).*

Cleaning of the C1-INH dedicated (b) (4) *(used for the collection of C1-INH* (b) (4) *is performed according to the same procedure as for* (b) (4) *used for the production of* (b) (4)

(b) (4) *products represent the worst case for cleaning of production equipment concerning the* (b) (4) *onto the equipment surface. This was shown in a separate study considering the removal of plasma products from* (b) (4) *surfaces (study no. IR-DIV-006-01). Equivalent amounts of different products were* (b) (4) *and it was demonstrated that* (b) (4) *products clearly show the lowest rate of protein recovery.*

Furthermore, the protein concentration of the (b) (4) *used in study CV-680-002 was* (b) (4) *significantly higher than the protein concentration of the C1-INH* (b) (4) *" with an* (b) (4) *between* (b) (4) *(in consideration of the extinction coefficient with* (b) (4) *equivalent to a protein concentration of* (b) (4)

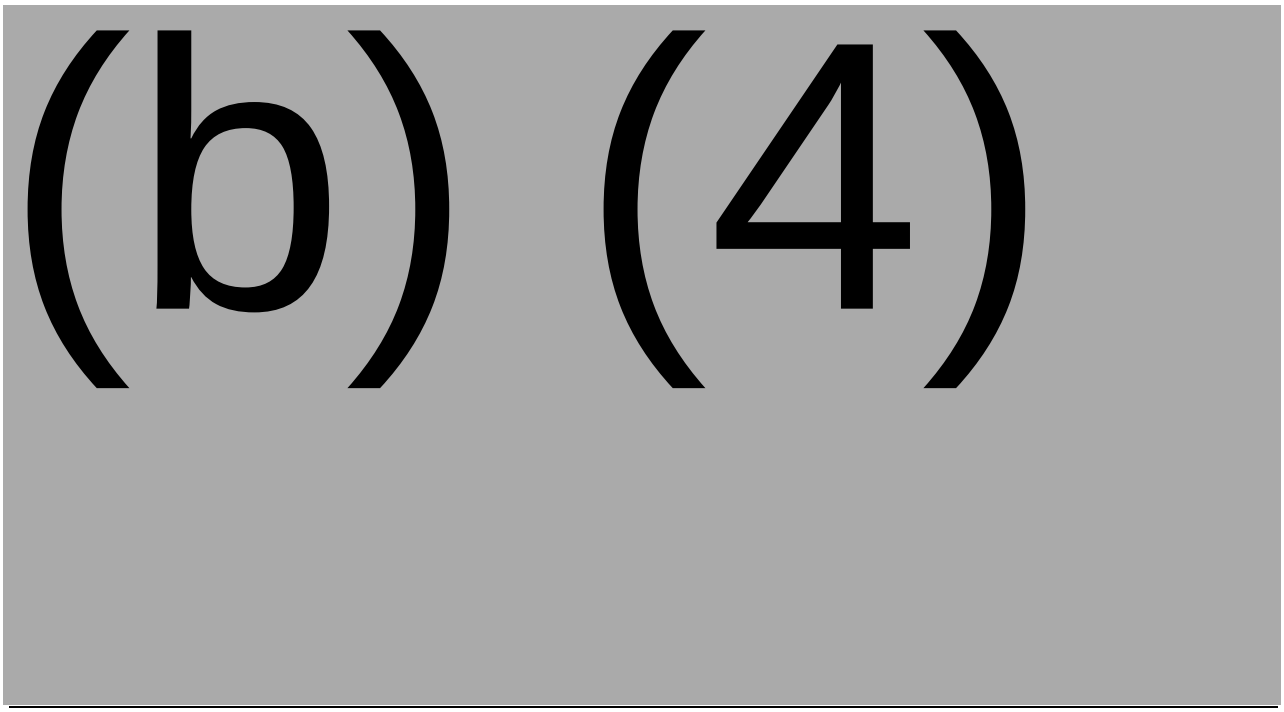
Review Assessment/ Comments: Worst Case scenario for (b) (4) appears scientifically sound based on rate of residue recovery and concentrations. No objectionable findings noted.

<Begin original text from Primary Memo>

3. Process Validation

Lyophilizers of (b) (4) 2000IU and (b) (4) 3000IU) were used and employed with (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 drug substance and drug product are as follows:



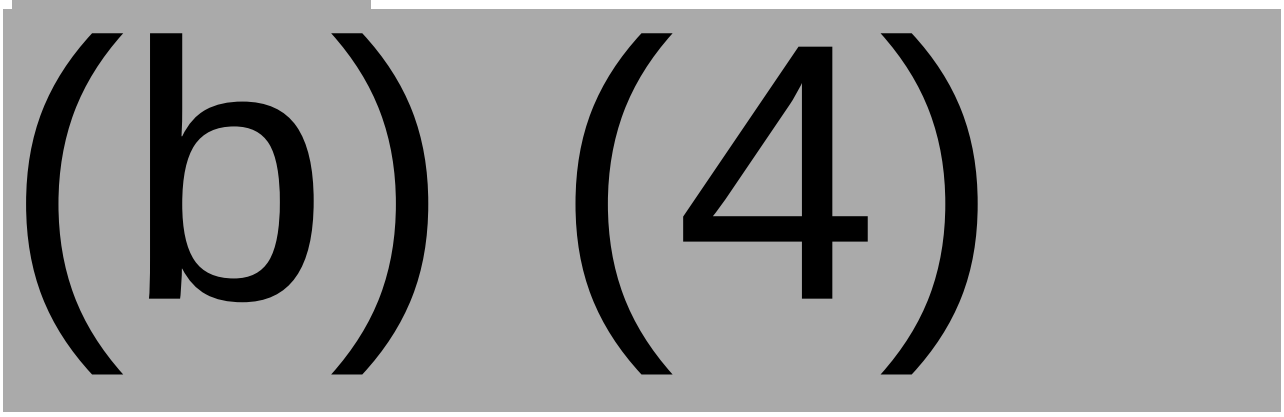
a. (b) (4) Production Process Validation

Per Protocol 900806-01, CSLB validated the manufacturing process of C1- esterase Inhibitor concentrate human according to manufacturing procedure (b) (4) . The preceding manufacturing process is described in production procedures (b) (4) This part of the manufacturing process was not changed and had already been validated previously.

The implemented changes only affect the (b) (4) manufacturing process. Starting after the (b) (4)

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

(b) (4)



Endotoxin content of the first consistency batch could not be determined (deviation 191486). The endotoxin value proved to be invalid due to an error during evaluation of the analytical results. Retest could not be performed. All other endotoxin values were well below the acceptance criterion.

All other values of the (b) (4) batches were within the acceptance criteria or expected ranges as defined in the process validation protocol 900806. The consistency batches yielded values that were equivalent to the comparison batches indicating that the change in batch size did not have any impact on the product PQA.

Each (b) (4) lot was filled into both new filling sizes 2000 IU and 3000 IU and tested according to Quality Control Procedure (b) (4) C1- Esterase-INH (2000IU/3000IU).

- From 001 68910: (b) (4) (2000 IU) & (b) (4) (3000 IU)
- From 002 68910: (b) (4) (2000 IU) & (b) (4) (3000 IU)
- From 003 68910: (b) (4) (2000 IU) & (b) (4) (3000 IU)

All lot release specifications including sterility and pyrogen content for the final product C1-esterase inhibitor concentrate (human) were fully met. Four Deviations were generated in the validation study as follows:

Category	Number
In-Process Control OOS	1
Equipment Related	2
Sampling and Testing	1

Review Assessment/Comments: The missing Endotoxin result was rated as not critical since the pyrogens test in the final product was compliant. For the (b) (4) consistency batch the amount of (b) (4) exceeded the predefined range. However, since the chemical parameters in the (b) (4) could still be adjusted to meet all requirements, this deviation was also rated as not critical for product and process validation. I defer the adequacy of that (b) (4) deviation to the Product Office Specialist.

Two additional deviations were issued for equipment that could not be used due to malfunction or late preparation respectively, but rated as not critical in regard to the product quality and the process validation. Those deviations appear minor and I agree with the assessment of no impact to validation. No OOS to endotoxin (b) (4) reported. No objectionable findings; However, I will clarify on where in the process that CSL monitors for (b) (4) .

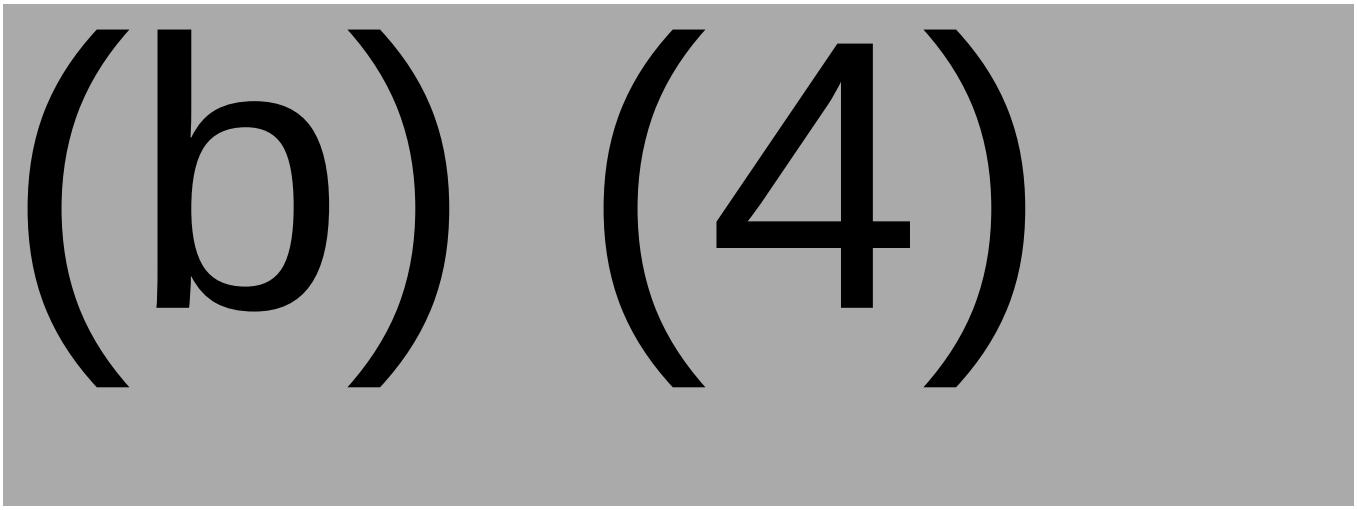
The following information request is being sent to the Firm to be evaluated in my Addendum Review:

1. 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 for the limit.

<End original text from Primary Memo>

CSLB Response

CSLB provided the following table as an attachment to their amendment:



Review Assessment/ Comments: CSLB provided evidence that (b) (4) is being monitored with both alert and actions limits qualified in microbial studies. No objectionable findings noted.

<Begin original text from Primary Memo>

4. 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) vial (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.

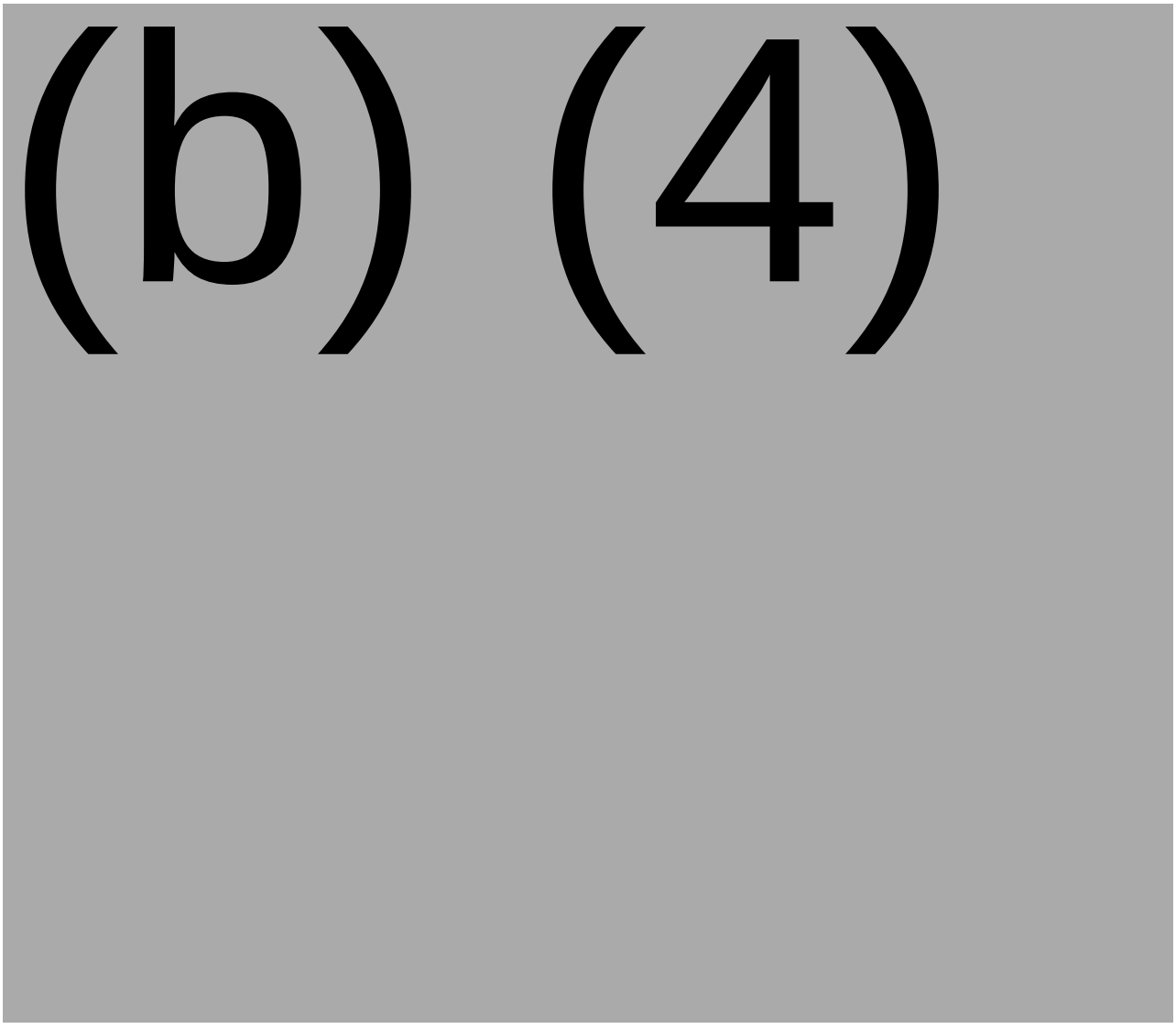
Single-dose colorless injection vials with a nominal size of (b) (4) are used for C1 Esterase Inhibitor Concentrate (human) lyophilized drug product. The containers are made of colorless, molded glass. All glass containers for C1 Esterase Inhibitor Concentrate (human) meet the requirements for type (b)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

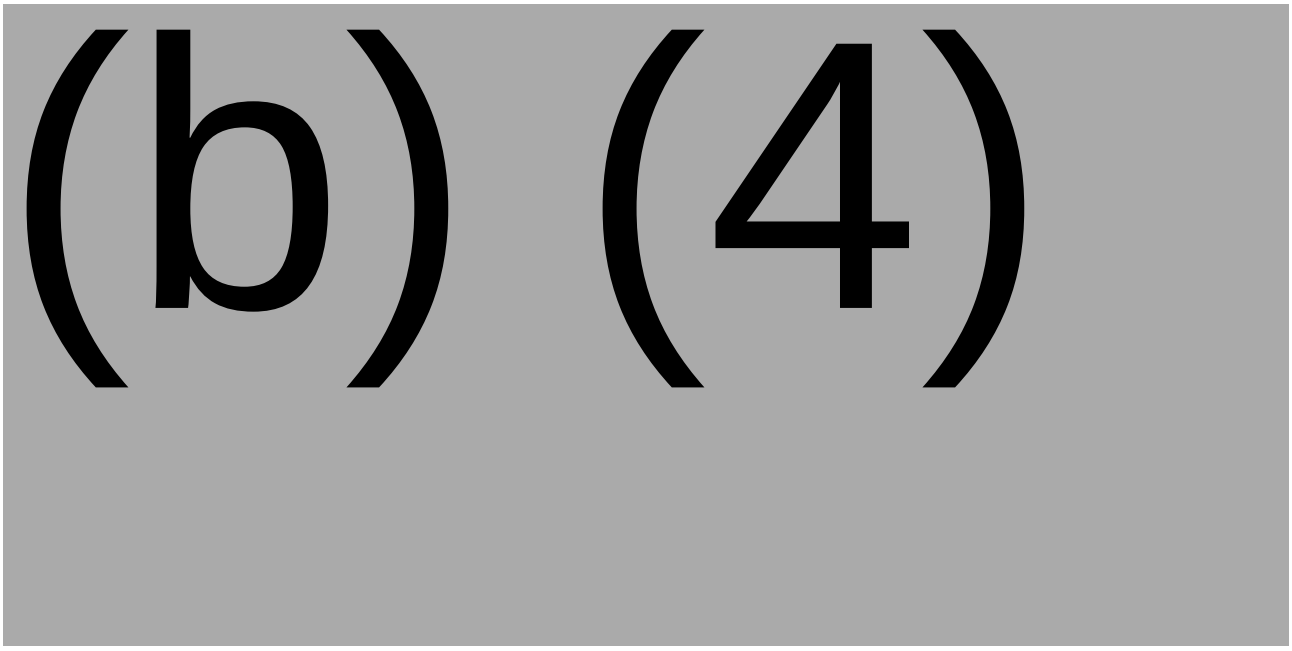
The vials are closed with ready-to-sterilize (b) (4) rubber stoppers that comply with Type (b) requirements of (b) (4) and the comparable requirements of chapter (b) (4) " of the current (b) (4). The stopper is not manufactured with natural rubber latex

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 (b) (4) glass occurs as follows:





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**

<End original text from Primary Memo>

CSLB Response:

In attachment 1 of their amendment CSL provided an summary of the detailed PQ documentation specifying the acceptance criteria, date of validation and summary of the results of the (b) (4) depyrogenation (b) (4) used for the (b) (4) Vials. The equipment is located on the (b) (4) floor of the licensed Building (b) (4). During the PQ runs no out of specification results occurred.

CSLB states that the complete PQ Certificates for (b) (4) could be provided upon request.

(b) (4)*: PQ Approval Date: 31 Oct 2014*

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

a. For the cleaning of vials in (b) (4), you reference the cleaning of (b) (4) vials. Please explain how this study is relevant to cleaning of (b) (4) and provide your scientific your scientific rationale for any worst case loads.
b. For the depyrogenation of vials in (b) (4), you reference the worst case load of (b) (4) vials. Please provide your scientific rationale for this worst case load.
c. Have you physically performed any qualification runs for (b) (4) vial cleaning or depyrogenation, or do plan to?

CSLB Response:

***2a**. Unfortunately, the referenced attachments regarding (b) (4) show an error. The cleaning study of (b) (4) was not done with (b) (4). For this study the relevant (b) (4) vial size was used. The referenced attachments regarding (b) (4) will be corrected accordingly and are available upon request. Therefore, a scientific rationale for any worst case loads is not deemed necessary.*

***2b.** The (b) (4) are defined as worst-case-load regarding depyrogenation. This is based on (b) (4) measurements during initial qualification by assessing the minimum lethality of (b) (4) placed inside the load. The relevant (b) (4) vials size was implemented by change control #156893 after initial qualification. Within this change a change qualification was carried out using the (b) (4) vial size. The results showed that the (b) (4) vial size was still determined to be the vial size with the minimum lethality.*

The following table shows the lethality of the various vial sizes used:

(b) (4)

***2c.** The qualification runs for (b) (4) vial cleaning or depyrogenation were performed physically as described in response 2a. and 2b.*

Review Assessment/ Comments: CSLB provided evidence of PQ studies performed or covered for (b) (4) depyrogenation of the (b) (4) vials. No objectionable findings noted.

<Begin original text from Primary Memo>
CCIT

CSLB validated the integrity of the primary packaging components (listed above) through (b) (4) supported by (b) (4) testing (b) (4) 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 Q-52-A07.

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 (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) test 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 Q-52-A07 for review

<End original text from Primary Memo>

CSLB Response:

CSLB provide a SOP Q-52-A07 in their amendment.

Review Assessment/ Comments: The SOP provides only high level information about the testing procedure, not product or vial size specific. **The following information request was sent to the Firm:**

In reference to your (b) (4) test:

1. **SOP, Q-52-A07, that you provided an amendment, does not include test parameters specific to the C1-INH (b) (4) vial filled units. Please provide the following for both vial sizes:**

- **The specific program (test cycle) used**
- **The amount of (b) (4) applied**
- **The defined period of time that the (b) (4) is monitored**
- **The specified pressure reference values that would indicate a leakage if exceeded**

2. **Please confirm that the (b) (4) test for the C1-INH (b) (4) vial filled units had been validated, and that testing parameters and acceptance limits are defined in a working document.**

CSLB Response:

1. *For the testing of closure systems with* (b) (4) *glass vials, the test program* (b) (4) *" is used. For the testing of closure systems with* (b) (4) *glass vials, the test program* (b) (4) *is used.*

   In both test programs the amount of (b) (4) *applied is* (b) (4) *The defined period of time that the* (b) (4) *is monitored is* (b) (4) *. The* (b) (4) *difference may not exceed* (b) (4) *for the testing of closure systems during that period of time.*

2. *The* (b) (4) *test is a simple and robust physical test method. Sample preparation is standardized to exclude environmental influences like humidity and room temperature. The testing device is qualified (IQ, OQ, PQ) as well as the vial size specific test programs. An additional sensitivity study demonstrates that leakage sizes up to* (b) (4) *in diameter can be detected with certainty. A system suitability test is performed at the beginning and at the end of the test series of a batch using the vial size specific control sample (vial completely filled with resin = positive sample) and the calibrated precision tester (to simulate a defined* (b) (4) *leakage = negative sample) connected by a* (b) (4) *with the test* (b) (4) *of the test device.*

   Testing parameters and acceptance criteria (e.g.: detection of an intact vial; detection of a vial with a simulated (b) (4) *leakage; detection of a vial with a simulated* (b) (4) *leakage; identification of a massive leakage (broken)) are defined and listed in the (additional) PQ documentation of the vial size specific test programs and subject to the change control procedure.*

Review Assessment/ Comments: CSLB provided evidence of a controlled and established procedure for (b) (4) testing. System suitability tests are performed with positive and negative control challenges. No objectionable findings noted.

<Begin original text from Primary Memo>

5. 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) *additional tests as* (b) (4) *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 introduce (b) (4) *customized optimizations to the Medimop standard presentation:*

- (b) (4)

Later a so called (b) (4) *improvement" 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) [redacted]

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:

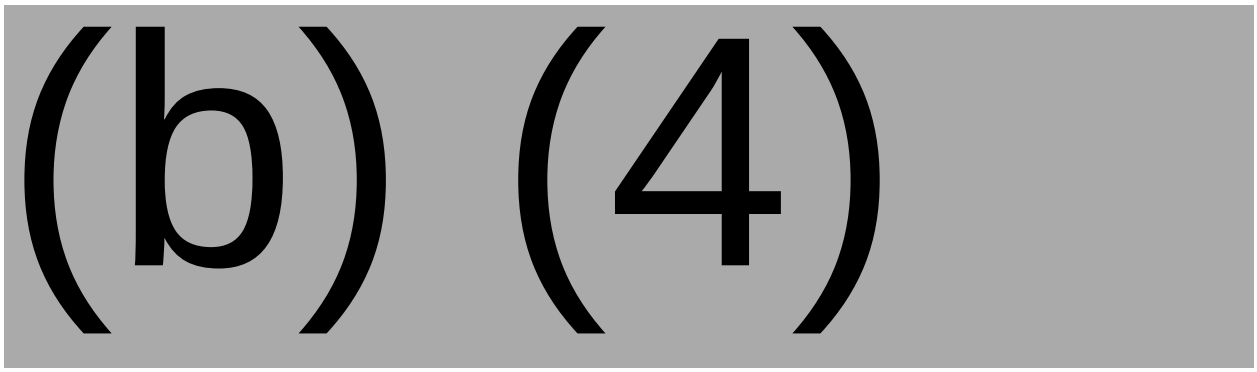
CFR Section 820.30: Design controls
The Mix2Vial (M2V) system was designed by Medimop Medical Projects Ltd. It enables a vial-to-vial transfer and mixing between two vials for the reconstitution of lyophilized drugs. The reconstituted drug product is available for immediate aspiration into the syringe 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



CSLB Response to #2

Time of introduction of optimization / improvement to the M2V presentation:
The bullet points (b) (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) .

Bullet point No. 5 is the introduction of an improved (b) (4) *of the device upon* (b) (4) . *The* (b) (4) *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* (b) (4)*). 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, <u>prior to making the changes</u>, 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.**

<u>Review Assessment/ Comments:</u> 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.

<End original text from Primary Memo>

<u>CSLB Response:</u>

On 06 January 2017, CSLB provided a response and requested a brief teleconference with FDA for advice on the proposed content of the Design History File for the Mix2Vial.

CSLB received FDA pre-meeting notes (13 Feb 2017) in advance of the 14 February 2017 teleconference. At the conclusion of the teleconference, CSLB was requested to amend the CSL830 BLA with our responses to the pre-meeting notes along with a Mix2Vial history document as related to the observation of (b) (4) " following reconstitution using Mix2Vial.

1. *CSLB is in the process of establishing a standard procedure for Design Controls, which will include the requirement for conducting Design Reviews and provide guidance for establishing DHFs. This procedure would be applied for Haegarda™. At the 14 February 2017 teleconference, FDA acknowledged the initiation of CSLB's design controls as part of standard procedures for combination products.*

2. *The DHF will focus on Haegarda™ but as part of the development history of the transfer device, the DHF will also reference studies performed with other CSLB licensed biologics as they influenced the decision-making of features of the transfer device. At the 14 February 2017 teleconference between representatives of FDA and CLSB, FDA agreed to the proposed content of the Haegarda™ DHF as presented in*

Table 1 of the 06 Jan 2017 response in 1.11.1 document.

In summary, FDA was in overall agreement with CSLB proposed content of the Mix2Vial/Haegarda™ Design History File (DHF) and offered additional advice:

- *The DHF should be a single compilation of electronic files/records, collated and readily available for audit on site in Marburg.*
- *Information/reports should be a prospective and retrospective collection of design history with one design review.*
- *CSLB commits to ensure the Medimop Quality Agreement remains effective, current with a copy included in the DHF.*

FDA agreed with CSLB proposal to have the DHF complete and closed by May 2017, in advance of the Haegarda™ launch.

3. *The current version of the Quality Agreement (effective date 06 May 2015) in place between CSL Behring and Medimop requires notification of changes as detailed below:*

"Supplier shall inform Customer of any changes that may affect the quality of the goods covered by this Agreement, including (if applicable) changes in the raw material or processing aids, changes in raw material suppliers, services, changes of production sites, changes of Supplier's specifications, changes of test methods and changes of subcontractors, comprehensively (b) (4) *in advance, so that Customer is able to review their impact. If necessary, Supplier will submit corresponding samples and reference materials.*

Notification of changes will be provided by the Supplier to Customer in writing and requires Customer approval. This information should be send to the following addresses:

For Products supplied to CSL Behring GmbH,
Germany: CSL Behring GmbH
Quality Assurance / Change Control
Emil-von-Behring-Straße 76
35041 Marburg, Germany

Before the change is implemented, Customer shall confirm acceptance of the change in writing within (b) (4) *days. If Customer fails to confirm its acceptance, this does not absolve Supplier of its liability to ensure compliance with the specified requirements. In case of changes to those specifications, both Parties will need to mutually agree in writing.*

Supplier must keep records of the introduction dates of all modifications/alterations. No new Purchase Orders will be accepted until the change is approved by the customer."

3a CSLB will revise above text to mention 510k amendments specifically.

4. *CSLB agrees that the* (b) (4) *is a critical quality attribute of the device. The* (b) (4) *of the Mix2Vial is ensured by the following measures:*

- (b) (4)

Furthermore, compliance is verified in (b) (4) *audits of Medimop's manufacturing process including* (b) (4)

5. *Berinert-P® is a plasma derived concentrate of complement C1 esterase inhibitor. The appearance of the reconstituted solution is colorless and clear. Antihemophilic factor/von Willebrand factor complex (human), Humate-P®, is a pasteurized, sterile and lyophilized concentrate of plasma-derived Factor VIII and von Willebrand Factor (vWF) protein. The appearance of the reconstituted solution is colorless and clear to slightly opalescent and in contrast to Berinert, may contain a few characteristic* (b) (4) *in accordance to the corresponding monograph of the* (b) (4)

Von Willebrand Factor protein is sensitive to mechanical stress (shear forces) and can cause the occurrence of (b) (4) *; in addition, particles can be formed at* (b) (4) *. To respect these specific properties, the transfer device used for dissolving the product* (b) (4) .

To ensure there was no formation of (b) (4) *, it was an imperative request for the Mix2Vial device to allow a cautious contact of the diluent to the surface of the* (b) (4) . *This was reached by a significant* (b) (4) .

Finally, all (b) (4) *, that may have been formed, are removed by a* (b) (4) *of the Mix2Vial device. Using a* (b) (4) *as in the former situation is not necessary and after* (b) (4) *of the Mix2Vial a* (b) (4) *to the reconstituted solution is possible.*

A functionality report that presents full comparability between the Mix2Vial and the Double Ended Needle transfer system (Research Report RR-023 – 061003 "Mix2Vials (b) (4) *assessment"), as well as a qualification report demonstrating equivalent compatibility between reconstitution appearance and the*

biological activity of the product ("Removal of (b) (4) *by the* (b) (4) *of M2V and Transfer Set Device after reconstitution of* (b) (4) *are available as part of the DHF.*

Review Assessment/ Comments: CSLB appears to be addressing all of our concerns for design controls. The (b) (4) issue appears to be related directly to the protein characteristics of the Factor VIII and von Willebrand Factor. CSLB appears to have suitably evaluated the current design of the Mix2Vial for use in the reconstitution of C1-INH. I suggest (b) (4) follow-up item. See section 6.