From: Cagungun, Nannette
Sent: Wednesday, December 21, 2016 4:02 PM
To: Michele.Walsh@cslbehring.com
Subject: Information Request_CMC/Facility_C1INH/CSL830

Dear Ms. Walsh:

We have the following additional CMC information request regarding 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.

Due to the holiday season, CSLB may respond to our information request by January 13, 2017. Please contact me at your earliest convenience if you are not able to respond by this date.

Sincerely,
Nannette Cagungun, MS, PD, RAC
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
U.S. Food and Drug Administration
Tel: 240-402-8267
nannette.cagungun@fda.hhs.gov.

From: Cagungun, Nannette
Sent: Friday, December 16, 2016 2:15 PM
To: Michele.Walsh@cslbehring.com
Subject: Information Request_CMC/Facility_C1INH/CSL830

Our Reference: BL 125606/0

Dear Ms. Walsh:

We are reviewing your June 30, 2016 biologics license application for C1 Esterase Inhibitor Subcutaneous (Human) for routine prophylaxis to prevent Hereditary Angioedema

attacks in adult and
adolescent patients. We are providing the following comments and request for additional information
to continue our review:

1. 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 (b) (4) until lyophilization.

You also state the b) (4) temperature in your recipe b) (4)

a. Is this storage at (b) (4) part of the b) (4) step? Please explain the
disparity in the temperature ranges.
b. How did you establish the b) (4) hold time?

2. Please provide a description (including manufacturer, item #, etc.) of the sterilizing filter used (in
(b) (4) .

a. Please provide summary of the filter qualification (or re-qualification) performed associated
with the more b) (4) .

3. Referencing your amendment, 125606/0.3 (received September 6, 2016): the Agency disagrees
with your position statement.

The Agency concludes that your product 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

Please provide this information 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)?)

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

* (b) (4)

a. Please provide any validation or where appropriate verification, review, and

approval of
these design changes before their implementation.

Please submit the requested information in an amendment to the file by Friday, January 6, 2017, or as
soon as possible referencing the date of this request. If you anticipate you will not be able to respond
by this date, please contact the Agency immediately so a new response date can be identified.

If you have any questions, please contact me at (240) 402-8267.

Sincerely,
Nannette Cagungun, MS, PD, RAC
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Office of Tissues and Advanced Therapies
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