From: Cagungun, Nannette
Sent: Thursday, May 11, 2017 4:23 PM
To: Michele.Walsh@cslbehring.com
Subject: Information Request_CMC_C1INH/CSL830

Importance: High

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 have the following request for additional information:

1. As stated in Information Request dated 3/20/17, your data do not support the proposed HAEGARDA specification for the (b) (4). Your current specification corresponds to a (b) (4). Such a specification is not acceptable.

a. Please develop a specification based on your data, the FDA and ICH guidance and your SOP 566255.

b. We also note that too broad specification may prevent you from performing a meaningful trend analysis. You stated that trends are flagged if the (b) (4) However, for limits established as the (b) (4) appears to be b) (4) . Please comment on the apparent negative trend, also, in the context of the apparently stable (b) (4) data and an apparently increasing trend observed for the protein content for the (b) (4) clinical lots for which data were provided in Section 3.2.S.2.6-2.

In response to the arguments that you used to support the proposed specification we note the following:

* The specifications are not set for groups of products but individually based on the clinical experience and manufacturing capability.
* Previous approvals and approvals in other countries do not justify setting specifications disregarding the data.
* SOPs should be followed. We note that you have SOP 566255 Setting of Specifications for New Development Products for Clinical Phase III and Commercial Manufacture which says “Limits should be based on data”, “The specification limits are to be set to cover compendial/regulatory requirements, the capability of the manufacturing process and the test variability”, and “Statistical procedures shall be applied to a valid, relevant and sufficiently large data set…” We also note that the SOP was effective on July 31, 2015, thus, before this BLA was submitted.
* (b) (4) 04/2016:2818 that you cite states that the minimum (b) (4) is (b) (4) . This is not a “recommended specification” as you say but the lowest standard established by (b) (4)

2. We note that a specification for sodium citrate is too broad taking into account your data. We note that the width of a licensed range for sodium citrate for Berinert is (b) (

mg/mL (Berinert specification: (b) (4) We also note that for HAEGARDA you proposed to (b) (4), i.e., to (b) (4). We note that in response to our comment you proposed to implement action limits at mean (b) (4). Nevertheless, you proposed to keep the broad specification. Please revise the specification based on your data.

3. Your residual moisture specification appears not to be acceptable. We note that you proposed not to change the specification and reassess it when more release data are available and the stability study 689-002US is completed in September 2018. However, we also note that CoA data for (b) (4) clinical lots provided in Amendment dated 1/31/17 (observed moisture range: (b) (4) HAEGARDA lots in the stability study with (b) (4) of data available (residual moisture b) (4) and Berinert 1500 stability data (Study 688-001US_688-002US, residual moisture range: (b) (4) at 36 months) do not support the proposed specification. Please explain what data are used to justify the proposed specification. Otherwise, please narrow the specification.

4. We note that in response to Comment 5 in IR dated 3/20/17 you stated that the in-process specification for (b) (4) for the (b) (4) is ? (b) (4) Please update the BLA, e.g., Section 3.2.S.2.4-1, Table 1: Critical PPs for the production of C1 Esterase Inhibitor Concentrate which currently says that a specification is (b) (4). Also, please establish an upper limit for (b) (4) based on the historical data.

5. You clarified that the b) (4) of (b) (4)

a. Please indicate where in the submission information on the (b) (4) range of the (b) (4)

b. Also, please discuss the criticality of this parameter value and provide supporting evidence.

6. Please clarify whether the conformance batches (b) (4) were produced before or after implementation of the b) (4) data in report IR-689-001-01 represent the purity of the current product manufactured with the b) (4)

7. We note that the final container product has an open ended specification for (b) (4) at release. Please add an upper limit and justify the b) (4) limits based on the historical data.

8. Please include the stability testing at b)(4) into your HAEGARDA stability program or change the storage conditions proposed in the Package Insert. “There should be a direct link between the label storage statement and the demonstrated stability of the drug product.” [ICH Q1A(R2)]

Please submit the requested information in an amendment to the file by Thursday, May 18, 2017, referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact me 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
Regulatory Project Manager
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.