From: Cagungun, Nannette
Sent: Monday, March 20, 2017 2:26 PM
To: Michele.Walsh@cslbehring.com
Subject: Information Request_CMC_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 have the following request for additional information:

1. We note that clinical lots final container (b) (4) results do not support the proposed specification for HAEGARDA (b) (4). The proposed specification is (b) (4). However, the results for the (b) (4) clinical lots provided in a response to Comment 22 (Amendment dated 1/31/17) are in the range of (b) (4). Also, we note a decreasing trend of the (b) (4) values of the clinical lots with time. Please, thus, address the following:
   a. Please narrow the specification to reflect the (b) (4) of the product administered during the clinical trial.
   b. Please explain the decreasing trend and discuss changes to the manufacturing process (if any) that may be responsible for the trend.
   c. Please provide an SOP on setting product specifications.

2. We note that the concentration of sodium citrate in HAEGARDA final container product (b) (4) is different from that in Berinert (b) (4). Also, we note that the range observed for the (b) (4) clinical lots (data provided in response to Comment 22 in Amendment dated 1/31/17) was (b) (4) with the (b) (4) appearing to be an outlier and the average was (b) (4). Thus, please address the following:
   a. Please clarify why the concentration of sodium citrate was changed.
   b. Please discuss the role of sodium citrate in the product and the impact of the change, including the impact on stability.
   c. Also, please reassess the specification based on the results obtained for the clinical lots and provide justification for the proposed range.

3. We note that the clinical lots final container residual moisture results (range of (b) (4) do not support the proposed specification (max. (b) (4). Moisture content may affect product stability. Please base the range on historical results.

4. We note that in the HAEGARDA manufacturing process a number of (b) (4) controls were (b) (4) from the (b) (4) process (Response to Comment 1, Amendment dated 9/6/16). With respect to this please take the following actions:
   a. As for (b) (4), please reinstate all the (b) (4) controls that you proposed to (b) (4). Such controls permit an assessment of the process consistency and allow early detection and/or prevention of manufacturing

problems that could compromise product safety and efficacy.
b. In a tabular format, please provide a history of product quality attributes routinely measured since the licensure of Berinert. Please use a format similar to that of Table 1 in study report IR-617-001-02. If any of the parameters were removed after the licensure, please inform under which supplement the removal was approved.
c. Please provide a study report that set a basis for establishing the routinely tested
parameters in the original Berinert BLA.
d. Also, please update and re-submit all documents which include information about the routinely measured in-process controls.

5. We note that (b) (4) is listed in Table 1: Critical PPs for
the production process of C1 Esterase Inhibitor Concentrate (BLA Section 3.2.S.2.4-1)
with a range of (b) (4) . However, we also note the following:
- This parameter appears not to be routinely measured in the HAEGARDA process (Table 1: List of In-Process Controls, BLA Section 3.2.S.2.4.2; Production Procedures (b) (4) , p.4; and (b) (4) , pp.19-20)
- This parameter is considered critical with respect to (b) (4)
(RA 689-001-01, p.28)
- (b) (4) eluate batches (out of (b) (4) and (b) (4) eluate (b) (4) (out of (b) (4)
which were used to manufacture process validation lots for the current BLA did not meet the OD range of (b) (4) . The results for the individual eluates exceeding the range were (b) (4) and for the eluate (b) (4) pp. 34-35). Also, we note that the acceptance criterion for this parameter for the validation lots was ? OD (b) (4) , p.23)
- The values of OD(b) (4) show an increasing trend. The range for individual eluate batches in a study performed in 2013 reported in IR-617-001-02 (pp.40-41) for Berinert appeared to be (b) (4) with an average of (b) (4), for Berinert 1500 in a study performed in 2012/2013 the range was (b) (4) with an average of (b) (4) (PV-688-003-02, p.17) and for HAEGARDA process in a study performed in 2015 the range and the average were (b) (4) and (b) (4), respectively (b) (4) , pp. 34).
- The (b) (4) range of (b) (4) studied in a (b) (4) study (b) (4) (b) (4) Evaluation of the Virus Filtration in the Manufacturing Procedure of Berinert P performed to assess the (b) (4) of process performance and (b) (4) was (b) (4) .
- You plan to re-evaluate the (b) (4) range within a (b) (4) study (BLA Section 3.2.S.2.4-1, p.2)

Please clarify and/or provide justification for the following:
a. What is the acceptance criterion for (b) (4) for

HAEGARDA?
b. Please reinstate this parameter as a routinely measured parameter in order to
meet the acceptance range and to ensure manufacturing consistency.
c. What caused an apparent increase of (b) (4) for Haegarda compared to Berinert process and Berinert 1500 process ((b) (4) ? Please provide the results of (b) (4) for the clinical lots and compare these results to the HAEGARDA process validation lots.
d. Considering a discrepancy between the protein concentration studied in the small scale virus (b) (4) studies and the levels of protein in HAEGARDA's (b) (4) , please provide (b) (4) study 15071552 referred to in response to Comment 18 (Amendment dated 1/31/17) and any other study reports that can be used in support of the virus filtration step (b) (4) claims listed in the PI.

e. What additional validation work is planned (BLA Section 3.2.S.2.4-1, p.2) and within what timeframe to ensure that the (b) (4) protein concentration has no adverse effect on the performance of virus filtration and virus (b) (4). Please justify the timeframe.

f. Please also discuss the impact of the (b) (4) protein concentration on the virus b) (4) during the (b) (4) chromatography step.

6. Please provide updated SOPs for the virus filtration step.

7. We note that the storage conditions proposed in the Package Insert are 2-30 °C. However, the stability studies have been performed to support product stability at 30 °C. Storage in the temperature range of 2-30 °C, requires supporting data for product stability at 2 °C. Please clarify how the stability of HAEGARDA at 2 °C has been or will be demonstrated.

8. HAEGARDA after reconstitution is (b) (4). Please discuss the content of protein aggregates in both products and provide information on the studies performed (if any) to quantify and characterize the amount of subvisible and visible particulate matter in the product.

9. Please discuss the risk of immunogenicity in relation to the presence of particulate matter, b) (4) concentration of the product (b) (4) different route of administration and frequency of administration compared to Berinert.

10. Your plan for reporting changes to the Berinert and HAEGARDA processes is not clear (CMC Section 1.11.1). Please note that changes affecting both processes for Berinert and Haegarda should be submitted to both BLAs.

11. Please provide (b) samples of each conformance lot, i.e., lots (b) (4) and a vial with diluent for each product sample. These samples should be sent to the following address:

Ewa Marszal
FDA/CBER
10903 New Hampshire Avenue, Bldg. 52-72, Rm. 4205
Silver Spring, MD 20993
Phone: 240-402-9726

Please submit the requested information in an amendment to the file by Monday, April 3, 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.

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN
INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are
not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that
any review, disclosure, dissemination, copying, or other action based on the content of this communication is not
authorized. If you have received this document in error, please notify the sender immediately by e-mail or phone.