Our Reference: BL 125606/0 January 13, 2016

CSL Behring GmbH
Attention: Mr. Kevin D. White
CSL Behring LLC
1020 First Avenue
PO Box 61501
King of Prussia, PA 19406-0901

Dear Mr. White:

Attached is a copy of the agenda for your December 20, 2016, Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to BL 125606/0 in your future submissions related to the subject product.

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

Sincerely,

Basil Golding, MD
Director
Division of Plasma Protein Therapeutics
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Mid-Cycle Communication Teleconference Summary

Application type and number: BL 125606/0
Product name: C1 Esterase Inhibitor Subcutaneous (Human)
Proposed Indication: For routine prophylaxis against Hereditary Angioedema in adolescent and adult patients.
Applicant: CSL Behring GmbH
Meeting date & time: December 20, 2016 at 10:00 AM
Committee Chair: Felice D'Agnillo, PhD
RPM: Nannette Cagungun, MS, PD, RAC

FDA Attendees:
Nannette Cagungun, MS, PD, RAC, Division of Regulatory Project Management, OTAT, CBER
Felice D'Agnillo, PhD, Division of Blood Components and Devices, OBRR, CBER
CDR Donald Ertel, M.S., MT(ASCP), ASQ CQA, Division of Manufacturing and Product Quality, OCBQ, CBER
Basil Golding, MD, Division of Plasma Protein Therapeutics, OTAT, CBER
Michael Kennedy, PhD, Division of Plasma Protein Therapeutics, OTAT, CBER
Hyesuk Kong, PhD, Division of Biological Standards and Quality Control, OCBQ, CBER
Ewa Marszal, PhD, Division of Plasma Protein Therapeutics, OTAT, CBER
Carolyn Renshaw, Division of Manufacturing and Product Quality, OCBQ, CBER
Deborah Trout, Division of Manufacturing and Product Quality, OCBQ, CBER

Contractor:
Christopher Sese, Eastern Research Group (ERG)

CSL Behring Attendees:
- Clinical: Debbie Bensen-Kennedy, Iris Jacobs, Ingo Pragst
- Statistics: Henrike Feuersenger
- PK: Dipti Pawaskar
- CMC: Karin Mueller-Stark
  - QC: Karl Fickenscher
  - QP: Peter Hofmann
  - VAL: Eckhard Schueler (Ramona Stauss, Uwe Nau)
  - Production: Wilfried Happel, Horst Boeder
- Safety: Sarah Mycroft
- Medical Affairs: Thomas Machnig
- Commercial: Hanno Waldhauser
- Non Clinical: Frank Schwoebel
- Project Management: Christiane Kolb
- Medical Writing: Daniel Wood
- Global Regulatory Affairs: KD White, Paula Clark, Zak Huang, Hartmut Landgrebe, Lori Mc Mahon and Michele Walsh

Agenda:

To discuss the progress of the review.

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the review committee to date.

   The review team has no significant issues/major deficiencies to communicate at this time. Further information/clarification will be requested to assist with the review of the CMC section of your application.

2. Information regarding major safety concerns.

   The review team has not identified any major safety concerns at this time.

3. Preliminary review committee thinking regarding risk management.

   The review team has no comments regarding risk management at this time.

4. Any information requests sent and responses not received

   We sent a CMC/Facility information request on December 16, 2016 for which we requested a response by January 6, 2017.

5. Any new information requests to be communicated

   - CMC Information Request
     - Assessment of (b) (4)
     - Timeline for additional updated stability data
     - Information regarding process validation studies and (b) (4)
     - Sample request for three vials of final product from each of the (b) (4) conformance lots (b) (4)
   - Update on clinical studies ongoing at time of BLA submission

6. Proposed date for the Late-Cycle meeting (LCM)

   The LCM between you and the review committee is currently scheduled for March 13, 2017.

   We intend to send the LCM meeting materials to you approximately 10 days in advance of the LCM.

If these timelines change, we will communicate updates to you during the course of the review.

7. Updates regarding plans for the AC meeting

There are no plans to present this BLA to BPAC at this time.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

Labeling Target Date: May 31, 2017

PMC Target Date: May 31, 2017

Additional Discussion:
In their email dated December 19, 2016, CSLB requested clarification for comments #3 and #4 of the Agency's December 16, 2016 information request (IR). These comments pertain to the Mix2 Vial device manufactured by Medimop and which is co-packaged with CSL830. CSLB indicated this transfer set is used in all CSLB lyophilized products on the market. According to CSLB, these products are not classified as a combination product and that CSL830 was not identified as such in any of the pre-application meetings with FDA. CSLB asked the Agency to re-review their response to the Agency's August 15, 2016 IR and confirm that CSL830 could be waived from the requirement.

The Agency maintains that CSL830 is a combination product, and CSLB confirmed that they were in agreement. As such, CSLB needs to be able to demonstrate compliance to cGMPs required for combination products. The Agency will work with CSLB to identify an alternative date if the latter cannot respond to the IR by the requested date. The Agency suggested that a streamlined approach to compliance to the cGMPs, as outlined in draft Guidance the *"Current Good Manufacturing Practice Requirement for Combination Products,"* may be applicable.

CSLB indicated they would respond to items #1 and #2 of the IR by January 6, 2017, but would request a short telecon with DMPQ to discuss their approach for addressing items #3 and #4 to ensure they are on the right track. They will communicate with the RPM regarding a date for this telecon. The Agency requested that CSLB provide, by January 6, 2017, a plan and timeline (including proposed teleconference date) for responding to IRs (Donald Ertel) #3 and #4.

CSLB asked if they could refer back to the 510k as part of the documentation. The Agency responded that it is CSLB's responsibility to create a design history file that includes risk assessment specific to this product. The Agency referred CSLB to the preamble of 21 CFR 820 for background and clarification on GMP requirements.

The Agency noted that, once the data is collated for cGMP compliance to this particular combination product, then CSLB has the opportunity to leverage existing data for their submissions of other products, and to support compliance inspections.

The Agency acknowledged that it is ok to leverage existing data in developing a design history file for a combination product that may not have been developed under design controls.

[Additional Note: An example: existing specifications may become part of the design output documentation; testing performed prior to distribution may be included as design verification and validation documentation.]

The Agency stated that CSLB does not need to prepare a development plan or conduct design review meetings for a currently marketed combination product. If device constituent is purchased, the combination product manufacturer is not required to retrospectively "design" the co-packaged device.

[Additional Notes for CSLB's consideration: Based on risk analysis/health hazard assessment, determine if prospective data is needed to assure safety and effectiveness. Leverage CAPA system for planning, implementation, effectiveness checks. Establish design history file (DHF) for the combination product.]

Before the telecon ended, CSLB asked the Agency to confirm the established name for CSL830 is C1 Esterase Inhibitor Subcutaneous (Human). FDA confirmed this is the established name of the product and is consistent with CBER's proper naming convention.