RECORD OF TELEPHONE CONVERSATION

Submission Information

Application Type	BLA
STN	125606/0.0
Review Office	OTAT
Applicant	CSL Behring GmbH / Lic. # 1765
Product	C1 Esterase Inhibitor Subcutaneous (Human)
Trans-BLA Group:	No

Telecon Details

Telecon Date/Time	14-FEB-2017 01:00 PM
Author	CAGUNGUN, NANNETTE
EDR	No
Post to Web	No
Outside Phone Number	
FDA Originated?	No
Communication Categories	OT -
Related STNs	None
Related PMCs	None
Telecon Summary	Discuss proposal for Design History File
FDA Participants	Nannette Cagungun, Donald Ertel, Ewa Marszal, Carolyn Renshaw, Debbie Trout, Bradley Dworak

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Applicant Participants	Marburg, Germany: Petra Hintz-Obertreis, Director Quality Bulk and Release QBR Christiane Kolb, Senior Project Manager Karin Mueller-Stark, RA Manager CMC Thomas Pfeifer, Senior Manager PRD Packaging and Devices King of Prussia, PA: Peter Douglas, Director Novel Technologies Project Management Tatyana Ilyina, Quality Manager, Combination Products and Medical Devices Sarah Mycroft, Director Clinical Safety Physician Baldev Rana, Associate Director Regulatory Regional Lead for North America Michele Walsh, RA Manager

Telecon Body:

CSLB had requested FDA to review and discuss in a teleconference the outline of their proposal for the Mix2Vial Design History File (DHF) in response to FDA's December 16, 2017 CMC information request. A telecon was scheduled for February 9, 2017.

On February 8, 2017, FDA provided points for discussion for the February 9, 2017, conference call. However the meeting did not take place because of a snowstorm that closed CSLB's offices in King of Prussia. The meeting was rescheduled for February 14, 2017.

CSLB provided preliminary comments to on February 13, 2017 to facilitate the discussion.

Please note: FDA Comment in **bold,** immediately followed by CSLB Comment.

1. **The Agency expects that you clearly establish your procedure for review of all the records in the DHF at all stages of development (in your case, that this device is appropriate for use with your product), and the reviews are documented and recorded in the DHF itself.**

CSLB Comment:
CSL Behring 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.

Additional Discussion:
FDA acknowledged CSLB's plan for establishing a standard procedure for Design Controls.

2. **The Agency expects that the records in the DHF 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. As example, 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 audit of active DHF binders in order to ensure that design projects are following the approved design plans.**

CSLB Comment:
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.
The DHF for HAEGARDA will be completed prior to marketing of the product and available for audit by May 2017.

We would like FDA to comment on the proposed content of the HAEGARDA DHF as presented in Table 1 of the 06 Jan 2017 response in 1.11.1 document. A copy of Table 1 has been included here to facilitate discussion.

3. **The Agency expects that since you do not manufacture the M2V constituent, that you have a Quality Agreement in place with Medimop that establishes a well-defined procedure for Medimop to notify you of changes (particularly those involving physical features and materials of construction) to the M2V, prior to making the changes, to allow for you to perform the appropriate design review.**

CSLB Comment:
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 six (6) months 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 thirty (30) working 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. Another Quality Agreement point-to-consider would be that you require that Medimop notify you of any proposed 510K amendment(s), if applicable, for the M2V to allow for you to perform the appropriate design review.

CSLB Comment:
CSL Behring will revise above text to mention 510k amendments specifically.

Additional Discussion:
FDA stated CSLB's plan to address Quality Agreement is acceptable. The plan has to be effective and up to date in case the facility has to be inspected.

4. The Agency considers (b) (4) to be a critical quality attribute of the (b) (4) Please provide details on how you verify that (b) (4) of the (b) (4) is being consistently met.

CSLB Comment:
CSL Behring agrees that the (b) (4) is a critical quality attribute of the (b) (4). The (b) (4) is ensured by the following measures:

- (b) (4)

Additional Discussion:
FDA indicated that CSLB's proposal for the content of the Mix2Vial Design History File seemed fairly comprehensive and pointed out the importance of including design reviews in the DHF.

CSLB noted that the documents in the DHF will be available for audit. FDA commented it will be a more effective audit if all components of the DHF are organized in one place. CSLB clarified that the (b) (4) audits are done on site in Marburg.

Table 1: Outline of a Design History File

Design input	Design output	Design verification	Design validation	Design change
Definition of technical profile, performance characteristics, safety requirements	Device description	Quality Control Procedures	Validation reports (device manufacturing process)	Design change history
Risk analysis	Specification, drawings	Functionality tests	Analysis of complaints from the market	Change control system
	Instructions for use	Compatibility (stability) studies	User tests	
		E/L studies		

FDA indicated the binder can either be paper or electronic. CSLB noted the timeline for completion of the DHF is May 2017.

CSLB will submit a BLA amendment that contains their responses to FDA's comments.

CSLB will provide a summary of the (b) (4) issue and resolution with (b) (4) following reconstitution using Mix2Vial, and its relevance to other products, if any, in an amendment by February 28, 2017.

CSLB noted this was the first time this product was identified as a combination product and asked if this was a global advice that could be applied to future products that use Mix2Vial. FDA said any product that uses the Mix2Vial is a combination product and will be subject to review during inspection. This is also true for legacy products.

Action Items:

CSLB will prepare an electronic DHF on site in Marburg which will be available for inspection. The following will be submitted to the BLA:

- DHF related to Mix2Vial.

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- Summary of the product (b) (4) issue with (b) (4) and the resolution process. They will provide the mitigation steps in a Quality amendment by February 28, 2017.

- CSLB will ensure that the Medipmo Quality Agreement remains current and will include a copy in the DHF.