

From: Maruna, Thomas
Sent: Tuesday, February 09, 2016 3:38 PM
To: 'Angela.Azzara@cslbehrlng.com'; KevinDarryl.White@cslbehrlng.com
Subject: February 9. 2016 Information Request - BLA 125591.0 - Please Respond By February 17. 2016

Importance: High

CSL Behrlng Recombinant Facility AG
Attention: Mr. Kevin Darryl White
February 9, 2016
Sent by email

Dear Mr. White:

We are reviewing your May 29, 2015 biologics license application (BLA) for the following:

STN	Name of Biological Products
125591/0	Antihemophilic Factor (Recombinant), Single Chain

We determined that the following information is necessary to continue our review:

1. Please plot the individual laboratory results for your product from the field study in a regression line graph of one-stage (OS) assay vs. chromogenic substrate (ChS) assay as you have done for Figures 1-8 and 1-9 on pages 30-33 in 2.7.1 Summary of Biopharmaceutical Studies (include data points with and without the correction factor applied). Additionally, with regard to Figures 1-8 and 1-9 on pages 30-33 in 2.7.1 Summary of Biopharmaceutical Studies, please submit two additional graphs for FVIII activity levels that re-graph and reanalyze the same data at the (b) (4) levels only (i.e., (b) (4)). The data is clumped at these levels and we want a reanalysis that spreads this data out, as these values are at the more critical levels. Please ensure that you provide the regression statistics (i.e., coefficient of determination) for all regression line graphs – including Figures 1-8 and 1-9 on pages 30 – 33 in 2.7.1 Summary of Biopharmaceutical Studies – with your response to this information request.
2. Given your proposal to use the ChS assay for potency assignment and labeling of your product, and the need for use of a conversion factor to align the FVIII activity measurements of the OS and ChS assays, please propose a communication strategy to be incorporated into your pharmacovigilance plan – in addition to the labeling strategy you have already proposed – to help to ensure the least amount of confusion on the part of providers when dosing and assessing the effectiveness of your product based on the OS assay.

3. In 5.3.1.4 Final Report on an International Comparative Field Study dated September 18, 2015, you have provided data and analyses based on the calculated FVIII activity from the in-house standard for calibration, but you have not provided data and analyses based on the standard human plasma or the product specific reference standards. Please provide these data and analyses.
4. Please clarify whether clinicians used the OS assay in monitoring/managing patients in the clinical studies, and if so, were the OS assay results locally derived (i.e., on-site and not at the CSL central lab)?
5. Please comment on the meaningfulness of the comparison to Advate in the field study, given that spiked values for your product were based on measured potency, whereas nominal potency was used for Advate, along with the fact that you included a dose adjustment analysis in the clinical trials.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your responses as an amendment to this file by February 17, 2016 referencing the date of this request.

The action due date for this file is May 28, 2016.

If you have any questions, please contact me.

Very Respectfully,

Thomas J. Maruna, MSc, MLS(ASCP), CPH

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