

STN 125350/0 Information Request - Hizentra, August 19, 2009

- **From:** Ko, Hon Sum
To: "Paula.Hines@csllbehring.com";
cc: Rana, Pratibha; Jain, Nisha;
Subject: RE: STN 125350/0 Information Request
Date: Wednesday, August 19, 2009 8:15:25 AM

Dear Dr. Hines:

You can submit all material together by Aug 28. We also had internal discussion on Monday about your pediatric data, and the conclusion was that you should request deferral despite having data on 3 children and 7 adolescents in the current BLA submission. You may seek approval of the BLA based on the 10 children and we shall follow the spirit of PREA in not holding up approval for the inadequacy of pediatric data in certain age subgroups. However, the information in the BLA is not likely to satisfy the Pediatric Review Committee, as acceptability criteria have been evolving upon accumulation of experience since FDAAA, and you should not base your decisions upon past BLAs.

Since you will actually have additional data of 18 children and 5 adolescents (making a total of 21 children and 12 adolescents), these data will have to be submitted for updated labeling post-approval (if approved by Feb 28, 2010), the best course for you to take is still requesting deferral.

Let me know if you need any further clarification.

Hon-Sum Ko

From: Paula.Hines@csllbehring.com [mailto:Paula.Hines@csllbehring.com]

Sent: Tuesday, August 18, 2009 12:36 PM

To: Ko, Hon Sum Cc: Rana, Pratibha

Subject: RE: STN 125350/0 Information Request

Dear Dr. Ko,

Thank you for the clarifications below. We have had internal discussions concerning our options in terms of the pediatric data. At this time, CSLB feels it is justified to provide a rationale to seek approval based on the 10 children. However, we request some additional time (1 week) to finalize and send this to FDA. Is it acceptable to FDA that we will submit the "rationale" by 28 August?

In the meantime, we can submit the responses to Q1 and Q2 by this Friday (21Aug) unless FDA prefers that we submit everything together.

Please let me know if the extension to next Friday (28Aug) is acceptable for Q3 and what is your preference for when to submit the responses to the other two questions. Thanks and best regards,
Paula

From: Ko, Hon Sum [mailto:HonSum.Ko@fda.hhs.gov]
Sent: Friday, August 14, 2009 8:15 PM
To: Hines, Paula US/KOP
Cc: Rana, Pratibha
Subject: RE: STN 125350/0 Information Request
Dear Dr. Hines:

1. If we provide a rationale as to why we think 10 pediatric subjects are enough to support use in children and adolescents, then does that mean we do not need a Deferral? Or should we do both (provide rationale and request Deferral)? In other words, we can seek approval based on 10 children (get this approved in the label) and then commit to provide additional pediatric data from the European study as soon as it's available?
 - o The 10 pediatric subjects include 3 children and 7 adolescents. The amount of information is not likely to support use in either age subgroup. Labeling presumably will mention their data with some qualifier that this is not adequate information (this is my tentative projecture and is not representing official verdict). If CSLB agrees that would be the case, CSLB can simply request Deferral and submit the remaining data post-approval as soon as they are available. There is no further need of providing a rationale.
2. Is this adequate time for FDA's assessment and incorporation into the IgPro20 label? Or will this automatically result in an extension of the review period (it is less than 3 months before the action due date of 28Feb10)?
 - o The purpose of Deferral is not to hold up approval if the adult data are adequate. The new information can be the subject of a supplement to change the label. If CSLB insists labeling with the additional information by submitting the assessment shortly before the due date (Feb 28), there are two possibilities. One is an extension as mentioned in the email, but it is more likely that it will not be reviewed at the present cycle, because that may hold up approval. It is important to note that the new data must not be simply available, but integrated with the existing data in order for the labeling to be complete. Thus having them available in January is not the only bar, but there is work in the integration, to the extent of updating the ISS and ISE.
3. Further a Pediatric Plan document is requested in Q #3 with the Deferral. We have submitted a Pediatric Assessment, including a request for a partial waiver in neonates and infants, in Module 1.9.1 of our BLA. What additional information is required to fulfill the Pediatric Plan document? We refer to the FDA guidance: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf>

- I do understand CSLB has a Pediatric Assessment document in Module 1. This cannot be taken as the Pediatric Plan per se. FDAAA has established the Pediatric Review Committee which now reviews all PREA Deferrals, and they require to see **a specific document by the title "Pediatric Plan"**. You have rightly referred to the guidance and in Section V.A., you will find the following recommendation: "A Pediatric Plan is a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that the applicant plans to conduct. The plan should also address the development of an age-appropriate formulation. Furthermore, it should address whether and, if so, under what grounds, the applicant plans to request a waiver or deferral under PREA." CSLB has essentially the needed information in Module 1 of the BLA, but simply needs to reorganize to fit the guidance and make the appropriate changes, especially if request for Deferral is to be made.

If you need any further clarification, please do not hesitate to be in touch with us.

Thank you.

Hon-Sum Ko.

From: Rana, Pratibha

Sent: Friday, August 14, 2009 6:57 PM

To: Ko, Hon Sum Subject: Fw: STN 125350/0 Information Request

From: Paula.Hines@csllbehring.com <Paula.Hines@csllbehring.com>

To: Rana, Pratibha

Cc: Elaine.Zumpino@csllbehring.com <Elaine.Zumpino@csllbehring.com>

Sent: Fri Aug 14 16:21:42 2009 Subject: RE: STN 125350/0 Information Request

Dear Pratibha,

Concerning Q #3 below:

I would like to clarify with FDA what is meant by a Deferral in terms **of the proposed label**. If we provide a rationale as to why we think 10 pediatric subjects are enough to support use in children and adolescents, then does that mean we do not need a Deferral? Or should we do both (provide rationale and request Deferral)? In other words, we can seek approval based on 10 children (get this approved in the label) and then commit to provide additional pediatric data from the European study as soon as it's available?

Additionally in regards to timing, we know that the final clinical study report for the European study, which will include data from an additional 18 children and 5 adolescents, will not be available **until Jan 2010**. Is this adequate time for FDA's assessment and incorporation into the IgPro20 label? Or will this automatically result in an extension of the review period (it is less than 3 months before the action due date of 28Feb10)?

Further a Pediatric Plan document is requested in Q #3 with the Deferral. We have submitted a Pediatric Assessment, including a request for a partial waiver in neonates

and infants, in Module 1.9.1 of our BLA. What additional information is required to fulfill the Pediatric Plan document? We refer to the FDA guidance:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf>

Therefore, we seek advice on how to appropriately respond to Q #3 and would like to discuss our options with FDA.

Best regards,

Paula

P.S. Please copy Elaine Zumpino on any email to me. I will be working from home on Monday, Aug 17 and cannot read secure email from FDA from home.

From: Rana, Pratibha [mailto:Pratibha.Rana@fda.hhs.gov]

Sent: Wednesday, August 12, 2009 4:43 PM

To: Hartmann, Paul US/KOP; Hines, Paula US/KOP

Subject: STN 125350/0 Information Request

To: Paul Hartmann

CSL Behring AG

Date: August 12, 2009

This is regarding your BLA submission STN 125350/0 for Immune Globulin Subcutaneous (Human), 20% Liquid, submitted to the Agency on April 30, 2009. FDA continues with the review of the referenced submission and requests CSL Behring AG to provide the following information.

1. To facilitate reviewing the submission, please submit electronic files in Microsoft Word for Sections 1 to 13 of each clinical study report (ZLB04_009CR, ZLB04_008CR, and ZLB06_003CR) in Microsoft Word.
2. Please provide an additional xpt file for adverse events showing (a) start time of immediate preceding infusion, (b) end time of immediate preceding infusion, (c) whether the event started between start time and within 48 hours of end of the infusion, and (d) whether event started between start time and within 72 hours of end of the infusion.
3. Please provide your rationale why 10 pediatric subjects' data are sufficient to support use of IgPro20 in children and adolescents. Since you will have additional data from European studies that include children and adolescents, please request a Deferral for submission. Please submit a Pediatric Plan document when you request for a PREA deferral for pediatric data submission.

Please submit a response to this request as an amendment to the file by August 21, 2009.

Thank you.

Pratibha Rana

Pratibha Rana, M.S.

Regulatory Project Manager

FDA/CBER/OBRR

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