

From: Maruna, Thomas  
Sent: Tuesday, May 17, 2016 10:59 AM  
To: 'Denloye, Aderonke O'  
Cc: Reed, Jennifer  
Subject: RE: Follow-up: May 3. 2016 (Clinical) Information Request

Importance: High

Aderonke,

We have reviewed the justifications you provided for excluding measurements of (b) (4) and osmolality as release specifications. As discussed in our teleconference on April 21, 2016, IG delivered by subcutaneous route still has the potential for adverse events related to thrombogenicity. We feel that measurements of (b) (4) and osmolality are useful measures of your product's quality and consistency. Information from these tests may aid in rapid identification of outlier lots, which could further limit patient risk. These considerations outweigh a desire to streamline specifications based on the Ph. Eur. monograph, or desire for a harmonized global specification. With these considerations in mind, we request the following commitments post-marketing:

1. Based on one year of manufacturing experience, please establish specifications for (b) (4), osmolality, (b) (4) for IGSC, 20% final product. Validation of tests, proposed specifications, and testing data will be submitted as a PAS by July 13, 2017. In the meantime, you may modify your Lot Release Protocol by adding these tests "For Information".
2. Please submit as a PAS the recalibrated (b) (4) assay reported as mIU (b) (4) using the (b) (4) international standard, and a proposed lot release specification based on manufacturing experience, within 12 months of BLA approval (September 13, 2017). In the meantime, please modify your Lot Release Protocol by adding the (b) (4) "For Information."

Respectfully,

Thomas J. Maruna, MSc, MLS(ASCP), CPH  
Lieutenant, U.S. Public Health Service  
Senior Regulatory Management Officer  
FDA/CBER/OBRR/IO

thomas.maruna@fda.hhs.gov  
Office: (240) 402-8454

From: Denloye, Aderonke O [mailto:Ade.Denloye@baxalta.com]  
Sent: Monday, May 16, 2016 8:16 PM  
To: Maruna, Thomas  
Subject: RE: Follow-up: May 3. 2016 (Clinical) Information Request

Dear Thomas:

Hope this finds you doing well. Thanks for your feedback to our draft response. We will review and make necessary revisions to address your comments provided below, and I will keep you posted of a submission date.

My understanding from the teleconference was that FDA would also provide a response today 16May2016 to our amendment submitted 9May2016 (SEQUENCE 0019) in which we provided the following:

? Baxalta justification for the not including (b) (4) , Osmolality and (b) (4) as release specification for IGSC, 20%  
? Proposal to PMC #2

When can we expect a response?

Best regards,  
Aderonke Denloye, MPH  
Associate Director, Global Regulatory Affairs

From: Maruna, Thomas [mailto:Thomas.Maruna@fda.hhs.gov]  
Sent: Friday, May 13, 2016 11:48 AM  
To: Denloye, Aderonke O  
Subject: Follow-up: May 3. 2016 (Clinical) Information Request

Aderonke,

We have reviewed your draft response regarding FDA information request (dated May 03, 2016). We have following comments:

1. We found the responses to question 1 and 3 are acceptable.
2. For this assay, LOQ is required for the (b) (4) which include (b) (4) . We disagree with your LOQ determination for

(b) (4) in response to the question 2. In the table 5, you found that a sample with (b) (4). Thus you calculated that the LOQ for (4). The LOQ of (b) (4) is calculated using a similar approach. Please provide your justification or a scientific reference article for such approach for the LOQ determination in a (b) (4) method.

If you conclude that LOQ for (b) (4) respectively, please provide data in support of your conclusion from samples, which contain (b) (4), respectively. The data should show adequate accuracy, precision, and (b) (4).

The figure 4 in your response is not adequate. Using ICH Q2(R1) equation  $LOQ = 10\sigma/S$  to determine the LOQ of either (b) (4) in a (b) (4) assay, multiple points are required for (b) (4) below your specification limit. Please provide adequate data to establish LOQ of your assay for both impurities.

3. Please provide the (b) (4) of lots (b) (4).  
Zoomed in figures may be necessary in order to clearly show the (b) (4).

Please let me know if you have any questions.

Respectfully,

Thomas J. Maruna, MSc, MLS(ASCP), CPH  
Lieutenant, U.S. Public Health Service  
Senior Regulatory Management Officer  
FDA/CBER/OBRR/IO  
thomas.maruna@fda.hhs.gov  
Office: (240) 402-8454

From: Denloye, Aderonke O [mailto:Ade.Denloye@baxalta.com]  
Sent: Friday, May 13, 2016 1:32 PM  
To: Maruna, Thomas  
Subject: RE: Follow-up: May 3. 2016 (Clinical) Information Request - BLA 125596.0 - Please Respond by May 6. 2016

Yes I now have revised tables that I can submit by Monday that include the NUMBER OF SUBJECTS for 170903.

Best regards,  
Aderonke Denloye, MPH  
Associate Director, Global Regulatory Affairs  
Baxalta US Inc.  
One Baxter Way  
Westlake Village, CA 91362 USA  
+1 805 372 3053 desk  
+1 805 372 3052 Facsimile  
ade.denloye@baxalta.com  
"A wise man learns from his own mistakes, but a genius learns from others."- Mark Twain

From: Maruna, Thomas [mailto:Thomas.Maruna@fda.hhs.gov]  
Sent: Friday, May 13, 2016 10:23 AM  
To: Denloye, Aderonke O  
Subject: RE: Follow-up: May 3. 2016 (Clinical) Information Request - BLA 125596.0 - Please Respond by May 6. 2016

Ade,

You appear to have addressed the NUMBER OF SUBJECTS for 160601 but I don't see the same information for 170903.

Tom

From: Denloye, Aderonke O [mailto:Ade.Denloye@baxalta.com]  
Sent: Friday, May 13, 2016 1:12 PM  
To: Maruna, Thomas  
Cc: Landow, Laurence  
Subject: RE: Follow-up: May 3. 2016 (Clinical) Information Request - BLA 125596.0 - Please Respond by May 6. 2016  
Importance: High

Dear Lt. Maruna & Dr. Landow:

Hope this finds you doing well.

Question 1:

Baxalta submitted SEQ 0021 on Monday 9 May 2016 and I believe the table provided within that amendment addresses Q1 below, could you please verify?

Question 2:

Tables 3 & 4 from SEQ 0014 submitted on 30Mar2016 will be updated to include the number of

subjects, please verify?

I will await your response prior to submitting this information as an amendment to the BLA, thanks.

Best regards,  
Aderonke Denloye, MPH  
Associate Director, Global Regulatory Affairs  
Baxalta US Inc.  
One Baxter Way  
Westlake Village, CA 91362 USA  
+1 805 372 3053 desk  
+1 805 372 3052 Facsimile  
ade.denloye@baxalta.com  
"A wise man learns from his own mistakes, but a genius learns from others."- Mark Twain

From: Maruna, Thomas [mailto:Thomas.Maruna@fda.hhs.gov]  
Sent: Thursday, May 12, 2016 3:25 PM  
To: Denloye, Aderonke O  
Cc: Landow, Laurence  
Subject: Follow-up: May 3. 2016 (Clinical) Information Request - BLA 125596.0 - Please Respond by May 6. 2016  
Importance: High

Baxalta US Inc.  
Attention: Ms. Aderonke Denloye  
May 12, 2016  
Sent by email

Dear Ms. Denloye:

We have just reviewed all of the March and April responses to our IRs. Most of the requests have been addressed except for the following:

1. For study 160601: Please draft a table of nonserious adverse events by absolute number of subjects (as opposed to proportion of subjects) per treatment cohort. This table should have (a) 6 columns labeled Classification, Part 1, Part 2, Part 3a, Part 3b and Extension (with appropriate sample size for each) and (b) 2 rows labeled local adverse reactions and systemic adverse reactions. The number of subjects, Preferred Term (where applicable), and severity of each adverse reaction in each study Part should be limited to an incidence  $\geq 5\%$ .

2. For study 170903, Safety Analysis Set, Table 3: Please include the number of subjects (as

opposed to annualized rate per subject) per treatment cohort for systemic related AEs, local related AEs, and infusional AEs.

Please respond via BLA amendment by May 16, 2016.

Respectfully,

Thomas J. Maruna, MSc, MLS(ASCP), CPH  
Lieutenant, U.S. Public Health Service  
Senior Regulatory Management Officer  
FDA/CBER/OBRR/IO  
thomas.maruna@fda.hhs.gov  
Office: (240) 402-8454

---

From: Maruna, Thomas  
Sent: Tuesday, May 03, 2016 12:34 PM  
To: 'Denloye, Aderonke O'  
Subject: May 3. 2016 (Clinical) Information Request - BLA 125596.0 - Please Respond by May 6. 2016  
Importance: High

Baxalta US Inc.  
Attention: Ms. Aderonke Denloye  
May 3, 2016  
Sent by email

Dear Ms. Denloye:

We are reviewing your September 14, 2015 biologics license application (BLA) to treat primary immune deficiency disorders associated with defects in humoral immunity for the following:

STN	Name of Biological Products
125596/0 Solution	Immune Globulin Subcutaneous (Human), 20%

We have determined the following information is required to continue our review:

1. Please specify the Integrated Summary of Safety Table number(s) from which the data for Table 3 and Table 4 in the PI were obtained.
2. For study 160601, please draft a table of nonserious adverse events by absolute number of subjects (as opposed to proportion of subjects). This table should have

(a) 6 columns labeled Classification, Part 1, Part 2, Part 3a, Part 3b and Extension (with appropriate sample size for each) and (b) 2 rows labeled local adverse reactions and systemic adverse reactions. The number of subjects, Preferred Term (where applicable), and severity of each adverse reaction in each study Part should be limited to an incidence  $\geq 5\%$ .

Please submit your responses as an amendment to this file by May 6, 2016 referencing the date of this request.

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

The action due date for these files is September 13, 2016.

Very Respectfully,

Thomas J. Maruna, MSc, MLS(ASCP), CPH  
Lieutenant, U.S. Public Health Service  
Senior Regulatory Management Officer  
Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Blood Research and Review  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
thomas.maruna@fda.hhs.gov  
O: (240) 402-8454  
www.usphs.gov

"THIS MESSAGE, INCLUDING ANY ATTACHMENTS, 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 immediately notify the sender by e-mail or phone.