RECORD OF TELEPHONE CONVERSATION

Submission Information

Application Type	BLA
STN	125614/0.0
Review Office	OVRR
Applicant	GlaxoSmithKline Biologicals / Lic. # 1617
Product	Zoster Vaccine Recombinant, Adjuvanted

Telecon Details

Telecon Date/Time	05-JUN-2017 09:21 AM
Author	NAIK, RAMACHANDRA
FDA Originated?	Yes
Communication Categories	IR - Information Request
Telecon Summary	CMC IR regarding Shingrix manufacturing and quality
FDA Participants	Ramachandra Naik, Michael Smith and Carmen Collazo-Custodio
Applicant Participants	Norris Pyle and Jody Gould

Telecon Body: E-mail message and IR attachment pasted below.

RECORD OF TELEPHONE CONVERSATION

From: Naik, Ramachandra
Sent: Monday, June 05, 2017 9:21 AM
To: 'Norris Pyle'
Cc: Collazo, Carmen; Smith, Michael (CBER); 'Jody Gould'
Subject: STN 125614/0: IR regarding manufacturing and quality

Dear Mr. Pyle,

Attached is a request for additional CMC information regarding STN 125614/0 (Zoster Vaccine Recombinant, Adjuvanted). Please provide your responses, in an amendment to STN 125614/0, by Monday, June 26, 2017.

Please confirm receipt of this message, and let us know if you have any questions or need additional information.
Regards,
Ram

Ramachandra S Naik, Ph.D.
Primary Reviewer/Regulatory Project Manager
Food and Drug Administration
CBER/OVRR/DVRPA/RRB3
10903 New Hampshire Avenue
Building 71, Room 3045
Silver Spring, MD 20993
Phone: (301) 796-2640
FAX: (301) 595-1244

RECORD OF TELEPHONE CONVERSATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
OFFICE OF VACCINES RESEARCH AND REVIEW
DIVISION OF VACCINES AND RELATED PRODUCT APPLICATIONS

Date: **June 5, 2017**

Pages: **7**

To: **Norris Pyle**
North American Regulatory Affairs, Vaccines
GlaxoSmithKline Biologicals
14200 Shady Grove Road
VR1500
Rockville, MD 20850
Telephone: (610) 917-4086 Fax: (240) 238-9822

From: **Division of Vaccines and Related Products Applications**
Office of Vaccines Research and Review
Point of Contact: Ramachandra Naik, Ph.D.
Regulatory Project Manager
10903 New Hampshire Ave., White Oak Bldg. 71
Silver Spring, MD 2993-0002
Telephone: (301)-796-2640 Fax: (301)-595-1124

STN: **125614/0**

Product: **Shingrix (Zoster Vaccine Recombinant, Adjuvanted)**

Subject: **Request for additional CMC Information**

Dear Mr. Pyle,

Our review of the information provided in your BLA dated October 21, 2016, for Zoster Vaccine Recombinant, Adjuvanted, is ongoing. We have the following request for additional information:

1. Regarding in-process testing of the gE Antigen (b) (4), gE Antigen (b) (4) $AS01_B$ Adjuvant for (b) (4), no limits appear to have been set for this process monitoring testing for commercial manufacturing. We recommend that you implement an action limit at each step that is in line with your process capability. Alternatively, you could implement an alert limit if the proposed action limit is well above the results for the PPQ lots. Please note that for (b) (4) testing that is performed (b) (4), the action limit should be below the (b) (4).

2. Regarding in-process testing of the $AS01_B$ Adjuvant during formulation for (b) (4), no limits appear to have been set for this process monitoring testing for commercial manufacturing. We recommend that you implement an action limit that is in line with your process capability for commercial manufacturing. Alternatively, you could implement an alert limit if the proposed action limit is well above the results for the PPQ lots.

3. Please clarify and describe the supplier(s) of the vials and flip-off caps used for the $AS01_B$ Adjuvant and gE Antigen.

4. The lyophilization cycle described in Figure 2 in *Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls - Filling and Lyophilization*, appears to include a design space for time, temperature and pressure for the various phases of the cycle. If this is correct, please clarify how this design space was qualified, such as describing the minimum/maximum runs that were performed, in order to support that gE Antigen lyophilized within this space will routinely be of acceptable product quality across each lot of product.

5. Regarding in-process testing of the gE Antigen FC for fill volume, no limits appear to have been set for commercial manufacturing. We recommend that you implement an action limit that is in line with your process capability for commercial manufacturing.

6. In follow-up to our email of March 13, 2017 requesting submission of release data on (b) (4) gE Antigen FC lots filled under the continuous (b) (4) filling duration as a BLA amendment in August 2017, please also provide the results of testing for (b) (4) for these lots at release as well as a summary of the results of the EM performed for the filling of these lots.

7. We note that you have provided extended sampling data for several lots of gE Antigen lyophilized in the (b) (4) lyophilizers proposed for use. Please provide product (b) (4) data to support that the lyophilizers' (b) (4) operate consistently during the lyophilization cycle used for the gE Antigen, or provide a justification of why such data is not necessary.

8. We note that CCIT for the gE Antigen Final Container was performed using the (b) (4) method and that the gE Antigen Final Container has a (b) (4), suggesting that this method might not be appropriate. Please clarify the reason for including the (b) (4), including if you consider the gE Antigen to be (b) (4) sensitive. Please also provide a rationale supporting that the (b) (4) method is appropriate to confirm integrity of the container closure system, or submit CCIT data that supports that the integrity of your container closure prevents (b) (4), if available.

9. Please clarify if there were any changes made to the following relevant aspects of Buildings (b) (4) due to the manufacture of the gE Antigen (b) (4), $AS01_B$ Adjuvant and gE Antigen in these buildings:

    a. The facility diagrams provided in the BLA
    b. The manufacturing rooms listed in the BLA
    c. The flows described in the BLA
    d. The environmental monitoring programs described in the BLA
    e. The routine monitoring of the water systems described in the BLA
    f. The routine monitoring of the gaseous systems described in the BLA
    g. The contamination and cross-contamination controls and procedures described in the BLA including the facility cleaning/disinfection/ decontamination agents and procedures, equipment cleaning/decontamination/sterilization agents and procedures, and the changeover/line clearance procedures

10. Please provide a description of the routine monitoring (limits and frequency) of the (b) (4) systems in Facility (b) (4) and in Buildings (b) (4).

11. Please clarify if the routine monitoring of the (b) (4) system in Facility (b) (4) includes monitoring of viables and non-viables. Please provide a description of the routine monitoring (limits and frequency) if it is performed or a rationale for why such monitoring is not needed.

12. We note that the (b) (4) in Facility (b) (4) is not currently monitored for viables due to an unexplained (b) (4) output flow. Please clarify the root cause of this issue and how it is being addressed.

13. Please provide the most recent routine monitoring data for the (b) (4) system in Facility (b) (4).

14. Please clarify if the validations of the (b) (4) in Facility (b) (4) provided in the BLA have been previously reviewed under an approved supplement or BLA, and provide the STN(s) and approval date(s).

15. We note that the cleaning validation (document VAS0000064009) covering the (b) (4) only includes (b) (4) runs for (b) (4) and that the (b) (4) used in these runs were not identified in the report. Please clarify the tanks that were used for these runs and if cleaning validations were performed for the other (b) (4), and provide the applicable study report(s) or a justification to support the cleanability of these (b) (4).

16. Regarding the cleaning validations performed for the (b) (4) used to clean product-contact equipment and materials used for the gE Antigen

(b) (4) manufacturing process (documents VAS0000089643, VAS0000089655, VAS0000089650, VAS0000089648, VAS0000089652, VAS0000089654, VAS0000089653 and VAS0000089646), please provide a table that clarifies the following items:

a. The (b) (4) used during the runs
b. The (b) (4) used during each run and how it relates to the (b) (4) the equipment will experience during commercial production (the same or more worst-case)

Finally, if a worst-case (b) (4) was used for the runs, please clarify why this (b) (4) is considered worst-case compared to the (b) (4) that would be experienced during commercial manufacturing.

17. The narrative text states that (b) (4) are used in Facility (b) (4) but only (b) (4) are identified. Please clarify (and identify) the actual number of decontamination (b) (4) used for the gE Antigen (b) (4) manufacturing process.

18. Regarding the following cleaning validations, the study reports state that various (b) (4) were established based upon these validations. However, the actual (b) (4) used during the runs to support the proposed (b) (4) were not supplied in the reports. Please provide the actual (b) (4) for these runs.

19. Regarding the qualifications of the manual cleaning and (b) (4) of material used for the gE Antigen (b) (4) manufacturing process in Facility (b) (4) (documents VAS0000064728, VAS0000064950, VAS0000064843 and VAS0000055834) and of the manual cleaning of reusable items in contact with QS-21 in Building (b) (4) (document (b) (4) VAS20110814), please clarify if for each of these validations the runs were performed by different operators.

20. We note that the EM program in Buildings (b) (4) includes (b) (4) sampling for viables in the (b) (4) but the locations and rationale for these (b) (4) is not provided. Please clarify.

21. Please clarify if the qualifications of the (b) (4) in Building (b) (4) (documents (b) (4) VAS20090864, (b) (4) VAS20090984, (b) (4) VAS20110619, (b) (4) VAS20110625, (b) (4) VAS0000079955 and (b) (4) VAS0000079958) submitted in the BLA have been previously submitted to CBER, and provide the applicable STN(s) and approval date(s).

22. Regarding the (b) (4) used for the manufacture of the $AS01_B$ Adjuvant in Building (b) (4), please clarify if this is a new piece of equipment and describe how it was qualified. If it is a new piece of equipment, please provide any applicable validation reports.

23. Please clarify how the (b) (4) used for the following cleaning validations is more worst-case than the (b) (4) the equipment would experience during commercial manufacturing:

    - Cleaning in (b) (4) used for the gE Antigen and/or $AS01_B$ Adjuvant manufacturing process in Building (b) (4) (documents (b) (4)).
    - Cleaning using (b) (4) of the (b) (4) formulation and (b) (4) used for the gE Antigen and/or $AS01_B$ Adjuvant manufacturing process in Building (b) (4) (documents (b) (4) VAS20110151, (b) (4) VAS0000056128, (b) (4), VA-0000068346 and (b) (4) VAS0000068432).
    - COP of (b) (4) used for the gE Antigen manufacturing process in Building (b) (4) (documents 20110694 and (b) (4)).
    - Manual cleaning of the filling manifold used for the gE Antigen manufacturing process in Building (b) (4) (document 20060471)

24. We note that the cleaning validation (document (b) (4) VAS0000068432) covering the COP of the (b) (4) dedicated to the manufacture of the $AS01_B$ Adjuvant in Facility (b) (4) only includes (b) (4) stations used in these runs were not identified. Please clarify the (b) (4) stations that were used for these runs and if cleaning validations were performed for the other (b) (4), and provide the applicable study report(s) or a justification to support the cleanability of these (b) (4).

25. Regarding the validation of the (b) (4) (document (b) (4) VAS20110321), the study report states that the equipment was (b) (4) with (b) (4) before cleaning. Please clarify the composition of (b) (4) and how it relates to the (b) (4) this equipment would experience during commercial manufacturing.

26. The Facility (b) (4) Comparability Protocol does not contain clearly defined acceptance criteria for the testing and validations that will be performed to support the qualification of the use of (b) (4), as recommended in the *Guidance for Industry Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information*. Please submit a revised Comparability Protocol that contains a description of the tests that will be performed and the acceptance criteria for these tests (such as in a table). Alternatively, the revised Comparability Protocol could confirm that the testing and acceptance criteria applied for the qualification of the use of (b) (4) will be the same as described in the BLA for (b) (4).

27. In reference to the information provided in the original submission for the BLA and in the amendments of December 21, 2016 (STN 125614/0/5) and March 30, 2017 (STN 125614/0/15) regarding the (b) (4) of the filling line (b) (4) and timing of set-up of the filling line, we have the following comments:

    a. Please provide the study reports for the aseptic process simulation runs described in the amendment of December 21, 2016 (STN 125614/0/5) that includes a description of any deviations.

    b. Please clarify if the aseptic process simulation runs described in the amendment of December 21, 2016 (STN 125614/0/5) were performed using the (b) (4) cycle and timing of set-up proposed in document *Process Performance Qualification Filling and Lyophilization – Annex 2* in the BLA original submission.

    c. Please provide a detailed description of how the sampling for residual (b) (4) including how frequently measurements are taken and the procedures for obtaining the measurements.

    d. In reference to the pre-read for the Type C meeting of December 10, 2015, held under INDs 13857 and 13879, you state that you observed under commercial production conditions (b) (4) levels up to (b) (4) remained inside the (b) (4), even after the test for the (b) (4) had been met. Please provide information/data to support that you can accurately determine the (b) (4) residual throughout your (b) (4).

e. In reference to the minutes of the Type B meeting of April 16, 2016 held under INDs 13857 and 13879, we acknowledge that CBER agreed that you would not need to revalidate your (b) (4) cycle based upon the changes to the aeration that you have proposed in document *Process Performance Qualification Filling and Lyophilization – Annex 2* in the BLA original submission, as long as none of the sterilization conditions or placement of equipment ((b) (4)) has changed. Therefore, please confirm that no changes to the placement of equipment ((b) (4)) were made for commercial manufacturing as this point does not appear to be mentioned in the BLA.

f. We note that as described in document *Process Performance Qualification Filling and Lyophilization – Annex 2* in the BLA original submission, you will be (b) (4) . We also note that you will not be implementing more sensitive measuring equipment under this BLA as described in the amendment of March 30, 2017 (STN 125614/0/15). Please provide information/data that supports that (b) (4) in order to confirm that you are capable of measuring the specified (b) (4) residual in your (b) (4) prior to set-up and filling.

Please provide your responses, in an Amendment to STN 125614/0, by Monday, June 26, 2017. We recommend that you restate each item and follow it with your explanation or clarification. Use of this format helps organize the relevant information and provides a self-contained document that facilitates future reference. If you have any questions about this communication, please contact Ramachandra Naik, Ph.D. or Michael Smith, Ph.D. at (301) 796-2640.