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
Trans-BLA Group:	No

Telecon Details

Telecon Date/Time	20-APR-2017 10:30 AM
Author	SMITH, MICHAEL
EDR	No
Post to Web	No
Outside Phone Number	857-207-4197
FDA Originated?	Yes
Communication Categories	IR - Information Request
Related STNs	None
Related PMCs	None
Telecon Summary	

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FDA Participants	• Paula Agger, Clinical Reviewer, OVRR/DVRPA/CRB2 • Carmen Collazo-Custodio, BLA Chair, Team Leader, OVRR/DVRPA/RRB3 • Marion Gruber, Director, OVRR • Andrea Hulse, Branch Chief, OVRR/DVRPA/CRB2 • Philips Krause, Deputy Director, OVRR • Ramachandra Naik, Regulatory Project Manager, OVRR/DVRPA/RRB3 • Michael Smith, Regulatory Project Manager, OVRR/DVRPA/RRB3 • Wellington Sun, Director, OVRR/DVRPA • Elizabeth Sutkowski, Branch Chief, OVRR/DVRPA/RRB3
Applicant Participants	• Ozzie Berger, VP, Head Regulatory Affairs RDC US • Dominique Descamps, Vice President, Head Clinical RDC Belgium • Brecht Geeraerts, Senior Manager, Clinical RDC Belgium • Jody Gould, PhD, Senior Director, North American Regulatory Affairs • Barbara Howe, VP and Director, Vaccines Medical and Clinical, US • Lidia Oostvogels, Director, Clinical and Epidemiology Project Leader Herpes Zoster Vaccine, Clinical RDC Belgium • Kimber Poffenberger, VP and Head, North American Regulatory Affairs • Amy Scott-Billman, VP and Head, Global Regulatory Affairs • Tamzin Tanner, Senior Manager, Global Regulatory Affairs • Fernanda Tavares, Director, Head of Safety Evaluation and Risk Management • Carla Vinals, Director, Global Regulatory Lead Herpes Zoster vaccine • Toufik Zahaf, Senior Manager, Lead Statistician Herpes Zoster Vaccine

Telecon Body:

Background: The mid-cycle meeting for STN 125614.0 was held on April 19, 2017, to update DVRPA and OVRR management on the review of the BLA. During the meeting,

the clinical review team noted that there are numerous problems with the BLA that are making it difficult to review the clinical section of the application in a timely manner (for example: omissions of data, erroneous data submitted, analyses which would help inform conclusions about safety-related outcomes were not provided for the pre-specified time period for SAE collection). It was also noted that numerous Information Requests (IRs) have been sent to the Applicant already, but there are concerns that additional IRs will need to be sent and that the Applicant has not applied their responses to these requests to include revision of similar outputs for other studies and/or documents. Management was concerned these review issues may have an impact on approval of the BLA during a first review cycle and requested a teleconference with the Applicant ahead of the mid-cycle communication that is scheduled for May 3, 2017.

Teleconference: CBER and GSK made introductions, and CBER explained that the purpose of the teleconference was to inform GSK of the serious issues that have been discovered during the clinical review of the BLA. Many of the issues found are regarding the review of the safety data/information for studies Zoster-006 and Zoster-022, the Integrated Summary of Safety (ISS) and the Summary of Clinical Safety (SCS), for example: omissions of data, erroneous tabulations submitted, data and analyses not presented on pre-specified time points. CBER noted that at the mid-cycle timeframe, reviewers are generally close to completion of an initial review of the BLA, but that due to the aforementioned issues the reviewer has been unable to complete a meaningful review. The issues appear to be systemic throughout the BLA submission requiring the CBER reviewers to perform quality control checks of the BLA in lieu of GSK having done this prior to the BLA submission. CBER also noted that it has generated and sent numerous Information Requests (IRs) to GSK and that reviewers are in the process of generating additional request for information without which we will be unable to complete the clinical review.

GSK acknowledged the IRs and acknowledged that errors were made. CBER provided the below specific examples of clinically-related issues that have been identified to date (please also see attached "Post-Applicant teleconference note" below for additional details):

- Several summary tables do not include proportions.

  Post meeting note – For example, see Zoster-006 CSR Table 23 and Zoster-022 CSR Table 20 (number of subjects vaccinated, completed and withdrawn).

- Several key outputs were not provided by System Organ Class (SOC), only by Preferred Terms (PT) for many events by time. In addition, some tabulations were not provided for time periods pre-specified for safety data collection (e.g., number/percentage of subjects with SAEs reported during Months 0-14, number/percentage of North American subjects in the main pooling reporting SAEs during Months 0 -14); an IR was previously sent to GSK on this issue.

- Comparative analysis of SAEs reported by subjects in the main pooling was provided in the SCS, but for the whole post-vaccination period, not for the pre-specified time period for the collection of SAEs (i.e., Month 0-14). Additional

timeframes might be useful, but if analyses are provided, it should be for the pre-specified time period that was listed in the protocol. Additionally, it appears that SAE reporting dropped off after the first year, which was as expected as unrelated and/or non-fatal SAEs were not pre-specified for collection beyond Month 14. SAE analyses beyond the pre-specified time period therefore may not be robust. CBER identified the following issues with the Standardized MedDRA Query (SMQ) analysis of most common SAEs in studies Zoster-006 and Zoster-022:

- It was not specified what events were analyzed (e.g., medically attended events, SAEs)
- If the analysis included only SAEs, the analysis should be for the pre-specified time for collection of these events (Months 0-14).

  Post- teleconference note *– If the analysis included medically attended events, the time period for analysis would be Months 0 – 8 as pre-specified for the collection of these events.*
- It was unclear as to the nature of the SMQ, if the query was broad or narrow or customized, or if a sub-SMQ was utilized for the analysis.
- It appears that the SMQs may not be standardized. For example, in the "cardiac arrhythmia" SMQ (with reference to the dataset with the SMQs), the PT sinus node dysfunction does not appear to be included in the CAR_ARR SMQ (i.e., sinus node dysfunction AEs are flagged as "N"), but sinus bradycardia appears to be included (flagged as a "Y"). This is not clear because these preferred terms are adjacent to each other in the broad Cardiac arrhythmia SMQ under the sub-SMQ of Disorders of sinus node function in MedDRA 18.0.

- There are errors in tabulations of subjects with events (e.g., number and proportions of subjects who died during particular time periods, number and proportions of subjects with Grade 3 unsolicited AEs during the 30 day post-vaccination period). Thus, the downstream enumerations (tabulations of these subjects for events by time and further by age group, region, causally associated) are likely also affected because of the initial error in tabulation. Furthermore, these errors not only affect the overall tabulations (number and percentage of subjects with an event by time, by region by time, by age by time, causally associated) but also the PT and SOC outputs associated with the various permutations.

  Post teleconference note *– Additionally, we have already communicated in a previous IR that some tabulations of subjects with events that occurred during the 30-day post-vaccination time period in the ISS could not be confirmed [e.g., number and percentage of subjects in each vaccination group reporting at least one SAE (TVC - main pooling analysis)]*.

GSK noted that when they receive an IR for one study, they usually provide a response regarding other studies too and apologized if this was not clear. GSK asked what they could do to help CBER complete a meaningful review.

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CBER noted that early in the review of the BLA GSK was contacted regarding the presentation of the ISS, i.e., it is 4,319 pages of tables without any descriptive text. At that time GSK assured CBER that the SCS was comprehensive and explained all of the tables in the ISS. However, the presentation of the safety data leaves the clinical reviewer to not only QC GSK's data, she also has to draw her own conclusions of the data. As a reminder, CBER stated that the primary responsibility of the clinical reviewer is supposed to be to verify the Applicant's conclusions not generate conclusions de novo. ***Post- teleconference note:*** *For clarity, the reviewer should be able to generate conclusions from the data provided by the Applicant.*

CBER commented that the next steps towards CBER being able to perform a meaningful clinical review include responding to any outstanding IRs and GSK addressing the below items:

- GSK will need to inform CBER on how they addressed the errors (for example, deaths) in the data and reports for studies Zoster-006, Zoster-022, the ISS (broad and main pooling) and the SCS. Additionally, GSK will need to provide the step-by-step process they used to determine if the identified errors affected any downstream analyses, and by extension which analyses were and were not affected.

- Comparative analyses and tabulations should be performed as pre-specified in the protocols. Additional analyses are acceptable, but tabulations and major analyses should be performed on what was pre-specified in the protocols.

CBER and GSK agreed to exchange summaries of this teleconference no-later-than Tuesday, April 25, 2017.

Action Items: CBER and the GSK agreed to exchange their summary of this teleconference no-later-than Tuesday, April 25, 2017. The Applicant requested a follow-up teleconference for a discussion on any potential clarifications or outstanding issues and Friday, April 28, 2017, was mentioned as a potential time for this teleconference.

Post-teleconference note: *GSK should provide stand-alone documents that summarizes all of the corrective actions taken, including links to the original individual sections, tables, text that required revisions.*