Mid-Cycle Meeting Summary

Application type and number: Original BLA, STN 125614/0
Product name: Shingrix (Zoster Vaccine Recombinant, Adjuvanted)
Proposed Indication: Prevention of herpes zoster (shingles) in adults aged 50 years and older
Applicant: GlaxoSmithKline Biologicals
Meeting date & time: April 19, 2017, 1:30 PM
Committee Chair: Carmen Collazo-Custodio, Ph.D.
RPMs: Ramachandra Naik, Ph.D. and Michael Smith, Ph.D.

Attendees:

Attendees: Review responsibility	**Committee Member**	**Attended**	**Team Leader/ Supervisor**	**Attended**
Chairperson	Carmen Collazo	✓	BC: Elizabeth Sutkowski	✓
Regulatory Project Manager	Ramachandra Naik	✓	BC: Elizabeth Sutkowski	✓
Regulatory Project Manager	Michael Smith	✓	BC: Elizabeth Sutkowski	✓
Clinical	Paula Agger	✓	TL: Meghan Ferris	✓
			BC: Andrea Hulse	✓
Clinical	Rebecca Reindel	✓	TL: Doran Fink	✓
			BC: Andrea Hulse	✓
Pharm/Tox reviewer	Nabil Al-Humadi	✓	Dave Green	
Pharm/Tox reviewer	Claudia Wrzesinski	✓	Dave Green	
Product	Shuang Tang	✓	Keith Peden	
			Philip Krause	✓
			Robin Levis	
Product	Marina Zaitseva	✓	Hana Golding	✓
Product, Consult assay reviewer	Hang Xie		Zhiping Ye	
Product Quality	Simleen Kaur		James Kenny	
			William McCormick	
Product Quality	Tao Pan	✓	Lokesh Bhattacharyya	
Product Quality	Alfred Del-Grosso	✓	Lokesh Bhattacharyya	
Product Quality	Noel Baichoo	✓	William McCormick	
Product Quality	Marie Anderson	✓	William McCormick	
Statistics, clinical and assays	Rong Fu	✓	TL: Tsai-Lien Lin	✓
			BC: Amelia (Dale) Horne	✓
Epidemiology/ Pharmacovigilance	Ravi Goud	✓	Deepa Arya	✓
DMPQ RPM	Debra Vause	✓	James Crim	
DMPQ (Facilities, CCIT, Inspector) Reviewer	Jeremy Wally	✓	BC: Qiao Bobo	
			TL: Anthony Lorenzo	
BIMO	Haecin Chun	✓	BC: Patricia Holobaugh	✓
APLB Labeling and PNR reviewer	Oluchi Elekwachi		BC: Lisa Stockbridge	
Labeling	Daphne Stewart		BC: Laraine Henchal	✓

Other Attendees:

Wellington Sun	Darlene Martin	Julianne Clifford
Katie Rivers	Erik Laughner	Laurie Norwood
Karen Farizo	Theresa Finn	John Eltermann
Douglas Pratt	Marion Gruber	Loris McVittie
Qun Wang		

1.0 BACKGROUND AND PURPOSE

BLA STN 125614/0 was submitted by GlaxoSmithKline Biologicals (GSK) on October 21, 2016.

The purpose of this meeting was to discuss the progress of the review; identify and present any substantive issues/major deficiencies and plans to address substantive issues; plan the remainder of the review including dates for further deliverables and interactions; obtain supervisory feedback; agree on the material to be communicated in the Mid-Cycle Communication telecon and determine which reviewers will participate in the MCC telecon to present their issues.

2.0 Review Timetable (milestones are in blue)

Review Milestone	Target Due Date
Submitted:	21-Oct-2016
Received:	21-Oct-2016
Committee Assignment:	31-Oct-2016
First Committee Meeting:	14-Nov-2016
Filing checklist/reviews complete:	30-Nov-2016
Filing Meeting:	6-Dec-2016
Filing Action:	20-Dec-2016
Deficiencies Identified:	3-Jan-2017
Draft Lot release protocol and Testing plan:	13-Apr-2017
Primary Draft Reviews & Reviewer Reports Due (4 days prior to Mid-Cycle meeting):	13-Apr-2017
Internal Mid-Cycle Meeting:	**19-Apr-2017**
Mid-cycle communication with applicant:	3-May-2017
PeRC Briefing materials due:	14-Jun-2017
PeRC Meeting:	28-Jun-2017
VRBPAC briefing pkg due to DFO:	11-Aug-2017
PLI Inspections completed:	22-Aug-2017
BIMO Inspections completed:	22-Aug-2017
Employee Officer list memo:	22-Aug-2017
Late cycle briefing pkg & VRBPAC briefing pkg to applicant:	23-Aug-2017
Final draft primary reviews with supervisory concurrence: (upload not required), due by LC meeting	31-Aug-2017
Late cycle meeting: (At least 12 days before VRBPAC)	31-Aug-2017

Review Milestone	Target Due Date
Press release (contact Maureen Hess):	6-Sep-2017
VRBPAC Meeting:	13-Sep-2017
Lot release protocol and Testing plan finalized:	21-Sep-2017
Final reviews & addenda signed & uploaded:	21-Sep-2017
Notify OCOD of pending approval:	21-Sep-2017
Labeling Comments to Applicant:	21-Sep-2017
Notify Applicant of PMC/PMR:	21-Sep-2017
Action Due Date (ADD):	20-Oct-2017 (21-Oct-2017 is Saturday)

Monthly Team Meetings and other meetings (scheduled already):

Meeting	Date and time
First Committee meeting	November 14, 2016 1:00 – 2:00 PM
Filing meeting	December 6, 2016 11:00 AM – 12:00 PM
DBSQC – OVRR in-support testing/review assignments	December 7, 2016 11:00 AM – 12:00 PM
DBSQC – OVRR: Discussion to clarify review responsibilities (DVP vs. DBSQC) for each of the adjuvant-related assays	March 7, 2017 11:0 AM – 12:00 PM
Internal Mid-Cycle meeting	**April 19, 2017 1:30 - 3:00 PM**
Mid-Cycle communication with Applicant	May 3, 2017 1:30 – 2:30 PM
PeRC paperwork preparation (OVRR IOD)	June 5, 2017 11:00 AM – 12:30 PM
PeRC presentation	June 28, 2017
Internal Late Cycle meeting	August 17, 2017 2:00 – 4:00 PM
VRBPAC rehearsal #1	21-Aug-2017 11:00 AM – 12:30 PM
VRBPAC rehearsal #2	28-Aug-2017 11:00 AM – 12:30 PM
External Late Cycle meeting with Applicant	August 31, 2017 1:00 – 3:00 PM
VRBPAC rehearsal #3	7-Sep-2017 1:00 – 2:30 PM
Monthly Committee meetings:	
January 2017	January 5, 2017 11:30 AM – 12:30 PM
February 2017	February 9, 2017 11:00 AM -12:30 PM
March 2017	March 7, 2017 9:00 AM – 10:30 AM
May 2017	May 16, 2017 11:00 AM – 12:00 PM
June 2017	June 22, 2017 11:00 AM – 12:30 PM
August 2017	August 2, 2017 1:00 - 2:00 PM
September 2017	September 14, 2017 11:10 AM-12:30 PM
Labeling meetings:	
Package Insert	May 8, 2017 11:00 AM – 12:30 PM
Carton and Container	May 11, 2017 1:00 – 2:30 PM
Package Insert	May 17, 2017 1:00 – 3:00 PM
Carton and Container	May 18, 2017 11:00 AM – 12:30 PM
Carton and Container	May 23, 2017 10:30 AM – 12:00 PM

Package Insert	June 7, 2017 2:00 – 4:00 PM
PLLR review of Section 8 (and 13)	June 8, 2017 11:30 AM – 12:30 PM
Package Insert	June 27, 2017 10:00 AM – 12:00 PM

Report and Discuss:

The Chair presented a brief overview of the submission followed by updates from individual reviewers (refer to **Attachment 1**).

1. **Reviewer Reports**

(a) Product - Antigen (Shuang Tang)

- No substantial issues identified; April 6, 2017, IR outstanding; expecting drafting additional IRs since the review is still ongoing
- To be reviewed: non-clinical studies and clinical assays
- Date the review will be completed: August 31, 2017

(b) Product - Adjuvant (Marina Zaitseva)

- No issues identified
- Date the review will be completed: July 1, 2017

(c) Product - Consult assay reviewer, CMI and HAI for clinical studies (Hang Xie)

- No issues identified
- Date the review will be completed: May 31, 2017

(d) Product Quality - Review of identity, antigenic activity and potency by (b) (4) **assay; purity by** (b) (4) **(Noel Baichoo)**

- No issues identified
- Date the review will be completed: May 31, 2017

(e) Product Quality - Review of the lot release protocol (LRP), testing samples and reagents (Marie Anderson)

- No issues identified
- Test samples and reagents were requested on March 29, 2017
- The review will be finalized after the LRP template review is completed; the LRP template is under review by Product Office and DBSQC reviewers
- Requested to schedule a meeting to further discuss the LRP

(f) Product Quality - Review of sterility and endotoxin test methods (Simleen Kaur)

- Review completed and the review memo uploaded

(g) Product Quality - Review of lot release assays for $AS01_B$ adjuvant system and their validation (Tao Pan)

- No issues identified

- Date the review will be completed: May 30, 2017

(h) Product Quality - Review of $AS01_B$ adjuvant system - Chemistry, Analytical Procedures and Validations (Alfred Del-Grosso)

- No issues identified
- Date the review will be completed: May 30, 2017

(i) Pharm/Tox (Nabil Al-Humadi and Claudia Wrzesinski)

- No issues identified
- Date the review will be completed: July 2017

(j) Epidemiology/Pharmacovigilance (Ravi Goud)

- No major issues identified
- The reviewer noted statistically significant increased rate of upper respiratory infection, and imbalance of polymyalgia rheumatica/temporal arteritis cases, and increased rate of gout and arthralgia in the vaccinated cohorts. He will further discuss these findings with the Clinical reviewer.
- Date the review will be completed: April 19, 2017

(l) BIMO (Haecin Chun)

- Five clinical sites/investigators were selected for inspections and BIMO issued the inspection assignment memo to ORA with the completion date of May 31, 2017.
- Inspection of site 79857 for Protocol Zoster-006 is complete. No 483 was issued and the Establishment Inspection Report (EIR) is pending receipt. The other four requested inspections are pending initiation. No issues identified at this time.
- BIMO will complete the final discipline review after all EIRs are received and reviewed.

(m)DMPQ Reviewer - Facilities, CCIT, Inspector (Jeremy Wally)

- No substantive review issues have been identified thus far; an IR is in preparation and will be ready to send to GSK after completion of the first draft review.
- The reviewer noted that as the drug product was filled (b) (4), and therefore, the (b) (4) method used for Container Closure Integrity Testing may not be appropriate. This issue will be addressed in the forthcoming IR.
- The reviewer noted that the adjuvant final containers are not being tested for endotoxin, and suggested that further discussion with the Product division is needed.
- The pre-license inspection of the labeling and packaging facility in (b) (4) will be waived.
- The January 2017 Team Biologics inspection of the (b) (4) DP manufacturing facilities in (b) (4) Rixensart, Belgium led to the issuance of an FDA Form 483 containing 28 observations. The lead inspector

recommended that the inspection be classified as OAI but the final classification of the inspection is pending.
  - If the inspection is classified as VAI (or NAI), the pre-license inspection of will be waived.
  - If the inspection is characterized as OAI, the facility would not be in compliance potentially requiring issuance of a Complete Response letter for this BLA.
- Date the review will be completed: As soon as possible based upon workload and receipt of the response to the forthcoming IR.

(n) Statistics - clinical and assays (Rong Fu)

- No substantial issues identified
- The following analysis results could not be verified:
  - Zoster-006: HZ VE in subjects ≥50 YOA at the final HZ analysis step (primary objective), as well as the HZ VE analysis at the final HZ analysis step by age stratum.
  - Zoster-006/022 pooled: subgroup analysis on PHN VE for age groups 50-59 and 60-69.

  These issues are not considered substantive because the reviewer's own analysis results are similar to those provided in the CSRs, therefore, not impacting the final conclusions.
- April 6, 2017, IR outstanding
- Formulating another IR to request the following:
  - Details (method, programing) on subgroup PHN VE analyses in ZOSTER-006
  - Explanations on change of statistical method for VE on reduction of the pain medication use in ZOSTER-006 and ZOSTER-022
- Date the review will be completed: June 16, 2017

(o) Clinical (Rebecca Reindel)

- No issues identified
- Date the review will be completed: May 15, 2017

(p) Clinical (Paula Agger)

- Presented an overview of the two pivotal clinical studies, eleven supportive studies and summaries submitted in the BLA and the review issues identified thus far (refer to **Attachment 2**). She informed the team that a major IR is outstanding. 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). Although several IRs have been sent to the Applicant already, 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 revisions of similar outputs for other studies and/or documents.

- Date the review will be completed: cannot determine at this time as substantive data submission is still anticipated in response to the IR sent, and errors and omissions are still being identified by the clinical and statistical reviewers.
- OVRR management was concerned that these review issues may have an impact on the 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.

2. **For PDUFA V Program submissions, indicate whether discipline review letters will be issued.** Clinical (Paula Agger), DMPQ (Jeremy Wally)
    - Since discipline review letters are used to convey preliminary notice of deficiencies found at the **conclusion of the discipline review** of an original BLA and the review is still ongoing, it is our understanding the this type of letter will not be issued.

3. **If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation.**
    - VRBPAC is scheduled for September 13, 2017.

4. **Determine whether Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed.** Paula Agger, Carmen Collazo-Custodio
    - Since the clinical review is not complete, the Committee did not determine whether PMRs, PMCs, or a REMS are needed.

5. **National Drug Code (NDC) assignments to product/packaging (excludes devices).**
    - Process has been initiated.

6. **Proper naming convention.**
    GSK was informed of the proper name (Zoster Vaccine Recombinant, Adjuvanted) on December 7, 2016.

7. **Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).** Jeremy Wally, Shuang Tang, Haecin Chun
    - For details, please refer to item # 1. Reviewer Reports, sections (l) BIMO (Haecin Chun) and (m) DMPQ Reviewer - Facilities, CCIT, Inspector (Jeremy Wally)

Review:

8. **Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones (e.g. Late-Cycle meeting, Advisory Committee, labeling discussion).**

- Late Cycle meeting with the Applicant: August 31, 2017
- VRBPAC meeting: September 13, 2017
- Labeling discussions: 8 meetings scheduled; first on May 8, 2017

9. Establish a labeling review plan and agree on future labeling meeting activities.
- Labeling discussions: 8 meetings have been scheduled; the first one will be held on May 8, 2017.

Confirm, as applicable:

10. Components Information Table was obtained and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements. If not complete, indicate date it will be completed.
- Request sent to CBERDCC DAT for the Component Information Table on April 12, 2017.

11. New facility information is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry.* If not complete, indicate date it will be completed.
- Completed.

12. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan
- Comments on the lot release protocol (LRP) were provided to GSK and a revised LRP is under review. Test samples and reagents were requested on March 29, 2017.

13. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid *JA 900.01*: *Unique Ingredient Identifier (UNII) Code* for additional information.
- Process has been initiated.

14. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision.
- Preparatory PeRC meeting (review team): June 5, 2017
- PeRC meeting scheduled: June 28, 2017

15. Action Items:
- Schedule a teleconference with GSK (clinical team and OVRR management) to discuss the issues regarding the clinical information submitted in the BLA
  Post-meeting note: Telecon with GSK was held on 4/20/2017 at 10:30 AM
- Prepare the Mid-Cycle Communication telecon agenda
- Draft IRs from the Product-Antigen, DMPQ, and Biostatistics disciplines

16. For applications subject to the PDUFA V Program:

- Agreement was reached to include issues related to the inspection of product manufacturing facilities, clinical and epidemiology/pharmacovigilance disciplines in the Mid-Cycle Communication telecon with the applicant.