DEPARTMENT OF HEALTH & HUMAN SERVICES

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Review and Research
Division of Viral Products

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From: Hang Xie, PhD, DVP/OVRR

To: **BLA STN 125614/0 File**
(SHINGRIX®– Zoster Vaccine Recombinant, Adjuvanted)
Carmen Collazo, PhD, Chairperson, DVRPA/OVRR
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Subject: **Review of intracellular staining (ICS) and hemagglutinin inhibition (HAI) assays used in clinical development of SHINGRIX®**

Sponsor: Glaxo Smith Kline (GSK)

Through: Zhiping Ye, PhD, DVP/OVRR

Cross-ref: IND 13857 (ICS assay)
IND 13879 (ICS assay)
BLA 125127 _ Fluarix® (HAI assay)
BLA 125163 _ FluLaval® (HAI assay)

Executive Summary and Recommendation

Glaxo Smith Kline (GSK) has submitted a Biologics License Application (BLA) for SHINGRIX®– a non-live, recombinant vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older.

The product is a sub-unit vaccine consisting of recombinant varicella zoster virus (VZV) glycoprotein E (gE) as antigen, combined with GSK's proprietary Adjuvant System $AS01_B$. The gE protein is provided in a lyophilized form in monodose vials (50 µg/dose). The $AS01_B$ (liquid) Adjuvant System is provided in separate monodose vials (0.5 ml/dose). The content of the $AS01_B$ vial is used to reconstitute the content of the gE vial immediately prior to intramuscular immunization.

US development of this vaccine was conducted under IND 13857 containing 12 Phase II and III pivotal or supportive clinical studies. The submission also includes data from two supportive studies conducted in immunocompromized adults conducted under IND 13879.

The current review memo is focused on (1) intracellular staining (ICS) assay used to assess cell-mediated immunity (CMI) in subjects administered with gE vaccines; and (2) hemagglutinin inhibition (HAI) assay used to determine the antibodies induced by unadjuvanted quadrivalent seasonal influenza vaccine (FLU-D-QIV) that was used as the concomitant vaccine in the Phase III clinical study ZOSTER-004.

The section covered is outlined below:
BLA125614/0
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

1. cmi-vzv-and-ge-gsk- CMI-VZV and gE (GSK)
2. cmi-vzv-and-ge-(b) (4)- CMI-VZV and gE (b) (4)
3. (b) (4)

BLA125614/a11 (IR responses to clarify previous submission of HAI SOPs and validation reports)
BLA125614/a12 (cross-references for HAI assay)

After a thorough review on SOPs and validation reports submitted, both ICS and HAI assays were found qualified for the clinical studies conducted.

Narrative Review

1. ICS assay

A flow cytometry-based ICS assay was performed to detect CD4+ and CD8+ T cell responses in subjects following vaccination with gE and VZV. The ICS SOPs provided are listed below:

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

6. CLABSOP 064 v2 Intracellular cytokine determination (b) (4))- original and English translation (Effective: 2/3/2011)

(b) (4)

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7. CLABSOP 064 v3 Intracellular cytokine determination (b) (4))- original and English translation (Effective: 2/10/2014)

(b) (4)

3 pages have been determined to be not releasable: (b)(4)

(b) (4)

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2. HAI assay

The Phase III ZOSTER-004 is a randomized, open-label study was designed to evaluate the immunogenicity and safety of HZ/su (the herpes zoster subunit candidate vaccine– 50 μg gE/AS01$_B$) when co-administered with GSK's seasonal influenza vaccine (FLU-D-QIV) in adults at ≥50 years of age. HAI assay was used to determine HAI titers in subjects following vaccination.

GSK provided the following HAI SOPs:

1. GSK SOP 9000009144 Version 13 "Haemagglutination Inhibition Assay in Assessment of Sera for Influenza Antibodies Using (b) (4)"- original and English translation (Effective: 2/7/2014)
2. GSK SOP 9000009144 Version 14 "Haemagglutination Inhibition Assay in Assessment of Sera for Influenza Antibodies Using (b) (4)"- original and English translation (Effective: 12/15/2014)

There were no major changes between Version 13 and Version 14 of GSK SOP 9000009144.

GSK also conducted strain-specific validation based on GSK SOP 9000009144 and provided the following validation reports:

1) FLU-(b) (4)-H1N1 v strain_PV_01 (Effective: 11/4/2009)
2) FLU(b) (4)_B/Brisbane/60/2008_MVR-01 (Effective: 3/9/2011)
3) FLU(b) (4)_B/Massachusetts/02/2012 (b) (4)01 (Effective: 8/7/2013)
4) FLU-(b) (4)_ A-Victoria-361-2011 (b) (4)_01 (Effective: 8/1/2012)
5) FLU(b) (4)_A/Texas/50/2012_(b) (4)_02 (Effective: 3/16/2015)

Comments: *Of note, GSK used (b) (4) /50 µl instead of standard (b) (4) /50 µl in this HAI SOP. Olga Zoueva and Zhiping Ye from DVP/OVRR reviewed the original (b) (4) HAI method submitted in BLA 125163/a176 and had no issues with using (b) (4) /50 µl in HAI assay. They completed the review on March 21, 2011.*

GSK also cross-references BLA125127/a775 (Sequence No. 0287) for the validation report FLU-(b) (4) -B Massachusetts 02 2012-(b) (4) -02, and BLA125127/a775.1 (Sequence No. 0294) for GSK SOP 9000009144. Zhiping Ye and Olga Zoueva reviewed both amendments and completed their review on October 31, 2016.

Additionally, GSK cross-references BLA 125127/a513 (Sequence No. 0107) for the validation reports FLU-(b) (4)-H1N1 V STRAIN-PV-01and FLU(b) (4)-B BRISBANE 60 2008-MVR-01, both of which were reviewed and completed by Olga Zoueva on December 5, 2012.

GSK cross-references BLA125163/a405 (Sequence No. 0232) for the validation reports FLU-(b) (4) - A Victoria 361 2011 -(b) (4) -01 and FLU-DRESDEN-A Texas 50 2012-(b) (4) -02, both of which were found acceptable by Ewan Plant from DVP/OVRR. His review was completed on June 27, 2016.

Please also see OBE statistical reviewer Dr. Rong Fu's memo for HAI assay validation and statistics.