Application Type	BLA Supplement
STN	125163/405
CBER Received Date	January 27, 2016
PDUFA Goal Date	November 26, 2016
Division / Office	DVRPA /OVRR
Committee Chair	Goutam Sen
Clinical Reviewer(s)	Sarah Browne
Project Manager	Laura Montague
Priority Review	No
Reviewer Name(s)	Charles (Yin Kiu) Cheung
Review Completion Date / Stamped Date	
Supervisory Concurrence 1	Tsai-Lien Lin, Team Leader Viral and Bioassay Team, Vaccine Evaluation Branch, Division of Biostatistics
Supervisory Concurrence 2	Dale Horne, Chief, Vaccine Evaluation Branch, Division of Biostatistics
Applicant	GlaxoSmithKline Biologicals
Established Name	Influenza Vaccine
(Proposed) Trade Name	FluLaval® Quadrivalent
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Influenza Virus Vaccine, 15µg HA per strain for a total of 60µg HA
Dosage Form(s) and Route(s) of Administration	Intramuscular Injection
Dosing Regimen	0.5 ml, 1 or 2 dose(s)
Indication(s) and Intended Population(s)	Active immunization against influenza in individuals 6 months of age and older.

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1. Executive Summary

GlaxoSmithKline submitted BLA125163/405 to seek approval of extending the indication of the FluLaval® seasonal quadrivalent inactivated Influenza vaccine to children 6 months to 35 months of age. The applicant performed four clinical studies to support this indication. To support immunogenicity evaluation, hemagglutination inhibition assays were used. The statistical reviewer evaluated 6 validation reports of these assays. The results demonstrated that the assay for A/Texas/50/2012 (Laval), B/Massachusetts/2/2012 (Laval), A/Texas/50/2012 (Dresden), and B/Massachusetts/2/2012 (Dresden) were fit for the intended use in this submission. The assays for A/Victoria/361/2011 and B/Hubei-Wujiagang/158/2009 used in Study-013 passed the acceptance criterion for specificity, which was the only parameter validated.

2. Clinical and Regulatory Background

GlaxoSmithKline (GSK)'s FluLaval® and FluLaval® Quadrivalent were approved on October 5, 2006 and August 15, 2013(BLA 125163/253), respectively. The current indication is for individuals 3 years of age and older. This BLA 125163/405 seeks to extend the indication to children 6 months to 35 months of age.
Immunogenicity was measured using the hemagglutination inhibition (HAI) assay. The HAI assay was originally validated in 2002 on influenza strains A/NewCaledonia/20/1999 (A/H1N1), A/Panama/2007/1999 (A/H3N2), and B/Shangdong/7/1997 (B/Victoria). The results of assay validation of A/Texas/50/2012 (Laval), B/Massachusetts/2/2012 (Laval), A/Texas/50/2012 (Dresden), B/Massachusetts/2/2012 (Dresden), A/Victoria/361/2011 (Dresden), and B/Hubei-Wujiagang/158/2009 (Dresden) were submitted to this BLA supplement.

3. SOURCES OF DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

3.1 Review Strategy

A total of 6 validation reports (4 from Dresden, 2 from Laval) were submitted. The reviewer summarized the validation approach and evaluated the results of the parameters validated.

3.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

From BLA 125163/405.0
- Module 5.3.5.4 – Method Validation Report for Haemagglutination Inhibition Test with the Influenza strain A/Texas/50/2012 wild type
- Module 5.3.5.4 – Method Validation Report for Haemagglutination Inhibition Test with the Influenza strain B/Massachusetts/2/2012 wild type
- Module 5.3.5.4 – Method Validation Report for Haemagglutination Inhibition Test with the H3N2 Influenza strain A/Texas/50/2012 wild type
- Module 5.3.5.4 – Method Validation Report for Haemagglutination Inhibition Test with the Influenza strain B/Massachusetts/02/2012 wild type
- Module 5.3.5.4 – Method Validation Report for Haemagglutination Inhibition Test with the H3N2 Influenza strain A/Victoria/361/2011 wild type

- Module 5.3.5.4 – Method Validation Report for Haemagglutination Inhibition Test with the Influenza strain B/Hubei-Wujiagang/158/2009 wild type
- Module 2.7.3 – Summary of Clinical Efficacy

4. DISCUSSION OF INDIVIDUAL STUDIES

4.1 Hemagglutination Inhibition Assays

The hemagglutination inhibition (HAI) assay was used to measure the immune response of subjects to different influenza virus strains in the vaccine. This assay is based on the principle that the hemagglutinin glycoprotein of the viruses agglutinates with red blood cells (erythrocyte), but antibodies specific to the glycoprotein can inhibit agglutination. In (b) (4)
. The HAI assay measures the titer as the highest dilution of serum that completely inhibits agglutination. Each sample is tested in duplicates, and the reportable titer is the geometric mean of the two titer values.

Intended use

The main study to support the proposed indication is FLU Q-QIV-022, which is a Phase III, observer-blind, randomized, controlled, multi-center trial to evaluate the immunogenicity and safety of GSK Biologicals' quadrivalent influenza vaccine candidate, GSK2282512A (FLU Q-QIV), compared to Sanofi Pasteur's quadrivalent influenza vaccine Fluzone® Quadrivalent, administered intramuscularly to children 6 to 35 months of age. Three other studies (FLU Q-QIV-021, FLU Q-QIV-013, and FLU Q-QIV-003) were used to provide supporting evidence for the proposed indication.

Validation

The validation reports of a subset of assays used in the clinical studies were submitted. For an assay which measures the content in a sample, the ICH Q2 (R1) recommends evaluating accuracy, precision, specificity, linearity, and range. For A/Texas/50/2012-Laval, B/Massachusetts/2/2012-Laval, A/Texas/50/2012-Dresden, and B/Massachusetts/2/2012-Dresden, the applicant evaluated all these parameters except accuracy because no standard serum with a defined titer for the seasonal strains is available. For A/Victoria/361/2011-Dresden and B/Hubei-Wujiagang/158/2009-Dresden, only specificity was evaluated because the applicant believed that only specificity could be statistically impacted by successive strain change. I recently reviewed the validation reports of the HAI assays for A/Texas/50/2012-Dresden and B/Massachusetts/2/2012-Dresden and determined these assays to be fit for use in BLA 125127/775 for Fluarix. The experimental designs (Table 1) and the results of validation (Table 2) are summarized.

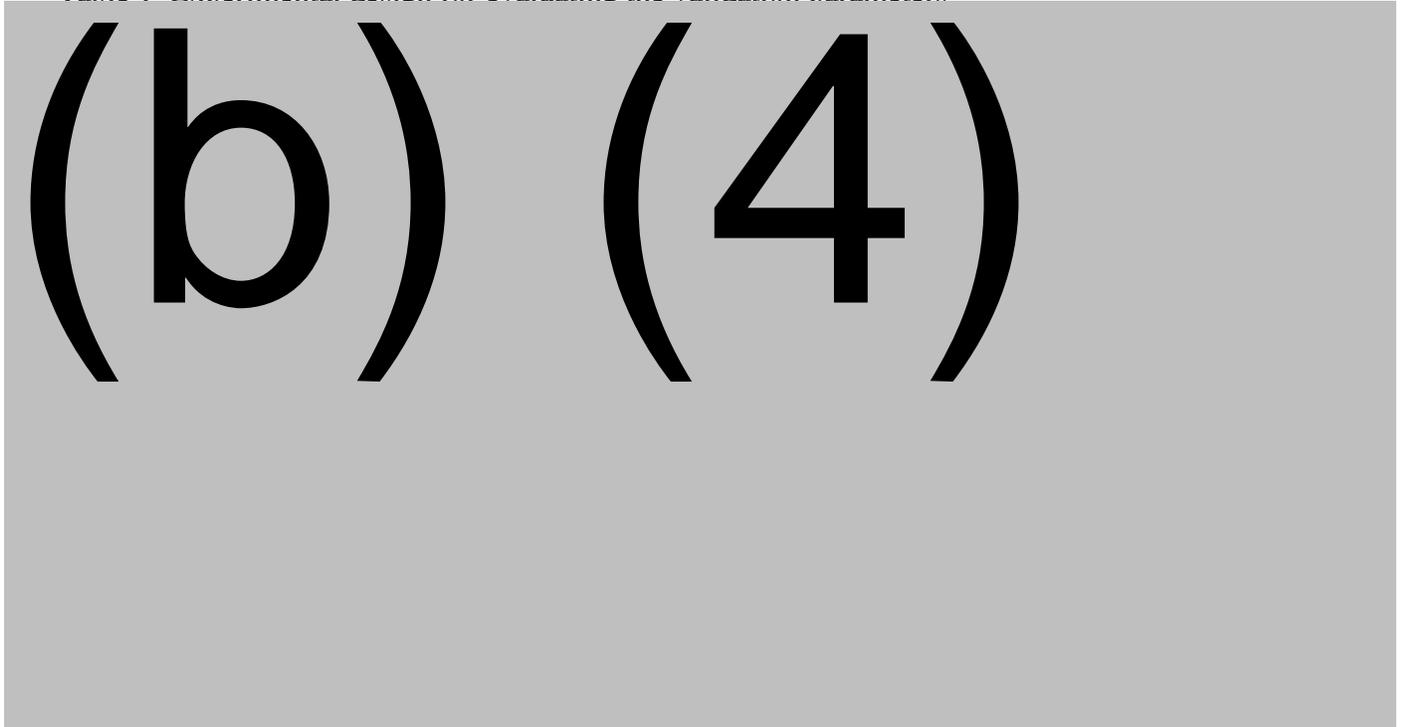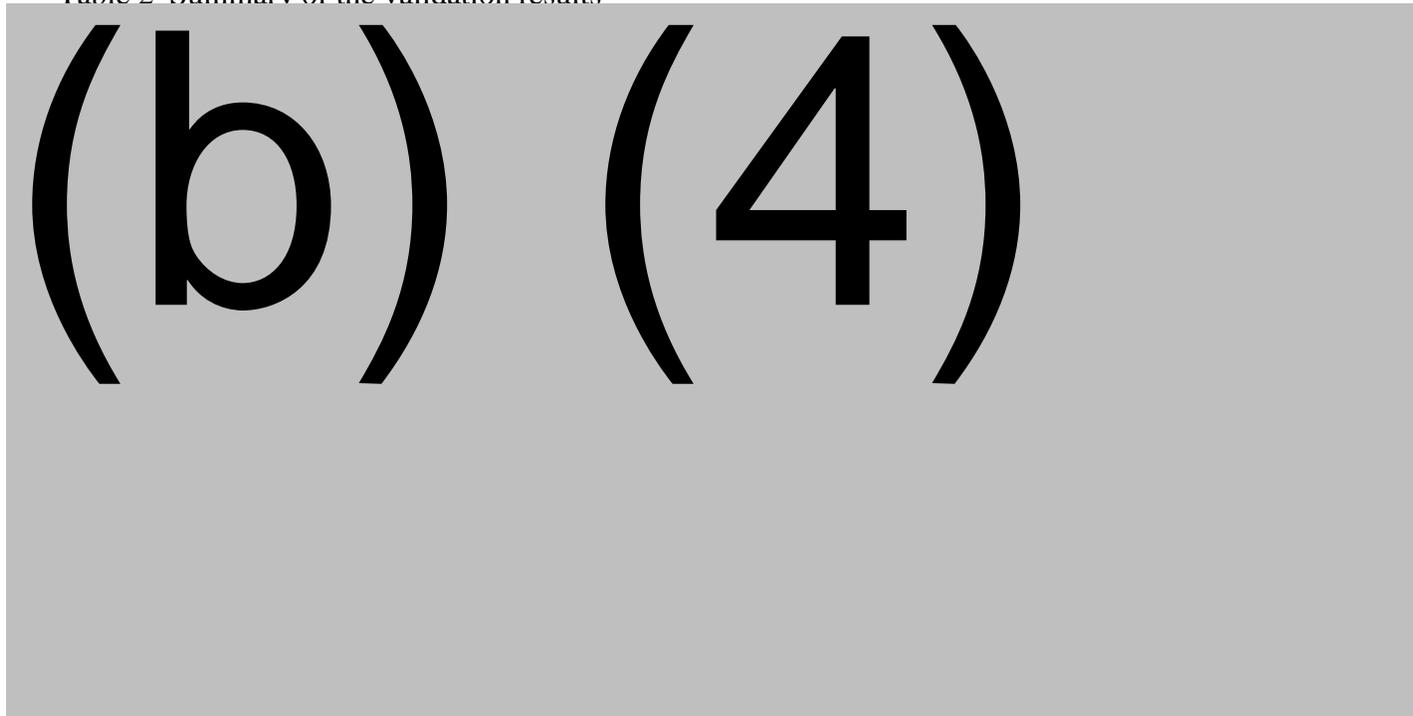Table 1. Experimental design for evaluating the validation parameters

(b) (4)

Table 2. Summary of the validation results

(b) (4)

<u>Specificity</u>:
Two approaches were used to evaluate specificity. The first approach evaluated whether presumably (b) (4)

(b) (4)   . The second approach
evaluated whether presumably (b) (4)

LOB:
The LOB analysis was performed only for A/Texas/50/2012 and B/Massachusetts/2/2012
at both Dresden and Laval laboratories. (b) (4)

Precision:
(b) (4) positive samples were tested with (b) (4)   technicians for (b) (4)   results
per sample). The (b) (4) was estimated using a (b) (4)

Reviewer's comments:
- *The Laval site has higher assay precision than the Dresden site for both
  A/Texas/50/2012 and B/Massachusetts/2/2012. The main cause appears to be
  higher variance in repeatability at Dresden (sponsor's reports).*
- *Precision was not evaluated covering the entire claimed range for
  A/Texas/50/2012 (Laval), B/Massachusetts/2/2012 (Laval), A/Texas/50/2012
  (Dresden), and B/Massachusetts/2/2012 (Dresden) (Tables 1 and 2).*

Linearity:
For each sample, (b) (4)

(sponsor's validation reports).

Reviewer's comment:
*Although the acceptance criterion was met for each assay, the A/Texas/50/2012 (Laval)
assay appears to display a pattern of slight nonlinearity, with overestimation of titers at
the low dilutions for both samples (Figure 1). The same assay at Dresden did not have
this issue (Figure 2).*

(b) (4)

5. CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The 6 assays passed all of the acceptance criteria for the parameters evaluated. I noted a few observations. First, the assays at Laval had higher precision than those at Dresden for both the A/Texas/50/2012 and B/Massachusetts/2/2012 strains. Second, the A/Texas/50/2012 (Laval) assay tended to slightly overestimate titers at the low dilutions, whereas the same assay at Dresden did not have this issue. Third, precision was not evaluated for the entire claimed range for A/Texas/50/2012 (Laval), B/Massachusetts/2/2012 (Laval), A/Texas/50/2012 (Dresden), and B/Massachusetts/2/2012 (Dresden).

5.2 Conclusions and Recommendations

The validation results suggest that the assays for A/Texas/50/2012 (Laval), B/Massachusetts/2/2012 (Laval), A/Texas/50/2012 (Dresden), and B/Massachusetts/2/2012 (Dresden) were fit for use in this BLA submission. The assays for A/Victoria/361/2011 and B/Hubei-Wujiagang/158/2009 used in Study-013 passed the acceptance criterion for specificity, which was the only parameter evaluated for these assays.