Application Type	Original BLA
STN	125748/0
CBER Received Date	June 4, 2021
PDUFA Goal Date	June 4, 2022
Division / Office	DVRPA /OVRR
Committee Chair	Luba K. Vujcic MS
Assay Reviewers	Tatiana Zagorodnyaya, MS Dmitriy Volokhov, DVM, PhD
Project Manager	Julianne C. M. Clifford, PhD
Priority Review	No
Reviewer Name(s)	Laura Thompson, PhD
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Ph.D. Concurring Reviewer VEB, DB, OBPV
	Tsai-Lien Lin, Ph.D. Chief, VEB, DB, OBPV
	John Scott, Ph.D. Director, DB, OBPV
Applicant	GlaxoSmithKline Biologicals
Established Name	Measles, Mumps and Rubella Virus Vaccine Live
(Proposed) Trade Name	PRIORIX
Pharmacologic Class	Vaccine
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder for Injectable Suspension, Subcutaneous
Dosing Regimen	0.5 mL
Indication(s) and Intended Population(s)	For active immunization for the prevention of measles, mumps, and rubella in individuals aged 12 months and older

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1. EXECUTIVE SUMMARY

The applicant submitted validation reports for all assays used in primary and secondary immunogenicity endpoints in their clinical studies to support the assessment of Priorix vaccine for measles, mumps, and rubella. Anti-measles, anti-mumps and anti-rubella virus antibody titers were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits. An additional evaluation by (b) (4) to measure the functional antibodies against mumps virus was performed in studies MMR-157 and MMR-161. However, the initial (b) (4) test used in study MMR-157 was an enhanced (b) (4), while the unenhanced (b) (4) was used later in a post-hoc analysis. Because the enhanced anti-mumps (b) (4) was only used in the phase II MMR-157 study, I did not review it. In addition, I did not review assays used in co-administration of vaccines because these are already approved vaccines.

For the anti-measles and anti-rubella ELISA assays, the applicant met all pre-specified criteria for validation. For anti-measles, the assessment of recovery of the titer from an expected titer showed high bias in several instances. However, there does not appear to be a trend in observed bias based on titer, as bias was not monotonic with titer. Other assay characteristics were ultimately determined as acceptable by assay reviewers.

For the anti-mumps ELISA assay, dilutability was not clearly shown due to missing operator results, large differences between some operator assays, deletion of outlying results, and patterns of increasing concentration with increasing dilution factor. The applicant was asked to provide clarification on the results and to justify linearity of the assay. However, because they no longer own the assay, the applicant has deferred to the current owner, who will provide responses to the master file. In addition, the applicant has deferred our request to re-evaluate tentative control limits on the slope of the standard curve.

For the anti-mumps (b) (4) assay, the applicant has stated that they met all pre-specified validation criteria. It is not clear that they have adequately demonstrated recovery, as the expected titer may not have been reliably estimated. However, linearity has been adequately demonstrated according to assay reviewers.

I defer to the assay reviewers as to the final acceptability of the validation results.

2. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

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

The following validation reports submitted in BLA 125748/0 were reviewed:

- Performance Characteristics and Validation (b) (4) Anti-Measles IgG (b) (4)

- Performance Characteristics and Validation (b) (4) Anti-Rubella IgG (b) (4)
- Performance Characteristics and Validation: (b) (4) assay using wild-type strain (b) (4) (v1 – 2011, v2 – 2014)
- Performance Characteristics and Validation: (b) (4) assay using wild-type strain (b) (4) (2008)
- Mumps (b) (4) Assay Wild Type Strain (b) (4)
- Validation of Mumps "Wild Type" IgG ELISA

The following information request (IR) responses were also reviewed:

- 1.11.3 Clinical Information Amendment Response to FDA IR 22 Dec 2017 submitted to IND 7229/0.614 on 10/13/2020
- 1.11.3 Clinical Information Amendment Response to FDA IR 25 Mar 2022 submitted to BLA 125748/0.32.

2.2 Table of Studies/Clinical Trials

Table 1 lists the immunogenicity assays that were used in the six MMR studies in BLA 125748/0.

Table 1: Immunogenicity assays for measles, mumps, and rubella used in the *Priorix* MMR U.S. CDP studies

Antigen	Assay method	Laboratory (Country)	Assay unit	Assay cut-off	Seroresponse threshold
Measles virus	ELISA	(b) (4) GSK (Belgium) (MMR-157 only)	mIU/mL	150	200
Rubella virus	ELISA	(b) (4) GSK (Belgium) (MMR-157 only)	IU/mL	4	10
Mumps virus	ELISA[a]	(b) (4)	EU/mL	5	10
Mumps virus	(b) (4)	GSK (Belgium)	ED_{50}	2.5	4
Mumps virus	(b) (4)	GSK (Belgium)	ED_{50}	24	51

ED_{50}=end-point dilution 50%; ELISA=enzyme-linked immunosorbent assay; EU=ELISA Unit; GSK=GlaxoSmithKline; IU=international unit; mIU=milli international unit; (b) (4) U.S.=United States.

(b) (4) to the assay used by Merck & Co, Inc to support licensure of *ProQuad*® (measles, mumps, rubella and varicella virus vaccine live) in the U.S.

[b] Enhanced (b) (4) was only used in the Phase II study MMR-157 and not reviewed in this memo.

Source: Table 1 in m2.7.1 Summary of Biopharmaceutic Studies

3. DISCUSSION OF INDIVIDUAL VALIDATION STUDIES

3.1 Validation of Anti-Measles ELISA

For the assay procedure, measles-specific IgG antibodies contained in (b) (4)

8 pages determined to be not releasable: (b)(4)

Source: Adapted from Tables 19 and 22 in Performance Characteristics and Validation (b) (4) *Anti-Measles IgG* (b) (4)

3.2 Validation of Anti-Rubella ELISA

For the assay procedure, a similar method as for anti-measles ELISA was used for the anti-rubella ELISA.

3.2.1 Assay Characteristics

(b) (4)

7 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

3.3 Validation of Anti-Mumps ELISA

For the assay procedure, the solid phase of the assay (b) (4)

20 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

4. CONCLUSIONS

I defer to the assay reviewers as to the final acceptability of the validation results.