Summary Basis for Regulatory Action

Date:	**June 3, 2022**
From:	Luba Vujcic, MS Review Committee Chair Division of Vaccines and Related Products Applications Office of Vaccines Research and Review
BLA/NDA STN:	125748/0
Applicant:	GlaxoSmithKline Biologicals SA
Submission Receipt Date:	June 4, 2021
Action Due Date:	June 4, 2022
Proper Name:	Measles, Mumps and Rubella Vaccine, Live
Proprietary Name:	PRIORIX
Indication:	For active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older.

Recommended Action: The Review Committee recommends approval of this product.

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Director, Product Office

Discipline Reviews	Reviewer / Consultant - Office/Division
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Other Review(s) not captured by above categories: • CDISC Consult	Brenda Baldwin, PhD, OVRR/DVRPA

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1. Introduction

On June 4, 2021, GlaxoSmithKline Biologicals SA (GSK) submitted a biologics license application (BLA) for a vaccine with the proposed proper name of Measles, Mumps, and Rubella Virus Vaccine, Live. The final proper name of the vaccine is Measles, Mumps, and Rubella Vaccine, Live, and the proprietary name of the vaccine is PRIORIX. It is a live attenuated trivalent measles, mumps and rubella (MMR) virus vaccine.

PRIORIX is indicated for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older. Each dose of the vaccine (approximately 0.5 mL) is administered subcutaneously. The first dose is administered at 12 through 15 months of age, and the second dose is administered at 4 through 6 years of age. If PRIORIX is not administered according to this schedule, and 2 doses of measles-, mumps- and rubella-virus vaccine are recommended for an individual, there should be a minimum of 4 weeks between the first and second dose. PRIORIX may be administered as a second dose to individuals who have received a first dose of another measles, mumps and rubella virus-containing vaccine.

PRIORIX consists of the Schwartz measles strain, the RIT 4385 mumps strain derived from the Jeryl Lyn strain, and the Wistar RA 27/3 rubella strain. Each virus strain is manufactured separately by propagation in either chick embryo fibroblasts cultures (for mumps and measles) or MRC5 human diploid cells (for rubella), (b) (4) The final product is a mixture of the purified viruses (b) (4) the stabilizer solution and lyophilized (freeze-dried) in single dose vials. The virus drug substances can be stored at (b) (4) for up to (b) (4) To manufacture the final drug product, the three monovalent drug substances are mixed with M-M-R stabilizer medium, (b) (4), filled into vials and lyophilized.

PRIORIX is supplied in a ten-dose configuration that contains ten single-dose vials of lyophilized vaccine antigen component and ten single-dose prefilled, ungraduated syringes of water for injection (WFI) diluent component. The lyophilized antigen component must be reconstituted with the sterile water diluent to form PRIORIX before use. It is reconstituted by adding the entire content of the prefilled syringe to the vial containing the lyophilized antigen component. After mixing the contents until the powder is completely dissolved to form PRIORIX, the entire contents of the reconstituted vaccine are withdrawn into the same syringe and administered subcutaneously. A single dose of vaccine, after reconstitution, is approximately 0.5 mL and contains a minimum of 3.4 $\log_{10}$ cell culture infective dose 50% ($CCID_{50}$) for the Schwarz measles strain, 4.2 $\log_{10}$ $CCID_{50}$ for the RIT 4385 mumps strain derived from the Jeryl Lynn strain and 3.3 $\log_{10}$ $CCID_{50}$ for the Wistar RA 27/3 rubella strain. Each dose also contains 32 mg of anhydrous lactose, 9 mg of sorbitol, 9 mg of amino acids, and 8 mg of mannitol as stabilizer. Each dose may also contain residual amounts of neomycin sulphate (≤25 mcg) from the manufacturing process. The vaccine does not contain any adjuvant or preservative.

The dating period for the lyophilized vaccine antigen is 24 months from the date of manufacture when stored at +5°C ± 3°C. After unlabeled vials are filled with the vaccine antigen and their contents are lyophilized, the vials can be stored for a maximum storage period of (b) (4) at 2°C - 8°C, allowing the performance of the 100% visual inspection. Following visual inspection, the vials can be stored for an intermediate period of up to (b) (4) Final labeling and packaging operations for the vials containing lyophilized vaccine antigen are performed when the vials are removed from (b) (4). The date of manufacture shall be defined as the date the vaccine antigen vials are removed from (b) (4) to begin final labeling and packaging operations. The dating period for each of the monovalent drug substances shall be (b) (4) when stored at (b) (4). The dating period for the sterile water diluent is 60 months from the date of manufacture when stored at +25°C (b) (4) The date of manufacture shall be defined as the date of filling of the diluent. The expiration date for the packaged product, consisting of lyophilized vaccine antigen component and sterile water diluent component, shall be the earlier expiration date of either component.

2. Background

M-M-R II, manufactured by Merck & Co, Inc, is currently the only MMR vaccine licensed in the US. This vaccine has been licensed since 1978 and is recommended by the Advisory Committee for Immunization Practices (ACIP) for the prevention of measles, mumps and rubella childhood illnesses. GSK initiated their measles, mumps, and rubella virus vaccine development in 1997 under IND. PRIORIX was developed following a specific clinical development plan (CDP) to demonstrate its effectiveness by evaluation of vaccine-specific antibody responses. In clinical studies, vaccine-specific antibody responses to measles, mumps, and rubella viruses following administration of PRIORIX were shown to be non-inferior to antibody responses induced by the licensed M-M-R II vaccine. The safety of PRIORIX was evaluated in 6 clinical studies, in which a total of **12,151** participants (**6,391** in the United States) received at least 1 dose of PRIORIX: **8,780** children (**4,148** in the United States) 12 through 15 months of age, **2,917** children (**1,950** in the United States) 4 through 6 years of age, and **454** adults and children (**293** in the United States) 7 years of age and older. Following product and clinical development, GSK requested 2 pre-BLA meetings in October of 2020, one dedicated to clinical aspects of their product development and the other concentrated on chemistry, manufacturing and controls (CMC) and facility plans.

PRIORIX was first registered in Germany in 1997 and is presently licensed in over 100 countries, including 30 European countries, Canada, Australia, and New Zealand.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. IND submission	July 8, 1997
2. End of Phase 2 meeting	December 19, 2011
3. Pre-BLA meetings	October 16, 2020 - Clinical October 26, 2020 - CMC & facilities

Regulatory Events / Milestones	Date
4. BLA 125748/0 submission	June 4, 2021
5. BLA filed	August 3, 2021
6. Mid-Cycle communication	December 2, 2021
7. Late-Cycle meeting	March 3, 2022 Cancelled by GSK
8. PeRC meeting	April 26, 2022
9. Action Due Date	June 4, 2022

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Manufacturing Overview

PRIORIX is a live, attenuated viral trivalent vaccine consisting of a mixture of the Schwarz measles strain, the RIT 4385 mumps strain derived from the Jeryl Lynn strain, and the Wistar RA 27/3 rubella strain. PRIORIX consists of the lyophilized vaccine antigen and sterile water diluent. The water diluent is used to reconstitute the lyophilized vaccine antigen prior to administration. Manufacture of the measles and rubella drug substances takes place at GlaxoSmithKline Biologicals (b) (4) , and manufacture of the mumps drug substance takes place at (b) (4) The final drug product will be manufactured, filled, lyophilized, labeled and packaged at (b) (4) GlaxoSmithKline Vaccines in (b) (4) . The sterile water diluent will be manufactured and filled at (b) (4) and labeled and packaged with the lyophilized vaccine antigen component at (b) (4) GlaxoSmithKline Vaccines in (b) (4)

Lyophilized Vaccine Antigen of PRIORIX

The lyophilized vaccine antigen contains three live attenuated viruses (measles, mumps and rubella). The master cells banks, working cells banks and virus master seeds used in the production of the vaccine were qualified for the absence of detectable extraneous agents. The sponsor presented information ensuring safety from BSE/TSE concerns. The final vaccine formulation does not contain any new or known hazardous excipients. Process performance qualification results showed the consistent elimination of all process residuals and impurities throughout the drug substance manufacturing process. Neomycin sulphate is used in the manufacturing process of PRIORIX at the (b) (4) stages of production of monovalent bulks.

The vaccine manufacturing process is robust, and the virus titers achieved are consistent. The applicant performs in-process and release testing of the vaccine and its intermediates at different stages of manufacturing to ensure that the product meets the pre-established specifications and manufacturing is consistent. The minimum release specifications of $10^{3.4}$, $10^{4.2}$, and $10^{3.3}$ log $CCID_{50}$/dose for measles, mumps and rubella vaccine viruses, respectively, are based on the assessed stability profile and correspond to the minimum titers guaranteed at the end of expiry period of 24 months under the

requested storage temperature of +5°C ± 3°C. These specifications were defined based on data from the clinical studies showing that the vaccine is immunogenic at those doses.

Lyophilized Vaccine Antigen Drug Substances (DSs)

Measles

Measles virus Schwarz strain is used for the preparation of measles monovalent bulks. This strain is approved by the WHO (Technical Report Series n°840, Annex 3, 1994) for vaccine production. In 1954, Enders and Peebles isolated this strain from a child named David Edmonston, who suffered from measles. The strain isolation used primary human kidney (24 viral passages) and primary human amnion (28 viral passages). The strain was adapted and propagated by six additional passages in embryonated chicken eggs (CE) and 13 passages in chick embryo fibroblasts (CEF). The chicken cells adapted strain, historically known as Edmonston A (1st generation attenuated virus) was still virulent for use as a vaccine. The Edmonston A vaccine strain was further attenuated by an additional 84 passages in CEF (19 passages at 35°C followed by 65 passages at 32°C) by Dr. Schwarz from the Dow Chemical Company (DCC). The newly created Schwarz strain was produced in 1963 and preserved by the DCC as an original master seed virus (MSV) with the reference identification SA3I1. In 1973, DCC produced a new MSV SA4I5 from SA3I1 by one further passage in CEF cultures. The GSK working seed virus (WSV) (b) (4)

After several years of production of the MMR vaccine (not for the US market) at GSK, due to the diminished quantity of the MSV (b) (4)

The manufactured measles monovalent bulk is a clarified viral suspension, stabilized in a (b) (4)

The manufacture of Bulk Drug Substance (BDS) is achieved in (b) (4)

Mumps

Currently, the two main mumps virus strains approved by the WHO for vaccination against mumps are Urabe Am9 and Jeryl Lynn. In September 1992, the applicant decided to suspend the distribution of their Urabe Am9 containing vaccines following reports of adverse reactions and decided to develop the Jeryl Lynn strain. The Jeryl Lynn stain has been sold by Merck Sharp & Dohme (MSD) for many years under the trade name MumpsVax. The strain was isolated by amniotic inoculation into chicken embryonated eggs and in cell cultures of CEF for a total of 17 passages. This passage level was chosen for routine vaccine preparation by MSD. The GSK MSV of strain RIT 4385 (lot (b) (4) was obtained after an additional (b) (4) in chicken embryo fibroblasts. The applicant stated that their previous clinical studies performed in children with trivalent measles, mumps and rubella vaccine demonstrated that the immunogenicity of the cloned vaccine strain RIT 4385 was comparable to MMR-II (which contains the MSD Jeryl Lynn mumps vaccine strain). An overview of the isolation and characterization of the mumps virus passage history and the genotypic characterization are provided in this BLA. The mumps monovalent bulk is a clarified viral suspension, stabilized in a (b) (4)

The manufacture of Bulk Drug Substance (BDS) is achieved in (b) (4)

Rubella

The attenuated Wistar RA 27/3 ("rubella abortus, 27th specimen, third explant") rubella virus strain is originated from infected human fetal tissue. The wild-type virus was isolated in human diploid (WI38) cells in 1964 and was attenuated by passage in the same substrate. This work was performed by Dr. S. Plotkin in the Wistar Institute, Philadelphia. Several ampoules, each containing approximately (b) (4) at the (b) (4) passage level, were received by the applicant (then known as SK-RIT) from Dr. Plotkin in 1981. One passage of this virus was performed in (b) (4)

(b) (4)

The manufacture of rubella Bulk Drug Substance (BDS) is achieved in (b) (4)

Lyophilized Vaccine Antigen Drug Product (DP)

Manufacturing Process

PRIORIX DP is prepared by combining measles, mumps and rubella BDSs with M-M-R stabilizer medium, (b) (4) . The stabilizer (b) (4) media are added during the formulation step to establish the exact composition of the formulated vaccine. Information on the composition of the stabilizer (b) (4) media is given below. The commercial manufacturing scale for the formulated Final Bulk is up to (b) (4) . The amounts of BDSs, DP stabilizer solution (b) (4) media in a formulation batch depend on the BDSs potencies and volume required to ensure that the DP potency is within specification at the time of release. The targeted size of a commercial lot is approximately (b) (4) vials corresponding to the maximal capacity of each of the freeze-dryers.

Overages

Overages of at least (b) (4) are incorporated during the formulation step. These overages are intended to guarantee the minimum declared virus titers along shelf life of the PRIORIX vaccine. Table 1 below presents End-of-Shelf Life (EoSL), lower and upper release limits for potency virus titers for PRIORIX vaccine.

Table 1: End-of-Shelf Life and Lower and Upper Release Limits (log $CCID_{50}$/dose) for Potency Virus Titers for PRIORIX Vaccine

Drug Substance	EoSL Limits*	Lower Release Limits*	Upper Release Limits*
Measles	3.4	(b) (4)	
Mumps	4.2		
Rubella	3.3		

*log $CCID_{50}$/dose

The manufacturing process of the PRIORIX vaccine is composed of the following steps: (i) formulation of the Final Bulk; (ii) filling and freeze-drying; (iii) labelling and packaging and (iv) transportation between manufacturing sites.

Bulk Drug Product Formulation Process

PRIORIX DP is manufactured as a sterile solution, aseptically filled into a single-dose 3.0 mL clear glass vial (b) (4) glass). During production of the monovalent bulk intermediates, (b) (4) . To produce the Final Bulk, the measles, mumps and rubella (b) (4)

(b) (4)

(b) (4)

Drug Product Filling and Lyophilization

(b) (4)

(b) (4)

Drug Product Labeling, Packaging and Transportation

(b) (4)

(b) (4)

Process Validation and Evaluation

The consistency of DP manufacturing during formulation, filling and lyophilization was confirmed through an analysis of the (b) (4) Process Performance Qualification (PPQ) lots of PRIORIX vaccine manufactured in 2012 at the (b) (4) facility. These PPQ lots were produced with the initial intent of supporting the registration of the (b) (4) site for the vaccine production for non-US markets. This PPQ information is now submitted to support the approval of the PRIORIX manufacturing process at the (b) (4) facility for the US market. Each lot was manufactured at (b) (4)

To validate the PRIORIX manufacturing process at the (b) (4) facility, the applicant performed the following validation studies:

(b) (4)

DP Specifications

The release tests, specifications and justification of the acceptance criteria for the assays used for release of PRIORIX vaccine at the Final Bulk, Final Container, and Final Product stages are described in the BLA and are shown in the Table 2 below. This testing confirms the absence of extraneous agents (i.e., sterility), verifies potency and identity, and provides a measure of quality and process consistency.

Table 2: Release Specifications for PRIORIX

Tests	**Acceptance criteria**
Vaccine Final Bulk	**--**
Sterility test (b) (4)	Absence of growth
Sterility test (b) (4)	Absence of growth
Bovine Serum Albumin content by (b) (4)	Not more than (b) (4)

Tests	Acceptance criteria
Vaccine Final Container*	--
Description	Whitish to slightly pink colored cake or powder contained in a glass vial sealed with a rubber stopper. After reconstitution with the diluent - clear peach to fuchsia pink colored solution.
Water content by (b) (4)	(b) (4)
Sterility test (b) (4)	Absence of growth
Sterility test (b) (4)	Absence of growth
Identity measles virus by (b) (4)	Positive
Identity mumps virus by (b) (4)	Positive
Identity rubella virus by (b) (4)	Positive
Potency measles virus by (b) (4)	(b) (4)
Potency mumps virus by (b) (4)	
Potency rubella virus by (b) (4)	
Potency measles virus by (b) (4)	
Potency mumps virus by (b) (4)	
Potency rubella virus by (b) (4)	
(b) (4)	
Vaccine Final Product	
Identity of measles by (b) (4)	
Identity of varicella by (b) (4)	
Description of WFI	
Identity (b) (4)	
Identity (b) (4)	

*After the lyophilization step
(b) (4)
(b) (4)

Stability

The stability profile of PRIORIX DP is assessed through the following stability studies:

- Long-term stability studies for up to 24 months at +5°C ± 3°C.
- Cumulative stability studies including (b) (4) 24 months at +5°C ± 3°C.

- Accelerated studies (193 days at (b) (4)
- Accelerated studies (30 days at (b) (4)
- In-use stability, to define the maximum temperature and time periods the reconstituted vaccine can be kept before administration (incubation of the reconstituted vaccine for up to (b) (4) at +5°C ± 3°C, testing at 8 (b) (4) hours).

The stability studies submitted in the BLA support:

- Long-term storage of PRIORIX Final Container (FC) for (b) (4) 24 months at +5°C ± 3°C.
- The recommended storage of the reconstituted vaccine for 8 hours incubation at +5°C ± 3°C after reconstitution.
- The implementation of the following manufacturing changes:
  - use of a new stopper for the container closure system used for the lyophilized vaccine (lots (b) (4)
  - transfer of the vaccine production to the (b) (4) site located in US (lots (b) (4)

Based on the available stability data, the applicant established a shelf-life of 24 months at +5°C ± 3°C for lyophilized PRIORIX in vials. Based on the in-use stability studies, the applicant proposes to use the reconstituted vaccine within a maximum of 8 hours storage at +5°C ± 3°C after reconstitution with WFI diluent. Beyond this storage period, the reconstituted vaccine should be discarded.

Analytical procedures used for the stability testing of PRIORIX along with their acceptance criteria are provided in Table 3 below.

Table 3: Tests and Acceptance Criteria for Stability Assessment of PRIORIX

Tests	Acceptance Criteria
Description	Whitish to slightly pink colored cake or powder contained in a glass vial sealed with a rubber stopper. After reconstitution with the diluent: clear peach to fuchsia pink colored solution.
(b) (4)	Between (b) (4)
Water content by (b) (4)	(b) (4)
Sterility test (b) (4)	Absence of growth
Sterility test (b) (4)	Absence of growth
Potency measles virus by (b) (4)	For stability purpose: Not less than 3.4 log $CCID_{50}$ per dose
Potency mumps virus by (b) (4)	For stability purpose: Not less than 4.2 log $CCID_{50}$ per dose
Potency rubella virus by (b) (4)	For stability purpose: Not less than 3.3 log $CCID_{50}$ per dose
Container closure integrity test	No (b) (4)

Comparability Protocols (CPs)

GSK submitted the following CPs in the BLA:

- Production, qualification and reporting of (b) (4) Rubella Working Virus Seeds to be used in the manufacture of rubella monovalent drug substance

- (b) (4) (i.e., Measles-Mumps-Rubella vaccine lot) to be used in the potency assay by (b) (4) testing procedure for the assay validity purpose only.

Under 21 CFR 601.12(e), approval of a comparability protocol may justify a reduced reporting category for a particular change. CBER reviewed these CPs and agreed with the reporting category of annual report for the changes specified in the CPs listed above.

WFI Diluent Component of PRIORIX

The diluent used to reconstitute the vaccine is WFI presented in a single-dose, pre-filled syringe for subcutaneous injection. It will be manufactured and filled at (b) (4) and labeled and packaged with the lyophilized antigen component at (b) (4) GlaxoSmithKline Vaccines, (b) (4) . The manufacturing process of the WFI diluent is composed of the following steps: (i) (b) (4) .

The WFI diluent is a clear solution, free from visible particles and is compliant with the (b) (4) monograph for sterile WFI. WFI is tested according to methods described in the (b) (4) monograph for sterile WFI. There are no excipients in the WFI diluent.

The WFI diluent planned to be packed with commercial PRIORIX vaccine is supplied in an ungraduated pre-filled syringe (PFS). The entire content of the ungraduated PFS is used to reconstitute the lyophilized PRIORIX vaccine. The applicant proposes that, after reconstitution, the same ungraduated syringe is used to withdraw and after needle change, to administer the entire contents of reconstituted vaccine. This whole content reconstitution/whole content administration (WC/WC) approach aims to consistently deliver a similar volume per dose and to guarantee that minimum potency titers are delivered independently of the variability that could arise from the manufacturing filling volume range for the WFI diluent. The target fill volume (b) (4) mL) for WFI diluent in the ungraduated prefilled syringe includes an overfill to compensate for liquid losses observed during reconstitution and administration of the vaccine and guarantees that minimum potency titers for measles, mumps and rubella are delivered in a dose of approximately 0.5 mL.

Composition

The diluent used to reconstitute the vaccine is WFI presented in a single-dose, pre-filled syringe for subcutaneous injection. The WFI diluent is a clear solution, free from visible particles and is compliant with the (b) (4) monograph for sterile WFI. The composition of the WFI diluent is provided in Table 4 below.

Table 4: Composition of the Drug Product (WFI Diluent)

Ingredients	Quantity per syringe *	Function	Reference/Monograph standard
Water for Injection	(b) (4) mL	Diluent	(b) (4) Sterile WFI

*Target fill volume is (b) (4) mL to guarantee a minimal volume of 0.5 mL of reconstituted vaccine per administered dose.

Microbiological Attributes

The WFI Bulk is manufactured according to GMP in controlled environmental conditions to minimize bioburden and to assure sterility of the Final Product. Areas are appropriately monitored for environmental air conditions. Equipment is cleaned or sterilized according to validated methods. The WFI Bulk entering the formulation of the WFI diluent is (b) (4) The WFI diluent Final Container is tested for sterility and endotoxin content according to Pharmacopoeia requirements (see Table 5 below).

Table 5: Release Specifications for WFI Diluent Final Container

Test/Procedure	Acceptance criteria
(b) (4)	(b) (4)
Particle Count	
Sterility test (b) (4)	
Sterility test (b) (4)	
Bacterial Endotoxin tests (b) (4)	
Water conductivity	
Extractable volume	

Compatibility

The compatibility of the WFI diluent with the container closure components is demonstrated through stability studies. In addition, the compatibility between the WFI diluent and the PRIORIX lyophilized vaccine has been validated by performing reconstitution of vaccine with WFI diluent, followed by potency testing. Potency testing was performed immediately and up to 8 hours after reconstitution. Results were provided in the BLA. All information was reviewed and found to be acceptable.

Stability

The dating period for the diluent component (Water for Injection) of Measles, Mumps and Rubella Vaccine, Live in the prefilled ungraduated syringes is 60 months from the date of manufacture when stored at +25°C (b) (4) The date of manufacture shall be defined as the date of filling of the diluent.

The PRIORIX Vaccine

Composition

As previously described, PRIORIX consists of one vial of lyophilized vaccine antigen that is reconstituted at the time of use with the whole contents (no less than 0.5 mL) of liquid from the accompanying vial of WFI diluent. A single dose of PRIORIX is approximately 0.5 mL, and it does not contain preservative. The composition of the reconstituted vaccine and the function of the ingredients are provided in Table 6.

Table 6: Composition of PRIORIX

Ingredients	**Quantity per dose[1]**
Active Ingredients	--
Live attenuated measles virus (Schwarz strain)	≥ $10^{3.4}$ log $CCID_{50}$
Live attenuated mumps virus (RIT4385 strain)	≥ $10^{4.2}$ log $CCID_{50}$
Live attenuated rubella virus (Wistar RA 27/3 strain)	≥ $10^{3.3}$ log $CCID_{50}$
Inactive Ingredients (Excipients)	--
Anhydrous lactose	32 mg
Mannitol	8 mg
Amino acids	9 mg
Sorbitol	9 mg

[1] Virus titer on the label. It corresponds to the minimum titer guaranteed at expiry. The vaccine is formulated to contain (b) (4) log $CCID_{50}$/dose for measles, mumps and rubella respectively.

As previously described, the dating period for the lyophilized vaccine antigen is 24 months from the date of manufacture when stored at +5°C ± 3°C. After unlabeled vials are filled with the vaccine antigen and their contents are lyophilized, the vials can be stored for a maximum storage period of (b) (4) at 2°C - 8°C, allowing the performance of the 100% visual inspection. Following visual inspection, the vials can be stored for an intermediate period of up to (b) (4) Final labeling and packaging operations for the vials containing lyophilized vaccine antigen are performed when the vials are removed from (b) (4) The date of manufacture shall be defined as the date the vaccine antigen vials are removed from (b) (4) to begin final labeling and packaging operations. The dating period for the sterile water diluent is 60 months from the date of manufacture when stored at +25°C (b) (4) The date of manufacture shall be defined as the date of filling of the diluent. The expiration date for the packaged product, consisting of lyophilized vaccine antigen component and sterile water diluent component, shall be the earlier expiration date of either component.

In-Use Stability of PRIORIX

In-use stability allows to define the maximum temperature and time periods the reconstituted vaccine can be kept before administration (incubation of the reconstituted vaccine for up to (b) (4) at +5°C ± 3°C, testing at 8 (b) (4) hours).

Analytical procedures used for the stability testing of PRIORIX vaccine along with their acceptance criteria and the justifications for the test are provided in table 7 below.

Table 7: Analytical Procedures Used for Stability Purpose*

Tests	**Acceptance Criteria**
Description	Whitish to slightly pink colored cake or powder contained in a glass vial sealed with a rubber stopper. After reconstitution with the diluent: clear peach to fuchsia pink colored solution.
(b) (4)	Between (b) (4)
Water content by (b) (4)	Not more than (b) (4)
Sterility test (b) (4)	Absence of growth
Sterility test (b) (4)	Absence of growth
Potency measles virus by (b) (4)	For stability purpose: Not less than 3.4 log $CCID_{50}$ per dose*
Potency mumps virus by (b) (4)	For stability purpose: Not less than 4.2 log $CCID_{50}$ per dose*
Potency rubella virus by (b) (4)	For stability purpose: Not less than 3.3 log $CCID_{50}$ per dose*
Container closure integrity test	(b) (4)

*The table indicates the specifications for the EoSL potency values that are being licensed in the United States.

Based on the in-use stability studies, the sponsor proposes to use the reconstituted vaccine within a maximum of 8 hours storage at +5°C ± 3°C after reconstitution with WFI diluent. Beyond this storage period, the reconstituted vaccine should be discarded. This proposal is acceptable and a statement regarding the maximum hold time for the reconstituted vaccine is included in the package insert.

Presentation and Packaging System

The vaccine will be supplied in a ten-dose configuration that contains ten single-dose vials of lyophilized antigen component and ten single-dose prefilled, ungraduated syringes of sterile water diluent component.

b. Testing Specifications

The analytical methods and their validations and /or qualifications reviewed for the PRIORIX drug substances and drug product were found to be adequate for their intended use.

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of PRIORIX™ vaccine are listed in the table below. The activities performed and inspectional histories are noted in the Table 8.

Table 8: Manufacturing Facilities Table for PRIORIX (Measles, Mumps and Rubella Vaccine, Live)

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/Results
GlaxoSmithKline Biologicals (b) (4) (b) (4) <u>Manufacturing Operations:</u> Measles: monovalent bulk DS; and Rubella: monovalent bulk DS	(b) (4)	(b) (4)	Waiver	DMPQ Pre-License Inspection, (b) (4) NAI[1]
GSK Vaccines (b) (4) (b) (4) <u>Manufacturing Operations:</u> Mumps: monovalent bulk DS	(b) (4)	(b) (4)	Waiver	Team Biologics Inspection (b) (4) NAI

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/Results
(b) (4) GlaxoSmithKline Vaccines (b) (4) Manufacturing Operations: DP formulation, filling, lyophilization, visual inspection; DP and WFI diluent labeling and packaging	(b) (4)	(b) (4)	Inspection	DMPQ Pre-License Inspection February (b) (4) VAI[2]
(b) (4) Manufacturing Operations: WFI diluent production and filling	(b) (4)	(b) (4)	Waiver	Team Biologics Inspection (b) (4) VAI

1 No Action Indicated
2 Voluntary Action Indicated

DMPQ performed a pre-license inspection (PLI) at GlaxoSmithKline Biologicals (b) (4) and a Form FDA 483 was not issued at the end of the inspection. The inspection was classified as NAI.

Team Biologics performed a surveillance inspection at GSK Vaccines (b) (4) in (b) (4), and a Form FDA 483 was not issued at the end of the inspection. The inspection was classified as NAI.

DMPQ performed a PLI at (b) (4) from (b) (4) and a Form FDA 483 was issued at the end of the inspection. All 483 issues were resolved, and the inspection was classified as VAI.

Team Biologics performed a surveillance inspection at (b) (4) in (b) (4), and a Form FDA 483 was issued at the end of the inspection. All 483 issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The drug product is filled into 3 mL (b) (4) glass vials (b) (4) with a bromobutyl rubber stopper (b) (4), and cap (b) (4). The applicant performed the container closure integrity testing at the GlaxoSmithKline Biologicals (b) (4) facility, employing the (b) (4) container closure integrity test method; all acceptance criteria were met.

The WFI diluent is filled into 1.25 mL (b) (4) glass syringe barrels with a styrene-butadiene rubber tip cap, bromobutyl rubber plunger stopper, syringe plunger rod and syringe backstop device. Container closure components are supplied by (b) (4). Container closure integrity testing was performed at the (b) (4) facility, employing the (b) (4) container closure integrity test method; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. A BLA is categorically excluded from environmental assessment requirements if the action does not increase the use of the active moiety. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

PRIORIX was first registered in Europe in November 1997, which was before the first preclinical guidance from the European Medicines Agency (EMA) or U.S. Food and Drug Administration (FDA). Good Laboratory Practice (GLP) toxicity studies were not performed with PRIORIX.

However, the applicant did perform a GLP toxicology study with the measles, mumps, rubella, and varicella (MMRV) vaccine called PRIORIX -TETRA, The MMR bulks used to formulate GSK's MMR and MMRV vaccines are the same. PRIORIX-Tetra is formulated to contain the same measles and rubella antigen content as PRIORIX and a higher amount of the mumps antigen than PRIORIX. In the submitted GLP toxicity study, *Rhesus* monkeys received a full human dose (0.5 ml/injection) containing either saline (control) or PRIORIX -TETRA subcutaneously on either SD 1 only, or on SD 1 and SD 36. No deaths or clinical signs attributed to the MMRV vaccine were observed. Local reactions at the injection sites did not reveal any signs of erythema, fissures, edema, scar formation or exfoliation. Body weight evolution and food consumption were unaffected by MMRV vaccine treatment. There were no treatment-related changes in rectal body temperature following inoculation with the MMRV vaccine. Ophthalmoscopy, electrocardiography, and blood pressure measurements revealed no treatment-related findings. No treatment-related findings were observed on clinical pathology parameters, organ weights, macroscopic examinations, or histopathology investigations.

PRIORIX contains live attenuated measles, mumps, and rubella viruses. The vaccine is contraindicated for use in pregnant women because infection during pregnancy with any

of the wild-type viruses is associated with maternal and fetal adverse outcomes. Therefore, no reproductive toxicology studies have been performed.

5. Clinical Pharmacology

Humoral immune responses against measles, mumps, and rubella viruses induced by PRIORIX were measured by enzyme-linked immunosorbent assays (ELISAs). IgG antibodies measured by the ELISAs used in clinical studies of PRIORIX have been shown to correlate with the presence of neutralizing antibodies that have been associated with protection.

6. Clinical/Statistical

a. Clinical Program

The Applicant has submitted data from 6 randomized clinical studies as part of this BLA to support the safety and effectiveness of PRIORIX in comparison to United States (US)-licensed M-M-R II vaccine [Merck & Co., Inc. (Merck)]. M-M-R II is the only trivalent combined MMR vaccine licensed in the US (since 1978) and is recommended for routine vaccination by the Advisory Committee on Immunization Practices (ACIP); thus, M-M-R II was the active comparator in all studies in the PRIORIX US Clinical Development Plan (CDP).

Five Phase 3 trials provide the primary data for the intended indication in individuals 12 months of age and older, as well as clinical data to support manufacturing consistency (lot consistency). One Phase 2 trial provided data to justify the mumps virus potency in the vaccine formulation used in the Phase 3 studies. These 6 trials (MMR-157, MMR-158, MMR-159, MMR-160, MMR-161, and MMR-162) enrolled participants ≥12 months of age at more than 400 sites in 11 countries, including the US. The total number of subjects for all studies that received PRIORIX was 12,151 of which 6,391 were from the US. The total number of subjects for all studies that received M-M-R II was 5,242 of which 2,689 were from the US.

Studies MMR-160, MMR-161, MMR-162, and MMR-157 evaluated a single dose of MMR vaccine in participants 12 through 15 months of age. Two Phase 3 studies assessed a second dose of MMR vaccine in older populations: study MMR-158 enrolled participants 4 through 6 years of age, and study MMR-159 enrolled participants ≥7 years of age. All studies evaluated safety (local and systemic adverse reactions, unsolicited adverse reactions, adverse events of specific interest and serious adverse events) descriptively. In all studies except MMR-159, age-appropriate ACIP-recommended routine vaccinations were concomitantly administered.

Phase 3 study MMR-160 evaluated both lot consistency and non-inferiority to M-M-R II in terms of immunogenicity. Phase 3 study MMR-161 evaluated the immunogenicity of PRIORIX at an end of shelf-life (EOSL) potency compared to M-M-R II and was the only study to administer 2 doses of MMR vaccine, spaced 6 weeks apart. Phase 3 study MMR-162 was primarily a safety study used to define maximum release potency limits. Phase 3 studies MMR-158 and MMR-159 evaluated the non-inferiority of PRIORIX compared to M-M-R II as a second MMR dose, after an MMR containing vaccine, in

terms of immunogenicity. Phase 2 study MMR-157 compared three lots of PRIORIX with different mumps potencies in a US population.

Clinical Serology Assays

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. The SOPs and their validations were reviewed and found to be adequate, and the assays were found to be suitable for their intended use. The parameters and validity criteria selected for the validation studies were adequate and were also reviewed by the statistician.

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 (b) (4), the applicant reported that pre-specified validation criteria were met. However, the analysis of dilutability of the ELISA assay experienced missing operator results, large differences between some operator assays, deletion of outlying results, and patterns of increasing concentration with increasing dilution factor. The applicant attributed the outlying results to sample-specific effects of dilution on estimated concentration and deferred any reanalysis to the current owner of the assay, who will provide responses to the master file. Therefore, despite meeting the pre-specified criteria, the linearity range of the ELISA assay may be updated.

Additionally, the applicant submitted validation reports for the following assays used in secondary immunogenicity endpoints in their concomitant use clinical studies:

- VZV IgG (b) (4) assay
- Hepatitis A (HAV) total antibody (b) (4)
- Poliovirus (b) (4)
- Diphtheria (DI) and Tetanus (TE) (b) (4)
- Acellular Pertussis (PT, FHA, and PRN) (b) (4)
- (b) (4) assay for the evaluation of immune response to the pneumococcal antigens
- Pneumococcal (b) (4)

The parameters and validity criteria of the assays were determined to be adequate, and the assays were found to be suitable for their intended use.

Effectiveness Study Results

Immunogenicity Analyses

Effectiveness of PRIORIX was inferred by demonstration of vaccine-specific antibody responses to measles, mumps, and rubella virus following administration of PRIORIX that were non-inferior to responses observed following M-M-R II. Antibody responses were assessed using validated immunological assays as described above. Both PRIORIX and M-M-R II contain the same strains for mumps (Jeryl-Lynn or a Jeryl-Lynn-derived strain) and rubella (Wistar 27/3 strain) and a similar lineage of measles strain derived from the Edmonston strain (Schwarz strain at GSK and Edmonston-Enders strain at Merck). Unless otherwise specified, immunogenicity objectives were to establish non-inferiority to MMR II as determined by the following: 1) lower limit (LL) of the two-sided 95% confidence interval (CI) of the seroresponse rate (SRR) difference (PRIORIX minus M-M-R II) of ≥-5% for each vaccine antigen; and 2) LL of the two-sided 95% CI of the geometric mean concentration (GMC) ratio (PRIORIX over M-M-R II) of ≥0.67 for each vaccine antigen.

Study MMR-160 was the main study evaluating the non-inferiority of PRIORIX compared to M-M-R II as a first MMR dose in healthy individuals 12 through 15 months of age. Non-inferiority was determined as described above with additional criteria of a seroresponse rate ≥90% for all vaccine antigens. The co-primary objectives to demonstrate immunological non-inferiority of PRIORIX to M-M-R II, were met. Secondary objectives evaluated concomitant vaccination with Varivax, Havrix, and Prevnar13. Lack of immune interference with concomitantly administered routine pediatric vaccines (Varivax, Havrix, and Prevnar 13) in PRIORIX as compared to M-M-R II was also demonstrated.

Study MMR-158 evaluated the non-inferiority of PRIORIX compared to M-M-R II as a second MMR dose in healthy individuals 4 through 6 years of age in participants who received study vaccine with or without administration of concomitant vaccines. Non-inferiority was determined as described above, though using the LL of the two-sided 97.5% CI. The primary objectives to demonstrate non-inferiority of PRIORIX to M-M-R II in terms of seroresponse rate and GMCs, when administered either with Kinrix and Varivax or alone, were met. Secondary objectives evaluated concomitant vaccination with Varivax and Kinrix vaccine. Lack of immune interference with concomitantly administered routine pediatric vaccines (Varivax and Kinrix) in PRIORIX as compared to M-M-R II was also demonstrated.

Study MMR-161 evaluated the End of Shelf Life (EOSL) potency for each antigen in PRIORIX in healthy 12 through 15-month-olds who received a first dose of either minimum potency PRIORIX, medium potency PRIORIX, or M-M-R II. Non-inferiority was determined as described above, though the LL of the two-sided 97.5% CI was used and the additional criteria of the seroresponse rate being ≥90% for all vaccine antigens was measured. The primary objectives to demonstrate non-inferiority of medium potency PRIORIX to M-M-R II as measured by ELISA for measles, mumps and rubella were met. Secondary objectives descriptively evaluated the immunogenicity of a second dose of MMR vaccine, where study participants who received a first dose of either PRIORIX or M-M-R II, received targeted release potency PRIORIX or M-M-R II, respectively, 6 weeks

later. Immune responses to PRIORIX or M-M-R II as a second dose were comparable among children enrolled in the US.

Study MMR-162 primarily evaluated safety of PRIORIX at the maximum potency release limits in children 12 through 15 months of age. Safety analyses are described below (see Section 7). The descriptive secondary immunogenicity analyses demonstrated comparable SRRs and point estimates for GMCs to the measles, mumps and rubella vaccine components.

Study MMR-159 demonstrated the non-inferiority of PRIORIX compared to M-M-R II as a second MMR dose in healthy individuals ≥7 years of age. Non-inferiority was determined as described above for the primary objective (GMCs) and the first secondary objective (SRR). The study met its predefined criteria for success for the primary objective and the first co-secondary objective.

Study MMR-157 was an exploratory Phase 2 study conducted in the US to descriptively assess the immunogenicity and safety of three lots of PRIORIX with different mumps virus potencies. The results supported the mumps potency of 4.2 $\log_{10}$ $CCID_{50}$ to be used in Phase 3 trials.

Lot Consistency

The Applicant satisfactorily demonstrated consistency of lot performance in Study MMR-160 based on pair-wise comparisons of GMCs and SRRs of three different lots of PRIORIX. Safety profiles across lots were also consistent.

Concomitant Vaccination

The safety and effectiveness of PRIORIX when administered concomitantly with ACIP-recommended routine childhood vaccines, Prevnar13, Havrix, and Varivax in 12 through 15-month-olds and Varivax and Kinrix in 4 through 6-year-olds, were evaluated in all relevant studies for the appropriate age groups as compared to M-M-R II concomitantly administered with the respective vaccines. Non-inferiority of PRIORIX to M-M-R II in terms of immune response for each antigen in the concomitantly administered vaccines was demonstrated. No evidence of immune interference to the antibody responses to the PRIORIX antigens and the antibody responses to the concomitantly administered vaccines was observed. Additionally, no notable increase in frequency or severity of reported adverse events (AEs) with concomitant administration was observed in PRIORIX as compared to M-M-R II.

The statistician confirmed the effectiveness analyses described above and concluded that overall, the primary immunogenicity and safety endpoints were largely met in the five Phase 3 studies.

Postmarketing

No safety signals have been identified to date that would justify a postmarketing study. For pediatric studies required by Pediatric Research Equity Act PREA (21 U.S.C. 355c), reference is made to the pediatric section of this document.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspections were issued for four domestic Clinical Investigators who participated in the conduct of protocol MMR-158 (115158), and three of the clinical investigators also participated in the conduct of protocol MMR-160 (115648). The inspections did not reveal substantive issues that impact the data submitted in this BLA.

c. Pediatrics

Under the IND, the Applicant submitted an initial Pediatric Study Plan (iPSP) on July 6, 2016, and an Agreed iPSP on January 6, 2017, which included a request for waiver of pediatric studies in infants <12 months of age. FDA concurred with the Agreed iPSP, acknowledged the plan to request the partial waiver, and provided a letter of agreement to the Applicant on January 26, 2017.

Under the Biologics License Application (BLA), the final Pediatric Study Plan was presented to the Pediatric Review Committee (PeRC) on April 26, 2022. Safety and effectiveness of PRIORIX have not been established in individuals younger than 12 months of age in the US. The Applicant's request for a partial waiver for those less than 12 months of age was accepted by PeRC because the candidate vaccine does not represent a meaningful therapeutic benefit and is not likely to be used in this age group. PeRC agreed that the pediatric assessment for PRIORIX was complete.

d. Other Special Populations

Pregnancy

PRIORIX is contraindicated for use in pregnant women because infection during pregnancy with the wild-type viruses is associated with maternal and fetal adverse outcomes.

Pregnancy should be avoided for 1 month after vaccination as per the Centers for Disease Control and Prevention. For women who are inadvertently vaccinated when pregnant or who become pregnant within 1 month of administration of PRIORIX, the healthcare provider should be aware of the following: Reports have indicated that contracting wild-type measles during pregnancy increases fetal risk. Mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion. Pregnant women infected with rubella are at increased risk for miscarriage or stillbirth, and their infants are at risk for congenital rubella syndrome.

Available data on inadvertent administration of PRIORIX to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

Lactation

The application did not contain data from clinical studies specifically addressing whether the vaccine viruses are excreted in human breast milk. The following language is included in the PRIORIX prescribing information based on literature reviewed:

It is not known whether the vaccine components of PRIORIX are excreted in human milk. Data are not available to assess the effects of PRIORIX on the breastfed infant or on milk production and excretion. Studies have shown that lactating postpartum women vaccinated with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. In the breast-fed infants with serological evidence of rubella virus vaccine strain antibodies, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PRIORIX and any potential adverse effects on the breastfed child from PRIORIX or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

Pediatric Sub-populations

Safety and effectiveness of PRIORIX in infants younger than 12 months of age have not been established.

Most infants receive passive protection against measles, mumps, and rubella in the form of antibodies from their mothers via trans-placental transmission. These antibodies can prevent vaccine virus replication if they are present when the vaccine is given and, thus, can cause the vaccine to be less effective. By 12 months of age, almost all infants have lost this passive protection. For this reason, the Indication and Usage will specify that the vaccine is indicated for use in individuals 12 months of age and older.

Immunocompromised Patients

Administration of PRIORIX poses a potential risk to immunocompromised individuals due to the live replication-competent virus strains contained in the vaccine. The following language is included in the PRIORIX prescribing information:

> Due to the risk of disseminated vaccine virus infection, do not administer to individuals with severe humoral or cellular (primary or acquired) immunodeficiency.

Geriatric Use

Clinical studies of PRIORIX did not include participants 65 years of age and older. The upper age limit across studies was 59 years. The Indication and Usage will not be restricted by an upper age limit; the data from study MMR-157 (age range: 7 to 59 years) are considered adequate to extrapolate safety and effectiveness to older persons.

7. Safety and Pharmacovigilance

Safety Results

Post-vaccination safety data were reviewed from over 12,000 PRIORIX recipients who were enrolled in the six randomized clinical trials. Overall, the most frequently (≥10%)

reported solicited local adverse reactions across age groups were injection site pain (12 to 41%) and erythema (11 to 25%); and in 4 through 6-year-olds, swelling (11%). The most frequently (≥10%) reported solicited systemic adverse reactions in 12 through 15-month-olds were irritability/fussiness (63%), loss of appetite (45%), drowsiness (45%), and in 4 through 6-year-olds were fever (35%); drowsiness (27%), fever (24%) and loss of appetite (21%). Rates of Serious Adverse Events (SAEs) following administration of PRIORIX as compared to M-M-R II were similar. The types of SAEs observed in the clinical trials were events that have been reported previously with other MMR-containing vaccines. All SAEs considered related to the administration of PRIORIX resolved without sequelae by the end of the study period. Across all six studies, there were 3 deaths throughout the entire study period: two deaths among PRIORIX recipients and 1 death among M-M-R II recipients. Upon careful review of the case narratives, it was determined that none were considered related to study vaccination by the clinical review team.

In study MMR-162, the primary objectives were to evaluate the incidence of fever at a potency used to define each antigen's maximum release limits when administered as a first dose to 12 through 15-month-old children. The co-primary safety objectives, to demonstrate that the two-sided 95% upper limit of the difference in fever rates (PRIORIX minus M-M-R II) did not exceed 5% for fever >39.0°C and 10% for fever ≥38.0°C, were met. Thus, safety of PRIORIX at the maximum release potency was considered acceptable.

Overall, the safety profile was similar to M-M-R II across studies.

Postmarketing Data

PRIORIX is currently approved in all EU countries as well as over 70 non-EU countries. Over 388 million doses have been distributed outside the U.S[1]. The submitted Periodic Benefit Risk Evaluation Report (PBRER) (reporting period: 05 May 2015 to 04 May 2018), dated 25 July 2018, was reviewed. Adverse reactions (ARs) reported in the post-marketing setting outside the US are summarized below in Table 9:

Table 9: Adverse Reactions Reported in the Postmarketing Setting Outside the US

System Organ Class (SOC)	Adverse Reactions
Infections and infestations	Meningitis, measles-like syndrome, mumps-like syndrome (including orchitis, epididymitis, and parotitis)
Blood and lymphatic system disorders	Thrombocytopenia, thrombocytopenic purpura
Immune system disorders	Anaphylactic reactions
Nervous system disorders	Encephalitis, cerebellitis, cerebellitis like symptoms (including transient gait disturbance and transient ataxia), Guillain-Barré syndrome, transverse myelitis, peripheral neuritis
Vascular disorders	Vasculitis (including Henoch-Schönlein purpura and Kawasaki syndrome)
Skin and subcutaneous tissue disorders	Erythema multiforme

System Organ Class (SOC)	Adverse Reactions
Musculoskeletal and connective tissue disorders	Arthralgia, arthritis

Pharmacovigilance Plan

The applicant submitted a pharmacovigilance plan (PVP) proposing routine pharmacovigilance (PV) activities, which includes the review and reporting of adverse reactions from the postmarketing setting, signal detection, periodic aggregate safety reports, and literature review. The applicant's summary of important identified risks, important potential risks, and missing information is summarized in Table 10.

Table 10: Summary of Safety Concerns

Safety Concern	Risk Minimization Activities
Important Identified Risks: None	• N/A
Important Potential Risks: None	• N/A
Missing Information: Use in pregnant or lactating patients	• Routine PV activities • Routine risk communication in USPI o The Highlights of Prescribing Information and Section 4.3 list pregnancy as a contraindication o Sections 8.1 and 8.2 summarize the lack of data regarding use of PRIORIX during pregnancy and/or lactation

There are no important identified or important potential risks in the submitted PVP. At the time of the PBRER dated 25 July 2018, important identified risks consisted of hypersensitivity, syncope/vasovagal response to injection, febrile convulsions, and immune thrombocytopenic purpura (ITP)/thrombocytopenia. There were no important potential risks. The applicant removed the four previously important identified risks from the safety specifications of the current PVP, stating that the risks are well-characterized, the frequencies have remained the same, are labeled, and do not require additional measures beyond routine pharmacovigilance. The applicant did not mention any ongoing studies in in the PVP that will yield additional safety information.

Assessment of Pharmacovigilance Plan

Overall, the clinical trial safety database does not indicate any new safety issues for PRIORIX which have not been previously described for MMR-containing vaccines. Hypersensitivity and syncope/vasovagal reactions can occur with any vaccine, while febrile convulsions and ITP/thrombocytopenia are known to occur with MMR-containing vaccines. Therefore, it is acceptable that the four previously important identified risks (hypersensitivity, syncope/vasovagal response to injection, febrile convulsions, and immune thrombocytopenic purpura (ITP)/thrombocytopenia) are no longer listed under the safety specifications of the current PVP.

8. Labeling

The proprietary name, PRIORIX, was reviewed by CBER's Advertising and Promotional Labeling Branch (APLB) on April 5, 2022 and found to be acceptable. CBER communicated this decision to the Applicant on May 2, 2022.

In our review, dated April 26, 2022, APLB examined the prescribing information, package, and container labels from a promotional and comprehension perspective. The package and container labels were found acceptable. On June 1, 2022, following an iterative review of additional revisions requested by the review committee, the applicant provided prescribing information that is acceptable from a promotional and comprehension perspective.

GSK submitted to CBER two versions of the revised container labels in response to CBER's comments in Amendments 40 and 43. GSK was notified on May 28, 2022, that the carton and container labels submitted in Amendment 43 on May 26, 2022, were acceptable and considered the Final Draft Labels. GSK subsequently submitted a revised carton label on June 1, 2022, superseding the May 26, 2022, version, and GSK was notified on June 2, 2022, that the carton label submitted in Amendment 45 on June 1, 2022, was acceptable and considered the Final Draft Label for the carton.

GSK submitted to CBER 4 versions of the PI (as amendments to the BLA) in response to CBER's comments in the following amendments: 125748/42, 125748/44, 125748/47 and 125748/48. The clean copy Word version of the PI submitted on June 3, 2002 (Amendment 48) was considered the Final Draft PI for approval. GSK was notified on June 3, 2022, that CBER considered the clean version of the PI included in Amendment 48 as the Final Draft PI for approval.

9. Advisory Committee Meeting

No advisory committee meeting was held since a similar vaccine from a different manufacturer has been on the market for many years, and FDA review of this submission did not identify concerns or issues which would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

With this BLA, the Applicant submitted clinical trial data from Phase 2 Study MMR-157 that utilized the lyophilized vaccine antigen in a vial plus the diluent in an ungraduated pre-filled syringe (PFS) presentation for use in the same Whole Content/Whole Content (WC/WC) approach for PRIORIX reconstitution and administration as specified in proposed product labeling for preparation of the vaccine for administration. The safety and immunogenicity data generated from this study using the ungraduated PFS presentation are consistent with the findings from Phase 3 clinical trials in which the vaccine was prepared for administration using a diluent supplied in a vial. The Phase 2 data provide evidence to support the commercial use of the diluent in an ungraduated PFS presentation and the Whole Content/Whole Content (WC/WC) approach for PRIORIX reconstitution and administration. The Applicant submitted a Use Related Risk Analysis (URRA) to their IND which included information that the ungraduated PFS

presentation has been used in PRIORIX marketed in other countries (e.g., PRIORIX Australia, AUS). Due to the similar presentation characteristics between PRIORIX US and PRIORIX AUS and the Applicant's report of the medication errors associated with use of PRIORIX AUS, the clinical reviewer assessed that the risk of medication errors associated with WC/WC administration is low. A formal consultation with the Division of Medication Error Prevention and Analysis (DMEPA) at CDER/FDA, will be completed post-licensure but is not considered essential for the approval of PRIORIX. Any recommendations from the DMEPA consultation will be communicated to the Applicant as appropriate.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the pre-clinical, clinical, and product-related data submitted in the BLA, the Review Committee recommends approval of PRIORIX for the labeled indication and usage.

b. Benefit/Risk Assessment

The applicant has submitted data to the BLA to support the safety and effectiveness of PRIORIX. Based on these data, the Review Committee agrees that the risk/benefit balance for PRIORIX is favorable and supports approval for use as a first dose in individuals 12 through 15 months of age and as a second dose in individuals 4 through 6 years of age.

c. Recommendation for Postmarketing Activities

No PMRs/PMCs have been identified for this submission.

12. References

1. Gershon AA, Marin M, Seward JF. Measles and mumps. In: Wilson CB, et al. eds. Remington and Klein's Infectious Disease of the Fetus and Newborn Infant. 8th ed. Philadelphia, PA: Elsevier; 2015:675-723.