CBER CMC BLA Review Memorandum

BLA STN 125748

PRIORIX [Combined Measles, Mumps and Rubella (MMR) Live (Attenuated) Viral Vaccine. A lyophilized single dose vial presentation to be reconstituted with water for injection provided in ungraduated prefilled syringes. Vaccine is a suspension for subcutaneous injection.]

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Abbreviations used:

BDS	Bulk Drug Substance
BSA	Bovine Serum Albumin
BSE	Bovine Spongiform Encephalitis
CCI	Container Closure Integrity
$CCID_{50}$	Cell Culture Infective Dose 50%
CCS	Container Closure System
CEF	Chick Embryo Fibroblasts
COAs	Certificate of Analysis
DP	Drug Product
DS	Drug Substance
EOSL	End of shelf-Life
FB	Final Bulk
FBS	Fetal Bovine Serum
FC	Final Container
FDP	Final Drug Product
GSK	GlaxoSmithKline
HDPE	High-density Polyethylene
HVF	Harvested Viral Fluids
LLA	Luer Lock Adaptors
LOD	Limit of Detection
LOQ	Limit of Quantitation
MCB	Master Cell Bank
MMR	Measles, Mumps and Rubella
MSV	Master Seed Virus
MT	Multi-tray
NVT	Neurovirulence Testing
PCMs	Process Contact Materials
Ph. Eur.	European Pharmacopoeia
PP	Poly propylene
QC	Quality Control
QR	Quality Release
RB	Roller bottles
RT	Reverse Transcriptase
RTS	Ready to Sterilize
SOP	Standard Operating Procedures
SPF	Specific Pathogen Free
TF	T-flasks
TSE	Transmissible Spongiform Encephalitis

ULOQ	Upper Limit of Quantitation
USDA	U.S Department of Agriculture
USP	United States Pharmacopoeia
WFI	Water for Injection
WSV	Working Seed Virus

1. BLA# STN 125748

2. APPPLICANT NAME AND LICENSE NUMBER
GlaxoSmithKline (GSK)

3. PRODUCT NAME/PRODUCT TYPE
PRIORIX [Combined Measles, Mumps and Rubella (MMR) Live (Attenuated) Viral Vaccine. A lyophilized single dose vial presentation to be reconstituted with water for injection provided in ungraduated prefilled syringes. Vaccine is a suspension for subcutaneous injection.]

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT
PRIORIX is a suspension for subcutaneous injection and is supplied as a sterile, lyophilized powder which is reconstituted at the time of use with the accompanying sterile water diluent. PRIORIX is a live attenuated viral trivalent vaccine consisting of a live attenuated measles virus (Schwarz Strain), live attenuated mumps virus (RIT 4385 Strain), and live attenuated rubella virus (Wistar RA27/3 Strain). The vaccine is manufactured by separate propagation of mumps and measles vaccine viruses in primary chick embryo fibroblasts cultures and rubella vaccine virus in MRC-5 human diploid cells. The viruses are harvested from the cell culture media, clarified by filtration, and (b) (4) . The three virus materials are then (b) (4), mixed with the appropriate volumes of dilution media and stabilizer medium and filled into vials. Filled vials are partially stoppered, lyophilized, capped, visually inspected, and stored at (b) (4) until labelling and packaging. The diluent for PRIORIX is sterile water for injection supplied in prefilled syringes. Vials and syringes are labelled, packaged, and stored between 36°F and 46°F (2°C and 8°C) in the original packaging to protect vials from light. The lyophilized antigens are presented in the form of a whitish to slightly pink powder. After reconstitution, each approximately 0.5-mL dose contains not less than 3.4 log10 $CCID_{50}$ of measles virus, 4.2 log10 $CCID_{50}$ of mumps virus, and 3.3 log10 $CCID_{50}$ of rubella virus. 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. After reconstitution, PRIORIX is a clear peach- to fuchsia, pink-colored liquid. PRIORIX does not contain preservatives. The first dose is administered at 12 to 15 months of age. The second dose is administered at 4 to 6 years of age.

5. MAJOR MILESTONES
Submission Date: 06/04/2021
Date of Filing Meeting: 07/19/2021
Filing Date: 08/03/2021
BLA Action Due Date: 06/04/2022

6. CMC/QUALITY REVIEW TEAM

Affiliation	Reviewer	Section/Subject Matter
CMC Reviewers	Dmitriy Volokhov, DVM, PhD Tatiana Zagorodnyaya, MS	Sections 2.2, 2.3, 2.4, 3.2.S, 3.2.P, 3.2.A.2, 3.2.A.3, 3.2.R, 4.2.1, and 5.3.1
OCBQ/DMPQ – Lead Inspector and Reviewer	Viviana Matta	The pre-approval inspection at (b) (4) doing business as GlaxoSmithKline Vaccines (b) (4) ; Pre-approval Inspection Report
Statistical Reviewer – assays	Laura Thompson	Module 1.11.3 Clinical Assays

DBPAP/LRSP Reviewer – assays	Eric Peng	Section 5.3.1 Clinical Assays (diphtheria, tetanus, and pertussis (PT, FHA, and PRN) assays)
DBPAP/LRSP Reviewer - assays	Mustafa Akkoyunlu	Section 5.3.1 Clinical Assays (Streptococcus pneumoniae assays)
OCBQ/DBSQC Reviewer	Claire Wernly	Sections 3.2.S.5.4 and 3.2.P.5.4 Sterility by (b) (4)
OCBQ/DBSQC Reviewer	Noel Baichoo	Sections 3.2.S.4.2, 3.2.S.4.3, 3.2.P.5.2, 3.2.P.5.3 and 3.2.R Cell Identity by (b) (4); Identity of Mumps, Measles, Rubella Viruses by (b) (4); Potency of Mumps, Measles, Rubella Viruses by (b) (4)
OCBQ/DBSQC Reviewer	Varsha Garnepudi	Section 3.2.R. LRP templates
OCBQ/DBSQC Reviewer	Hsiaoling Wang	Sections 3.2.P.5.4 and 3.2.R Description/Appearance, (b) (4) Water Content by (b) (4)
Labeling – Carton, Container	Alisa Gilliard, Daphne Stewart	Section 1.14.1 Draft Labeling

7. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
06/04/2021	STN 125748/0 (the original submission)	Reviewed
12/17/2021	STN 125748/16 (responses to CMC IRs dated November 9, 2021)	Reviewed
02/11/2022	STN 125748/20 (responses to CMC IRs dated January 14, 2022)	Reviewed
03/28/2022	STN 125748/30 (responses to CMC IRs dated March 11, 2022)	Reviewed
04/08/2022	STN 125748/31 (responses to CMC IRs dated March 11, 2022)	Reviewed
04/19/2022	STN 125748/33 (responses to CMC IRs dated March 11, 2022)	Reviewed
04/24/2022	STN 125748/34 (responses to CMC IRs dated April 15, 2022)	Reviewed
04/25/2022	STN 125748/35 (responses to CMC IRs dated April 18, 2022)	Reviewed
04/29/2022	STN 125748/36 (responses to CMC IRs dated April 26, 2022)	Reviewed

8. REFERENCED REGULATORY SUBMISSIONS (e.g., IND, BLA, 510K, MASTER FILE, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
IND 7229 (Priorix)	GlaxoSmithKline Biologicals (b) (4)	The original IND for this vaccine	Not applicable	Information was reviewed, assessed and documented.
MF (b) (4)	(b) (4)	(b) (4) Glass Pre-fillable Syringe (PFS)	Yes	Information was reviewed, assessed, and documented.
MF (b) (4)	(b) (4)	Rubber Compounds	Yes	Information was reviewed, assessed, and documented.
IND (b) (4)	GlaxoSmithKline Biologicals (b) (4)	Clinical serological assays	Not applicable	Information was reviewed, assessed, and documented.

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
IND 008461 (Boostrix)	GlaxoSmithKline Biologicals SA	Clinical serological assays	Not applicable	Information was reviewed, assessed, and documented.
IND (b) (4) (Synflorix)	GlaxoSmithKline Biologicals SA	Clinical serological assays	Not applicable	Information was reviewed, assessed, and documented.
IND (b) (4)	GlaxoSmithKline Biologicals SA	Clinical serological assays	Not applicable	Information was reviewed, assessed, and documented.
IND 010663 (Kinrix)	GlaxoSmithKline Biologicals SA	Clinical serological assays	Not applicable	Information was reviewed, assessed, and documented.
IND 003200 (Havrix)	GlaxoSmithKline Biologicals SA	Clinical serological assays	Not applicable	Information was reviewed, assessed, and documented.
IND 014151 (Hiberix)	GlaxoSmithKline Biologicals SA	Clinical serological assays	Not applicable	Information was reviewed, assessed, and documented.
BLA 125614 (Shingrix)	GlaxoSmithKline Biologicals SA	Clinical serological assays	Not applicable	Information was reviewed, assessed, and documented.

9. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

GSK submitted this BLA seeking approval of combined Measles, Mumps and Rubella (MMR) live (attenuated) viral vaccine (tradename: PRIORIX). PRIORIX is a vaccine indicated for active immunization for the prevention of measles, mumps and rubella in individuals 12 months and older. We have reviewed the CMC sections and preclinical studies.

PRIORIX is a live attenuated Measles, Mumps and Rubella (MMR) viral trivalent vaccine consisting of the Schwarz measles strain, the RIT 4385 mumps strain derived from the Jeryl Lynn 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 a single dose vial presentation to be reconstituted with water for injection (WFI) provided in ungraduated prefilled syringes. PRIORIX vaccine is a suspension for subcutaneous injection with no added adjuvant or preservatives. The minimum volume of reconstituted vaccine is 0.5 mL per administered dose. Each 0.5 mL dose of vaccine 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.

It is important to note that, once the final DP vials are filled, following a storage period of maximum (b) (4) at 2-8°C allowing to perform the 100% visual inspection, the vials are stored for an (b) (4) period up to (b) (4). Final labelling and packaging operations are performed when vials are removed from the freezer. At this point, the actual shelf life of 24 months at a storage temperature of 2-8°C starts. The date of manufacture for PRIORIX is defined as the date the vials are removed from (b) (4) to begin final labelling and packaging operations.

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 upstream stages of production of monovalent bulks.

The vaccine manufacturing process is robust, and the virus titers achieved are consistent. The sponsor 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. Release testing for final drug product (freeze-dried) includes potency (virus concentration), virus identification, bacterial and fungal sterility, physical appearance, (b) (4) and residual water content.

The acceptance specifications for the potency of the vaccine in formulation are (b) (4) and (b) (4) log $CCID_{50}$/dose for measles, mumps and rubella, respectively. The (b) (4) release specifications of $10^{3.4}$, $10^{4.2}$, and $10^{3.3}$ log $CCID_{50}$/dose for measles, mumps and rubella, respectively, are based on the assessed stability profile and corresponds to the minimum titer guaranteed at the end of expiry period (i.e., a shelf-life of the vaccine) 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.

Based on the information submitted in the BLA, we recommend approval of the product.

For all tables and figures in this memo, if help is needed for 508 compliance, transcriptions are available upon request. Please contact the Division of Viral Products at 240-402-7302.

B. RECOMMENDATION

I. APPROVAL

a. List of Drug Substances (DSs) and Drug Product (DP) manufacturing facilities:

- **Manufacture of measles DS:** GlaxoSmithKline Biologicals (b) (4)
- **Manufacture of mumps DS:** GSK Vaccines (b) (4)
- **Manufacture of rubella DS:** GlaxoSmithKline Biologicals (b) (4)
- **Manufacture of the Final DP:** (b) (4)

b. List of approvable Comparability Protocols:

- Comparability Protocol – Future Rubella Working Seeds, Section 3.2.R “Regional Information, Comparability Protocol Rubella WS”

c. Post-Marketing Commitments Not Subject to The Reporting Requirements Under Section 506B

None.

d. List of Post-Marketing Agreements (PMAs):

None.

e. Considerations for Inspectional Follow-up (e.g., flagging inspectional issues for future surveillance inspections)

- Review of stability results for the completed DS and DP lots.
- Review of storage conditions and inventory control for WCB, MSV, and WSV vials.
- Certificates of analysis for all media and solutions used for cell culture, viral culture, viral harvest, clarification, and stabilization stages of manufacturing of all three drug substances – measles, mumps, and rubella.

f. Considerations for Clinical Follow-up (e.g., flagging issues for future surveillance)

None.

g. Lot release requirements

The lot release protocol (LRP) is provided (in the original BLA submission and amendments 35) and found to be acceptable.

II. COMPLETE RESPONSE (CR)

Not applicable.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Tatiana Zagorodnyaya/Biologist/DVP: CMC reviewer	Concur	
Dmitriy Volokhov/Research Microbiologist/DVP: CMC reviewer	Concur	
Mustafa Akkoyunlu/Research Biologist/DBPAP: bacteriological assays reviewer	Concur	
Eric Peng/Biologist/DBPAP: bacteriological assays reviewer	Concur	
Robin Levis/Deputy Director/DVP	Concur	

Review of CTD

Module 3

3.2.S DRUG SUBSTANCE MEASLES

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

Proper Name: Compendial name: Measles vaccine (live), *Vaccinum morbillorum vivum.* WHO recommended name: Live attenuated measles vaccine, Schwarz strain; sponsor name: Measles vaccine, strain Schwarz; Tradename: not applicable.
Abbreviated Name: not applicable

Structure: The measles virus is a member of the genus *Morbillivirus* that belongs to the family of *Paramyxoviridae*. The virus is pleomorphic and is 100 to 300 nm in diameter and roughly spherical in shape. The viral envelope carries surface peplomers with a length of 9 to 15 nm that are composed of the viral transmembrane hemagglutinin (H) and fusion (F) glycoproteins. On the inside surface of the envelope is the matrix or membrane (M) protein, which is thought to interact with H and F and with the nucleocapsid to play a key role in virion maturation. The nucleocapsid has a helical structure, consists of the primary nucleocapsid protein (N), which surrounds the genomic RNA and of the phospho- (P), and large (L) protein bound to RNA. The nucleocapsid is packed within the envelope in the form of a symmetrical coil. Virions may also contain actin from the cellular cytoskeleton, which is involved in the final steps of budding from the plasma membrane of the infected cell. The measles genome, about 16,000 ribonucleotides in length, is composed of a single-stranded, non-infectious, non-segmented RNA of negative polarity. The measles viral genome encodes six major structural proteins from the six genes and additional two non-structural proteins from the P gene.

General properties: 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 (see Table 1). The GSK working seed virus (WSV) (b) (4) has then been produced by a (b) (4) of the MSV (b) (4) in CEF at (b) (4). After several years of production of the MMR vaccine (not for the US market) at GSK, (b) (4) the stock, the sponsor decided to use this WSV (b) (4), produced by a (b) (4) of this master seed (b) (4) in CEF at (b) (4). Table 1 shows the passage history of the strain.

The manufactured measles monovalent bulk is **a clarified viral suspension**, stabilized in a solution containing sorbitol, lactose, amino acids and inorganic salts. The measles monovalent bulk is stored at (b) (4) until further use.

Table 1: Schwarz Measles Vaccine: Passage History of Strain

Name and Address of Site	Passage History
Laboratory of Dr. J.F. Enders Children's Hospital Medical Centre Boston, Mass. USA	**Edmonston** (starting material) 24 passages - human kidney cells 28 passages - human amnion cells 6 passages - embryonated eggs 13 passages - CEF **Edmonston A Strain** (final material)
Laboratory of Dr. A.F. Schwarz and Production Division, Dow Chemical Company, Zionsville, Indiana, USA	**Edmonston A Strain** (starting material) 19 passages - CEF (culture at 35°C) 65 passages - CEF (culture at 32°C) **Schwarz Vaccine** (final material)
Laboratory of Dr. A.F. Schwarz and Production Division, Dow Chemical Company, Zionsville, Indiana, USA	**Schwarz Vaccine** (starting material) the Dow Chemical Company: master seed lot: SA3I1 1 passage - CEF (culture at 32°C) **Master seed lot: SA4I5** (final material)
GSK Biologicals Rixensart and GSK Biologicals (b) (4)	**Master seed lot: SA4I5** (starting material) (b) (4) passage - CEF (Culture at (b) (4) **Previous Working seed lots** (b) (4) (final master seed) (b) (4) passage - CEF (Culture at (b) (4) **Final Working seed lot** (b) (4)

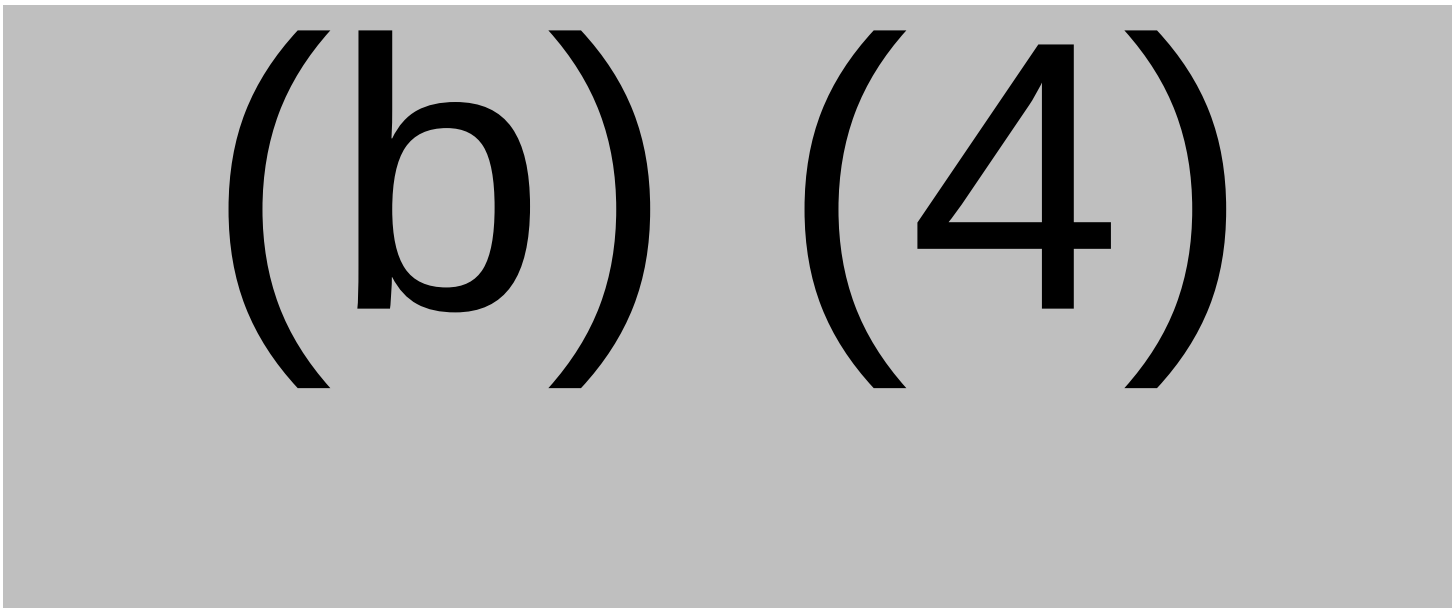
3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The facilities responsible for manufacturing, testing and storage of the measles virus MSV, WSV, and Bulk Drug Substance (BDS) are presented in table 2 below. The table also includes information on the sites where the release and stability testing are performed on different intermediates of the BDS such as the control cells, harvested viral fluids and harvested control fluids.

(b) (4)

(b) (4)



3.2.S.2.2 Description of Manufacturing Process

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

(b) (4)

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

Module 3

3.2.S DRUG SUBSTANCE MUMPS

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

Proper Name: Compendial name: Mumps vaccine (live) *Vaccinum parotitidis vivum*. WHO recommended name: Live attenuated Mumps vaccine, Jeryl Lynn strain; sponsor name: Mumps vaccine, strain Jeryl Lynn. Tradename: not applicable

Abbreviated Name: not applicable

Structure: The mumps virus is classified as a member of the genus *Paramyxovirus* in the family *Paramyxoviridae*. Mumps virions are pleiomorphic with particle size ranging from 100 to 600 nm. These enveloped particles contain helical nucleocapsids that encase a single-stranded, non-segmented negative-sense ribonucleic acid (RNA) genome of 15.3 kb. The virus contains six major structural proteins: the nucleocapsid-associated protein (NP), a phosphoprotein (P) and limited amounts of a high-molecular-weight (L) protein that are also associated with the nucleocapsid; a membrane or matrix (M) protein; and two glycoproteins, a hemagglutinin-neuraminidase (HN) and a fusion (F) protein. The order of the genes encoding these proteins is 3' NP-P-M-F-SH-HN-L 5'.

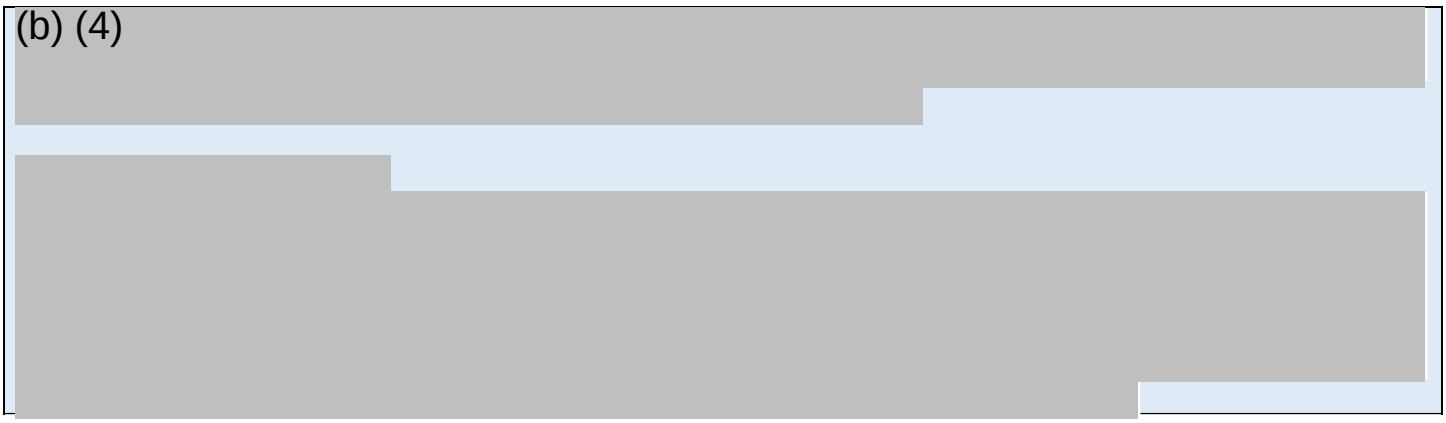
General properties: Currently, the two main mumps virus strains approved by the WHO for vaccination against mumps are Urabe Am9 and Jeryl Lynn. In September 1992, the sponsor decided to suspend the distribution of their Urabe Am9 containing vaccines following reports of side effects and decided to develop 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 sponsor 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 and described in Section 3.2.S.3.1 "Elucidation of Structure and Other Characteristics". The mumps monovalent bulk is **a clarified viral suspension**, stabilized in a solution containing sorbitol, lactose, amino acids and inorganic salts. The mumps monovalent bulk is stored at (b) (4) until further use.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The sites responsible for manufacturing, testing and storage of the MSV, WSV, and BDS are presented in table 35 below. The table also includes information on the sites where the release and stability testing are performed on different intermediates of the BDS such as the control cells, harvested viral fluids and harvested control fluids.

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



Module 3

3.2.S DRUG SUBSTANCE RUBELLA

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

Proper Name: Compendial name: Rubella vaccine (live), *Vaccinum rubellae vivum*. WHO recommended name: Live attenuated rubella vaccine, RA27/3 strain; sponsor name: Rubella vaccine, strain RA27/3. Tradename: not applicable

Abbreviated Name: not applicable

Structure: The rubella virus belongs to the family *Togavirus*. It is a spherical and rather small particle that measures 60-70 nm in diameter. Individual virions consist of a 30-nm electron-dense core surrounded by a lipid envelope. A distinctive electron-lucent zone is found between the virus core and envelope that distinguishes rubella virus from the other togaviruses. The core of each virion contains a message-sense (positive-polarity), single-stranded RNA genome composed of approximately 10,000 nucleotides.

General properties: The attenuated Wistar RA 27/3 ("rubella abortus, 27th specimen, third explant") rubella virus strain is originated from infected human fetal tissue. The wild 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 $10^{4.5}$ virus (lot H9080) at the 25th passage level, were received by the sponsor (then known as SK-RIT) from Dr. Plotkin in 1981. One passage of this virus was performed in MRC-5 cell cultures, gave rise to the rubella Pre-Master Seed Virus (pre-MSV) batch (b) (4) in MRC-5 cells to produce:

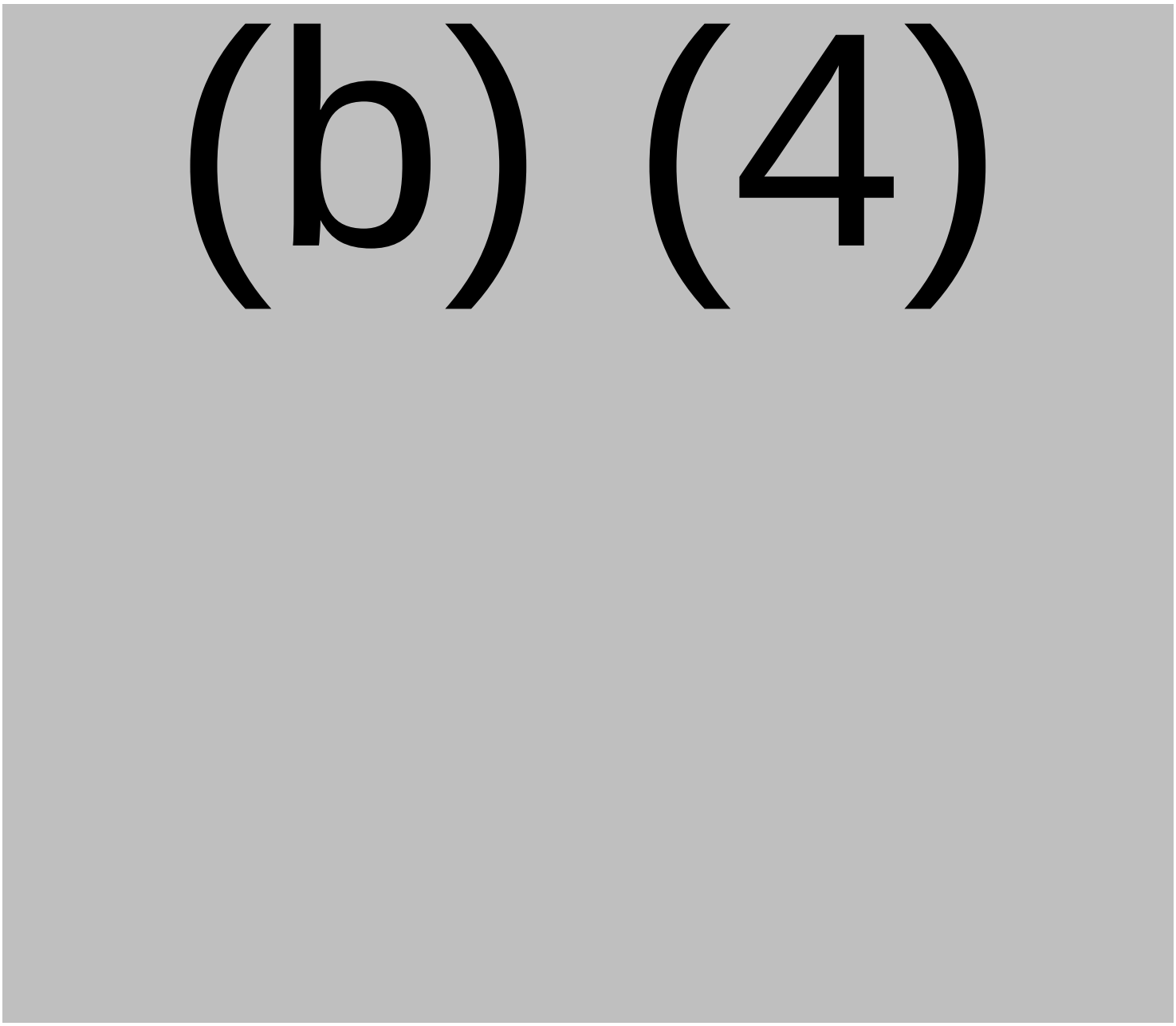
- the rubella WSV lots (b) (4), which were previously used as rubella WSVs.
- and the lot (b) (4), also referred to as the rubella MSV.

The rubella MSV lot (b) (4), is currently used for the production of rubella WSVs. The rubella Drug Substance is produced (b) (4) passages from virus isolation).

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The sites responsible for manufacturing, testing and storage of the Master/Working Cell Bank, MSV, WSV, and Bulk Drug Substance (BDS) are presented in table 63 below. The table also includes information on the sites where the release and stability testing are performed on different intermediates of the BDS such as the control cells, harvested viral fluids and harvested control fluids.



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(b) (4)

(b) (4)

3.2.P DRUG PRODUCT
3.2.P DRUG PRODUCT, PRIORIX VACCINE
3.2.P.1 Description and Composition of the Drug Product

The vaccine Drug Product (DP) is a suspension for subcutaneous injection with no added preservative manufactured by aseptic addition of the Bulk Drug Substances (BDSs) to the Drug Product Stabilizer Solution, which consists of the excipients as indicated in table 92 below. The vaccine kit consists of two components: (i) the lyophilized measles, mumps and rubella antigens presented in single-dose 3 mL glass vial, and (ii) the Water for Injection (WFI) diluent provided in single-dose prefilled ungraduated syringe. The glass vial is stoppered with bromobutyl rubber stopper and capped with aluminum cap. Prior to reconstitution, the lyophilized drug product is a whitish to slightly pink colored cake or powder. The vaccine is reconstituted by adding the entire contents of the supplied container of WFI diluent to the vial containing the powder. After reconstitution with the WFI diluent the vaccine is a clear peach to fuchsia pink colored solution. The minimum required volume of reconstituted vaccine is 0.5 mL per administered dose. The composition of the final DP per 0.5 mL dose is provided in the table 92 below.

Table 92: Composition of the Final Drug Product

Active Ingredients	**Quantity per dose[1]**	**Function**	**Reference/Monograph standard**
Live attenuated measles virus (Schwarz strain)	≥ $10^{3.4}$ log $CCID_{50}$	Immunogen	In-house[2]
Live attenuated mumps virus (RIT4385 strain)	≥ $10^{4\ 2}$ log $CCID_{50}$	Immunogen	In-house[2]
Live attenuated rubella virus (Wistar RA 27/3 strain)	≥ $10^{3\ 3}$ log $CCID_{50}$	Immunogen	In-house[2]
Inactive Ingredients (Excipients)	**Quantity per dose[1]**	**Function**	**Reference/Monograph standard**
Anhydrous lactose	32 mg	Stabilizer	(b) (4)
Mannitol	8 mg	Stabilizer	(b) (4)
Amino acids	9 mg	Stabilizer	In-house[3]
Sorbitol	9 mg	Stabilizer	(b) (4)

Note: [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. [2] Please refer to Section

3.2.S.4.1 “Specification Me”, Section 3.2.S.4.1 “Specification Mu”, Section 3.2.S.4.1 “Specification Ru”. [3] Please refer to Section 3.2.P.4.1 “Amino Acids MMR”.

3.2.P.2 Pharmaceutical Development
3.2.P.2.1 Components of the Drug Product
3.2.P.2.1.1 Drug Substance
3.2.P.2.1.2 Excipients

The Bulk Drug Substances (BDSs) active ingredients consists of the Schwarz measles strain, the RIT 4385 mumps strain, and the Wistar RA 27/3 rubella strain. Each virus strain is obtained by propagation in either chick embryo fibroblasts cultures (for mumps and measles) or MRC5 human diploid cells (for rubella), (b) (4) The final DP contains four excipients: anhydrous lactose, mannitol, amino acids and sorbitol. Those excipients ensure stabilization of the live measles, mumps and rubella viruses during the freezing and drying processes. No excipients of animal or human origin are used.

3.2.P.2.2 Drug Product

(b) (4)

The quantities of excipients included in the PRIORIX vaccine used for US clinical studies were based on the previous formulation from other viral vaccines manufactured by GSK. As stability of the PRIORIX vaccine was demonstrated throughout the product development with this specific formulation containing mannitol, sorbitol, lactose and amino acids excipients, no additional formulation development was performed. The sponsor stated that the WHO Technical Report Series No. 962, 2011, Annex 3, “Guidelines on Stability Evaluation of Vaccines” was used to define the lower release limits that guarantee the minimum viral potency titers up to the expiry of PRIORIX vaccine. The minimum viral potency titers guaranteed up to the expiry of PRIORIX vaccine were defined during clinical development and they correspond to the End of Shelf-Life (EoSL) specification limits. Those specification limits were defined by calculating the mean potencies observed for (b) (4) clinical lot (MMR-161 study) throughout its stability study at (b) (4). The upper release limits are derived from long-term stability data at (b) (4) for the maximum potency titer lot (or the high potency formulation lot) used during clinical development (b) (4) clinical lot used for MMR-162 clinical study). Long-term stability data for the (b) (4) clinical lots are presented in section 3.2.P.8.3 “Compilation Historical Stability Data MMR”. These data were reviewed and found to be acceptable.

3.2.P.2.2.2 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 93 below presents EoSL, lower and upper release limits for potency virus titers for PRIORIX vaccine.

Table 93: End-of-Shelf Life and Lower and Upper Release Limits (log $CCID_{50}$/dose) for Potency Virus Titers for PRIORIX Vaccine

Drug Substance	Units	EoSL limits	Lower Release Limits	Upper Release Limits
Measles	log $CCID_{50}$/dose	3.4	(b) (4)	(b) (4)
Mumps		4.2	(b) (4)	(b) (4)
Rubella		3.3	(b) (4)	(b) (4)

3.2.P.2.2.3 Physicochemical and Biological Properties

Potency, identity, (b) (4), water content, and sterility are tested as part of the PRIORIX DP release specifications. As a part of the Vaccine Final Product release, identity (b) (4) and identity (b) (4) tests are performed on the WFI pre-filled syringes included in the vaccine kit. These tests and acceptance criteria are described in section 3.2.P.5. The PRIORIX vaccine is presented as a freeze-dried (lyophilized) product. This is a whitish to slightly pink colored cake or powder with water content not more than (b) (4). The lyophilized DP must be reconstituted with WFI diluent prior to use. Upon reconstitution, the vaccine is a clear peach to fuchsia pink colored solution and is essentially free from visible particles. The (b) (4) of the reconstituted vaccine is between (b) (4) The other DP release specifications include sterility, identity of measles, mumps and rubella viruses, potency of measles, mumps and rubella viruses at the time of release and after (b) (4) days at (b) (4) as recommended the (b) (4) "Measles, Mumps, and Rubella Vaccine (Live)". The tests and acceptance criteria are described in section 3.2.P.5 "Control of Drug Product, MMR".

3.2.P.2.3 Manufacturing Process Development

To produce the DP, the measles, mumps and rubella monovalent bulks are (b) (4) with the appropriate volumes of dilution media and stabilizer. The quantity of each BDS used is calculated in order to achieve the target virus titer after lyophilization. The resulting Final Bulk is then filled into glass vials and lyophilized. The current manufacturing process applied for PRIORIX vaccine production is described in Section 3.2.P.3.3 of this memo.

The major historical change in the production of PRIORIX prior to clinical development in the USA was (b) (4) used as an excipient from the vaccine formulation. This change is described in section 3.2.P.2.2.1 of this memo. The sponsor also stated that the stability data obtained from (b) (4) PRIORIX vaccine lots (non-US lots) formulated (b) (4) also demonstrated a satisfactory stability profile (since these lots were tested not under this BLA, their stability data are not shown).

During the clinical development of PRIORIX in the USA, several changes were made to the manufacturing process between Phase II and Phase III clinical studies, including the implementation of a (b) (4) for the container closure system used for the lyophilized vaccine, as well as (b) (4) from the Rixensart manufacturing site in (b) (4)

manufacturing site in (b) (4) . These changes are summarized in table 94 and described below.

(b) (4)

(b) (4)

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

- Implementation of automated visual inspection of Final Product vials.

Details on these equipment changes are provided in table 8, in section 3.2.P.2.3 “Manufacturing Process Development, Development History” of this BLA, and reviewed by the DMPQ reviewer on this file.

Changes to the Testing Strategy During Development
During the clinical development of the vaccine, some of the analytical procedures applicable to Final Bulk and Final Container quality release testing have been changed. An overview of these changes is presented in table 96 below.

Table 96: PRIORIX Final Bulk and Final Container Release Modifications

Sample Type	Tests and methods	Modification	Rationale
Final Bulk	Bovine Serum Albumin Content by (b) (4)	Modified method	As agreed with CBER, a modified, more robust, semi-quantitative BSA (b) (4) test was revalidated and implemented.
Final Container	(b) (4)	Replacement with (b) (4) method for water content	The (b) (4) method has been determined to be equivalent to the (b) (4) method for moisture content and has replaced the (b) (4) method.
	Water Content by (b) (4)	Acceptance criterion revised	Acceptance criterion was revised from (b) (4) to align with global specification.
	Identity measles virus by (b) (4)	Replaced method	These serological methods were replaced by a (b) (4) based method.
	Identity mumps virus by (b) (4)		
	Identity rubella virus by (b) (4)		
	Potency measles virus by (b) (4)	Acceptance criteria revised	Not less than (b) (4) log $CCID_{50}$ per dose and not more than (b) (4) log $CCID_{50}$ per dose, based on EoSL potency calculations using the medium potency lots used in the MMR-161 clinical study and the stability data of the maximum potency lots used in MMR-162 clinical study. Change in testing format from (b) (4) .
	Potency mumps virus by (b) (4)		Not less than (b) (4) log $CCID_{50}$ per dose and not more than (b) (4) log $CCID_{50}$ per dose, based on EoSL potency calculations using the medium potency lots used in the MMR-161 clinical study and the stability data of the maximum potency lots used in MMR-162 clinical study. Change in testing format from (b) (4) .
	Potency rubella virus by (b) (4) *		Not less than (b) (4) log $CCID_{50}$ per dose and not more than (b) (4) log $CCID_{50}$ per dose, based on EoSL potency calculations using the medium potency lots used in the MMR-161 clinical study and the stability data of the maximum potency lots used in MMR-162 clinical study. Change in testing format from (b) (4) .
	Neomycin sulphate content by (b) (4)	Removed	Currently, the harvest stabilizer as well as the media used at formulation do not contain neomycin sulphate. A quantitative (b) (4) based method was qualified to

			evaluate neomycin content in Final Container as a characterization test on (b) (4) batches of PRIORIX drug product. Of note, the PPQ and the (b) (4) commercial batches will also be tested with this method as characterization test only.
	(b) (4)	Acceptance range revised	(b) (4)

* Of note, the (b) (4) first commercial batches were erroneously released with a Lower Release Limit (LRL) acceptance criterion of "Not less than (b) (4) log CCID50 per dose" defined based on the variability of (b) (4) testing format while (b) (4) testing format is applied for commercial lots. The (b) (4) testing format variability leads to a LRL acceptance criteria of "Not less than (b) (4) log CCID50 per dose".

For the clinical batches, the BSA content was measured by a (b) (4) method which was replaced with a (b) (4) method using the same antibody reagents. The description of this method “Modification of Bovine Serum Albumin Content by (b) (4)” is provided in the measles BDS section in this memo. The (b) (4) procedure was applied routinely during release testing and is described in section 3.2.P.5.2 “Bovine Serum Albumin Content by (b) (4) MMR”, and the validation of this procedure is described in section 3.2.P.5.3 “Bovine Serum Albumin Content by (b) (4) MMR”. All information about the (b) (4) method was reviewed and found to be acceptable.

3.2.P.2.4 Container Closure System

The DP container closure system consists of the primary packaging components listed in the table 97 below.

Table 97: Primary Packaging of PRIORIX Drug Product

Component	Description
Vial	3.0 mL clear glass vial (b) (4) glass, meets the requirements of (b) (4) Glass Containers for Pharmaceutical Use and (b) (4) Glass containers for pharmaceutical use")
Vial Stopper	(b) (4) ready to sterilize (RTS) bromobutyl rubber stopper; meets the requirements of (b) (4) Elastomeric Closures for Injections and (b) (4) . Rubber closures for containers for freeze-dried powders"
Vial flip-off cap	Aluminum cap

Note: The vial flip-off cap is not in contact with the DP and is not sterilized.

The suitability of the container closure system for the DP is demonstrated by the following:
• Compendial testing (according to the (b) (4) and the International Organization for Standardization (ISO) standards applied for the primary packaging components
• Assessment of extractables and leachables

Suitability of the container closure system is further demonstrated by the following studies presented in other sections, as indicated:

- Container Closure Integrity [Section 3.2.P.2.4].
- Container Closure System [Section 3.2.P.7].
- Stability Summary and Conclusion [Sec. 3.2.P.8.1] and Stability Data [Section 3.2.P.8.3].
- The protection from light requirement is fulfilled by the opaque secondary packaging component [Section. 3.2.P.2.4].

The extractable study was performed on the bromobutyl rubber stoppers. The sponsor stated that they did not perform an extractable study on their 3.0 mL clear glass vial due to the chemical inertness of (b) (4) glass. The glass vials and the bromobutyl rubber stoppers have been evaluated for leachables, and the results are discussed in section 3.2.P.2.4. The aluminum seal cap is not evaluated for extractables and leachables since it does not come into contact with product during product filling, storage or distribution. The assessment of extractables and leachables for this container closure system was performed and found to be acceptable (see section 3.2.P.2.4).

During the product life cycle, the stoppers composition was changed and the chlorobutyl rubber stoppers used to seal glass vials in the production of Phase II clinical lots were replaced with bromobutyl rubber stoppers, which were introduced into Phase III clinical lots production and in commercial manufacture. This change was justified by the fact that the (b) (4) stopper is less subject to moisture uptake during the washing cycle than the initial container stopper, and it was validated by the production of (b) (4) vaccine consistency lots which were followed in long term stability (see sections 3.2.P.5.4 "Batch Analysis, Clinical MMR" and 3.2.P.8.3 "Stability Data, Compilation Historical Stability Data MMR"). The data provided for the container closure system were

reviewed and found to be acceptable. The container closure system has also been reviewed by the DMPQ reviewer on this BLA.

3.2.P.2.5 Microbiological Attributes
The PRIORIX vaccine is a sterile vaccine with no added preservative. The DP is manufactured by aseptic addition of sterile BDS and the DP Stabilizer Solution. The formulated bulk is aseptically filled into vials. Sterility testing is included as part of release testing for every lot. Process simulations verify the robustness of the aseptic processing steps. Additional integrity of the filled vials is provided by Container Closure Integrity (CCI) Validation [see section 3.2.R].

3.2.P.2.6 Compatibility
Compatibility of PRIORIX vaccine DP with the selected vial and stopper container closure system (CCS) is demonstrated by development of the container closure system and Drug Product stability studies (see Section 3.2.P.8.1 "Stability Summary and Conclusion MMR"). The compatibility of PRIORIX vaccine DP with the process contact materials (single use or on-site sterilized) during the manufacturing process was reviewed by the DPMQ reviewer on this BLA submission. The process contact materials were confirmed to be appropriate for use and pose no risk of extractables and leachables.

Overall Reviewer's Assessment of Section 3.2.P.2:
The information provided is acceptable. To support this, the comments below were submitted to the sponsor. The responses provided by the sponsor in amendment 30,34 and 36 are considered acceptable (see below).

Agency Question 1:
In Section 3.2.P.2.3 "Manufacturing Process Development, Development History MMR", in table 8 you stated that the test for neomycin sulphate content by (b) (4) was removed because currently, the harvest stabilizer as well as the media used at formulation do not contain neomycin sulphate. However, in sections 3.2.S.2.3 "Control of Materials, Material and Solutions, Me, Mu, Ru", the data provided for the compositions of the growth media, the maintenance media, (b) (4) solutions and (b) (4) buffer used for production of measles, mumps and rubella harvests indicate the presence of neomycin sulphate. Please clarify how the residual neomycin sulphate will be controlled during the routine commercial production of PRIORIX for the US market.

Company Response 1:
The sponsor confirms the presence of neomycin sulfate in the compositions of the growth media, the maintenance media, (b) (4) solutions and (b) (4) buffer used in the (b) (4) production steps of measles, mumps and rubella bulks. The sponsor also confirmed its absence in the harvest stabilizer (b) (4) steps) and in the media used for formulation. A theoretical worst-case evaluation of the residual neomycin sulfate content in the PRIORIX formulation was conducted. Results of this evaluation is summarized in table 1 below and allows for an estimation of maximum (b) (4) of neomycin sulfate/dose of PRIORIX vaccine.

Table 1: Worst case evaluation of neomycin sulfate content in PRIORIX final container[1]

(b) (4)

[1]Only residue from the Viral Culture, estimation of 10% of leftover (worst case).

Additionally, as mentioned in BLA section 3.2.P.5.5 "Characterization of Impurities", a (b) (4) based method was developed and qualified to evaluate neomycin content in (b) (4) batches of PRIORIX vaccine FC. The results (presented in BLA in section 3.2.P.5.5 Characterization of Impurities) indicate that the average of neomycin content in these batches is (b) (4), which corresponds to (b) (4)/dose (0.5 mL) and thus well below the acceptable level from a toxicological point of view (i.e.: (b) (4) infant). Data on the (b) (4) PRIORIX vaccine FC batches demonstrate that residual neomycin sulphate is under control. Based on these low residual neomycin concentration values, the sponsor deems appropriate to not continue the routine testing for neomycin content at release of the PRIORIX vaccine FC.

Reviewer's Assessment:
The response is acceptable.

Agency Question 2:
In your response to CBER Question 3 in amendment 125748/0030, in Table 5, you mentioned the use of Stabilizer (b) (4) ". This is the first time this solution is referred to in the BLA. Also, in your response to CBER Question 6 in this amendment, in Table 6, you referred to it as "M-M-R stabilizer medium (b) (4)". Please clarify the correct name for the Stabilizer, if it is referred to in any other way in the BLA, and what do the abbreviations (b) (4) mean?

Company Response 2:
The sponsor acknowledges the unclarity of the different names provided in the amendment 125748/0031 for the same stabilizer medium. The sponsor wishes to clarify that (b) (4) and M-M-R stabilizer medium (b) (4)) all refer to the same M-M-R stabilizer medium used during formulation. As presented in the section 3.2.P.3.3 "Formulation MMR" of the original BLA, the Composition of the stabilizer mainly contains lactose and mannitol and represent the origin of the (b) (4) part of the name. The (b) (4) part of the name refers to the respective volumes of the bulks versus the volume of the stabilizer (called here T for "Tampon" – the French word for buffer) in the final formulated bulk of the MMR vaccine. Indeed, as presented in different sections of the file, a filling dose of MMR vaccine corresponds to (b) (4) of formulated bulk before lyophilization. within these (b) (4) is coming from the bulk (b) (4) reserved for Measles and Mumps and (b) (4) for Rubella) and (b) (4) volume) is coming from the stabilizer itself (b) (4) For sake of clarity, the sponsor acknowledges that the terminology "M-M-R stabilizer medium" is the correct name and should have been used across the BLA and in any amendments.

Reviewer's Assessment:
The response is acceptable.

Agency Question 3:
In your table for composition of MMR PRIORIX vaccine you indicated amino acids as 9 mg per dose. Please provide an updated table with approximate concentration for each amino acid per dose for the product. Please also provide the source of origin for each of the amino acids.

Company Response 3:
The sponsor wants to clarify this total amount of 9 mg of amino acids has several origins. During the formulation of the PRIORIX vaccine, the final bulk is produced by mixing the different monovalent bulks (i.e., mumps, measles and rubella monovalent bulks) with (b) (4) of media containing amino acids: stabilizer medium (M-M-R stabilizer medium) and dilution medium (Measles-Mumps dilution medium and Rubella dilution medium). Dilution media have the same composition as the bulks (except that there is no antigen and no neomycin sulphate). For further details regarding the composition of each medium, please refer to sections 3.2.S.2.3 "Materials and Solutions Me", 3.2.S.2.3 "Materials and Solutions Mu", 3.2.S.2.3 "Materials and Solutions Ru" and 3.2.P.3.3 "Formulation MMR". Table 2 below summarizes the total quantities of amino acids per PRIORIX dose. Each vial of PRIORIX vaccine is filled with (b) (4) of PRIORIX final bulk. Within those (b) (4) of final bulk, there are (b) (4) of a blend of amino acids called amino acids for injection sourcing from the different aforementioned media and monovalent bulks. Additionally, there are (b) (4) of (b) (4) coming from the mumps bulk, the measles bulk, and the Measles-Mumps dilution medium as well as from the rubella bulk and Rubella dilution medium. Although (b) (4) is not part of the stabilizer medium used at formulation, these additional (b) (4) are taken into consideration to calculate the total amount of amino acids per dose in the Composition table of the vaccine presented in the section 3.2.P.1 "Composition MMR" in this BLA.

(b) (4)

The composition of this commercially available amino acids for injection is provided in table 3 below. It contains a mixture of (b) (4) amino acids. It is important to note that most of these amino acids are from vegetal origin and none of them are derived from animals. The detail of the origin for each of them is also provided in table 3.

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

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The sites responsible for manufacturing, testing, packaging, labeling, release, and storage of PRIORIX Drug Product are presented in the table 98 below.

Table 98: Manufacturing, Testing, Packaging and Release Sites for PRIORIX Drug Product

Name and Address of Site	Responsibility
(b) (4) GlaxoSmithKline Vaccines, (b) (4)	• Formulation, filling and lyophilization of the PRIORIX vaccine • Visual inspection of the PRIORIX vaccine • Quality Release testing of the Final bulk, Final Container and Final Product[1] • QA release of Final Product • Labeling and packaging operations for the PRIORIX vaccine and diluent • Warehousing operations
GlaxoSmithKline Biologicals (b) (4). (b) (4)	• Quality Release of the Final bulk and Final Container[1] • Stability testing of Final Container • Warehousing operations
(b) (4)	• Warehousing and distribution

[1] The site is not necessarily performing all the QC release tests at each of the indicated steps, please refer to section 3.2.P.5.2 "Overview MMR" for clarification about the QC site conducting each test.

3.2.P.3.2 Batch Formula

PRIORIX DP is prepared by combining measles, mumps and rubella BDSs with M-M-R stabilizer medium, measles/mumps dilution medium and rubella dilution medium. The stabilizer and dilution media are added during the formulation step to establish the exact composition of the formulated vaccine. Information on the composition of the stabilizer and dilution media is given below in section 3.2.P.3.3. The commercial manufacturing scale for the formulated Final Bulk is up to (b) (4) . The amounts of BDSs, DP stabilizer solution and dilution 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 composition of the final DP is provided in table 92 above. The batch formula for a representative commercial PRIORIX Final Bulk (lot (b) (4) manufactured in the (b) (4) facility, is provided as an example in table 99 below. Targeted size of commercial lot is approximately (b) (4) vials corresponding to the maximal capacity of each of the freeze-dryers.

Table 99: Representative Commercial Batch Formula for PRIORIX Final Bulk Lot (b) (4)

Components	(b) (4)
Live attenuated measles virus (Schwarz strain)	
Live attenuated mumps virus (RIT4385 strain)	
Live attenuated rubella virus (Wistar RA 27/3 strain)	
M-M-R Stabilizer Medium	
Measles/Mumps Dilution Medium	
Rubella Dilution Medium	

Total Volume	(b) (4)

N/A, Not applicable

Four PPQ lots were manufactured at the (b) (4) site to validate the commercial process. Details are provided in section 3.2.P.5.4 of this memo.

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:
The information provided is acceptable. However, the comment below was submitted to the sponsor. The response provided by the sponsor in amendment 30 is considered acceptable (see below).

Agency Question:
In section 3.2.P.3.3 "Description of Manufacturing Process and Process Controls, Formulation" you mentioned the commercial manufacturing scale for the formulated Final Bulk is up to (b) (4) . Please clarify the validated formulation batch range to be used for the commercial manufacturing of PRIORIX.

Company Response:
The sponsor acknowledges the fact that section 3.2.P.3.3 "Formulation MMR" in BLA states "up to (b) (4)" as commercial manufacturing scale for the formulated Final Bulk. We wish to clarify that the PRIORIX vaccine being a lyophilized vaccine, the volume of the formulated final bulk prepared during the manufacturing process is based on freeze dryers load (approx. (b) (4) vials for PRIORIX), accounting for inherent process hold up volumes and sampling volumes. The entire formulation process (including its volume) is considered to be validated by the compliance of the PPQ lots release test results with their specifications at the final container level. Per the PPQ validity criteria, more than (b) (4) . A formulated final bulk target batch size of (b) (4) was used, with an allowed target batch size within (b) (4) of that volume considered as being validated during the PPQ campaign. The historical maximum formulated target batch size used in (b) (4) for routine PRIORIX production is (b) (4) It is important to note that the Continued Process Verification of the PRIORIX process provides the continual assurance that the PRIORIX process (including the PRIORIX formulated volume) remains in a validated state.

Reviewer's Assessment:
The response is acceptable.

3.2.P.3.3 Description of Manufacturing Process and Process Controls
The manufacturing process of the PRIORIX vaccine is composed of the following steps: (b) (4)

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

(b) (4)

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M-M-R stabilizer medium

The composition of the M-M-R stabilizing medium (also known as the DP stabilizing solution or PRIORIX stabilizing medium) is shown in Table 100 below.

Table 100: PRIORIX Stabilizer Medium

Solution/material	Composition	Final concentration/amount of ingredients	Analytical reference
PRIORIX stabilizer medium (b) (4)	Lactose	(b) (4)	
	Mannitol		
	Amino acids for injection		
	(b) (4)		
	WFI		

The release criteria for the DP Stabilizer Solution components are provided in section 3.2.P.4 "Control of Excipients, MMR", were reviewed and found to be acceptable.

Drug Product Filling and Lyophilization

The Final Bulk (FB) is aseptically filled under (b) (4)

The primary packaging components of each lot are representatively sampled and stored under quarantine until they have been tested by Quality Control (QC) and released for use in production by Quality Assurance (QA), according to written procedures. The primary packaging components were reviewed by the DMPQ reviewer on this BLA.

(b) (4)

- (b) (4)

Drug Product Labelling, Packaging and Transportation

Vials and WFI syringes are labelled (b) (4)

(b) (4)

Batch Numbering System

1) Unlabeled Final Container

The batch numbering system for DP lots are as follows.

For Final Bulk:

- (b) (4)

For the vaccine in Final Containers (FC), a letter is added to the FB number to specify the sequential filling and lyophilization number.

(b) (4)

2) Labelled and Packed Final Container (Final Product)

The commercial PRIORIX Final Container (FC) vial, the commercial WFI diluent FC syringe and the commercial cardboard box are each labelled with a different single 5-digit alpha numeric lot number according to sponsor's internal procedures. The lot number is generated randomly by the SAP system and consists of both letters and numbers (e.g., XD3A2). A same lot of unlabeled PRIORIX FC can be labelled with a different 5-digit alpha numeric lot number and combined with the same WFI diluent FC lot which keeps the same 5-digit alpha numeric lot number. The batch numbering system for the WFI diluent FC in syringe is described in section 3.2.P.3.3 below.

The following describes how an expiration date is assigned to the combo box, the PRIORIX vial and the WFI diluent:

- Cardboard box: Expiry date – earliest date between expiry date of the vaccine and expiry date of the WFI Diluent.
- The PRIORIX vial: Expiry date – expiry date of the vialed vaccine.
- The WFI Diluent syringe: Expiry date – expiry date of the WFI Diluent.

Controls implemented within the sponsor's product management software ensure that distinct lot numbers are used within an NDC (National Drug Code), i.e., the same lot number is not re-used within a single NDC. These same controls also ensure that a lot number is not re-used for a different sponsor's product, i.e., the same lot number is not re-used for a different NDC.

Overall Reviewer's Assessment of Section 3.2.P.3.3:

The information provided is acceptable. However, the comments below were submitted to the sponsor. The responses provided by the sponsor in amendment 30 are considered acceptable (see below).

Agency Question 1:
We recommend that you provide the PRIORIX DP manufacturing flow charts for all manufacturing processes, including charts for the Formulation, Filling and Lyophilization, showing all in-process and release tests, CPPs and hold times. In addition, please indicate, the total time for the manufacture of the DP and the time ranges (in hours or days) required for each step within the DP production.

Company Response 1:
Please find below the Drug Product (DP) manufacturing flow chart and the list of tests performed at each manufacturing step:

- Figure 4: "PRIORIX Drug Product Manufacturing Flow chart with steps durations, tests and CPPs" is provided in section 3.2.P.3.3 in this memo above.
- Table 4: "Tests performed at the different process steps during PRIORIX Drug Product Manufacturing" is provided in amendment 30.

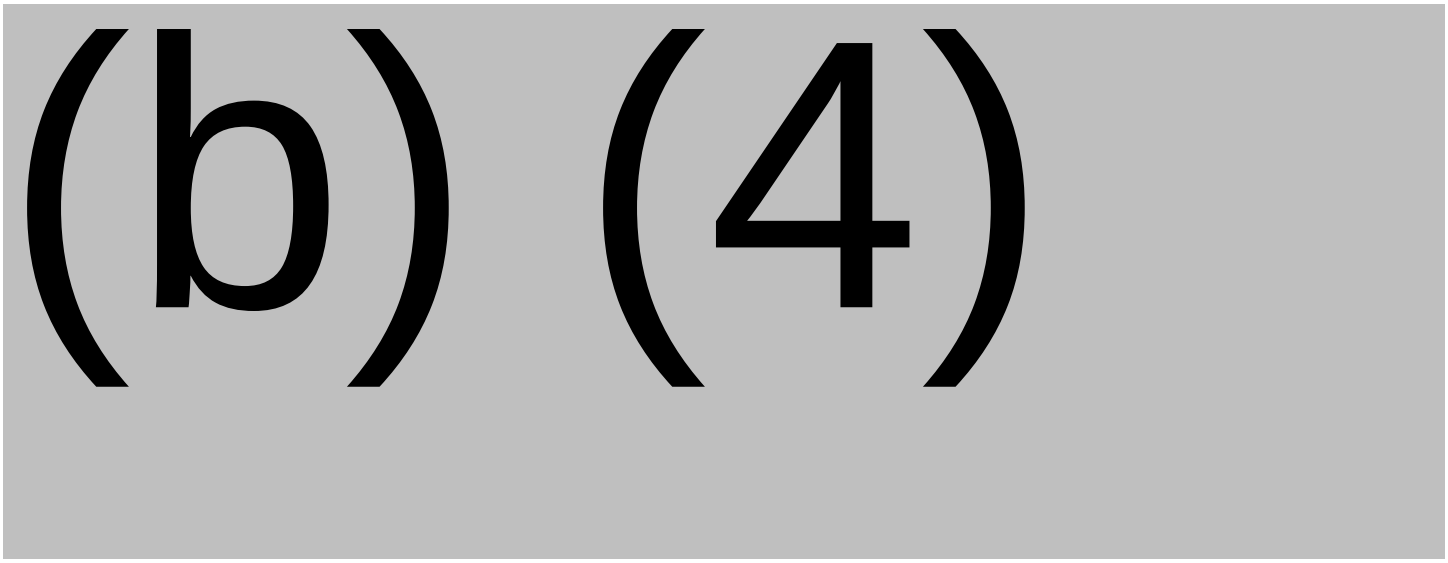
As requested, this flow chart details the in-process and release tests, the CPPs, hold times (storage exceeding (b) (4) and the total time for each step within the DP production when available. Of note, total liquid time for the manufacture of the DP is limited to (b) (4)

Reviewer's Assessment:
The response is acceptable.

Agency Question 2:
In section 3.2.P.3.3 "Description of Manufacturing Process and Process Controls, Formulation MMR" you mentioned: "The Final Bulk can be stored at (b) (4) for a maximum of (b) (4) hours in a (b) (4), in order to increase manufacturing flexibility". Please provide data to support the (b) (4)-hour Final Bulk hold time at (b) (4).

Company Response 2:
The sponsor acknowledges the CBER's request of supportive data for the Final Bulk maximum storage duration of (b) (4) hours at (b) (4) in a (b) (4). The hold time supporting data has been generated through downscale studies, where the effect of final bulk storage at (b) (4) in a (b) (4) on measles, mumps and rubella potency was evaluated at the time points shown in Figure 1 below. Final bulk samples are collected at the specified timepoints and then frozen at (b) (4) until testing. Of note, final container samples are sampled in the final bulk at specified timepoints, lyophilized and then tested. Please refer to Figure 2, Figure 3 and Figure 4 below for measles, mumps and rubella potency in trivalent Final Bulk (FB) and Final Container (FC) during storage at (b) (4), respectively.

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



3.2.P.3.4 Controls of Critical Steps and Intermediates

In this BLA, the description of the product control strategy for the production process of the DP is presented in section 3.2.P.2.3 “Manufacturing Process Development, Control Strategy”. The controls implemented for routine manufacturing of the DP have been validated and are provided below. These controls represent CQAs and PAs. Several of the identified process parameters are classified as CPPs when they have an impact on CQAs. These CPPs could also have an impact on PAs. The process parameters are classified as manufacturing process parameters (MPPs) when they have an impact on a PA only. CQAs and CPPs were used for process validation. Any deviation from CQAs or CPPs in routine manufacturing will require investigation. CQAs are tested as a part of release of the DP and are defined in the table 101 below. Table 101 summarizes the information provided in this BLA in section 3.2.P.2.3 “Manufacturing Process Development, Control Strategy, MMR” in tables 1, 3-10. The data presented in the column “Specifications” in the table 101 was originally provided in this BLA in section 3.2.P.5.6 "Justification of Specifications, Overview MMR".

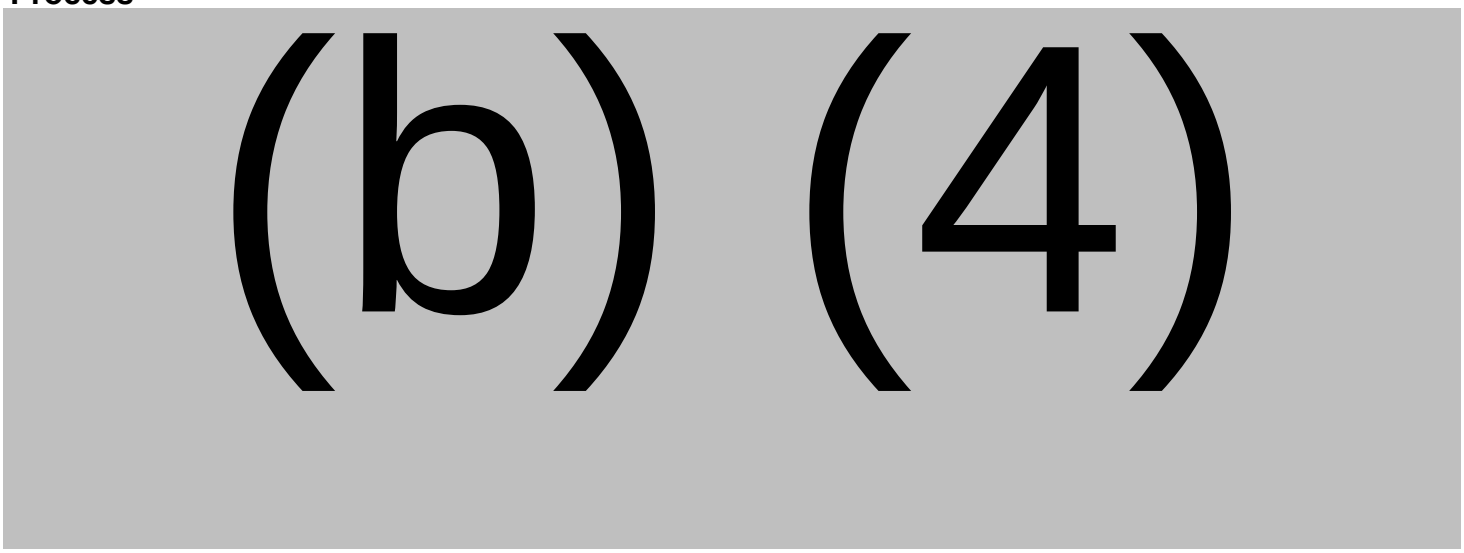
Table 101: Critical Quality Attributes (CQAs) for PRIORIX Drug Product

Product Quality Attribute	Testing strategy	Matrix	Specification
Potency	Potency measles virus by (b) (4)	Final Container	Not less than (b) (4) log $CCID_{50}$ per dose and not more than (b) (4) log $CCID_{50}$ per dose
	Potency mumps virus by (b) (4)		Not less than (b) (4) log $CCID_{50}$ per dose and not more than (b) (4) log $CCID_{50}$ per dose
	Potency rubella virus by (b) (4)		Not less than (b) (4) log $CCID_{50}$ per dose and not more than (b) (4) log $CCID_{50}$ per dose
	Potency measles virus by cell (b) (4)		The virus concentration is not more than (b) (4) log lower than the initial value

	Potency mumps virus by cell (b) (4)		The virus concentration is not more than (b) (4) log lower than the initial value
	Potency rubella virus by (b) (4)		The virus concentration is not more than (b) (4) log lower than the initial value
Identity	measles virus identity by (b) (4)	Final Container	Positive
	mumps virus identity by (b) (4)		Positive
	rubella virus identity by (b) (4)		Positive
Sterility	Sterility test (b) (4)	Final Bulk, Final Container	Absence of growth
	Sterility test (b) (4)		Absence of growth
Description	Quality Decision: Particulate Matter by Visual Inspection	Final Container	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
Neomycin sulphate content	N/A*	Final Container	N/A*
(b) (4)	Quality Release (QR): (b) (4)	Final Container	Between (b) (4)
Water content by (b) (4)	QR of Stopper: Stopper Moisture Content QR: Water Content by (b) (4)	Final Container	(b) (4)
Bovine Serum Albumin (BSA) content	BSA content by (b) (4)	Final Bulk	(b) (4)

*Based on the low residual neomycin concentrations values, the routine testing for neomycin content will not be performed to release the PRIORIX Final Container. Refer to section 3.2.P.5.5 “Characterization of Impurities” in this BLA for a discussion of why this test is no longer necessary.

Table 102: Critical Process Parameters (CPPs) for PRIORIX Drug Product Manufacturing Process



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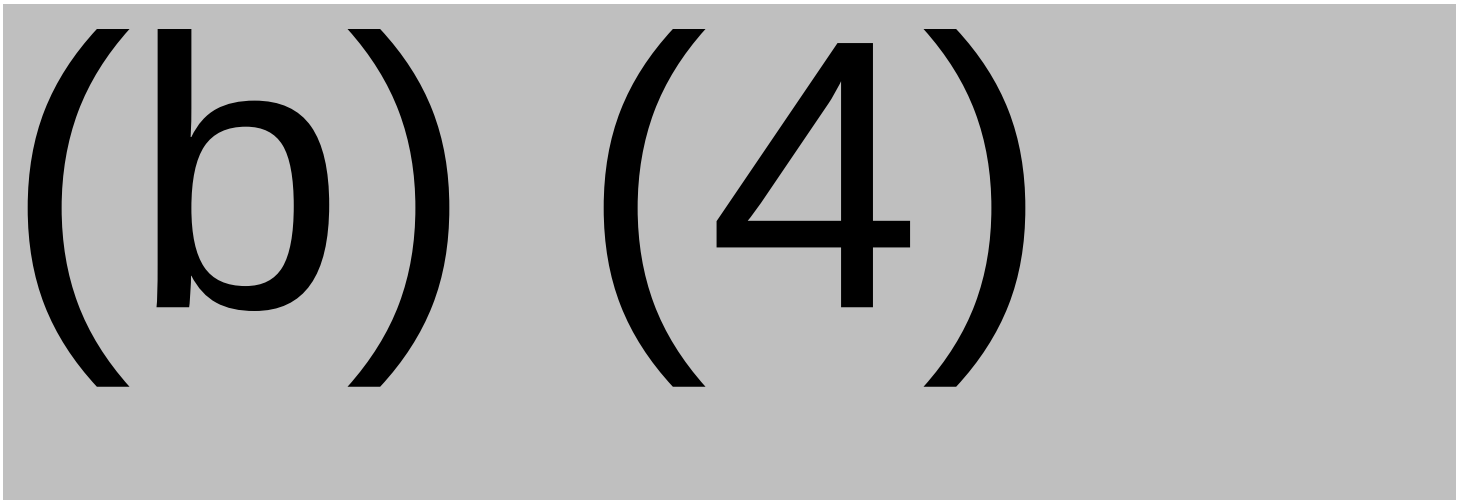


The DP production control strategy also defines PAs, which is the Process Yield and Visual Inspection Rejection Rate at the Final Container step. The full description of these parameters can be found in section 3.2.P.2.3 “Manufacturing Process Development, Control Strategy, MMR” in this BLA.

Process controls are applied during the manufacturing process of PRIORIX DP and are classified in two categories: (i) in-process Quality Decision (QD) test that is used to demonstrate that the process is controlled, and (ii) in-process Monitoring (PM) test that is used for process consistency evaluation and for data accumulation (to be used in case of investigation).

In-process QD Test

Test for particulate matter by visual inspection at the FC stage with the acceptance criteria “Essentially free from extraneous visible particulates after reconstitution with WFI”. The sponsor stated that the test is performed according to the (b) (4) (General Chapters – Physical tests (b) (4) Visible Particulates in Injections). The QD test results for the PRIORIX FC commercial lots (b) (4) are provided in table 1 in section 3.2.P.3.4 “Control of critical steps and Intermediates, In-process Quality Decision Tests Batch Analysis Data MMR” of the BLA. All results met the current specification.

In-process PM Test

Test for Container Closure Integrity Test to be carried out during routine commercial production of PRIORIX vaccine at the Final Container stage. The analytical procedure for this test is provided in section 3.2.P.8.3 “Stability Data, Analytical Procedures MMR” in this BLA, and is also described in section 3.2.P.8.3 in this memo below.

There are no intermediates produced for PRIORIX DP. QR tests are performed at the Final Bulk, Final Container and Final Product stages (refer to details in section 3.2.P.5.1 in this memo).

Overall Reviewer’s Assessment of Section 3.2.P.3.4:

The information currently provided for DP Controls of Critical Steps and Intermediates is acceptable. However, the comments below were submitted to the sponsor. The responses provided by the sponsor in amendments 30 and 34 are considered acceptable (see below).

Agency Question 1:
We note that Section 3.2.P.3.5 “Process Validation and/or Evaluation” for all (b) (4) PPQ DP lots you have not provided (i) Evaluation of Critical Process Parameters (CPPs) and (ii) Evaluation of In-process controls. Please submit these data to the BLA. For a better presentation of these data, please send us this information in tabular format alongside with your conclusions.

Company Response 1:
The sponsor acknowledges the CBER´s request for the provision of (i) Critical Process Parameters (CPPs) observed and (ii) In-process controls tests results for all (b) (4) PPQ DP batches. To answer this question, critical process parameters and acceptable ranges listed and originally submitted in BLA in the 3.2.P.2.3 “Control Strategy MMR” section have been used as the basis for the PPQ batch parameters data provided in table 103 of section 3.2.P.3.4 in this memo. The In-process controls tests results for all (b) (4) PPQ lots are provided in table 104 of section 3.2.P.3.4 in this memo. The sponsor wishes to clarify that some of the CPPs and in-process controls established at the time of the PPQ campaign were different than the current CPPs, provided in section 3.2.P.2.3 “Control Strategy MMR” in BLA. Indeed, as explained in BLA in section 3.2.P.3.5 “Process Performance Qualification Annex MMR”, the risk score defined for each process parameter (and therefore the identification of CPPs and MPPs) is reviewed and updated throughout the process design, process performance qualification and continued process verification stages as knowledge is acquired. CPPs in force at the time of the PPQ campaign are therefore provided in table 105 of section 3.2.P.3.4 in this memo, while the related in-process controls are provided in table 104 of section 3.2.P.3.4 in this memo, alongside with current in-process controls. It shall be noted that all the Critical Process Parameters for all (b) (4) PPQ DP lots are within the acceptable ranges, both the CPPs established at the time of the PPQ campaign and the current CPPs. Additionally, In-process controls tests results of the PPQ batches show consistency and are within the acceptance criteria, whenever applicable.

Reviewer’s Assessment:
The response is acceptable.

Agency Question 2:
We noted that in section 1.11.1 of your Response to FDA request on March 11, 2022 (amendment 0030) in your response to CBER Question 1, you said: “The Sponsor wishes to clarify that some of the CPPs and in-process controls established at the time of the PPQ campaign were different than the current CPPs, provided in section 3.2.P.2.3 Control Strategy MMR”. However, the given titles to Tables 1 and 3 are provided as: Table 1: “Current in-process parameters (i.e., CPPs), acceptable ranges, and ranges observed during MMR PPQ batches production.” Table 3: “Relevant in-process parameters (i.e., CPPs), acceptable ranges, and ranges observed during MMR PPQ batches production, as established at the time of PPQ campaign.” Please clarify whether in-process parameters are equivalent to CPPs.

Company Response 2:
The sponsor would like to clarify that in the given titles of Table 1 and 3 of section 1.11.1 Quality Information Amendment for our response to FDA request on March 11, 2022 (amendment 0030) the term "in-process parameters" are equivalent to CPPs.

Reviewer's Assessment:
The response is acceptable.

3.2.P.3.5 Process Validation and/or Evaluation
The consistency of DP manufacturing during formulation, filling and lyophilization are confirmed through an analysis of the (b) (4) 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 full scale including formulation, filling and lyophilization of approximately (b) (4) **vials**.

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

1. (b) (4)

(b) (4)

.

(b) (4)

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

(b) (4)

(b) (4)

.

(b) (4)

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

The excipient used in PRIORIX vaccine are anhydrous lactose, sorbitol, mannitol and amino acids for injection, and they are used for the stabilization of the DP.

Table 111: Excipients in PRIORIX Vaccine

Excipient	Ingredient	Ingredient Concentration	Reference/Monograph standard
Drug Product Stabilizers	Anhydrous lactose	32 mg	(b) (4)
	Mannitol	8 mg	
	Amino acids	9 mg	
	Sorbitol	9 mg	

Anhydrous lactose purchased from commercial suppliers, is manufactured from milk sourced in USA and complies with the current editions of the (b) (4) Sorbitol purchased from commercial suppliers complies with the current edition of the (b) (4) . Mannitol purchased from commercial suppliers complies with the current editions of the (b) (4) . The QR testing of amino acids for injection is performed according to sponsor's Monograph (b) (4) and is summarized in table 112 below.

(b) (4)

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

Quality release testing for anhydrous lactose, sorbitol and mannitol are performed by suppliers using the analytical procedures described in the relevant pharmacopoeia monographs. Therefore, the analytical methods are considered validated and covers the justification of the specifications. The methods used for the QR testing of amino acids for injection are provided in section 3.2.P.4.2 "Analytical Procedures, Amino Acids for Injection" in this BLA, were reviewed and found to be acceptable. Procedures for the QR testing of amino acids for injection have been validated according to

pharmacopoeia requirements, when applicable, and specifications have been set based on pharmacopoeia monographs which cover the justification of the specifications.

3.2.P.4.4 Justification of Specifications
Specifications and justifications for tests performed for the DP excipients (stabilizers) are also provided in section 3.2.P.4.4. The information is reviewed and found to be adequate.

3.2.P.4.5 Excipients of Human or Animal Origin
There is no excipient of human origin in the vaccine. The only excipient of animal origin is anhydrous lactose (ruminant-derived material - milk). Milk is sourced from USA and is deemed fit for human consumption.

3.2.P.4.6 Novel Excipient
There are no novel excipients in PRIORIX vaccine.

Overall Reviewer's Assessment of Section 3.2.P.4:
The information provided is acceptable. However, the comments below were submitted to the sponsor. The responses provided by the sponsor in amendment 30 are considered acceptable (see below).

Agency Question 1:
No certificates of analysis for the lots of anhydrous lactose, sorbitol and mannitol used for the manufacture of the DP PPQ lots for the PRIORIX vaccine are provided in the BLA. Please submit certificates of analysis for these excipients.

Company Response 1:
The sponsor acknowledges the absence of Certificates of Analysis (CoA) for the lots of anhydrous lactose, sorbitol and mannitol used for the manufacture of the PRIORIX PPQ lots production in the BLA original submission. The CoAs of all these excipients were submitted in 3.2.R Regional Information section of the PRIORIX BLA. A summary providing a clear correspondence between the vendor and the GSK batch numbers for the anhydrous lactose, sorbitol and mannitol used in the production of the PRIORIX Drug Product PPQ lots is provided in table 7 of amendment 30. Links to the annexed GSK CoAs are also provided within this summary table 7 of amendment 30.

Reviewer's Assessment:
The response is acceptable.

Agency Question 2:
Amino Acids for injection (as one of the excipients of your vaccine) contain (b) (4) . Please provide the estimated content of these impurities in the final dose of the vaccine and a risk assessment based on toxicological threshold for exposure to these impurities in adults and children.

Company Response 2:

The sponsor wishes to clarify that in the 9 mg of “Amino Acids” mentioned in the 3.2.P.1 Composition MMR are including (b) (4) of “Amino Acids for injection”. The 3.2.P.4.1 Amino Acids MMR is only applicable for the (b) (4) of “Amino Acids for Injection”. This value of (b) (4) /dose of vaccine of Amino Acids for Injection combined with the release specifications provides a worst-case estimation of the (b) (4) content per dose, see table below.

(b) (4)

Toxicological assessment

A conservative approach is taken and daily limits (Threshold of Toxicological Concern (TTC) and Permitted Daily Exposure (PDE)) for long term exposure are used (not considering less than a lifetime exposure in case of intake via vaccinations). Assessment of all impurities is performed in accordance to (b) (4). The assessment of elemental impurities is made in accordance with the (b) (4) adopted in 2019. The mass adjustment assumes an arbitrary adult human body mass for either sex of (b) (4). It is recognized that some patients weigh less than (b) (4) these patients are considered to be accommodated by the built-in safety factors used to determine a PDE and that lifetime studies were often used. For lead, the pediatric population is considered the most sensitive population, and data from this population were used to set the PDE. Therefore, the PDEs are considered appropriate for pharmaceuticals intended for pediatric populations.

(b) (4)

(b) (4)

Reviewer's Assessment:
The response is acceptable.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

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 113 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 113: Justification of Release Specifications for PRIORIX Vaccine

Tests	Acceptance criteria	Justification
Vaccine Final Bulk		
Sterility test (b) (4) Sterility test (b) (4)	Absence of growth	The acceptance criteria are based on (b) (4), 21 CFR 610.12, (b) (4)
Bovine Serum Albumin content by (b) (4)	(b) (4)	The acceptance criterion is established according to the (b) (4) "Measles, Mumps, and Rubella Vaccine (Live)", which requires BSA content of "not more than (b) (4) per single human dose, determined by a (b) (4) method".
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.	The acceptance criterion is established according to the (b) (4) "Measles, Mumps, and Rubella Vaccine (Live)".
Water content by (b) (4)	(b) (4)	The acceptance criterion is established according to the (b) (4) "Measles, Mumps, and Rubella Vaccine (Live)", which requires water content of "(b) (4) cent, determined by the (b) (4) determination of water".
Sterility test (b) (4)	Absence of growth	The acceptance criteria are based on (b) (4) 21 CFR 610.12, (b) (4)

Sterility test (b) (4)		
Identity measles virus by (b) (4)	Positive	This test is performed to confirm the presence of the measles virus.
Identity mumps virus by (b) (4)	Positive	This test is performed to confirm the presence of the mumps virus.
Identity rubella virus by (b) (4)	Positive	This test is performed to confirm the presence of the rubella virus.
Potency measles virus by (b) (4)	(b) (4)	The lower release limit is derived from the EoSL potency as defined during clinical development of the PRIORIX vaccine (MMR-161 study, see Module 2.5 "Clinical Overview", Section 4, in this BLA) and the WHO stability evaluation guideline. The upper release limit is derived from the outcome of clinical study MMR-162 using maximum potency titer lot and from related long term (b) (4) stability data. See Section 3.2.P.5.6 "Potency Measles Virus by (b) (4) MMR" in this BLA.
Potency mumps virus by (b) (4)	(b) (4)	The lower release limit is derived from the EoSL potency as defined during clinical development of the MMR vaccine (MMR-161 study, see Module 2.5 Clinical Overview, Section 4, in this BLA) and the WHO stability evaluation guideline. The upper release limit is derived from the outcome of clinical study MMR-162 using maximum potency titer lot and from related long term (b) (4) stability data. See Section 3.2.P.5.6 "Potency Mumps Virus by (b) (4) MMR" in this BLA.
Potency rubella virus by (b) (4)	(b) (4)	The lower release limit is derived from the EoSL potency as defined during clinical development of the MMR vaccine (MMR-161 study; see Module 2.5 Clinical Overview, Section 4, in this BLA) and the WHO stability evaluation guideline. The upper release limit is derived from the outcome of clinical study MMR-162 using maximum potency titer lot and from related long term (b) (4) stability data from the maximum potency titer lot used during clinical development. See Section 3.2.P.5.6 "Potency Rubella Virus by (b) (4) MMR" in this BLA.
Potency measles virus by (b) (4)	(b) (4)	The acceptance criterion is established according to the (b) (4) "Measles, Mumps, and Rubella Vaccine (Live)".
Potency mumps virus by (b) (4)	(b) (4)	The acceptance criterion is established according to the (b) (4) "Measles, Mumps, and Rubella Vaccine (Live)".
Potency rubella virus by (b) (4)	(b) (4)	The acceptance criterion is established according to the (b) (4) "Measles, Mumps, and Rubella Vaccine (Live)".

(b) (4)	(b) (4)	The acceptance criterion is established based on a median of (b) (4) selected as the target.
Vaccine Final Product		
Identity of measles by (b) (4)	Positive	This test is performed to confirm the presence of the measles virus and the absence of the varicella virus. To ensure the correct vaccine has been included in the package, an identity test is performed to confirm identity of the vaccine and to distinguish it from other products at the (b) (4) site. The duplex measles and varicella (b) (4) is used to confirm both the presence of measles and absence of varicella viruses in PRIORIX Final Product.
Identity of varicella by (b) (4)	Negative	
Description of WFI	Clear, colorless liquid, free from visible particles	This test is performed to confirm the absence of visible particles in the WFI pre-filled syringe.
Identity (b) (4)	(b) (4)	This test is performed to confirm the absence of (b) (4) in the WFI pre-filled syringe.
Identity (b) (4)	(b) (4)	This test is performed to confirm the absence of (b) (4) in the WFI pre-filled syringe.

(b) (4).

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:
The information provided is acceptable. However, the comments below were submitted to the sponsor. The responses provided by the sponsor in amendments 30 and 34 are considered acceptable (see below).

Agency Question 1:
We note that the identity tests for measles, mumps and rubella are performed on the Vaccine Final Container (Section 3.2.P.5.1, Table 2). However, it is not clear if these tests are performed after all labeling operations are concluded, as required by 21 CFR 610.14. Please clarify. If the identity tests are performed on the drug product after all labeling operations are concluded, if not, please institute these tests on labeled final container product.

Company Response 1:
The sponsor would like to clarify that the identity tests for measles, mumps and rubella listed in the release testing panel provided in Table 2 of section 3.2.P.5.1 "Specifications MMR" in the BLA are not performed after labelling and packaging operations. In this table the sponsor provided the release testing plan performed at the end of the production after the (b) (4) step. It is important to note that, once produced, (b) (4) allowing to perform the 100% visual inspection, the vials are (b) (4). Labelling and packaging operations are performed only at the (b) (4), **where the actual shelf life of 24 months at a storage temperature of 2-8°C starts**. At the time of the labelling operations, as described in the Table 3 of the section 3.2.P.5.2 "Overview MMR" in the BLA, a duplex measles and varicella identity by (b) (4) test is performed on the finished product (labelled product). This test allows to comply with the 21 CFR 610.14, requirements as it is "specific for each product "and allows to "distinguish it (i.e., PRIORIX Vaccine) from any other product being processed in the same laboratory (b) (4)

(b) (4) The sponsor deems not necessary to conduct further additional identity tests for mumps and rubella on the vaccine finished product. Indeed, in order to confirm the correct identity of the PRIORIX vaccine, the acceptance criteria for this test, as presented in the Table 3 of the section 3.2.P.5.1 "Specifications MMR" in BLA should be "Positive" for the Identity of Measles and "Negative" for the Identity of Varicella. This combination of acceptance criteria allows the distinction between the PRIORIX vaccine from any other vaccine packaged at the (b) (4) site.

Reviewer's Assessment:
The response is acceptable.

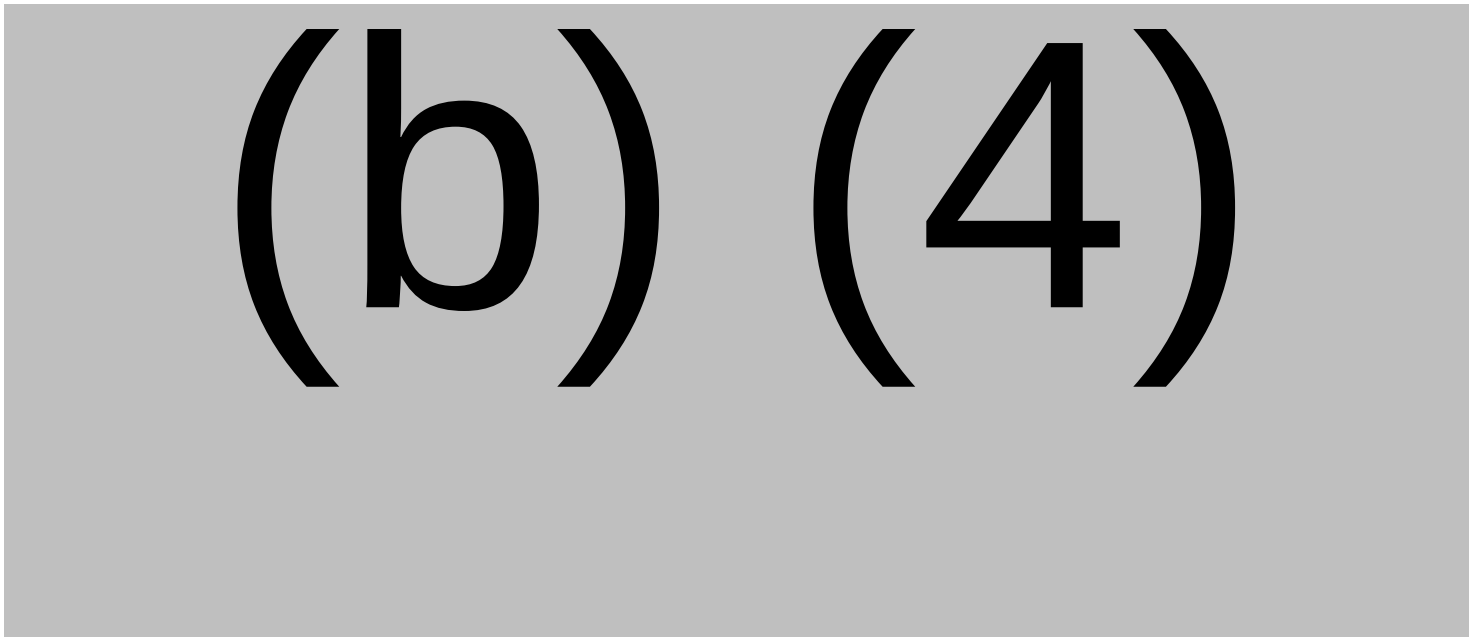
Agency Question 2:
Your response to CBER Question 9 in amendment 125748/0030 (Response to CBER IR dated 11Mar2022 – CMC") is generally acceptable. However, it is not clear how you track the non-yet-labeled vials of PRIORIX commercial lots stored for a period of maximum of (b) (4) Since other vaccine products (e.g., (b) (4) Priorix for the non-US market) may be concurrently processed in the same facility, you should have a reliable tracking system, which should guarantee a clear distinguish between the non-yet-labeled vials (until the labeling and packaging operations) of PRIORIX commercial lots for the US market and other vialed products. Please clarify.

Company Response 2:
The sponsor would like to explain the tracking system used to control and identify the unlabeled individual vials until the labeling and packaging operations of Priorix commercial lots for the US market and other vialed products. Product and materials are managed at each processing step using SAP (validated material management system). An Order Edition which declares the lot of product to be processed is issued. The process order is used at each process step to verify that it is the appropriate material and that it is available for use. (b) (4) . This label is used for subsequent material verification at a later step against the order edition. Additionally, Priorix vaccine vials use a unique color flip cap, different than the color flip cap of other vaccines products (e.g., (b) (4) that is controlled with order edition.

Reviewer's Assessment:
The response is acceptable.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures
The release test methods that are common between the (b) (4) DP (potency, identity, sterility tests and BSA content by (b) (4)) are previously described in section 3.2.S.4.2. The tests specific to the DP are described below. The references for the analytical procedures used for QR testing and the validation and verification data for the release analytical procedures at Final Bulk, Final Container and Final Product stages are provided in the table 114 below. Majority of the QR tests is performed at the (b) (4) testing site. The tests performed at the (b) (4) testing site are also indicated in this table below.

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



Description
The test consists in examining visually the appearance of the product to be characterized. The characteristics to be observed are: the absence of particles, the aspect of the cake, opalescence, the color, the time of reconstitution (if required), the time of sedimentation, turbidity, color of sediment/color of supernatant (if required). Analytical procedure is provided in section 3.2.R “R SOP Description MMR” was reviewed and found to be acceptable.

Water Content by (b) (4)
This method is based on the (b) (4)

This method and the validation results for this method were also reviewed by a DBSQC reviewer assigned to this BLA submission, and the method is suitable for its intended use.

(b) (4)

Identity Measles and Varicella by (b) (4)
The identification of measles and varicella viruses in the FDP samples is performed (b) (4) This method and the validation results for this method were also reviewed by a DBSQC reviewer assigned to this BLA submission, and the method is suitable for its intended use.

Description of Liquid WFI
Parameters of description specifications are visually examined.

Identity (b) (4)
A description of the method can be found in (b) (4) .

Identity (b) (4)
A description of the method can be found in (b) (4) .

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:
The information provided is acceptable. Validation reports and detailed descriptions (or SOPs) of all non-compendial test methods are provided in the BLA, reviewed and found to be acceptable. The methods validations/qualifications were adequately performed to assure that these methods are suitable for their intended purpose.

3.2.P.5.4 Batch Analyses
General information including the dates of manufacture and batch size of the PRIORIX vaccine lots used for the clinical development in the US as well as PRIORIX vaccine lots produced for commercial purpose is provided in table 115 below.

Table 115: PRIORIX Final Container Lots – General Information

Lot Number	Container	Lot size	Filling date	Manufacturing sites	Context
(b) (4)	3 mL vial closed with bromobutyl	(b) (4)	(b) (4)	Rixensart	Phase 2 clinical study (MMR-157)

	D/12 rubber stopper				
(b) (4)	3 mL vial closed with bromobutyl (b) (4) stopper	(b) (4)	(b) (4)	Rixensart	Phase 3 clinical studies (MMR-158, MMR-159, MMR-161 and MMR-162)
	3 mL vial closed with bromobutyl (b) (4) stopper			(b) (4)	Phase 3 Clinical study (MMR-160)[1] Clinical & PPQ lots
	3 mL vial closed with bromobutyl (b) (4) stopper			(b) (4)	Commercial launch

[1] Lot (b) (4) manufactured as additional PPQ lot. This lot was not used in clinical studies.

The QR testing results at Final Bulk and Final Container stages for the (b) (4) PRIORIX vaccine lots used in Phase II MMR-157 clinical study, for (b) (4) PRIORIX vaccine lots used for Phase III Clinical Studies MMR-158, MMR-159, MMR-161 and MMR-162 are provided in section 3.2.P.5.4 "Batch Analyses, Clinical MMR" in this BLA. Filling of those clinical lots took place at the Rixensart site (Belgium). The results of all QR tests comply with the acceptance criteria at the time of testing.

The QR testing results for the (b) (4) PRIORIX PPQ lots, at Final Bulk and Final Container stages are provided in table 116 below. Filling of PPQ lots took place at the (b) (4) site. (b) (4) of those vaccine lots (lots (b) (4) were used as consistency batches in Phase III MMR-160 clinical study.

Table 116: Batch Analysis Data – PPQ lots Filled in (b) (4) Building

Tests/Procedures	Acceptance Criteria**	Results
FINAL BULK		(b) (4)
Sterility test (b) (4)	Absence of growth	
Sterility test (b) (4)	Absence of growth	
Bovine Serum Albumin content by (b) (4)	(b) (4)	
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	(b) (4)
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)	Not less than (b) (4) log $CCID_{50}$ per dose	
Potency mumps virus by (b) (4)	Not less than (b) (4) log $CCID_{50}$ per dose	
Potency rubella virus by (b) (4)	Not less than (b) (4) log $CCID_{50}$ per dose	
Potency measles virus by (b) (4)	The virus concentration is not more than (b) (4) log lower than the initial value.	
Potency mumps virus by (b) (4)	The virus concentration is not more than (b) (4) log lower than the initial value.	
Potency rubella virus by (b) (4)	The virus concentration is not more than (b) (4) log lower than the initial value.	
Neomycin sulphate content by (b) (4)	Not more than (b) (4) per dose	
(b) (4)	(b) (4)	

*Identity of the vaccine viruses in PPQ lots was performed by (b) (4), however, the commercial lots are (and will be) tested for identity by (b) (4). Please see the table below for the commercial lots. **The table indicates the specifications that are being licensed in the United States.

The QR testing results at Final Bulk and Final Container stages for the (b) (4) commercial batches of PRIORIX vaccine, produced in (b) (4) are also provided in table 117 below.

Table 117: Batch Analysis Data - Commercial Lots Filled in (b) (4) building

Tests/Procedures	Acceptance Criteria	Results
FINAL BULK		(b) (4)
Sterility test (b) (4)	Absence of growth	
Sterility test (b) (4)	Absence of growth	
Bovine Serum Albumin content by (b) (4)	No more than (b) (4) per dose (0.5mL)	
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)	Not more than (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)	Not less than (b) (4) log $CCID_{50}$ per dose. Not more than (b) (4) log $CCID_{50}$ per dose.			
Potency mumps virus by (b) (4)	Not less than (b) (4) log $CCID_{50}$ per dose. Not more than (b) (4) log $CCID_{50}$ per dose.			
Potency rubella virus by (b) (4)	Not less than (b) (4) log $CCID_{50}$ per dose[3]. Not more than (b) (4) log $CCID_{50}$ per dose.			
Potency measles virus by (b) (4)	The virus concentration is not more than (b) (4) log lower than the initial value			
Potency mumps virus by (b) (4)	The virus concentration is not more than (b) (4) log lower than the initial value			
Potency rubella virus by (b) (4)	The virus concentration is not more than (b) (4) log lower than the initial value			
(b) (4)	(b) (4)			

[1] Result is the mean of (b) (4) vials, tested in (b) (4) sessions. [2] Result is the mean of (b) (4) vials, tested in (b) (4) session.
[3] As mentioned in the section 3.2 P.2.3 "Development History MMR" in this BLA, the LRL was erroneously set at (b) (4) Log $CCID_{50}$ per dose instead of (b) (4) Log $CCID_{50}$ per dose for the three first commercial PRIORIX batches.

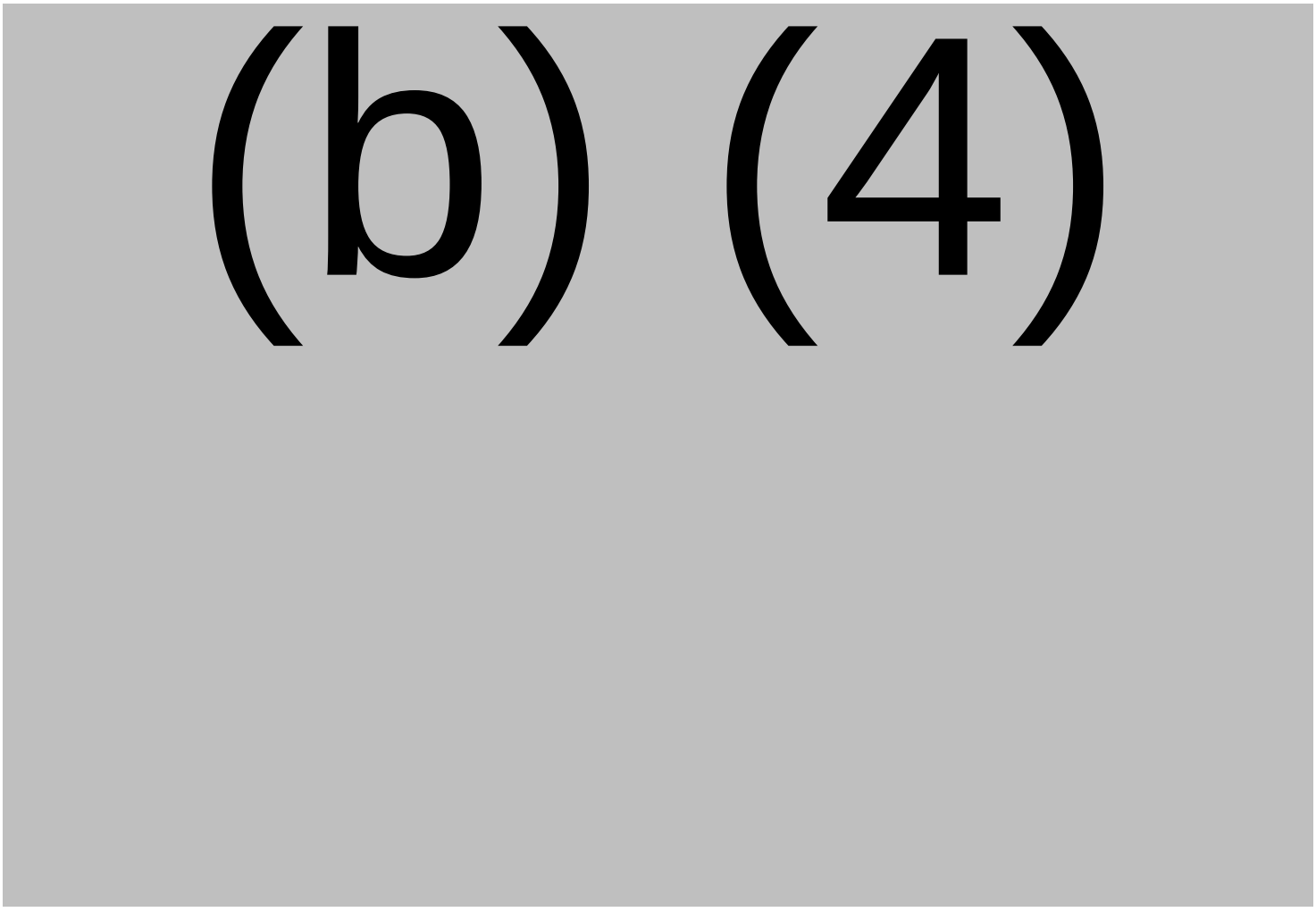
3.2.P.5.5 Characterization of Impurities

The impurities that could potentially be present in the PRIORIX FC would derive from the manufacturing process of the measles, mumps, and rubella monovalent bulks as no impurities are generated by the formulation/filling process. Those impurities originating from the bulks production processes are described in sections 3.2.S.3.2 above.

Potential impurity in the PRIORIX vaccine FB is residual BSA. The culture medium used during the production of (b) (4). The formulated FB is tested for residual BSA according to

the specification provided in sections 3.2.P.5.1 and the analytical procedure described in section 3.2.P.5.2 above. The validation of this analytical procedure is provided in section 3.2.P.5.3 “Bovine Serum Albumin Content by (b) (4) in this BLA, and results from the clinical and commercial vaccine batches are presented above in section 3.2.P.5.4 for clinical, PPQ and commercial batches. The justification of specifications for the residual BSA content in the FB is provided in section 3.2.P.5.6 above.

Potential impurity in the PRIORIX vaccine FC is residual neomycin. This antibiotic used during production of the BDSs. Based on toxicological assessments, the acceptable daily intake of neomycin sulphate is (b) (4) infant. Since 1997 and the registration of the vaccine in Europe, neomycin sulphate has been removed from stabilizers used for the DP formulation and this potential residual neomycin could therefore be only derived from the manufacturing process of the monovalent bulks. A quantitative (b) (4) based method was developed and qualified to evaluate neomycin content in (b) (4) batches of PRIORIX vaccine and the results are provided in table 118 below. The results obtained indicate that the average of neomycin content in these batches is (b) (4) , which would correspond to (b) (4) (0.5mL) and below the acceptable level from a toxicological point of view.



(b) (4)

Therefore, the sponsor stated that the analysis of (b) (4) batches of PRIORIX vaccine demonstrates that the limit of neomycin per single dose is never reached in a representative sampling of PRIORIX vaccine batches. Based on these low residual neomycin concentration values, the routine testing for neomycin content will not be performed to release the PRIORIX FC.

Potential impurity in the PRIORIX vaccine FC is endotoxin, which is not tested on the Final Container of the DP. However, the rationale for absence of endotoxin test for the release of the Final Container was part of the June 2016 Type C meeting during the vaccine development under IND 7229 (Question 5, Section 9.4 of the Type C Briefing Document, submitted 18 May 2016, eCTD sequence 0574). In the CBER Written Responses dated 16 June 2016, CBER agreed with GSK's position that endotoxin testing is not required on the Final Container since the manufacturing process design and control strategy sufficiently minimizes the potential risk for bacterial endotoxin contamination of the vaccine. CBER also agreed that endotoxin testing is not needed on the Final Container of the DP during the CMC Pre-BLA communication with the sponsor in December 2020.

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:
The information provided is acceptable. All DP specifications were met. Release testing results support consistency of product manufacture. Impurities are adequately controlled.

3.2.P.6 Reference Standards or Materials
For measles, mumps and rubella potency tests performed for the release of the PRIORIX DP, the internal control used is a trivalent Measles-Mumps-Rubella vaccine lot. This internal control is used in the potency by (b) (4) testing procedure for validity purpose but not to act as a relative standard to determine the viral potency titers of the tested lot. There are no reference materials used for determining the viral potency titers of the DP. Comparability protocols for replacement of internal control material (i.e., Measles-Mumps-Rubella vaccine lot) are provided in this BLA in sections 3.2.R "Internal Control Comparability Protocol Potency Test Me, Mu" and 3.2.R "Internal Control Comparability Protocol Potency Test Ru". The Comparability protocols were reviewed and found to be acceptable.

3.2.P.7 Container Closure System
The PRIORIX DP container closure system consists of a 3 ml vial container, (b) (4) ready to sterilize (RTS) vial stopper and vial flip-off cap. The vial primary packaging is provided in section 3.2.P.2.4 "Container Closure System" in this memo above. The vial containers and vial stoppers are (b) (4) that meets (b) (4). requirements. The vial containers, vial stoppers and vial flip-off caps are received separately, and their assembly is carried out during the filling, lyophilization and packaging operations. The vial containers are (b) (4) . The vial stoppers were previously submitted to the FDA and reviewed under Master File (MF) (b) (4). This information was also reviewed by the DMPQ reviewer on this BLA.

Overall Reviewer's Assessment of Sections 3.2.P.6 and 3.2.P.7:
The information provided is acceptable. The DP container closure system is safe for its intended use. However, the comment below was submitted to the sponsor. The response provided by the sponsor in amendment 30 is considered acceptable (see below).

Agency Question:
In Section 3.2.P.6 "Reference Standards or Materials, MMR" you mentioned the usage of a trivalent Measles-Mumps-Rubella vaccine lot as the internal control for measles, mumps and rubella potency tests. Please provide information on the qualification of this reference lot and the COA for this trivalent lot.

Company Response:
The MMR trivalent lot used as current Internal Control (IC) for the measles, mumps and rubella potency test performed for the release of PRIORIX Drug Product is the lot (b) (4). Please find the CoA of this lot annexed to this Response to question. As mentioned in BLA in section 3.2.P.6 "Reference standards or Materials", the comparability protocols for replacement of IC material (i.e., MMR vaccine lot) are provided in sections 3.2.R "R Internal Control Comparability Protocol Potency Test Me, Mu" in this BLA and 3.2.R "R Internal Control Comparability Protocol Potency Test Ru" in this BLA. As explained in these 2 sections, qualification of a new IC lot is based on the evaluation of (b) (4). Based on this approach, the measles, mumps and rubella potency titers of the MMR DP IC lot (b) (4) have been determined as (b) (4) log $CCID_{50}$/dose for measles, mumps and rubella respectively. The (b) (4) independent values used for the calculation of the potency titer for each antigen are listed in Table 10 of amendment 30. In 2017, (b) (4) for mumps IC titer, an investigation was opened and concluded that a re- evaluation of mumps titer of the IC was necessary. The titer was therefore re-evaluated based on all the data routinely generated between June 2015 and May 2017 (i.e., (b) (4) values, see Table 11 in amendment 30). Based on these values, the potency average for mumps was determined as (b) (4) log $CCID_{50}$/dose.

Reviewer's Assessment:
The response is acceptable.

3.2.P.8 Stability
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data
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, which allows to define the maximum temperature and time periods the reconstituted vaccine can be kept before administration (b) (4) of the reconstituted vaccine for up to (b) (4) hours at +5°C ± 3°C, testing at 8 (b) (4) hours).

All PRIORIX vaccine lots included in stability studies are described in table 119 below.

Table 119: General Information on PRIORIX Lots followed in Stability Studies

Lot	Date of manufacture	Batch size (vials)	Use	Type of stability study	Stability data currently available	Study status	Stability data
(b) (4)			Clinical – Phase II	Long-term stability studies (24 months at (b) (4)	24 months	completed	Section 3.2.P.8.3 Compilation Historical Stability Data MMR
			Clinical – Phase III Registration of a new stopper	Cumulative stability studies (12 months at (b) (4) +5°C ± 3°C)	(b) (4)	completed	Section 3.2.P.8.3 Compilation Historical Stability Data MMR
			Clinical – Phase III Registration of a new stopper	Cumulative stability studies (12 months at (b) (4) +5°C ± 3°C) Accelerated stability (30 days at (b) (4)	(b) (4)	completed	Section 3.2.P.8.3 Compilation Historical Stability Data MMR Section 3.2.P.8.3 Accelerated Stability Data MMR
			Clinical – Phase III	Long-term stability studies (b) (4)	(b) (4)	completed	Section 3.2.P.8.3 Compilation Historical Stability Data MMR
			Clinical – Phase III	Cumulative stability studies (24 months at (b) (4) +5°C ± 3°C) Accelerated stability (30 days at (b) (4)	(b) (4)	completed	Section 3.2.P.8.3 Compilation Historical Stability Data MMR Section 3.2.P.8.3 Accelerated Stability Data MMR
			Clinical – Phase III	Long-term stability studies (b) (4) Long-term stability studies (b) (4)	(b) (4)	completed	Section 3.2.P.8.3 Compilation Historical Stability Data MMR
			PPQ/ Registration of the Marietta site	Long term stability studies (24 months at +5°C ± 3°C). Cumulative stability studies (b) (4) followed by 24 months at +5°C ± 3°C). Accelerated stability studies (b) (4) In-use stability studies (reconstitution followed by storage at +5°C ± 3°C for up to (b) (4)	24 months real time, (b) (4) cumulative	completed	Section 3.2.P.8.3 Long-term Stability Data PPQ MMR, Section 3.2.P.8.3 Cumulative Stability Data PPQ MMR, Section 3.2.P.8.3 Accelerated Conditions Stability Data PPQ MMR, and Section 3.2.P.8.3 In-Use Stability Data PPQ MMR

(b) (4)	Commercial	Long-term stability studies (24 months at +5°C ± 3°C). Cumulative stability studies ((b) (4) at +5°C ± 3°C). Accelerated stability studies (193 days at (b) (4) Accelerated stability studies (30 days at (b) (4) In-Use stability studies (up to (b) (4) at +5°C ± 3°C)	9 months	ongoing	Section 3.2.P.8.3 Long-term Stability Data commercial MMR, Section 3.2.P.8.3 Cumulative Stability Data Commercial MMR, Section 3.2.P.8.3 Accelerated Conditions Commercial MMR, and Section 3.2.P.8.3 In-Use Stability Data Commercial MMR

*Manufactured according to clinical process, but not actually used in clinic.

The stability studies presented in table 119 above support:

- Long-term storage of PRIORIX 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 sponsor 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 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.

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 120 below.

Table 120: Analytical Procedures used for Stability Purpose*

Tests	Acceptance Criteria	Analytical Procedure and Validation[1]	Justification for the Test
Description[2]	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.	Please refer to Section 3.2.R R SOP Description - MMR	Parameter that may indicate changes in product quality with potential effects on efficacy and safety.
(b) (4)	Between (b) (4)	Please refer to Section 3.2.R R SOP (b) (4) - MMR	Parameter that may indicate changes in product quality with potential effects on efficacy and safety.

Water content by (b) (4)	(b) (4)	Please refer to Section 3.2.P.5.2 Water Content by (b) (4) MMR and Section 3.2.P.5.3 Water content by (b) (4) .	Parameter that may indicate changes in product quality with potential effects on efficacy and safety
Sterility test (b) (4)	Absence of growth	Please refer to Section 3.2.R R SOP Sterility tests by (b) (4) - Me, Ru, MMR, Section 3.2.R R Verification Sterility tests by (b) (4) - MMR FC	Safety test selected for real time and cumulative studies at least at beginning and end of shelf-life. Test not relevant for accelerated and for in use condition.
Sterility test (b) (4)	Absence of growth		
Potency measles virus by (b) (4)	For stability purpose: (b) (4)	Please refer to Section 3.2.P.5.2 Potency Measles Virus by (b) (4) MMR and Section 3.2.P.5.3 Potency Measles Virus by (b) (4)	Stability indicating test
Potency mumps virus by (b) (4)	For stability purpose: (b) (4)	Please refer to Section 3.2.P.5.2 Potency Mumps Virus by (b) (4) MMR and Section 3.2.P.5.3 Potency Mumps Virus by (b) (4)	Stability indicating test
Potency rubella virus by (b) (4)	For stability purpose: (b) (4)	Please refer to Section 3.2.P.5.2 Potency Rubella Virus by (b) (4) MMR and Section 3.2.P.5.3 Potency Rubella Virus by (b) (4)	Stability indicating test
Container closure integrity test	(b) (4)	Please refer to section 2 and Section 3.2.R R Validation CCIT for Stability - MMR	Safety test, performed for real time and cumulative studies at beginning and end of shelf-life.

[1]Verification data for (b) (4) methods. [2]Test is considered as a simple test, and therefore does not need to be validated, in alignment with the sponsor's internal procedures. *The table indicates the specifications for the EoSL potency values that are being licensed in the United States.

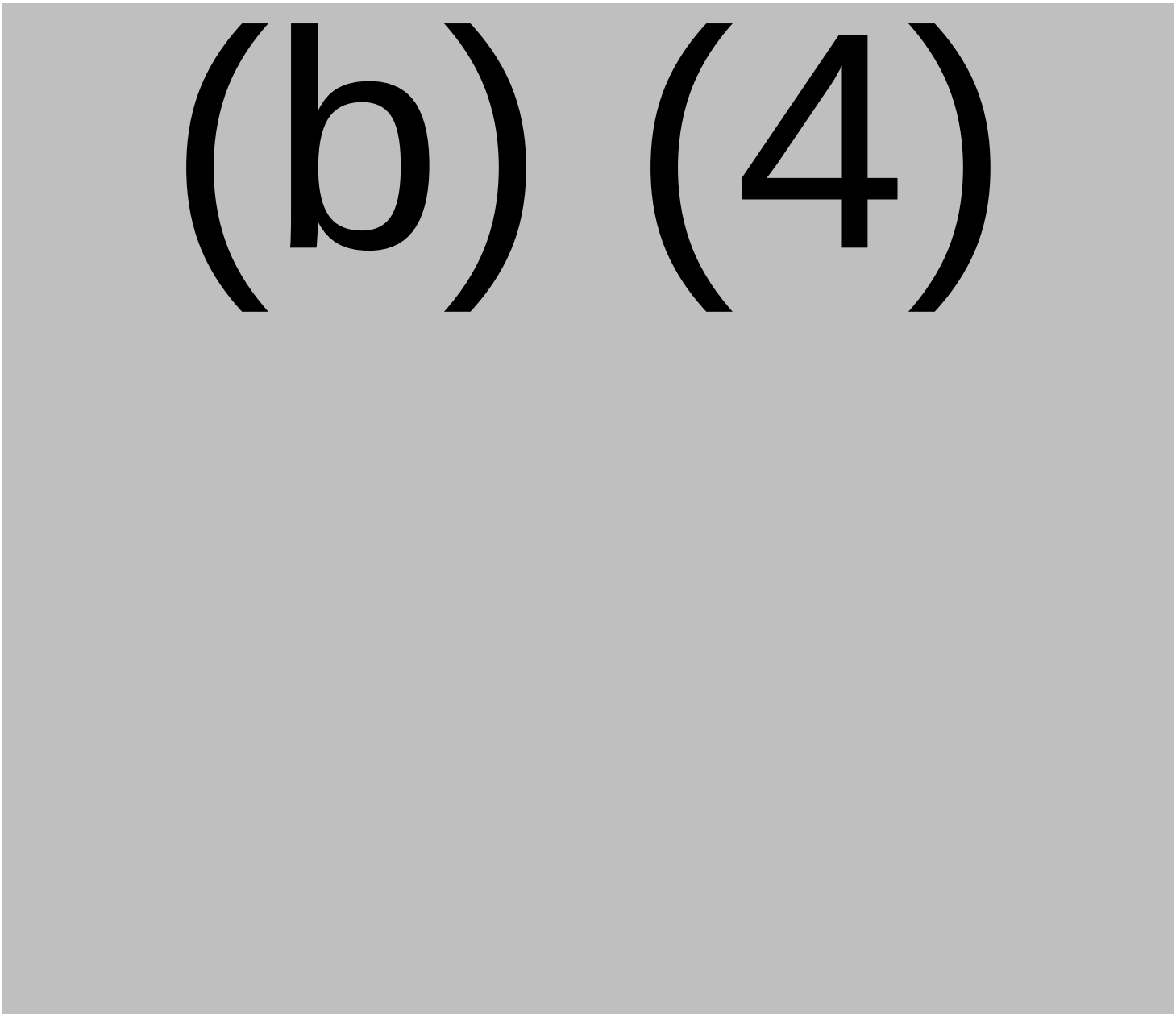
Analytical procedures used for additional stability testing performed on the clinical PRIORIX lots only are provided in table 121 below.

Table 121: Analytical Procedures used for Stability Purpose – Clinical Study Materials Only

Tests	Acceptance Criteria	Analytical Procedure	Justification for the Test
General safety – Abnormal toxicity on Guinea pigs	No weight loss, no abnormal reaction	21 CFR 610.11[1]	Safety test, test performed for real time studies at end of shelf-life.
General safety – Abnormal toxicity on mice	No weight loss, no abnormal reaction	21 CFR 610.11[1]	Safety test, test performed for real time studies at end of shelf-life.

[1]Testing performed according to compendial method, required at the time of clinical lot stability testing. Requirement for this method has since been eliminated.

(b) (4) PPQ lots of PRIORIX vaccine (b) (4) produced at the (b) (4) site were evaluated in a real time and real condition stability study at +5°C ± 3°C for 24 months to demonstrate that the product consistently retains its quality characteristics throughout its claimed shelf-life (24 months at +5°C ± 3°C). Additionally, this stability study supports the transfer of the process for formulation, filling, lyophilization, capping, and visual inspection of the vaccine to the (b) (4) site. The FC lots entering the stability program were filled in glass vials closed by a vial rubber stopper which are identical to the container closure system used during commercial manufacture. The stability samples have been positioned in inverted position. Stability samples were shipped for QC stability storage and testing at the (b) (4) site in (b) (4) .



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

(b) (4)

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

The (b) (4) commercial lots of PRIORIX vaccine (b) (4) produced at the (b) (4) site for registration of PRIORIX for the US market are followed in several stability studies. The sponsor is committed to complete the following ongoing long-term, cumulative, accelerated and in-use stability studies according to the stability plan given in order to:

- Demonstrate that the product consistently retains its quality characteristics throughout its claimed shelf-life (+5°C± 3°C for up to 24 months): real time and real conditions stability studies consisting of storage of the FC at +2°C to +8°C for up to 24 months (see table 1 in section 3.2.P.8.2 "Post-Approval Stability Protocol and Stability Commitment, MMR" in this BLA).
- Demonstrate that the cumulative storage (maximum (b) (4) 24 months at +5°C ± 3°C) has no impact on the quality of the vaccine: cumulative stability study including storage up to (b) (4) and by up to 24 months at +2°C to +8°C (see table 2 in section 3.2.P.8.2 "Post-Approval Stability Protocol and Stability Commitment, MMR" in this BLA).
- define the maximum time period the reconstituted vaccine can be kept before administration: in-use stability (b) (4) of the reconstituted vaccine for (b) (4) at +2°C to +8°C) (see table 3 in section 3.2.P.8.2 "Post-Approval Stability Protocol and Stability Commitment, MMR" in this BLA).

The sponsor is committed to complete stability testing and assessment for one batch per year of PRIORIX vaccine. The stability studies will be performed according to the stability plan given in table 128 below, in order to support the storage of PRIORIX FC at +2°C to +8°C for up to 24 months.

Table 128: Commercial Stability Protocol to support the storage of PRIORIX Final Container at +2°C/+8°C

Product	PRIORIX Final Container			
Container	3 mL glass vials closed with 13 mm RTS vial stoppers for lyophilized formulations			
Sample position	Inverted			
Storage temperature	+2°C/+8°C			
Time points	Release –12– 24 months			
Tests and methods	Please refer to Section 3.2.P.8.3 "Stability Analytical Procedures MMR" for information regarding the analytical procedures used for stability purpose only.			
		Time points (months)		
Tests	**Acceptance criteria**	**0**	**12**	**24**
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.	Release T0 Data	x	x
(b) (4)	(b) (4)		x	x
Water Content by (b) (4)	(b) (4)		x	x

Sterility test (b) (4)	Absence of growth		-	x
Sterility test (b) (4)	Absence of growth		-	x
Potency Measles virus by (b) (4)	For stability purpose: Not less than 3.4 log $CCID_{50}$ per dose*		x	x
Potency Mumps virus by (b) (4)	For stability purpose: Not less than 4.2 log $CCID_{50}$ per dose*		x	x
Potency Rubella virus by (b) (4)	For stability purpose: Not less than 3.3 log $CCID_{50}$ per dose*		x	x
Container closure integrity test	(b) (4)		NA	x

NA - indicates that the test is not planned at the time point. *The table indicates the specifications for the EoSL potency values that are being licensed in the United States.

Overall Reviewer's Assessment of Section 3.2.P.8:
The information provided is acceptable. However, the comments below were submitted to the sponsor. The responses provided by the sponsor in amendments 30, 34 and 36 are considered acceptable (see below).

Agency Question 1:
We note that in section 3.2.P.8.3 "Stability Data, Cumulative Stability Data PPQ, MMR" in table 1, the acceptance criteria provided for potency are given inaccurately. Please comment.

a. You stated in the table (b) (4) log $CCID_{50}$, (b) (4) log $CCID_{50}$ and (b) (4) log $CCID_{50}$ per dose" for the measles, mumps and rubella, respectively, refer to the (b) (4) storage at (b) (4). We think that for the (b) (4) storage at (b) (4) you should use the release specifications of "not less than (b) (4) log $CCID_{50}$, (b) (4) log $CCID_{50}$ and (b) (4) log $CCID_{50}$ per dose" for the measles, mumps and rubella, respectively.
b. You stated in the table "not less than (b) (4) log $CCID_{50}$, (b) (4) log $CCID_{50}$ and (b) (4) log $CCID_{50}$ per dose" for the measles, mumps and rubella, respectively, refer to the stability storage at (b) (4). We think that for the stability storage at (b) (4) you should use the EoSL potency values that are being licensed in the United States, i.e., "not less than 3.4 log $CCID_{50}$, 4.2 log $CCID_{50}$ and 3.3 log $CCID_{50}$ per dose" for the measles, mumps and rubella, respectively.
c. In all your tables, please use only either the release or EoSL specifications that are being licensed in the United States, but not the worldwide specifications. Please, revise your tables accordingly, and re-submit the corrected tables.

Company Response 1:
The sponsor agrees with the general comment from CBER about some unclarity on the acceptance criteria provided for the potency tests in the cumulative stability study of the PRIORIX PPQ lots.
a) With respect to the acceptance criteria for the (b) (4) of storage at (b) (4), the sponsor does not agree with CBER's proposal to consider the release acceptance criteria for the first month of storage at (b) (4). The sponsor considers that the EoSL acceptance criteria should apply for the full stability plan (with the exception of the release time point) irrespective of the storage temperature. This approach has been proposed in the cumulative stability plan of the (b) (4) commercial batches provided in the original BLA submission (see 3.2.P.8.2 "Ongoing Stability Studies MMR" in tnis BLA). The sponsor acknowledges that this approach was not clearly reflected in the cumulative stability of

the PPQ batches and proposes to update the section submitted accordingly (see response to Question 12b) of amendment 30 below). Please also refer to the response to question 12c) of amendment 30 below for the rational to keep the non-US acceptance criteria for the stability studies launched on the PRIORIX PPQ lots.

b) The sponsor agrees with CBER's suggestion to consider the EOSL acceptance criteria instead of the Release acceptance criteria, as mentioned in the 3.2.P.8.3 "Cumulative stability data PPQ MMR" submitted in the original BLA, for the time points generated during the period storage at (b) (4) in the cumulative stability study. Indeed, as mentioned above, the sponsor considers that the EoSL acceptance criteria should apply for the full stability plan (with the exception of the release time point) irrespective of the storage temperature and proposes to update, with this answer the above mentioned 3.2.P.8.3 "Cumulative stability data PPQ MMR" to correctly reflect this approach within the BLA

c) With respect to the request from CBER to consider either the US release or EOSL acceptance criteria instead of the non-US acceptance criteria for the cumulative stability studies launched on the PRIORIX PPQ batches, the sponsor wants to bring to CBER's attention that the PRIORIX PPQ batches were produced at (b) (4) in 2012. The batches were released at that time according to non-US release acceptance criteria in the context of the registration of the site as an additional manufacturing site for the production of PRIORIX vaccine for non-US markets. The representativity of these batches for the US market was discussed and agreed during the MMR US Type C meeting of May 2020 (IND #07229). It is important to note that, as explained in the Briefing document for the type C meeting, while the PPQ batches produced in 2012 at (b) (4), are representative from a process point of view of the PRIORIX US vaccine, the volumes of monovalent bulks are slightly different than in the PRIORIX US vaccine to meet the higher release and EoSL potency acceptance criteria intended for the US market. As a consequence, the sponsor does not deem appropriate to align the Release and EOSL acceptance criteria of the PRIORIX PPQ batches to the PRIORIX US release and acceptance criteria. In order to support the stability of the PRIORIX US vaccine, additional stability studies have been launched on the (b) (4) commercial lots (b) (4) The data available to date are provided in the "3.2.P.8.3 Commercial" sections of the BLA.

Agency Question 2:
In section 3.2.P.8.3 "Stability Data, Cumulative Stability Data PPQ, MMR", please:

a. Clarify whether tables 1 and 2 represent two independent stability studies or table 2 represents a continuation of the stability study presented in table 1?
b. Clarify if the stability data for potency (log CCID (b) (4) per dose for stability at (b) (4)) in table 2 are corresponded to the release specifications and applied for the (b) (4) storage at +5°C or are they also applied for the followed by (b) (4) storage at +5°C ± 3°C?
c. Clarify if stability data for potency after (b) (4) storage at (b) (4) storage at (b) (4) provided are the end of shelf-life specifications?
d. Provide the final investigation report for the deviation related to the measles potency value of (b) (4) log $CCID_{50}$ per dose for the PPQ lot (b) (4) at (b) (4) months. This lot failed the acceptable EoSL value for the US, which should be not less than 3.4 log $CCID_{50}$ per dose.

Company Response 2:
a) The sponsor clarifies that Table 1 and Table 2 for the section 3.2.P.8.3 “Stability Data, Cumulative Stability Data PPQ, MMR” submitted in the BLA, represent a single stability study. Within this study, the (b) (4) lots have been stored for (b) (4) 24 months at +5°C.

b) The sponsor acknowledges the unclarity about the acceptance criteria included in the section 3.2.P.8.3 “Cumulative stability data PPQ MMR” relative to the cumulative stability study of the PRIORIX PPQ batches. As discussed above in the Response to question 12 of amendment 30, the sponsor considers that the EoSL acceptance criteria should apply for the full stability plan (with the exception of the release time point) irrespective of the storage temperature and therefore submits within this answer an updated 3.2.P.8.3 “Cumulative stability data PPQ MMR” section to correctly reflect this approach within the BLA.

c) as per response to point b).

d) The sponsor clarifies that the PRIORIX PPQ batches (b) (4) were produced and tested taking into account non-US acceptance criteria. As presented in table below which summarizes the differences between worldwide and the US potency acceptance criteria applied for the PRIORIX vaccine, the Measles potency EoSL acceptance criteria for the non-US market is “Not less than (b) (4) log10 $CCID_{50}$/dose” (highlighted in bold in the table). As a consequence, at the time of the stability study, the batch (b) (4), presenting a Measles potency titer at (b) (4) time point of (b) (4) log10 $CCID_{50}$/dose, met the non-US EoSL acceptance criteria and no deviation was opened at that time. The statistical analysis concluded an out of trend which was explained by the variability of the method. It is important also to note that, to reduce this variability, as mentioned in the Table 8 of the section 3.2.P.2.3 “Development History MMR” in this BLA, the testing format of the Measles potency test has been changed from a (b) (4) session (b) (4) applied in 2012 to a (b) (4) sessions format (b) (4) that is currently applied.

(b) (4)

Agency Question 3:
We note that in section 3.2.P.8.3 “Stability Data, Cumulative Stability Data PPQ, MMR”, the title of Table 1 states “Cumulative Stability Results of MMR Final Container Stored (b) (4) however, the Introduction of this document states:

(b) (4) lots of MMR vaccine (b) (4) produced during PPQ campaign at (b) (4) site and used in Phase III clinical study MMR-160, have been followed in a cumulative stability study including storage for (b) (4) 24 months storage at +5°C ± 3°C." Please clarify this discrepancy. Please also confirm that the maximum shelf life of DP commercial lots will be (b) (4) months, i.e., (b) (4) 24 months storage at +5°C ± 3°C.

Company Response 3:
The sponsor wishes to clarify that the cumulative study performed on the PRIORIX PPQ lots was performed with the following design: (b) (4) by 24 months at +5°C ± 3°C. In section 3.2.P.8.3 "Cumulative Stability Data PPQ MMR", Table 1, are presented the data for the timepoints of the (b) (4). On the other hand, Table 2 presents the data for the timepoints as of (b) (4) after release, until (b) (4) of storage. Please refer to Table 2 in amendment 34 for a tabular presentation on the stability data presentation in this section. The sponsor acknowledges that this initial stability plan is a worst case as compared to the actual life cycle of the product. Indeed, according to internal operating procedure, (b) (4) after the production date. Therefore, the maximum shelf-life of commercial PRIORIX DP lots will be of (b) (4) 24 months at +5°C ± 3°C. Stability data of the PPQ lots, up to (b) (4), are considered as worst case and therefore as supportive of the (b) (4) shelf-life. Please note that for commercial lots the cumulative stability protocol defined is: (b) (4) 24 months at +5°C ± 3°C, as mentioned in section 3.2.P.8.2 "Ongoing Stability Studies MMR" and 3.2.P.8.3 "Cumulative Stability Data Commercial MMR" in this BLA.

Agency Question 4:
Your responses to CBER Questions 12 and 13 in amendment 125748/0030 (Response to CBER IR dated 11Mar2022 – CMC") are generally acceptable, however, we would like to clarify the following:

- a) During the MMR US Type C meeting in May 2020 (under IND 7229/605), which you mentioned in your response 12c, we have not discussed or not agreed that the non-US shelf-life potency values for the DP, which were originally assigned to the PPQ batches (b) (4) in 2012, are acceptable to support the registration of the US shelf-life potency values for Priorix DP for the US market under the BLA.
- b) As mentioned in our previous CBER Question 13d, the shelf-life potency value for measles of (b) (4) log CCID50 per dose for the PPQ lot (b) (4) at (b) (4), is considered an unsatisfactory potency value for the US market because the shelf-life potency value for measles for this vaccine for the US market to be registered under the BLA is 3.4 log CCID50 per dose. Please also note that PPQ lot (b) (4) met the US potency value acceptance criteria for measles, mumps and rubella at release.

To support the requested shelf life, please place an additional (b) (4) commercial lots of Priorix DP (in addition to PRIORIX commercial lots (b) (4) on long term stability testing and provide the data when available.

Company Response 4:

The sponsor acknowledges the CBER's request for placing (b) (4) additional commercial lots of the DP in long term and cumulative stability studies and commits to provide stability data on these (b) (4) lots when they will be available.

Agency Question 5:
In the original BLA you provided stability results for PRIORIX commercial lots (b) (4) for up to 9 months. Please provide updated stability data for these batches which we believe should be available for the 12- and 18- month time points. In addition, please clarify how the additional stability information for these lots will be provided post-approval.

Company Response 5:
As mentioned in the "Note to Reviewer" submitted in this BLA in sequence 001, page 12, paragraph 7, 12-month, 18-month and 24-month stability data were planned to be provided in May 2022, May 2022 and November 2022, respectively. 12-month and 18-month stability data are currently under statistical analysis. The sponsor proposes to submit these data by the 29th of April. Of note, this additional stability information will be submitted as amendments to the BLA.

Agency Question 6:
In the original BLA you provided stability results for PRIORIX commercial lots (b) (4) for up to 9 months. Please provide updated stability data for these batches which we believe should be available for the 12- and 18-month time points. In addition, please clarify how the additional stability information for these lots will be provided post-approval.

Company Response 6:
In amendment 36 to this BLA, the sponsor provided 12-month and 18-month stability data for three commercial lots of PRIORIX vaccine (b) (4) The information presented in this BLA in sections 3.2.P.8.1 "Stability Summary and Conclusion MMR", 3.2.P.8.3 "Cumulative Stability Data MMR" and 3.2.P.8.3 "Long Term Stability Data Commercial MMR", was reviewed and found to be acceptable.

Reviewer's Assessment:
The responses are acceptable.

3.2.P DRUG PRODUCT, WFI DILUENT
3.2.P.1 Description and Composition of the Drug Product
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 USP monograph for sterile WFI. The composition of the WFI diluent is provided in the table 129 below.

Table 129: Composition of the Drug Product (WFI Diluent)

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

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

The WFI diluent is filled in 1.25 mL glass syringe. The immediate packaging material used for the container closure system is provided in table 130 below.

Table 130: Container Closure System

Presentation	Container	Closure
Prefilled syringe	1.25 mL syringe (b) (4) glass barrel) with luer lock adaptors and (b) (4) rubber tip caps	Bromobutyl (b) (4) rubber plunger stopper

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

The diluent used for reconstitution of the lyophilized vaccine solely contains WFI. WFI is tested according to methods described in the (b) (4) monograph for sterile WFI. The specifications are presented in section 3.2.P.5.1 in this memo. There are no excipients in the WFI diluent.

3.2.P.2.2 Drug Product

The WFI diluent solely contains sterile WFI, therefore, no other components are presented.

3.2.P.2.2.1 Formulation Development

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. For further simplification, the sponsor proposes that, after reconstitution, the same ungraduated syringe is used to withdraw and after needle change, to administer the entire content of reconstituted vaccine. This whole content reconstitution/whole content administration approach aims at consistently delivering 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) for WFI diluent in ungraduated prefilled syringe including an overfill to compensate liquid losses observed during reconstitution and administration of the vaccine guarantees that minimum potency titers for measles, mumps and rubella are delivered in a dose of approximately 0.5 mL.

3.2.P.2.2.2 Overages

There are no overages for this product. An overfill, the volume filled in each syringe (b) (4) is in slight excess to ensure that the minimum recoverable volume release criterion for the reconstituted vaccine (0.5 mL) is met.

3.2.P.2.2.3 Physicochemical and Biological Properties
The physicochemical properties of WFI diluent are consistent with (b) (4) monograph for Sterile WFI. The WFI diluent has no inherent biologic activity and is use solely for the reconstitution of the lyophilized PRIORIX vaccine.

3.2.P.2.3 Manufacturing Process Development
During the US clinical development of the vaccine, changes to the WFI diluent manufacturing process and presentation were introduced. These changes included (b) (4) prefilled syringes presentation for PPQ and commercial lots. (b) (4), as summarized in table 131 below.

(b) (4)

The original manufacturing of WFI diluent in PFSs was performed at the Rixensart site. The manufacturing process to produce the WFI diluent in PFSs was (b) (4) for the production of PPQ and commercial lots. The prefilled syringes, their characterization and aseptic filling were reviewed by the DMPQ reviewer on this BLA.

The major changes occurred between the initial implementation of the WFI syringe filling process at the Rixensart site and manufacturing process applied at (b) (4) are detailed below:

- (b) (4)

Clinical Development
The Phase II MMR-157 study was performed using a lyophilized vial of PRIORIX vaccine to be reconstituted with WFI diluent filled in ungraduated syringes. The instructions for reconstitution and administration mentioned at that time correspond to the proposed whole contents/whole contents (WC/WC) approach for commercial product. In the Phase III clinical trials (MMR-158 to MMR-162), the PRIORIX vaccine was still presented as a lyophilized vaccine in a vial that required reconstitution with WFI diluent, though the diluent was filled in a vial for these studies. The sponsor's instructions for administration in these clinical studies were also to inject the whole content of diluent from the vial into the vial of lyophilized vaccine, to withdraw the reconstituted vaccine and to administer the whole content to the subject. As Phase III clinical studies were performed by using a WFI diluent filled in glass vials,

an experiment was performed to determine if the range of vaccine volume and therefore the viral potency titers that are administered to the subject when WFI diluent is filled in PFS are similar to those administered for Phase III studies. Several measurements were performed in this study to assess:

- The volume of WFI diluent withdrawn from the PFS and used for the reconstitution of the lyophilized vaccine.
- The volume of reconstituted vaccine withdrawn from the vial into the PFS before administration.
- The volume of reconstituted vaccine administered to the subject.
- The comparative volume administered to the subject when using prefilled syringes vs. glass vials as used for Phase III clinical studies.
- And ultimately the minimal and maximal mumps, measles and rubella potency titers that could be administered to the subject.

(b) (4)

(b) (4)

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(b) (4)

3.2.P.2.4 Container Closure System

The WFI diluent container closure system consists of a syringe barrel 1.25 mL that are received from the supplier (b) (4) assembled with (b) (4) rubber tip caps, rigid caps and luer lock adaptors (LLA). During filling operations, syringe barrels are sealed with plunger stoppers. During packaging operations, a (b) (4) The syringes are then packed in boxes. Testing of the container closure integrity by (b) (4) was validated to demonstrate that the container closure system (CCS) maintains its integrity upon long-term storage of the vaccine. The information for (b) (4) WFI Final Container lots (b) (4) at release and after 60 months of storage at +25°C is provided in table 1 in section 3.2.P.2.4 "Pharmaceutical development, Container Closure System WFI Diluent". All information has been reviewed and found to be acceptable.

The safety of the container closure components is evaluated through extractable and leachable studies. (b) (4) glass has a high hydrolytic resistance. Thus, no extractables and leachables assessment is conducted on the syringe barrel of the 1.25 mL PFS, in accordance with the sponsor's procedures for extractables as well as based on (b) (4) general Chapter (b) (4) Pharmaceutical Dosage Forms. The evaluation of the extractables was performed on the (b) (4) bromobutyl rubber plunger stopper and the (b) (4) styrene-butadiene rubber tip cap which in addition to the glass syringe barrel, are the 1.25 mL PFS components in contact with the WFI diluent drug product. Extractable compounds were identified and quantified in accordance with sponsor's SOP.

1.25 mL (b) (4) glass syringe filled with WFI and closed with (b) (4) tip-cap and (b) (4) plunger stopper (referred to as the sample) were used for the evaluation of leachables. The syringe samples are stored in a (b) (4) position during the ageing. A blank solution of WFI diluent, which does not have any contact with the CCS is sampled under sterile conditions and aged simultaneously as reference. Blank is stored upright in a glass bottle with Teflon lined screw cap (i.e., inert container) and came from the same batch as the one used for the filling of the syringes. The rubber tip cap and bromobutyl rubber plunger stopper have been in contact with WFI diluent up to 5 years at room temperature (b) (4) which correspond to the registered shelf-life for WFI diluent.
The toxicological assessments of the extractable and leachable compounds were made according to the "Guideline on the limits of genotoxic impurities" of the European Medicines Agency, June 2006 (EMEA/CHMP/QWP/251344/2006), in which it is recommended to use a Threshold of Toxicological Concern (TTC). "A TTC value of (b) (4) intake of a genotoxic impurity is considered to be associated with an acceptable risk for most pharmaceuticals." The safety of residuals present at above the TTC

was evaluated in accordance with the (b) (4) procedure. The assessment of extractables and leachables for this CCS was performed and found to be acceptable. See section 3.2.P.2.4 "Pharmaceutical development, Container Closure System, WFI Diluent" in this BLA for details. The data provided for the container closure system were reviewed and found to be acceptable. This information was also reviewed by the DMPQ reviewer on this BLA.

3.2.P.2.5 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. (b) (4)

The WFI diluent Final Container is tested for sterility and endotoxin content according to (b) (4) requirements.

3.2.P.2.6 Compatibility

The compatibility of the WFI diluent with the container closure components is demonstrated through stability studies (see details in section 3.2.P.8.3 "Real Time Stability Data WFI Diluent" in this BLA). 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 are provided in section 3.2.P.8.3 "In-use Stability Data PPQ MMR for MMR Drug Product" in this BLA. All information was reviewed and found to be acceptable.

Overall Reviewer's Assessment of Section 3.2.P.2:
The information provided is acceptable.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The name and address of all manufacturers including contractors, or third parties involved in the manufacture, testing and QA release of the WFI diluent and a brief description of the responsibilities of each manufacturer are provided below in table 134.

Table 134: Facility Information

Site Name	Site Address	Specific Manufacturing Responsibilities or Type of Testing
(b) (4)	(b) (4)	• Production and filling of the WFI diluent • Quality Release and Stability testing of WFI diluent

(b) (4)	(b) (4)	• Warehousing operations
(b) (4)	(b) (4)	• Warehousing operations
(b) (4)	(b) (4)	• Warehousing operations
GlaxoSmithKline Biologicals (b) (4)	GlaxoSmithKline Biologicals (b) (4)	• Commercial Stability testing of WFI diluent • Warehousing operations
(b) (4) GlaxoSmithKline Vaccines	(b) (4) GlaxoSmithKline Vaccines (b) (4)	• Labeling and packaging operations for the MMR vaccine and WFI diluent • Quality Release testing of Final Product • QA release of Final Product • Warehousing operations
(b) (4)	(b) (4)	• Warehousing and distribution

3.2.P.3.2 Batch Formula

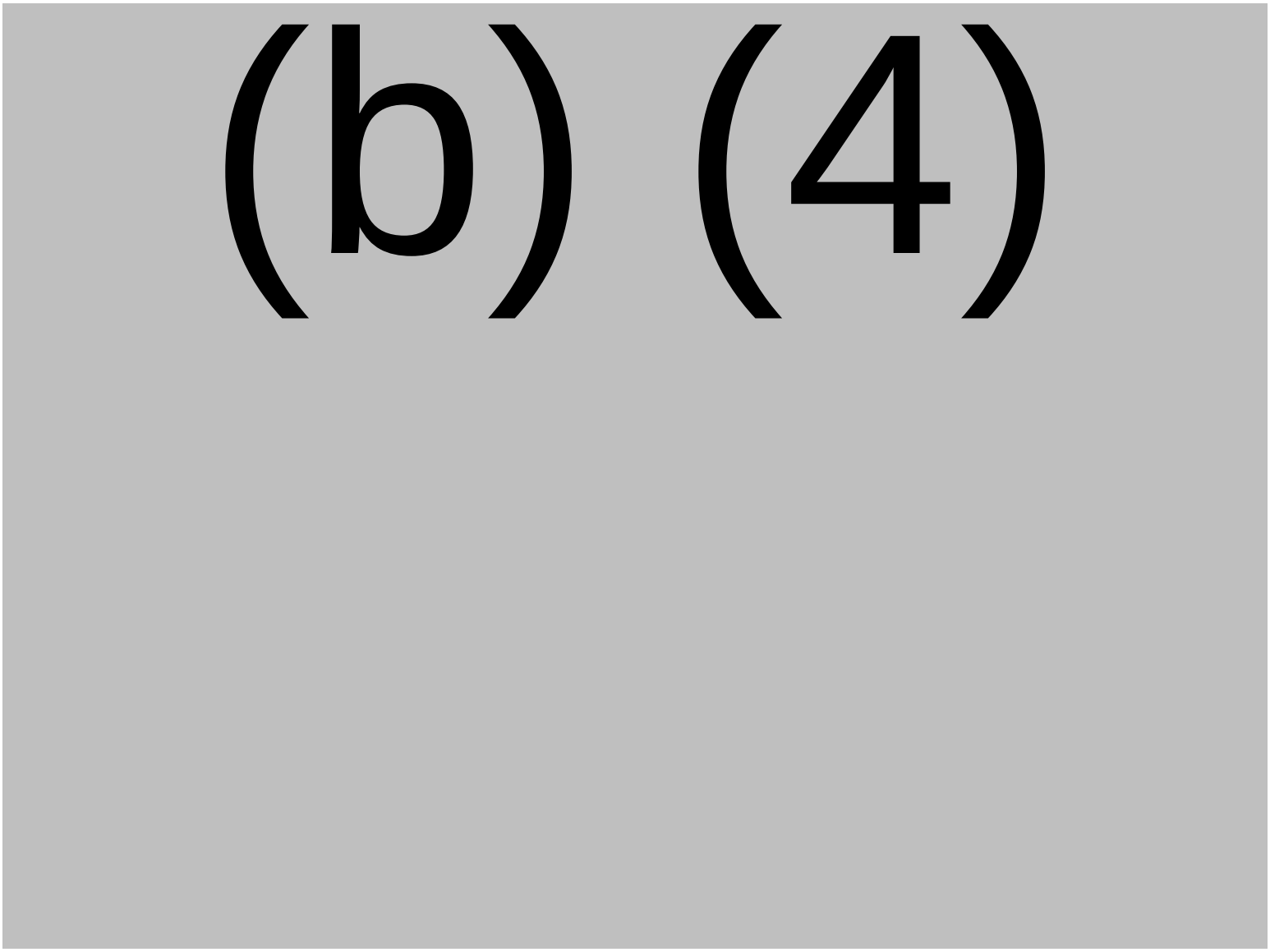
Water for Injection is the only component in WFI diluent commercial batch manufactured at (b) (4) . The batch size of a commercial batch of WFI diluent Final Bulk is (b) (4) corresponding to a Final Container batch size of about (b) (4) prefilled syringes.

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:
Agency Question:
Company Response:

3.2.P.3.3 Description of Manufacturing Process and Process Controls

The manufacturing process of the WFI diluent is composed of the following steps: (i) WFI production; (ii) receipt and storage of untested packaging material; (iii) preparation of syringes; (iv) filling operations;

(v) inspection and storage; (vi) shipment to the sponsor; (vii) plunger fitting/packaging. A general overview of WFI diluent manufacturing processes is provided in figure 5 below.



(b) (4)

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(b) (4)

Plunger Fitting and Packaging
The final manufacturing and packaging steps of the sterile syringes are described in section 3.2.P.3.3 “Description of Manufacturing Process and Process Controls, PRIORIX Vaccine” in this memo above.

Drug Product Inspection, Storage and Transportation
The autoclaved, filled syringes are 100% visually inspected for volume, integrity defects, and visible particles with an automatic visual inspection machine. Inspected and approved containers are placed in boxes and stored at the warehouse at (b) (4), awaiting labelling and packaging. The labelled and sterile syringes from the (b) (4) site are transported to the (b) (4) site, and then from the (b) (4)

site to the (b) (4) site for final packaging. See section 3.2.A.1 “Cold Chain Transport and Validations” in this BLA for details for the shipping procedures.

Batch Numbering System
The rules defining the batch numbering system for WFI diluent lots are as follows:

- (b) (4)

3.2.P.3.4 Controls of Critical Steps and Intermediates
Process monitoring (PM) tests, as in-process controls, are applied during the WFI diluent manufacturing process and are used for process consistency evaluation. Process consistency and performance are monitored through consistency ranges established for the in-process controls and through release testing. QR tests are performed at the WFI diluent Final Container and the packaged PRIORIX Final Product stages. PM tests to be carried out during routine commercial production of WFI diluent are presented in table 135 below. There is no intermediate in WFI diluent production.

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.4:
The information provided is acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

The consistency of DP during the manufacturing process are confirmed through an analysis of the PPQ batches. The (b) (4) WFI PPQ batches were manufactured by (b) (4) at its manufacturing site in Belgium, in 2011, at commercial scale resulting in approximately (b) (4) PFSs per batch (see table 136 below for details). These consecutive batches were produced to ensure that the product quality and process performance were consistent. The validation and/or evaluation studies were performed by (b) (4)

(b) (4)

(b) (4) .

(b) (4)

(b) (4)

(b) (4)

These (b) (4) PPQ batches were 100% visually inspected followed by acceptance quality limit (AQL) sampling and inspection. The results complied with the acceptance criteria. The holding time has also been validated during the manufacturing of the (b) (4) consistency batches: (b) (4) end of filling and (b) (4) .

The sponsor stated that because the WFI diluent is (b) (4) , aseptic process simulation studies are not required to assure sterility of the WFI FC. WFI diluent (b) (4) validation was based on (b) (4) . The details are presented in section 3.2.P.3.5 "Validation of (b) (4) WFI Diluent" and were reviewed by the DMPQ reviewer on this BLA.

Overall Reviewer's Assessment of Section 3.2.P.3.5:
The information provided is acceptable.

3.2.P.4 Control of Excipients
3.2.P.4.1 Specifications
The WFI diluent does not contain any excipients.

Overall Reviewer's Assessment of Section 3.2.P.4:
The information provided is acceptable.

3.2.P.5 Control of Drug Product
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

The specifications for release of the WFI diluent in FC (i.e., in prefilled syringes) include those described in the (b) (4) for Sterile WFI. An overview of the QR testing and justifications of the acceptance criteria for each QR test conducted on commercial WFI diluent FC are provided below in table 139.

Table 139: Justification of Release Specifications for WFI Diluent Final Container

Test/Procedure	Acceptance criteria	Justification
(b) (4)	(b) (4)	(b) (4) .
Particle Count	Not more than (b) (4) and not more than (b) (4) per syringe	The specification for the determination of Particle Count is set according to (b) (4)
Sterility test (b) (4)	Absence of growth	The specification for Sterility test (b) (4) is set according to (b) (4)
Sterility test (b) (4)	Absence of growth	The specification for Sterility test (b) (4) is set according to (b) (4)
Bacterial Endotoxin tests (b) (4)	(b) (4)	The specification for Bacterial Endotoxin is set according to (b) (4)
Water conductivity	(b) (4)	The specification for Water conductivity is set according to (b) (4)
Extractable volume	(b) (4)	The proposed range is defined to ensure that each dose of the Final Product delivered after reconstitution of the lyophilized MMR with the WFI diluent is approximately 0.5 mL. The proposed range is based on statistical assessment which considered the variability of the filling line, the volume loss due to the whole content/whole content administration instructions and the variability of the analytical method. Details are provided in this section below and in Section 3.2.P.5.6 "Extractable Volume WFI" in this BLA.

The acceptance criterion for extractable volume was defined considering the sponsor's instructions for reconstitution and administration of the PRIORIX vaccine. Based on data generated to assess the mean volume of reconstituted vaccine and hence, the viral potency titers that can be administered to the subject (see section 3.2.P.2.3 "Manufacturing Process Development WFI Diluent" in this memo above), the proposed acceptance criterion is between (b) (4), as even after rounding, the extractable volumes between (b) (4) will still ensure the administration of appropriate viral potency titers.

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:
The information provided is acceptable.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures
The references for the analytical procedures used for released testing of the WFI diluent FC and the verification data for some compendial methods are provided in 3.2.R "Regional Information sections"

in this BLA and are presented in table 140 below. The tests performed in accordance with official pharmacopoeia monographs are considered to be validated.

(b) (4)

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

The information provided is acceptable.

3.2.P.5.4 Batch Analyses

General information including the dates of manufacture and batch size of the WFI diluent lots used for the clinical development in the US as well as PPQ WFI lots is provided in table 141 below. Batch analysis results for WFI batches are presented in the indicated sections. The sponsor stated that all these batches have been tested according to the sponsor's internal SOPs at the time of release testing and all complied with the accepted specifications.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The QR testing results for the WFI diluent in syringes utilized for the Phase II MMR-157 Clinical Study and the QR testing results for the (b) (4) Phase III WFI diluent clinical batches filled in glass vials provided in section 3.2.P.5.4 “Batch Analyses Clinical WFI Diluent” were reviewed and found to be acceptable.

3.2.P.5.5 Characterization of Impurities

The WFI diluent meets the (b) (4) requirements with respect to impurities ((b) (4) and endotoxin). The specifications are given in table 139 above. No impurities are generated by the filtration/filling process.

Overall Reviewer’s Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:
The information provided is acceptable. All DP specifications were met. Release testing results support consistency of product manufacture.

3.2.P.6 Reference Standards or Materials
No reference standard is used for the Quality Control testing of WFI diluent.

3.2.P.7 Container Closure System
The WFI diluent container closure system consists of a syringe barrel 1.25 mL that are received from the supplier, assembled with (b) (4) rubber tip caps, rigid caps and luer lock adaptors (LLA). They are received clean, siliconized and sterile from the supplier and tested at the (b) (4) site. During filling operations, syringe barrels are (b) (4) . Durin (b) (4) The syringes are then packed in boxes.
The glass prefillable syringes from (b) (4) and the syringe rubber compounds from (b) (4) were submitted to the FDA under the Master File (MF) (b) (4) and MF (b) (4), respectively. Additional information on the container closure system is provided in section 3.2.R "Medical Devices" in this BLA. The information has been reviewed by the DMPQ reviewer on this BLA.

Overall Reviewer's Assessment of Sections 3.2.P.6 and 3.2.P.7:
The information provided is acceptable. The DP container closure system is safe for its intended use.

3.2.P.8 Stability
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data
The stability profile of WFI diluent is assessed through the following stability studies:
- Long-term stability studies for up to 60 months at +25°C (b) (4).
- In-use stability study to demonstrate compatibility with PRIORIX vaccine.

Analytical procedures used for stability testing of WFI diluent include those used for routine QR and are described in sections 3.2.P.5.2 and 3.2.P.5.2 in this memo above. All lots included in stability studies are described in table 143 below.

Table 143: General Information on WFI Diluent Lots Followed in Stability Studies

Lot	Production Date	Batch size (number of prefilled syringes) *	Use	Type of stability study	Stability data currently available	Study status	Stability data
(b) (4)			PPQ, Registration of (b) (4) site	Long-term stability studies (60 months at +25°C (b) (4)	60 months	completed	see Section 3.2.P.8.3 Real Time Stability Data WFI Diluent

* Including QC samples and rejects

Based on the available stability data, the sponsor established a shelf-life of 60 months at +25°C (b) (4) for WFI Diluent filled in the prefilled syringes. The sponsor stated that no changes in product quality were observed over this storage period. All information has been reviewed and found to be acceptable.

(b) (4) PPQ batches of WFI diluent produced at (b) (4) were evaluated in a real time and real condition stability study to confirm the shelf-life and to demonstrate that the product consistently retains its quality characteristics throughout its claimed shelf-life or storage period of 60 months at +25°C (b) (4). The WFI diluent batches entering the stability program were filled in 1.25 mL glass syringes with a (b) (4) bromobutyl rubber plunger stopper and a (b) (4) styrene-butadiene rubber tip cap, which are identical to the container closure system components to be used during routine manufacture. The stability samples have been positioned in a horizontal position. Table 144 below provides an overview of these stability data.

Table 144: Real Time and Real Condition Stability Results - WFI Diluent FC stored up to 60 Months at +25°C ± 2°C

Tests	Acceptance criteria	Units	Batches	Time points									
				0	3	6	9	12	18	24	36	48	60
(b) (4)	(b) (4)	N/A	(b) (4)										
Water Conductivity	Not more than (b) (4)	ms/cm											
Sterility test (b) (4)	Absence of growth	N/A											
Sterility test (b) (4) C)	Absence of growth	N/A											
Bacterial Endotoxin test	(b) (4)	IU/mL											

- Indicates that the test is not planned at the time point

(b) (4) batches of WFI diluent produced at (b) (4), were evaluated in an in-use stability study. For the in-use study, (b) (4) lot of PRIORIX FC (b) (4) was reconstituted with the different lots of WFI diluent and was evaluated to confirm the recommended temperature and time period the reconstituted vaccine can be kept before administration. The WFI diluent lots and the PRIORIX FC lot entering this in-use study are provided in table 145 below with their respective manufacturing date and batch size. The diluent lots were selected at different age with the aim to cover the 60-month shelf-life upon storage of the WFI diluent in real time and real condition.

Table 145: WFI Diluent and PRIORIX vaccine Lots Used for In-Use Stability

Lot ID	Product	Manufacturing Date	Lot Size
(b) (4)	WFI diluent	(b) (4)	
	WFI diluent		
	WFI diluent		
	PRIORIX		

In addition to the WFI diluent lots produced by (b) (4) , a reference diluent corresponding to (b) (4) . filtered water for injection is evaluated for comparison. The WFI diluent entering the stability program were filled in 1.25 mL glass syringes with a (b) (4) bromobutyl rubber plunger stopper and a (b) (4) styrene-butadiene rubber tip cap which are identical to the container/closure system components to be used during routine manufacture. For in-use condition study, the PRIORIX vaccine lot was reconstituted with WFI lots and tested immediately after reconstitution and following storage of the reconstituted vaccine for 8 hours at 5°C ± 3°C. After reconstitution, vials containing reconstituted vaccine are stored in a vertical position. Table 146 below provides the in-use stability data.

Table 146: In-use Stability Results of PRIORX FC stored at 5°C ± 3°C after reconstitution with WFI Diluent from (b) (4)

Tests	Acceptance criteria	(b) (4)
Potency Measles Virus by (b) (4)	Not less than 3.4 log $CCID_{50}$ per dose[1]	
Potency Mumps Virus by (b) (4)	Not less than 4.2 log $CCID_{50}$ per dose[1]	
Potency Rubella Virus by (b) (4)	Not less than 3.3 log $CCID_{50}$ per dose[1]	

[1]The table indicates the specifications for the EoSL potency values that are being licensed in the United States. [2]Reconstituted vaccine 0h indicates testing immediately after reconstitution. [3]In-use 8h indicates reconstitution followed by storage at 5°C ± 3°C for 8 hours

The sponsor stated that the in-use stability results obtained comply with specifications and the difference observed between the potency value obtained directly after reconstitution and the one obtained after reconstitution and storage for 8h at 2-8°C is within the potency method variability (i.e., ±

(b) (4) log $CCID_{50}$). The results obtained with WFI lots from (b) (4) are comparable to the one obtained with the WFI reference.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

There is currently no ongoing real time stability study for the WFI diluent. The sponsor is committed to complete stability testing and assessment for (b) (4) WFI FC batch per year. The stability studies will be performed according to the stability plan given in table 147 below to support the storage of WFI FC at +25°C for up to 60 months.

Table 147: Commercial Stability protocol to support the storage of WFI Diluent FC at +25°C

Product	WFI diluent Final Container						
Container	The WFI diluent is filled in 1.25 mL pre-filled glass syringe (USP (b) (4) glass)						
Sample position	Horizontal						
Storage temperature	25°C (b) (4)						
Time points	Release – 12 – 24 – 36 – 48 – 60 months						
Tests and methods	please refer to: Section 3.2.P.5.2 *Overview WFI Diluent* for a description of the analytical procedures used for both Quality Release and stability testing						
Tests	**Acceptance criteria**	**Time point (months)**					
		0	**12**	**24**	**36**	**48**	**60**
Sterility test (b) (4)	Absence of growth	X	X	X	X	X	X
Sterility test (b) (4)	Absence of growth	X	X	X	X	X	X
Container closure integrity testing[2]	(b) (4)	-[1]	-[1]	-[1]	-[1]	-[1]	X

[1]Test not planned at this time point. [2]Please refer to section 3.2.P.2.4 “Container Closure System WFI Diluent”, chapter 3.3 in this BLA for the analytical method description.

Overall Reviewer’s Assessment of Section 3.2.P.8:
The information provided is acceptable. However, the comment below was submitted to the sponsor. The response provided by the sponsor in amendment 34 is considered acceptable (see below).

Agency Question:
We note that in section 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment for WFI Diluent you proposed the testing time points at release and 60 months only. We recommend you perform this testing on an annual basis. Please update your Table 1 in this section accordingly.

Company Response:
The sponsor acknowledges the CBER’s request for a testing on an annual basis for the Water For Injection (WFI) Diluent and confirms the stability testing of the WFI Diluent on an annual basis, as per the stability protocol presented in table 147 above in this memo. Section 3.2.P.8.2 “Post-Approval Stability Protocol and Stability Commitment WFI” in this BLA has been updated accordingly.

Reviewer’s Assessment:
The response is acceptable.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

We did not review this section, except for specific equipment which comes into contact with the DS and DP such as container closure systems and filtration systems.

3.2.A.2 Adventitious Agents Safety Evaluation

See section 3.2.S.2.3 in all three DSs and section 3.2.P.4 above for assessment of materials of biological origin in the DSs and in the DP, respectively. Cell substrates, cell banks, virus seeds, and raw materials used during manufacture of PRIORIX vaccine were rigorously tested, using validated methods, to provide high confidence that extraneous agents are not present in the DP.

To provide adequate assurance of viral, bacterial and fungal safety, the adventitious agents control strategy, in accordance with the (b) (4) Guideline, includes the following approaches to control the potential contamination of products:

- Sourcing appropriate materials from approved suppliers and ensuring that raw materials of human or animal origin are not a source of adventitious agent contamination that may be infectious and/or pathogenic for humans.
- Testing of the starting materials to demonstrate that no adventitious agent is detected at the seeds and cell banks level.
- Testing at appropriate stages of production to ensure that no bacterial, fungal and viral adventitious agents are detected in the DS batches and in the DP lots.

To ensure the safety of the Final Product, a safety evaluation of the raw materials, with respect to adventitious agents, has been performed. This includes information related to:

- The origin of the raw materials used during Cell Bank System development or routine manufacturing process
- Available Certificates of Analysis (COA) information.
- For animal-derived raw materials, the risk of Transmissible Spongiform Encephalopathy (TSE) contamination from the materials of ruminant origin used in the manufacture of PRIORIX (see table 148 below) is considered negligible due to the origin of the raw materials.

(b) (4)

The testing for adventitious agents is performed at appropriate stages of production from the starting materials to the final product. The sponsor stated that these testing confirmed that no viral, bacterial and fungal adventitious agents are detected at any stage of the process.

Viral Clearance Studies
There is no dedicated viral inactivation or clearance step in the PRIORIX manufacturing process as the vaccine is a live virus vaccine.

Overall Reviewer's Assessment of Section 3.2.A.2:
The information provided is acceptable.

3.2.A.3 Novel Excipients
There is no novel excipient in either PRIORIX vaccine or in the WFI diluent.

Overall Reviewer's Assessment of Section 3.2.A.3:
The information provided is acceptable. Section 3.2.A.3 does not exist in this BLA.

3.2.R Regional Information (USA)

- **Executed Batch Records**

The executed batch records for completed PPQ DS lots are presented as follows:

- Measles – (b) (4) .
- Mumps – (b) (4) .
- Rubella – (b) (4) .

The executed batch records for PPQ DP lots are presented as follows:

- PRIORIX vaccine – (b) (4) Formulation, (b) (4) Filling and Lyophilization, and (b) (4) Manual Visual Inspection batch records.
- WFI Diluent – (b) (4) Release batch records.

All submitted batch records were reviewed and found to be acceptable. The executed batch records for PRIORIX batch number (b) (4) (final bulk) and (b) (4) (final container) were also reviewed during the (b) (4) , Pre-License Inspection (PLI) of (b) (4) GlaxoSmithKline Vaccines located at (b) (4) (see the Pre-License Inspection Report for details). (b) (5)

- **Method Validation Package**

Method validation protocols and validation reports were reviewed and discussed in sections 3.2.S.4.2.and 3.2.S.4.3 **"**Analytical Procedures and Validation of Analytical Procedures for Drug Substances" and 3.2.P.5.2 and 3.2.P.5.3 for Drug Products. All submitted data were reviewed and found to be acceptable.

Overall Reviewer's Assessment of Combination Products Section:
The information provided is acceptable.

- **Comparability Protocols**

(b) (4)

Overall Reviewer's Assessment of Section on Comparability Protocols:
The information provided is acceptable. However, the comments below were submitted to the sponsor. The responses provided by the sponsor in amendments 20 and 30 are considered acceptable (see below).

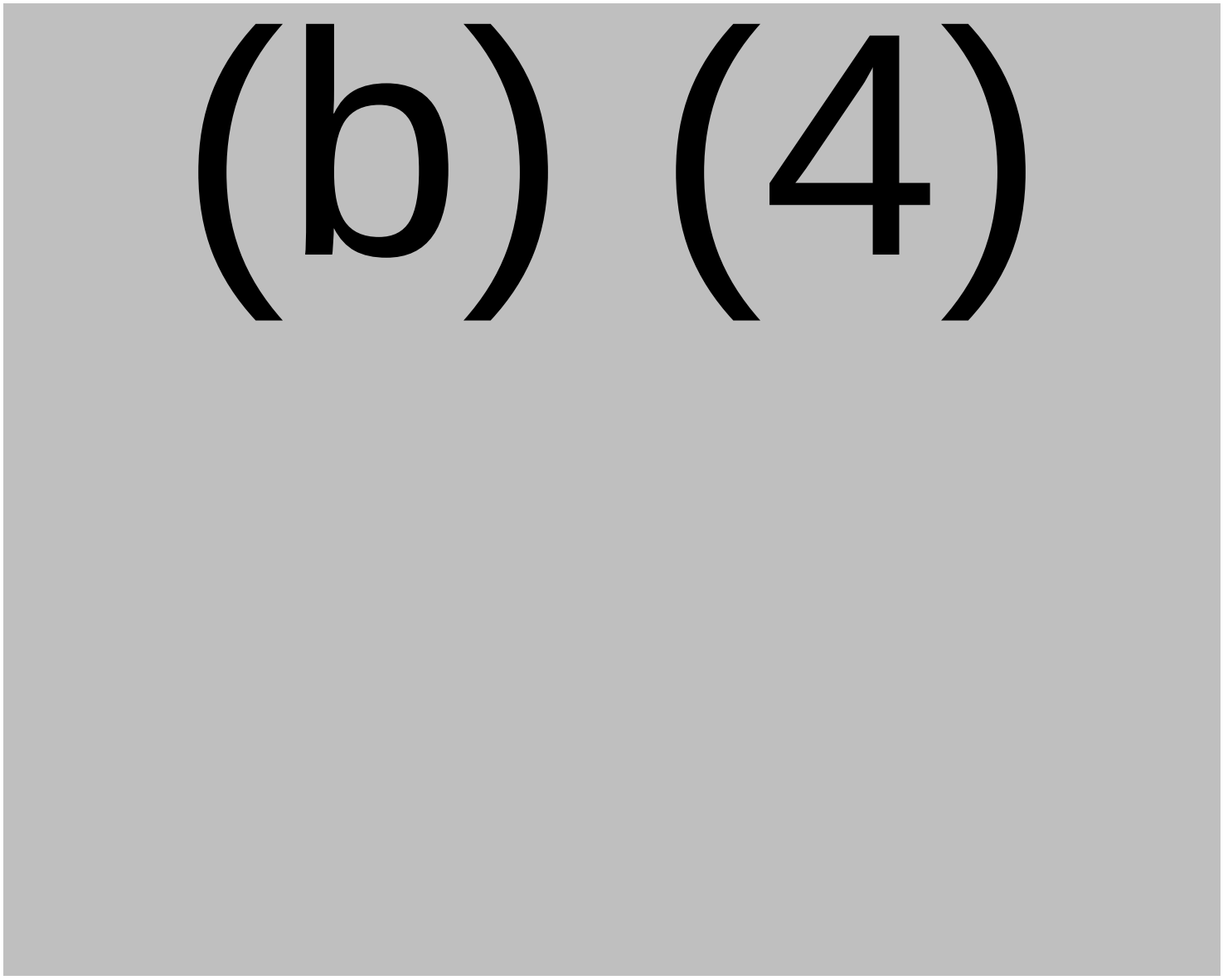
Agency Comment 1:
We note that in Section 3.2.R "Regional Information" you submitted the Comparability Protocol for qualification of (b) (4) . During the BLA review, do you plan to submit similar Comparability Protocols for qualification of (b) (4) Please clarify.

Company Response 1:
The Company acknowledges the submission of a comparability protocol for the qualification of (b) (4) only and (b) (4) neither during the BLA review (b) (4)

(b) (4)
.

Agency Comment 2:
In section 3.2.R "Regional Information, Comparability Protocol – (b) (4) you mentioned a production, qualification and reporting of (b) (4) . It is not clear if you intend to use the (b) (4) Please clarify.

Company Response 2:
The sponsor clarifies that according to details provided in the chapter 2 of section 3.2.R "Regional information, Comparability Protocol" within the BLA, the Master Seed (MS) (b) (4) is used to produce any lots of rubella Working seeds and subsequently to produce rubella monovalent bulk established at passage (b) (4) from virus isolation. This is in line with the Figure 1 of the section 3.2.S.2.3 "Master Seed History and Manufacture Ru" of BLA and is shown in the figure below.



Other eCTD Modules
Module 1

A. Environmental Assessment
The sponsor also requested a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(a). This BLA meets the requirements of a categorical exclusion under 21 CFR §25.31(a). Thus, the sponsor's request for Environmental Assessment Exclusion is acceptable.

B. Labeling Review
Full Prescribing Information (PI):

We reviewed and commented on the product-related sections of the PI listed below. Please see the approved PI for information on the following sections:

- Dosage Forms and Strengths
- Description
- Clinical Pharmacology/Mechanism of Action
- How Supplied
- Storage and Handling

Reviewer's Assessment: *The above sections of the Full Prescribing Information are acceptable.*

Modules 4 and 5

Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical Study Endpoints

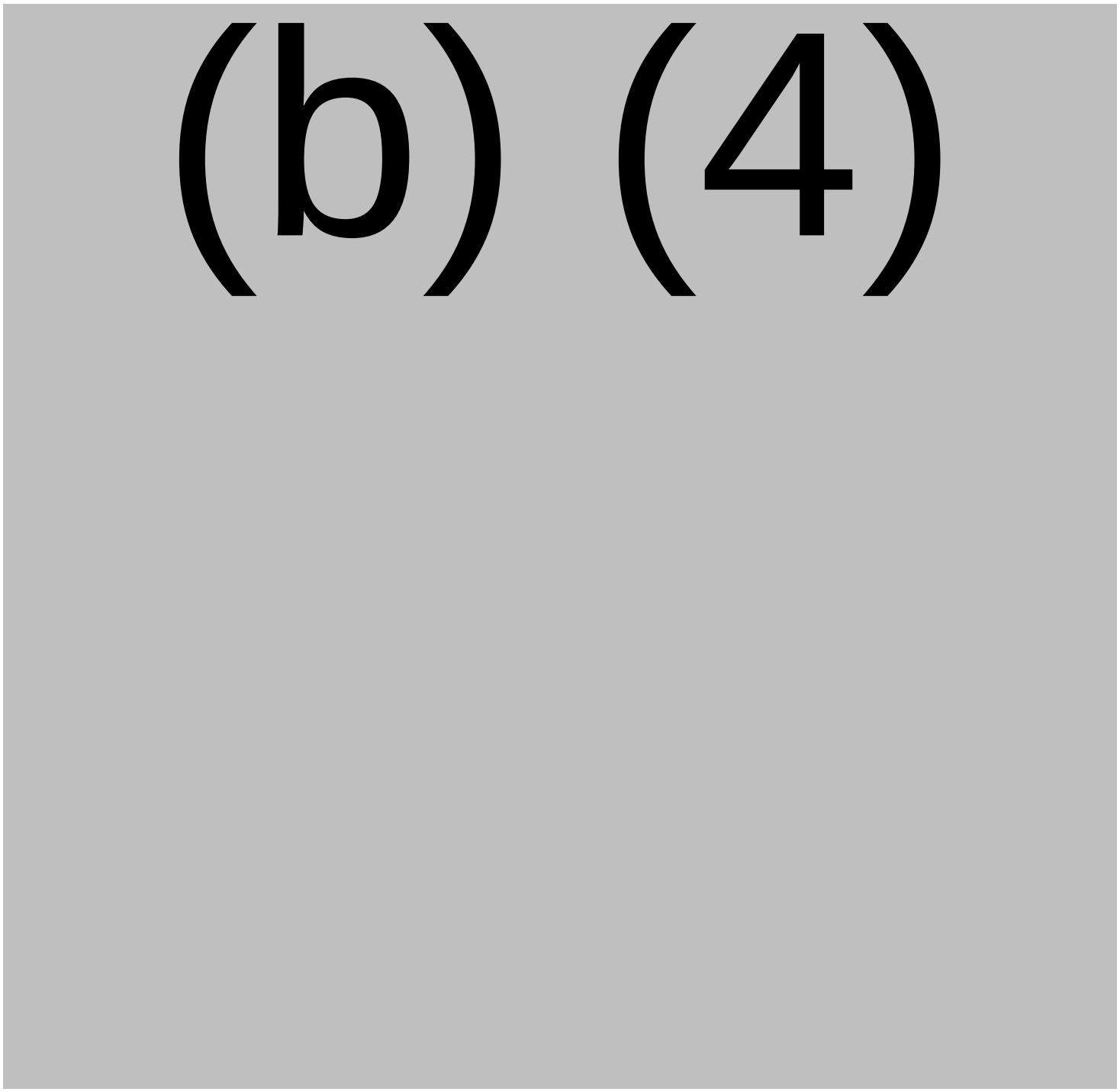
Immunological and virological assays were used to assess the vaccine clinical performance. The clinical assays that have been used in support of primary and secondary clinical immunological endpoints and/or have been used consistently throughout clinical development, are the following:

- ELISA for the qualitative detection and quantitative determination of IgG antibodies to measles virus.
- (b) (4) for detection and measurement of the neutralizing antibodies to mumps virus.
- Enhanced (b) (4) for detection and measurement of the neutralizing antibodies to mumps virus.
- ELISA for the qualitative detection and quantitative determination of IgG antibodies to mumps virus.
- ELISA for the qualitative detection and quantitative determination of IgG antibodies to rubella virus.
- (b) (4) for the qualitative detection and quantitative determination of IgG antibodies to varicella-zoster virus.
- (b) (4) for the measurement of total antibody to hepatitis A virus.
- (b) (4) for detection and measurement of the neutralizing antibodies to poliovirus type 1, 2 and 3.
- (b) (4) for the quantitation of IgG antibodies to Corynebacterium diphtheriae diphtheria toxoid.
- (b) (4) for the quantitation of IgG antibodies to Bordetella pertussis filamentous hemagglutinin.
- (b) (4) for the quantitation of IgG antibodies to Bordetella pertussis outer membrane protein pertactin.
- (b) (4) for the quantitation of IgG antibodies to Bordetella pertussis pertussis toxin.
- (b) (4) for the quantitation of IgG antibodies to Clostridium tetani tetanus toxoid.
- (b) (4) for the measurement of total IgG antibody to Streptococcus pneumoniae polysaccharides.

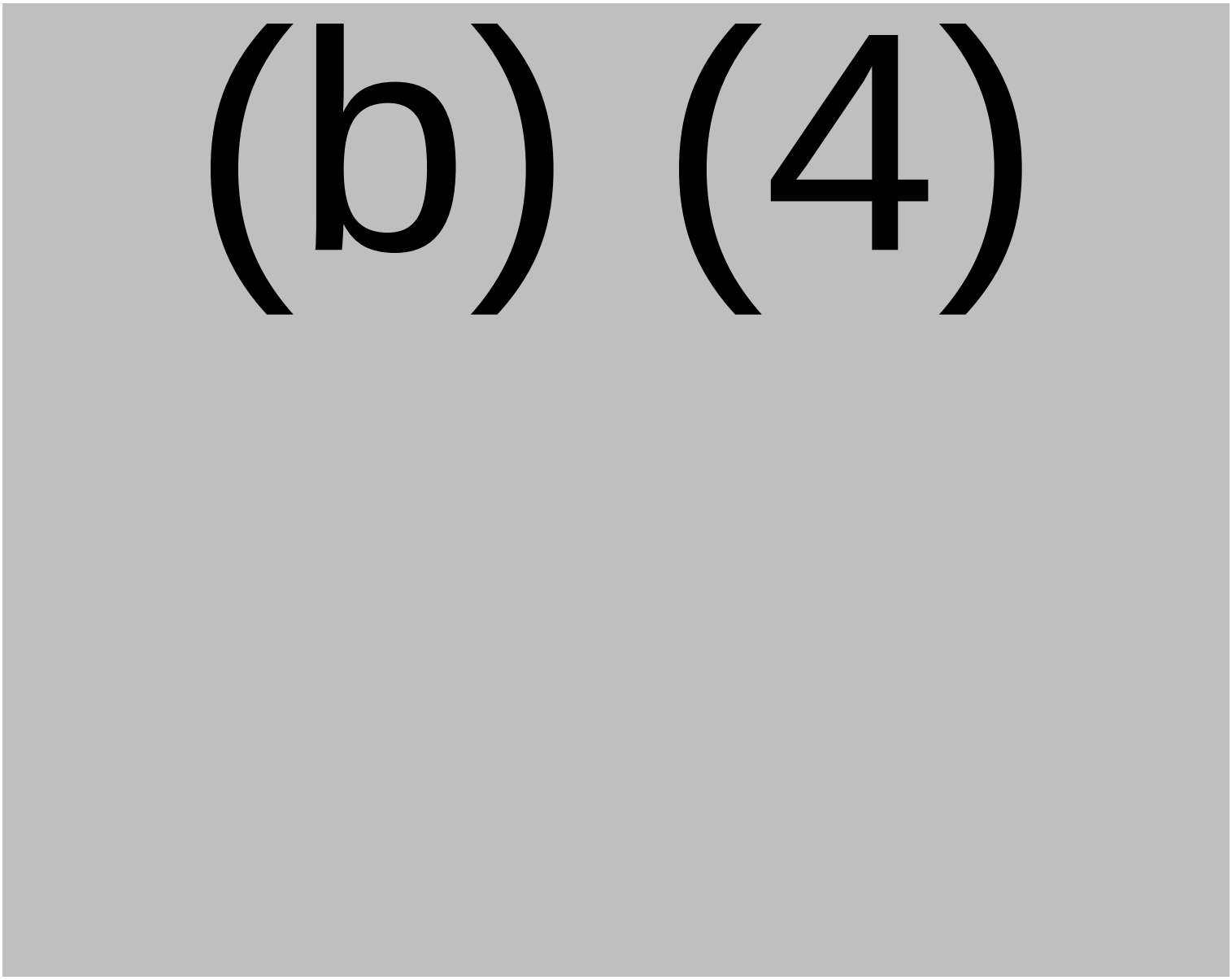
ASSAYS FOR CLINICAL IMMUNOGENICITY ENDPOINTS FOR VIRAL ANTIGENS

The PRIORIX vaccine induced humoral immune responses as measured by the anti-measles, anti-mumps and anti-rubella enzyme-linked immunosorbent assays (ELISA), have been evaluated in all Phase II and III clinical studies. The mumps induced immune response has also been measured by mumps (b) (4) in two studies (MMR-157 and MMR-161). Other

assays to evaluate humoral immune responses to the co-administrated vaccines have also been used in three studies (MMR-157, MMR-158 and MMR-160). All assays were validated and the full validation reports and standard operating procedures (SOPs) for these assays are provided in Module 5.3.1.4 in this BLA. Table 149 below presents the validation documents and SOPs for the clinical immunogenicity assays submitted in this BLA.



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



The SOPs and their validations were reviewed and found to be adequate. The parameters and validity criteria selected for the validation studies are adequate and were also reviewed by the statistician for the clinical assays assigned on this BLA. The following is a summary of the protocols mentioned in table 149 above.

ASSAYS FOR PRIMARY CLINICAL IMMUNOGENICITY ENDPOINTS

Measles IgG Enzyme Linked Immunosorbent Assay (ELISA)

ELISA assays developed by (b) (4) (SOP 9000005555 version 01) and (b) (4) (SOPs 9000005555 versions 02 and 03) companies were used in clinical study MMR-157 (Phase II), and the ELISA developed by (b) (4) (SOP 9000005555 version 04) was used in clinical studies MMR-158,

MMR-159, MMR-160, MMR-161 and MMR-162 (Phase III). These SOPs were successfully validated and previously reviewed and agreed under IND 7229.

Purpose: The ELISA was used for the qualitative detection and quantitative determination of IgG antibodies to measles virus in human serum.

Principle: Measles specific IgG antibodies contained in the (b) (4)

(b) (4)

(b) (4)

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

Reviewer's Assessment: *The parameters and validity criteria selected for the validation studies are adequate and were reviewed by the statistician for the clinical assays assigned on this BLA. The measles ELISA assay is suitable for its intended use.*

Mumps Enhanced (b) (4)

Enhanced (b) (4) assay developed by the sponsor (SOP 9000005552 version 06) was used in clinical study MMR-157 (Phase II), The SOP was successfully validated and previously reviewed and agreed under IND 7229. The enhanced (b) (4) assay used by GSK until 2011.

Purpose: Mumps enhanced (b) (4) assay was used to detect and measure the neutralizing antibodies to mumps virus in the human sera. The assay has been developed using the mumps wild type virus, strain (b) (4) (received from the NIBSC). The assay utilized guinea pig complement (GPC) and anti-human IgG antibody for the potentiation of the virus-antibody neutralization reaction.

Principle: (b) (4)

The mumps enhanced (b) (4) was validated for the assessment of antibody responses in clinical study MMR-157 (Phase II). The following parameters were assessed using positive control and incurred samples: prozone effect, LOD, LLOQ, technical cut-off, analytical range, precision (CV repeatability, CV reproducibility, CV total, duplicate to single determination – CV total), specificity and interferences (for details, see document "MUPRNPCV04" in section 5.3.1.4 in this BLA). Table 152 below provides the executive summary of the validation data corresponding to the validation reports for the mumps enhanced (b) (4). All parameters met their acceptance criteria.

(b) (4)

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

(b) (4)

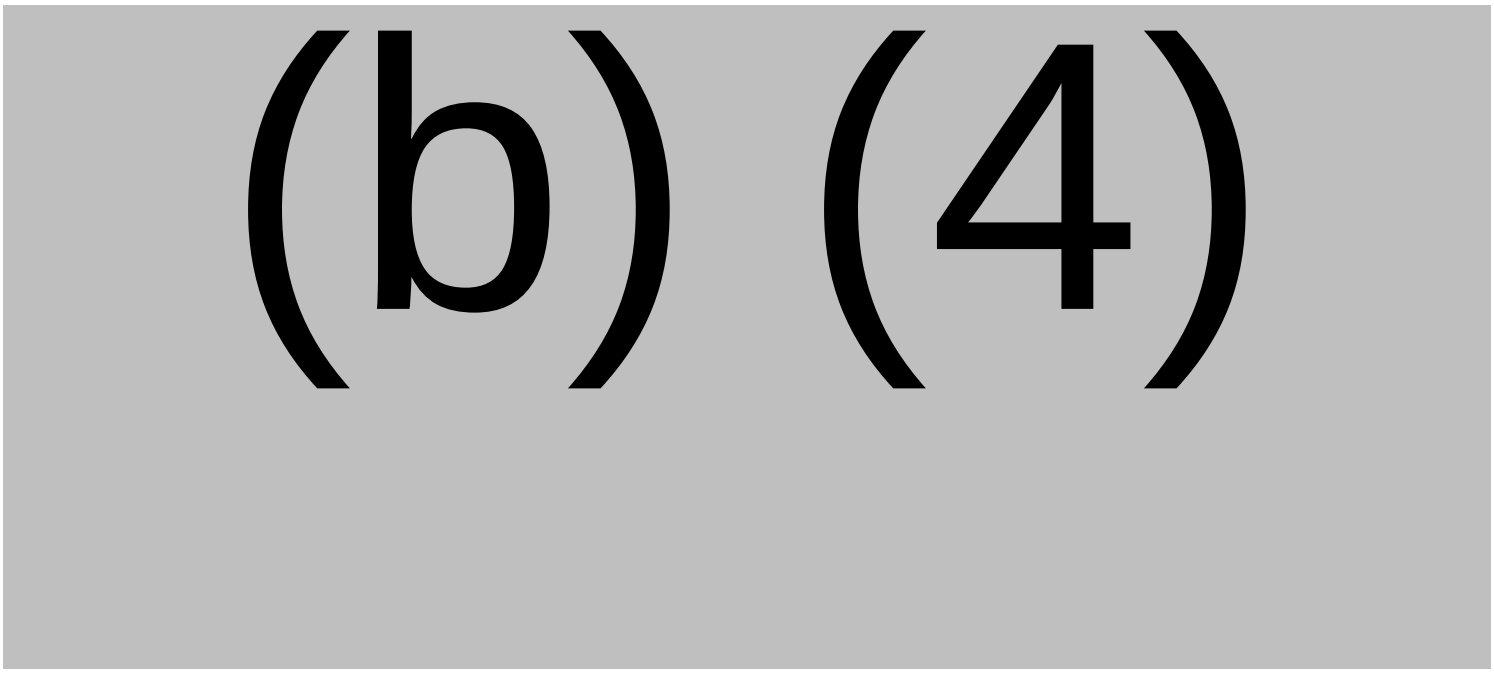
The GSK enhanced (b) (4) assay data were compared with results generated by ELISA and (b) (4) assays used in the (b) (4) The sponsor stated that its enhanced (b) (4) assay displayed a good agreement (88.8%) with the (b) (4) results.

Reviewer's Assessment: *The parameters and validity criteria selected for the validation study are adequate and were reviewed by the statistician for the clinical assays assigned on this BLA. The enhanced* (b) (4) *assay is suitable for its intended use.*

Mumps (b) (4)
(b) (4)

(b) (4)

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



Reviewer's Assessment: *The parameters and validity criteria selected for the validation study are adequate and were reviewed by the statistician for the clinical assays assigned on this BLA. The enhanced* (b) (4) *assay is suitable for its intended use.*

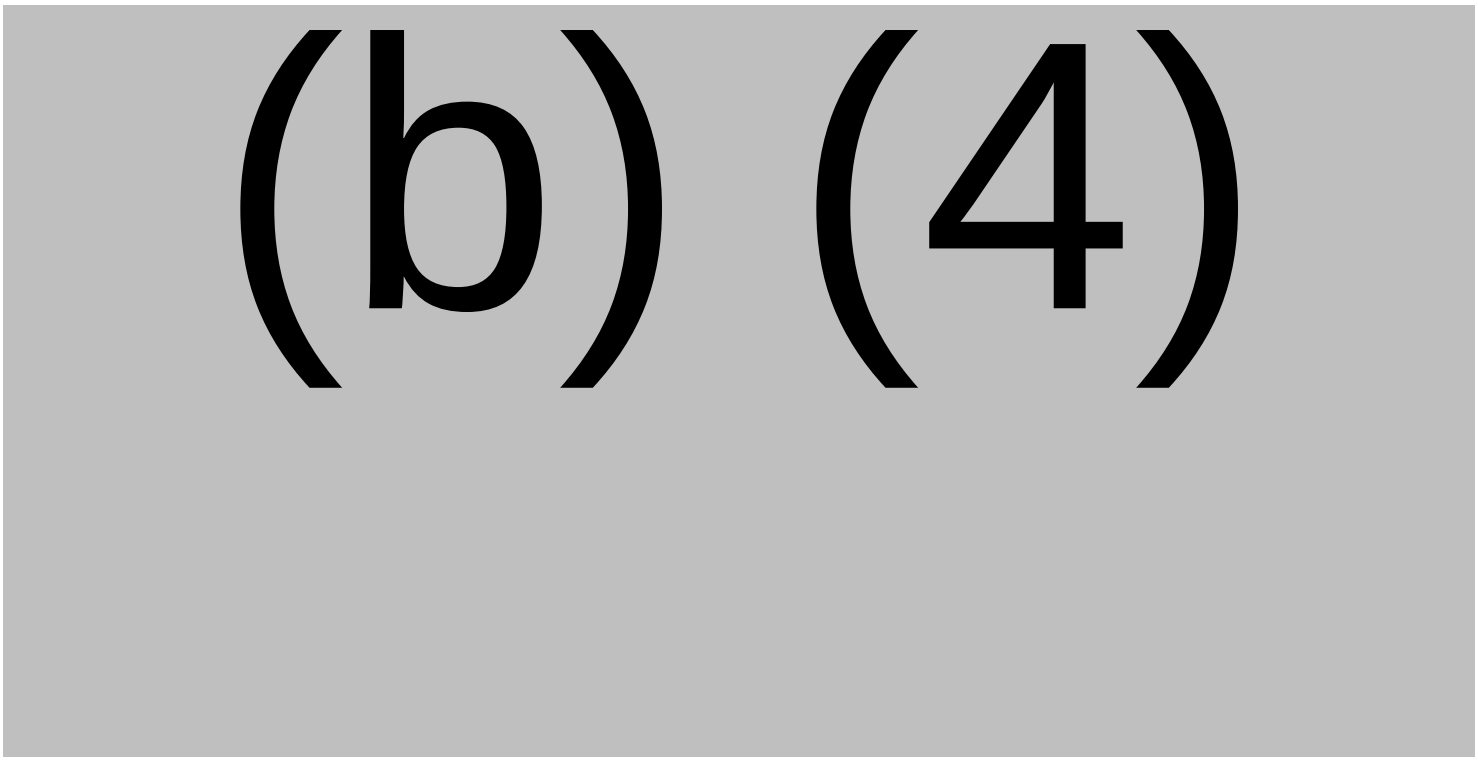
Mumps Wild Type (WT) IgG ELISA

The mumps WT IgG ELISA assays developed by (b) (4) were used in clinical study MMR-157 (SOP VBL.3633_5.0) and in the clinical studies MMR-158, MMR-159, MMR-160, MMR-161 and MMR-162 (SOP VBL.3633_7.0). These assays were successfully validated and previously reviewed and agreed under IND 7229.

Purpose: The mumps WT IgG ELISA was used for the qualitative detection and quantitative determination of IgG antibodies to mumps virus in human serum or plasma.

(b) (4)

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



Reviewer's Assessment: *The parameters and validity criteria selected for the validation studies are adequate and were reviewed by the statistician for the clinical assays assigned on this BLA. The mumps WT IgG ELISA assay is suitable for its intended use.*

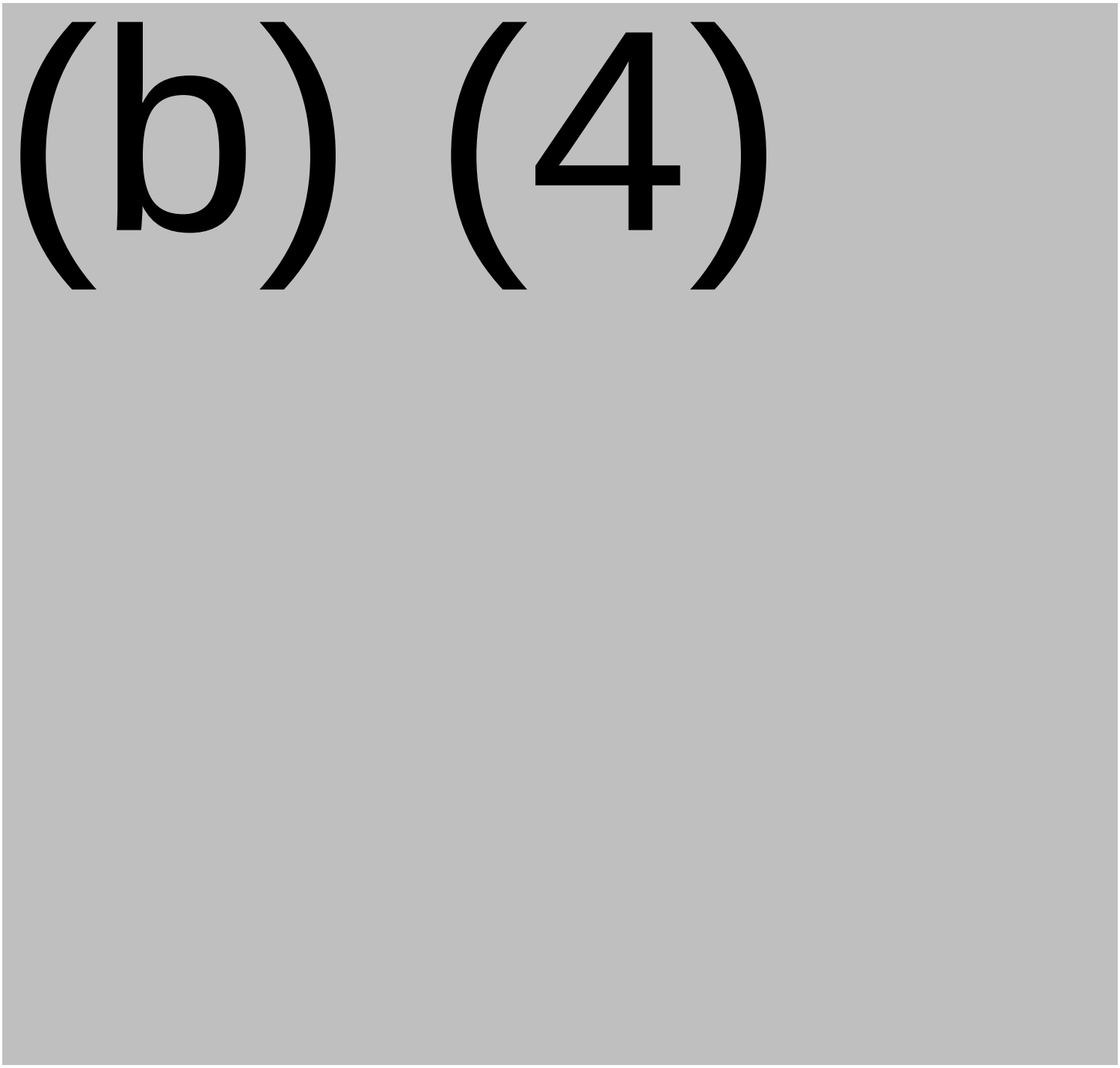
Rubella IgG ELISA

ELISA assays developed by (b) (4) (SOP 9000005553 version 01) and (b) (4) (SOPs 9000005553 version 02) were used in clinical study MMR-157, and the ELISA developed by (b) (4) (SOP 9000005553 version 04) was used in clinical studies MMR-158, MMR-159, MMR-160, MMR-161 and MMR-162. These SOPs were successfully validated and previously reviewed and agreed under IND 7229.

Purpose: The ELISA was used for the qualitative detection and quantitative determination of IgG antibodies to rubella virus in human serum.

Principle: Rubella specific IgG antibodies (b) (4)

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



Reviewer's Assessment: *The parameters and validity criteria selected for the validation studies are adequate and were reviewed by the statistician for the clinical assays assigned on this BLA. The rubella IgG ELISA assay is suitable for its intended use.*

ASSAYS FOR SECONDARY CLINICAL IMMUNOGENICITY ENDPOINTS

The following vaccines were co-administered in the Phases II and III clinical studies:

- In MMR-157 Phase II clinical study (randomized, observer blind, controlled, multicenter), the sponsor assessed the immunogenicity and antibody persistence following vaccination with PRIORIX vaccine versus MMR-II vaccine (Merck & Co., Inc.) as a first dose, both administered subcutaneously at 12-15 months of age, and concomitantly with Havrix (hepatitis A vaccine (HAV)), Varivax (varicella vaccine (VV)) and Prevnar 13 (pneumococcal conjugate vaccine (PCV)) but at separate injection sites.
- In MMR-158 Phase III clinical study (observer-blind, randomized), the sponsor evaluated non-inferiority of a second dose of PRIORIX vaccine versus a second dose of MMR-II vaccine when administered with and without the diphtheria, tetanus, acellular pertussis and inactivated polio (DTaP-IPV) vaccine and the varicella vaccine (Varivax) to healthy children four to six years of age.
- In MMR-160 Phase III clinical study (randomized, observer-blind, controlled, multinational), the sponsor evaluated the immunogenicity and safety of PRIORIX vaccine compared to MMR-II vaccine as a first dose, both co-administered with Varivax, Havrix and Prevnar 13 (subset of children) to healthy children 12 to 15 months of age.
- In MMR-161 Phase III clinical study (randomized, observer-blind, controlled, multinational), the sponsor evaluated the immunogenicity and safety of PRIORIX vaccine at an end of shelf-life potency compared to MMR-II, when both are co-administered with Varivax, Havrix and Prevnar 13 (subset of children), and given on a two-dose schedule to healthy children in their second year of life.
- In MMR-162 Phase III clinical study (randomized, observer-blind, controlled, multinational), the sponsor evaluated the immunogenicity of PRIORIX vaccine compared to MMR-II, as a first dose, both co-administered with Varivax, Havrix (all subjects) and Prevnar 13 (US subset) in healthy children 12 to 15 months of age.

All secondary immunogenicity objectives were evaluated using the assays described below.

Varicella Zoster Virus (VZV) IgG (b) (4)

The (b) (4) assays developed by (b) (4) (SOP 9000005570 version 01) was used in clinical study MMR-157, and the (b) (4) developed by (b) (4) (SOP 9000005570 version 02 and version 06) were used in clinical study MMR-157, MMR-158 and MMR-160. These assays were successfully validated and previously reviewed and agreed under IND 7229.

Purpose: The (b) (4) was used for the qualitative detection and quantitative determination of IgG antibodies to VZV in human serum.

(b) (4)

(b) (4)

Reviewer's Assessment: *The parameters and validity criteria of the assay are adequate. The VZV IgG* (b) (4) *assay is suitable for its intended use.*

Hepatitis A (HAV) total antibody (b) (4)

The (b) (4) assays developed by (b) (4) (SOP 9000005542 version 02) was used in clinical study MMR-157, and the (b) (4) developed by (b) (4) (SOP 9000005542 version 03 and version 04) were used in clinical study MMR-157 and MMR-160. These SOPs were successfully validated and previously reviewed and agreed under IND 7229.

Purpose: The HAV (b) (4) was used for the quantitative measurement of total antibodies against HAV in human serum.

(b) (4)

(b) (4)

Reviewer's Assessment: *The parameters and validity criteria of the assay are adequate. The HAV IgG* (b) (4) *assay is suitable for its intended use.*

Poliovirus (b) (4)

The poliovirus (b) (4) assays for serotypes 1, 2 and 3 was developed by the sponsor to assess the antibody responses to these three polio serotypes. The (b) (4) assay SOP 9000005576 version 06 was used in clinical study MMR-158. This SOP was successfully validated and previously reviewed and agreed under IND 7229.

Purpose: The poliovirus (b) (4) assay used to the quantitative measurement of neutralizing antibodies to polio types 1, 2 and 3 viruses in the human sera.

(b) (4)

Reviewer's Assessment: *The parameters and validity criteria of the assay are adequate. The Poliovirus* (b) (4) *assay is suitable for its intended use.*

Diphtheria (DI) and Tetanus (TE) (b) (4)

The Diphtheria, Tetanus, and acellular Pertussis serological assays were used to evaluate potential interference with concomitantly administered licensed vaccines recommended in the adolescent population in the Phase 3 study MMR-158. The (b) (4) assays used to the quantitative measurement of IgG antibodies to DI and TE in the human sera.

(b) (4)

The DI and TE (b) (4) were previously reviewed under the sponsor's IND 7229 and IND 8461.203 for BOOSTRIX. All parameters met their acceptance criteria.

Reviewer's Assessment: *The parameters and validity criteria of the assay are adequate. The DI and TE* (b) (4) *assays are suitable for their intended use.*

Acellular Pertussis (PT, FHA, and PRN) (b) (4)

The (b) (4) assays used to the quantitative measurement of IgG antibodies to PT, FHA, and PRN in the human sera.

Principle: The principle and procedure for the PT, FHA, and PRN (b) (4) are similar. Briefly, antigen (PT, FHA, or PRN) is used (b) (4)

Review of the acellular Pertussis (b) (4) for assessing antibody concentrations and booster responses were previously reviewed under IND 8461.203 for BOOSTRIX. All parameters met their acceptance criteria. Information was requested from GSK on February 16, 2022, regarding the performance of the DI, TE, PT, PRN, and FHA serological assays from the time of validation through their use for testing of samples for the clinical study MMR-158. GSK provided assay stability data for DI, TE, PT, PRN, and FHA (b) (4) under STN 125748/0.21. GSK notes that assay stability is routinely monitored using Quality Control (QC) samples for which pre-defined acceptance ranges were previously determined. The data support the stability of the assays during their use in MMR-158.

Reviewer's Assessment: *The parameters and validity criteria of the assay are adequate. The acellular pertussis (PT, FHA, and PRN)* (b) (4) *assays are suitable for their intended use.*

(b) (4)

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Pneumococcal (b) (4)
(b) (4)

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In an IR sent on 4 November 2021, the sponsor was asked whether the SOP and the validation information for the pneumococcal (b) (4) was submitted for CBER review in a previous IND. In their response dated 23 November 2021 (STN 125748/14), the applicant indicated that the SOP and validation reports were previously submitted to IND 14151. The sponsor also submitted the SOP and the validation report to STN 125748/14. The assay was previously reviewed under IND 14151. The assay was adequately validated for its intended use and the assay performance was stable between 2006 and 2013.

Reviewer's Assessment: *The parameters and validity criteria of the assay are adequate. The pneumococcal* (b) (4) *assay is suitable for its intended use.*

Overall Reviewer's Assessment of Relevant Sections of Module 5 (clinical assays):
The information provided is acceptable. The parameters and validity criteria selected for the validation studies are adequate and were reviewed by the statistician for the clinical assays assigned on this BLA. Validation results assure that methods used are suitable for their intended purpose. However, the comments below were submitted to the sponsor. The responses provided by the sponsor in amendment 32 are considered acceptable (see below).

Agency comment 1:
We note that in section 5.3.1.4 "Summary of Clinical Assay Validation Documents and SOPs" in table 1, for some of the viral assays used in clinical studies, you listed more than one SOP version (or their appendices) and/or validation documents. Please clarify.

a. Please provide a table reflecting the exact SOP(s) and the corresponding validation report(s) used for each clinical study, as well as the effective dates for these SOP(s) and validation report(s).
b. Please note that for the mumps ELISA, the validation report (Validation of Mumps "Wild Type" IgG ELISA (SOP No.910-0096)) does not match the SOPs VBL.3633_7.0 or VBL.3633_5.0, which are indicated in the table.
c. We note that none of the validation reports refer to the specific SOP for what validation data they represent. Please revise your table accordingly or present this data in a separate table.

Company response 1:
1a) In the initial Priorix BLA submission (STN # 125748, seq0001), Table 1 of the Summary of Clinical Assay Validation Document and SOPs located in m5.3.1.4, listed all SOPs and validation documents that were effective during the testing period of each clinical study. As clinical testing might have lasted for several months, changes to the initial versions have occurred for these documents. Table 2 and Table 3 of the Summary of Clinical Assay Validation Document and SOPs provided a summary of the changes between the different versions of SOPs and validation reports. Please note that while reviewing the Summary of Clinical Assay Validation Document and SOPs, some inconsistencies and discrepancies were identified for some of the listed documents in Table 1 and Table 3. Table 1 and Table 3 were therefore corrected (for the updated list of validation document and SOPs see table 149 in section "Modules 4 and 5" in this memo above), and the amended Summary of Clinical Assay Validation Document and SOPs is included in m5.3.1.4 of this submission to replace the initial version. To indicate to CBER the corrections made in this document, the amended version is also included with revisions indicated in track change in m1.11.3 of this submission. Consequently, the Measles ELISA SOP 9000005555 version 03 and the Mumps ELISA SOP VBL.3633_5.0 (from (b) (4) , should be deleted from the initial submission. As GSK is not the owner of the Mumps ELISA (b) (4) SOP VBL.3633_6.0 now to be added, GSK has asked the current assay owner to submit this SOP through their master file. In addition, the SOP Mumps PRNT SOPs 9000024353 V6 and 9000024353 V7 have now been added.

1b) GSK acknowledges that for study MMR-157, SOP VBL.3633_5.0 is erroneously listed, whereas SOP VBL.3633_6.0 is used for mumps ELISA testing in this study. This is now corrected in Table 1 and Table 3 of the amended Summary of Clinical Assay Validation Document and SOPs. Therefore, SOP VBL.3633_5.0 is deleted from the Priorix BLA. For clarification on SOP VBL.3633_6.0, see response to Question 15a. Furthermore, GSK confirms that the SOPs VBL.3633_6.0 and VBL.3633_7.0 are correctly linked to the validation report entitled: Validation of Mumps "Wild Type" IgG ELISA (SOP No.910-0096)". This can be clarified as follows: the SOP number in the title of the validation document (SOP No.910-0096) refers to the former procedure in use by the third-party laboratories that have developed the assay. The SOP number changed to VBL.3633 when (b) (4) became the owner of the assay. As no changes were made to the validation report from the validation period until the end of clinical testing, the title of the document remained unchanged. Please note that SOP VBL.3633_6.0 is a proprietary document of the assay owner and is identical to the SOP VBL.3633_7.0 already submitted in the initial Priorix BLA; the main difference between both versions being the qualification of a new antigen lot (as indicated in Table 3 of the Summary of Clinical Assay Validation Document and SOPs in m5.3.1.4).

1c) GSK confirms that Table 1 is correct and links the validation documents with their respective SOPs. The effective date indicated for each document in the new Table 1 submitted in the amended Summary of Clinical Assay Validation Document and SOPs, allows to identify the corresponding document in use during a specific period.

Reviewer's Assessment:
The response is acceptable.

Agency comment 2:
In Section 5.3.1.4, please submit the following missing assay validation information:

a. For validation of the measles ELISA, mumps enhanced (b) (4), mumps WT IgG ELISA and rubella ELISA, please provide the final validation data (for the assays used for analysis of clinical samples submitted under BLA) for each assay in a tabular format reflecting the samples used (number of samples, from which study and time point), assay validation parameters, summary of procedures, acceptance criteria used, and the final validation results. Please include information on the controls used during validation. Tables with the final validation data are not presented in any of the named validation reports.
b. We note that in section 5.3.1.4, in the mumps (b) (4) validation report "MUMPS90/LO1_MN_MVR_02", the following information was missing in the table "Executive summary": no data was presented in the Results cell for the monoplicate vs duplicate parameter; no data was presented in the Design cells for the cut-off, replicate zone, analytical range and specificity parameters; and no data was presented in the Criteria cell for the cut-off parameter. Please edit your table accordingly and re-submit an updated table.

Company response 2:
2a) As requested by CBER, the tables 1-6 of amendment 32 present executive summaries of the validation data for each assay referred to in Question 2a. above. These tables include information regarding the samples used and the quality controls, the validation parameters tested, the procedure and acceptance criteria as well as validation results. These tables presented in section "Modules 4 and 5" of this memo as follows:

- Table 150 and Table 151 provide the executive summary of the validation data corresponding to the validation reports for Measles ELISA version 1 and version 2, respectively.
- Table 152 provides the executive summary of the validation data corresponding to the validation reports for the Mumps enhanced (b) (4);
- Table 154 provides the executive summary of the validation data corresponding to the validation reports for the Mumps WT IgG ELISA (completed by (b) (4) as former assay owner during the testing period in MMR US CDP studies), and
- Table 155 and Table 156 provide the executive summary of the validation data corresponding to the validation reports for the Rubella ELISA version 1 and version 2, respectively.

2b) The table "Executive summary" in the mumps (b) (4) validation report "MUMPS90/LO1_MN_MVR_02" has been updated with the requested information as presented in Table 153 of this memo above.

Reviewer's Assessment:
The response is acceptable.

Agency comment 3:
In Section 5.3.1.4 "Reports of Bioanalytical and Analytical Methods for Human Studies" you submitted SOPs for measles ELISA assays developed by (b) (4) (SOP 9000005555 version 01) and (b) (4) (SOPs 9000005555 versions 02, 03, 04). The submitted validation documents "(b) (4) and (b) (4) provide the validation

data related to the use of the (b) (4) kit purchased from (b) (4). The validation documents for the (b) (4) measles ELISA assays are not provided in the BLA. Please submit validation documents for the (b) (4) measles ELISA assays used in clinical studies MMR-158, MMR-159, MMR-160, MMR-161 and MMR-162.

Company response 3:
GSK would like to clarify that the (b) (4) Measles ELISA from (b) (4) and the (b) (4) Measles ELISA correspond to the same test. Indeed, (b) (4) first developed the commercial Measles ELISA ((b) (4) acquired (b) (4) and thereby became owner of this Measles ELISA test (b) (4)

Reviewer's Assessment:
The response is acceptable.

Agency comment 4:
We note that in the validation reports (b) (4) and (b) (4) you demonstrated the specificity by competition with a homologous measles antigen but did not demonstrate the specificity by competition with heterologous antigens. Please comment.

Company response 4:
GSK acknowledges that in the above-mentioned validation reports, the specificity of Measles and Rubella ELISAs were only assessed by competition with a homologous antigen. Although heterologous specificity is part of the current GSK requirements for assay development, the heterologous competition analysis was not routinely performed at the time of validation of the Measles and Rubella (b) (4) ELISAs (during 2007– 2008). Please note that the Measles and Rubella (b) (4) ELISAs are no longer commercially available and therefore, additional specificity experiments cannot be conducted. Both Measles and Rubella ELISA assays' validation were considered as acceptable by CBER at the Type C Meeting, held in April 2012 and further follow-up communication (in amendment 32, see paragraphs 1.3, 1.4.1 and 1.4.2 of section m2.7.1 "Summary of Biopharmaceutic Studies and Associated Analytical Methods").

Reviewer's Assessment:
The above-mentioned validation reports were previously reviewed by CBER in 2012. The specificity by competition with heterologous antigens for measles and rubella has not been demonstrated, which is a limitation of the methods. The response is acceptable.

Agency comment 5:
Please provide the list of abbreviations used in your validation report "Validation of Mumps "Wild Type" IgG ELISA (SOP No.910-0096)".

Company response 5:
GSK provides below the list of abbreviations used in the validation report together with their corresponding definitions.

Abbreviation	Definition
OD	Optical density
DOD	Delta optical density
DF	Dilution factor
% RSD	% Relative standard deviation
CI	Confidence interval
Mab	Monoclonal antibody
TCC	Tissue culture control
LS Mean	Least-Square mean
LN	Natural log

Reviewer's Assessment:
The response is acceptable.

Agency comment 6:
We note that in section 5.3.1.4, for the mumps WT IgG ELISA, some validated assay characteristics (e.g., extravariability, standard curve modeling, assay ruggedness to operator, control samples and dilutability) are different when compared to the measles and rubella ELISAs. Please comment.

Company response 6:
The main reason behind the differences in some validated assay characteristics between Measles and Rubella ELISAs (performed at GSK) on one hand, and the Mumps WT IgG ELISA (performed at (b) (4) on the other hand is that Measles and Rubella ELISAs were commercially available assays (see response to Question 3 above) for which GSK has performed additional characterization to ensure that the assays were fit for purpose before proceeding to testing of clinical samples. However, the Mumps WT IgG ELISA available at (b) (4) is an assay which was fully developed by a third-party based on their own internal requirements and specifications. GSK has therefore not performed any additional assay characterization for the Mumps WT IgG ELISA. The documents (validation report and SOPs) related to the Mumps WT IgG ELISA were submitted to CBER in the context of the Priorix BLA and the assay characteristics were addressed and considered as acceptable by CBER in previous consultations (in amendment 32, see paragraphs 1.3 and 1.4.3 of section m2.7.1 "Summary of Biopharmaceutic Studies and Associated Analytical Methods").

Reviewer's Assessment:
The response is acceptable.

Agency comment 7:
In Section 5.3.1.4 "Reports of Bioanalytical and Analytical Methods for Human Studies" you submitted SOPs for rubella ELISA assays developed by (b) (4) (SOP 9000005553 version 01) and (b) (4) (SOPs 9000005553 versions 02, and 04). The validation documents (b) (4) and (b) (4) provide the validation data related to the use of the (b) (4) kit purchased from (b) (4). The validation documents for the (b) (4) rubella ELISA assays are not provided in the BLA. Please submit validation documents for the (b) (4) rubella ELISA assays used in clinical studies MMR-158, MMR-159, MMR-160, MMR-161 and MMR-162.

Company response 7:
As in the response to Question 3 above, GSK would like to clarify that the (b) (4) Rubella ELISA from (b) (4) and the (b) (4) Rubella ELISA correspond to the same test. Indeed, (b) (4) first developed the commercial Rubella ELISA (b) (4) and thereby became owner of the Rubella ELISA test (b) (4)

Reviewer's Assessment:
The response is acceptable.

Agency comment 8:
In Section 5.3.1.4 "Summary of Clinical Assay Validation Documents and SOPs" in table 1 you provided information about SOPs and validation reports for the Varicella Zoster Virus (VZV) IgG ELISA assay used in the MMR-157, MMR-158, and MMR-160 clinical studies. However, in Section 5.3.5.1 in the reports for MMR-161 and MMR-162 studies you also mentioned the co-administration of the Varivax vaccine. Please provide information on the SOPs and validation reports for the qualitative detection and quantitative determination of anti-VZV IgG antibodies in individuals vaccinated with Varivax in MMR-161 and MMR-162 studies if different from those previously submitted. Please update information to include all clinical studies where this assay was used.

Company response 8:
GSK would like to clarify that in the Phase 2 study MMR-157 and the Phase 3 studies MMR-160, MMR-161 and MMR-162, all subjects aged 12-15 months of age received one of the 2 MMR vaccines co-administered with Hepatitis A vaccine (Havrix), Varicella vaccine (Varivax) and pneumococcal conjugate vaccine (PCV 7, Prevnar in the study MMR-157 and PCV 13, Prevnar 13 in the Phase 3 studies) according to the routine vaccination schedule in this age group in US. However, the immunogenicity of these co-administered vaccines, including Varivax and Havrix, was only evaluated in the Phase 2 study MMR-157 and the Phase 3 study MMR-160. Therefore, no serology testing for co-administered vaccines was performed in the studies MMR-161 and MMR-162.

Reviewer's Assessment:
The response is acceptable.

Agency comment 9:
In Section 5.3.1.4 "Summary of Clinical Assay Validation Documents and SOPs" in table 1 you provided information about SOPs and validation reports for the hepatitis A (HAV) (b) (4) assay used in the MMR-157 and MMR-160 clinical studies. However, in Section 5.3.5.1 in the reports for MMR-160, MMR-161 and MMR-162 studies, you also mentioned the co-administration of the Havrix vaccine. Please provide information on the SOPs and validation reports for the quantitative measurement of total antibodies against HAV in individuals vaccinated with Havrix in MMR-160, MMR-161 and MMR-162 studies if different from those previously submitted. Please update information to include all clinical studies where this assay was used.

Company response 9:

GSK refers to the response to Question 8.

Reviewer's Assessment:
The response is acceptable.

Agency comment 10:
In Section 5.3.1.4 of the validation report "MUPRNPCV04" for the mumps enhanced (b) (4) you mentioned that the assay data were compared with results generated by (b) (4) and (b) (4) assays used in the (b) (4) . Please specify the date when this comparison was performed and a reason for comparison of your validated assay to the (b) (4) assays.

Company response 10:
As there is no assay considered the "gold standard" in the mumps serology field, GSK's enhanced (b) (4) was descriptively compared with the (b) (4) used at the (b) (4) , to benchmark the sensitivity of GSK's enhanced Mumps (b) (4) used in study MMR-157 of the MMR US CDP [Gans, 2001]. The exploratory comparison of GSK's enhanced (b) (4) with (b) (4) was completed before August 2003.

Reviewer's Assessment:
The response is acceptable.

Agency comment 11:
Please provide any available data demonstrating assay performance over time for the measles (ELISA), mumps (ELISA, (b) (4) rubella (ELISA), varicella-zoster (b) (4), hepatitis A (b) (4) and poliovirus (b) (4) serological assays used in the clinical studies described in this BLA submission.

Company response 11:
As requested by CBER, the quality control (QC) charts for the positive QC samples used for the measles (ELISA), mumps (ELISA, (b) (4)), rubella (ELISA), varicellazoster (b) (4), hepatitis A (b) (4) and poliovirus (b) (4) serological assays are provided in amendment 33 to this BLA. According to the GSK assay stability monitoring process, the performance of the assays over time is routinely monitored using QC samples for which a pre-defined acceptance range (also named "control limits" corresponding to upper and lower limits of the acceptance range) was determined. The QC samples are included in each assay run and their value, when falling in the pre-defined acceptance range, validates the data of the run. For some clinical studies, sample testing has been carried out by third-party laboratories. Although the QC charts provided by external partners have different format than those built at GSK Biologicals laboratories (GSK), both include the same information. These charts illustrate the performance stability over time of the different assays from their validation until the end of sample testing in the MMR US CDP studies part of the Priorix BLA (STN 125748). Note that for the mumps ELISA, the QC charts are not provided in this response as detailed in paragraph 2) of amendment 33: QC charts for the mumps "wild type" IgG ELISA.

Reviewer's Assessment:

The assay performance information provided in amendment 33 was reviewed and found to be acceptable.

PHARMACOLOGY STUDIES (SECTION 4.2.1)

Immunogenicity and Efficacy (Challenge) Studies

Many aspects of the preclinical evaluation of these vaccine viruses have been studied in academic and industry laboratories in a variety of animal models. Data from these studies have been published over an extended period of time from 1965-2000 (for the published references, see section 4.2.1.1 in the BLA). Despite the development of several animal models for the individual vaccine components, no common non-human host has been identified for the evaluation of the MMR vaccine. Table 157 below provides the list of the animal species sensitive to each virus. While not all animal species listed are relevant in terms of disease, they may support replication of the viruses and be suitable for immunogenicity and toxicity studies. The data from pharmacological studies are presented in this BLA in section 2.4 “Nonclinical Overview – MMR".

Table 157: The animal species susceptible to measles, mumps and rubella viruses

Measles	Mumps	Rubella
***Rhesus* monkey**	***Rhesus* monkey**	***Rhesus* monkey**
Marmosets	Marmosets	Marmosets
Cynomolgus monkey	Cat	African green monkey
Squirrel monkey*	Rabbit	Rabbit
Transgenic mice	Suckling mice	Mice
Cotton rat	Ferret	Ferret
Chick embryo	Guinea pig	Baboons
	Suckling rat	Rat
	Chick embryo	Chimpanzee
	Dog	
	Hamster	

Note: Rhesus monkey is the most commonly used species

PRIORIX vaccine was first registered in Europe in November 1997, before the first preclinical guidance from the European Medicines Agency (EMA) “Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines”, came into force in 1998. Furthermore, none of the active ingredients or excipients in PRIORIX vaccine are novel. Consequently, Good Laboratory Practice (GLP) toxicity studies were not performed for PRIORIX. However, tests for the measles, mumps and rubella working seeds have been conducted in animals, including neurovirulence tests in monkeys, which are described in this memo.

In addition, the effects of single or repeated subcutaneous injection of GSK’s measles, mumps, rubella and varicella (MMRV) vaccine [Priorix-Tetra], have been evaluated in a pivotal GLP toxicity study in the Rhesus monkey with demonstration of the vaccine immunogenicity in this species. It should be noted that the MMR bulks used to formulate GSK’s PRIORIX and MMRV vaccines are the same; consequently, the residuals in both vaccines are also the same. Priorix-Tetra is formulated to contain the same measles and rubella antigen content as PRIORIX, the same varicella antigen content as GSK’s varicella vaccine [Varilrix], although it contains five times more mumps than PRIORIX. With

respect to the excipients, Priorix-Tetra contains the same excipient levels as PRIORIX and contains in addition ¾ of the excipient content of Varilrix. Therefore, since Priorix-Tetra contains a higher amount of the mumps antigen and a higher level of excipients than PRIORIX, it is the sponsor's position that the GLP toxicity study with Priorix-Tetra is also applicable for the nonclinical safety evaluation of PRIORIX.

Vaccine immunogenicity in Rhesus Monkeys
To demonstrate the vaccine immunogenicity during the study in Rhesus monkeys, a quantification of antibodies against measles, mumps, rubella and varicella viruses was performed in individual sera. Administration of the Priorix-Tetra vaccine resulted in 100% seroconversion to rubella virus while all saline recipients were seronegative. Furthermore, 100% seroconversion was also demonstrated for varicella although 2 out of 8 monkeys had positive pre-immunization values. For mumps, the seroconversion rate was low (1 out of 8 monkeys) and, for measles, there was an unexpected pre-existing immunity. The sponsor stated that the results for mumps and measles seroconversion illustrate the limitation of the animal model used.

Secondary Pharmacodynamics and Pharmacokinetics
No secondary pharmacodynamic and no pharmacokinetic studies were performed according to the "Note for Guidance on Preclinical Pharmacological and Toxicological testing of vaccines" (CPMP/465/95) and WHO Guidelines on Nonclinical Evaluation of Vaccines (WHO, 2005).

Neurovirulence Study
The tests for the measles, mumps and rubella working seeds have been conducted in animals, including neurovirulence test in monkeys. See section 3.2.S.2.3 of each Drug Substance in this memo for results of neurovirulence testing.

Toxicology
The effects of single or repeated subcutaneous injection of Priorix-Tetra were evaluated in a pivotal GLP-compliant toxicity study (b) (4) in Rhesus monkeys. The study was conducted by (b) (4). The subcutaneous route of administration was used since that is the intended route of human administration in the US. Briefly, single or multiple subcutaneous injections of Priorix-Tetra were well tolerated in the Rhesus monkey. No treatment-related toxic effects were observed on clinical signs, body weight evolution, food consumption, hematology, clinical chemistry, body temperature, ophthalmoscopy, electrocardiography, blood pressure, organ weights, macroscopic or microscopic examinations. Based on these results, single or repeated subcutaneous injection of the full human dose of Priorix-Tetra in Rhesus monkeys was considered to be a no observed adverse effect dose level. The study report (b) (4) is provided in section 4.2.3.2 "Repeat Dose Toxicity" in this BLA.

Overview and Conclusions
The sponsor stated that they have demonstrated in Rhesus monkeys the absence of unexpected histopathological changes in the central nervous system that could be attributable to unusual neurotropism of the mumps strain or to extraneous neurotropic agents and the absence of toxicity of single or repeated subcutaneous injection of Priorix-Tetra. **Up to the date, more than 380 million**

doses of PRIORIX having been distributed worldwide. Based on a large safety database from clinical studies and a broad post-marketing safety surveillance experience, PRIORIX has a well-established safety profile and a favorable benefit/risk profile in humans. From the limited data that are available in women vaccinated with PRIORIX during pregnancy, no safety concern was raised. Furthermore, no novel excipients are used in the PRIORIX formulation. Based on these arguments, no reproductive and developmental toxicity studies were conducted with PRIORIX as was agreed with CBER in the Type C meeting of 6 June 2017, and as included in the agreed investigational pediatric study plan (aiPSP). The sponsor considers that it has adequately demonstrated the safety of its measles, mumps and rubella vaccine, PRIORIX, in animals and more precisely, the safety of the mumps virus strain RIT 4385. The sponsor mentioned that the non-clinical data are consistent with the clinical safety profile for PRIORIX, which shows that vaccine is well-tolerated and induces the appropriate immunological protection in human subjects.

Overall Reviewer's Assessment of Relevant Sections of Module 4 (clinical pharmacology):
The information provided is acceptable. The preclinical evaluation of this vaccine virus has been studied in different animal models, including non-human primates, and has been demonstrated to be safe, immunogenic, and effective.

UNII assignment: We concur with the list of ingredients for PRIORIX as identified by the Substance Registration System (SRS) team.