CBER CMC BLA Review Memorandum

BLA STN 125748/0

Measles, Mumps and Rubella Virus Vaccine Live

Viviana Matta / Consumer Safety Officer/ CBER/OCBQ/DMPQ/MRB2

1. BLA#:
STN 125748/0

2. APPPLICANT NAME AND LICENSE NUMBER
GlaxoSmithKline Biologicals, Lic.# 1617

3. PRODUCT NAME/PRODUCT TYPE
Non-Proprietary/Proper/USAN: Measles, Mumps and Rubella (MMR) Virus Vaccine Live
Chemical/Biochemical: Measles (Schwartz strain; CEF), Mumps (RIT 4385 strain; CEF) and Rubella (Wistar RA 27/3 strain; MRC-5) Vaccine, Live, Attenuated
Proprietary: PRIORIX

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT
Live attenuated vaccine, 0.5 mL solution for subcutaneous injection indicated for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older.

5. MAJOR MILESTONES
06/06/2017 Type C meeting (clinical, non-clinical, and CMC)
05/01/2020 Type C Written Response Only (WRO) (CMC)
10/16/2020 Type B preBLA WRO (non-clinical, clinical)
10/26/2020 Type B preBLA WRO (CMC, facilities)
11/18/2020 Follow-up responses to clinical preBLA
12/14/2020 Follow-up responses to CMC/facilities preBLA
06/04/2021 Application received
08/03/2021 Filing action due
12/04/2021 Mid-cycle communication
02/17/2022 Late-cycle meeting
06/04/2022 First action due 06/04/2022

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Viviana Matta, OCBQ/DMPQ/MRB2	CMC/Facilities
Ekaterina Allen, OCBQ/DMPQ/MRB2	CMC/Facilities

7. INTER-CENTER CONSULTS REQUESTED
N/A

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
06/04/2021	STN 125748/0	Original application
11/19/2021	125748/0.13 (eCTD 0014)	Response to DMPQ IR#1

Date Received	Submission	Comments/ Status
12/17/2021	125748/0.16 (eCTD 0017)	Response to DMPQ IR#2
03/07/2022	125748/0.23 (eCTD 0024)	Response to DMPQ IR#3
05/06/2022	125748/0.39 (eCTD 0040)	Response to DMPQ IR #4

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4)	Glass prefillable syringe (PFS)	Yes	NA
DMF (b) (4)	(b) (4)	(b) (4) compounds; (b) (4) washing process	Yes	NA
IND7229	GlaxoSmithKline	Measles, Mumps, Rubella Vaccine, Live Attenuated, (PRIOrix)	NA	NA

Additionally, clinical serological assays from the following previously submitted GSK files is cross-referenced: IND (b) (4) IND (b) (4) (Boostrix), IND (b) (4) IND (b) (4) IND 003200 (Havrix), IND 014151 (Hiberix), and BLA 125614 (Shingrix).

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

The firm, GlaxoSmithKline Biologicals, submitted this original BLA, standard 12-month review for licensure of the product. The drug product is a live attenuated vaccine, 0.5 mL suspension for subcutaneous injection. The vaccine is packaged with two components: a lyophilized preparation containing Measles, Mumps and Rubella antigens in a monodose vial and water for injection (WFI) diluent provided in a monodose pre-filled syringe.

To support the BLA, the firm provided facility information, equipment description and qualifications, cleaning validations, computer systems, container closure and container closure integrity, manufacturing process description and process validation including aseptic process simulation studies. During the review, four information requests were issued by DMPQ. The firm responses were reviewed and deemed acceptable. Additionally, a pre-license inspection of drug product manufacturer, (b) (4) GlaxcoSmithKline (b) (4) was performed from (b) (4) A two item Form FDA 483 was issued. The firm's response was reviewed

and deemed acceptable; the inspection was classified as Voluntary Action Indicated (VAI). The inspection of the other facilities including drug substance manufacturers, GlaxoSmithKline Biologicals (b) (4) GlaxoSmithKline Biologicals (b) (4) and GSK Vaccines (b) (4) in addition to diluent manufacturer, (b) (4) were waived on basis of an acceptable compliance history.

B. RECOMMENDATION

I. APPROVAL

Based on the information provided in the original submission, the corresponding amendments with information under DMPQ purview, an acceptable outcome to the pre-license inspection and provided all OVRR issues are resolved, approval is recommended.

II. COMPLETE RESPONSE (CR)

NA

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Viviana Matta, Reviewer OCBQ/DMPQ/MRB2		
Ekaterina Allen, Reviewer OCBQ/DMPQ/MRB2		
Anthony Lorenzo, Branch Chief OCBQ/DMPQ/MRB2		
Carolyn Renshaw, Acting Director OCBQ/DMPQ		

Review of CTD

Table of Contents

Module 3

3.2.S DRUG SUBSTANCE

Please note that this product has three drug substances (DS). The information relevant to a particular DS is indicated in the subsequent sections as follows:

- Measles (ME)
- Mumps (MU)
- Rubella (RU)

3.2.S.2 Manufacture

(b) (4)

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

(b) (4)

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

MMR vaccine is a suspension for subcutaneous injection without added preservative. The vaccine is intended for active immunization for the prevention of measles, mumps, and rubella in individuals aged 12 months and older. The vaccine consists of two components:

- Lyophilized preparation containing the measles, mumps, and rubella antigens, presented in a monodose 3 mL glass vial closed with a bromobutyl rubber stopper and aluminum cap.
- Water For Injection (WFI) diluent in a monodose 1.25 mL glass (b) (4) prefilled syringe for subcutaneous injection with luer lock adaptors and (b) (4) rubber tip

caps. The syringe is closed with bromobuthyl (b) (4) rubber plunger stopper and is supplied with the vial containing powder. The diluent is a clear solution, free from visible particles and compliance with the (b) (4) monograph for sterile WFI. Target fill volume is (b) (4) to guarantee a minimal volume of 0.5 mL of reconstituted vaccine. Entire contents of WFI syringe is used for reconstitution.

.

Each dose of the vaccine is composed as follows:

- Active substances, i.e. immunogens (minimum titer guaranteed at expiry/titer range as formulated, log $CCID_{50}$):
  - Live attenuated measles virus (Schwarz strain) (NLT (b) (4)
  - Live attenuated mumps virus (RIT4385 strain) (NLT (b) (4)
  - Live attenuated rubella virus (Wistar RA 27/3 strain) (NLT $10^{3.3}$ /(b) (4)
- Excipients (stabilizers):
  - Anhydrous lactose, 32 mg
  - Mannitol, 8 mg
  - Amino acids, 9 mg
  - Sorbitol, 9 mg

3.2.P.2.5 Microbiological Attributes

MMR vaccine is a sterile vaccine with no added preservatives. Sterility of the vaccine is ensured via validated aseptic manufacture per GMP in controlled environment, validated cleaning / sterilization of the equipment, sterile filtration of all media/solutions, use of WFI, sterility testing of final bulk and final container, and CCS integrity demonstrated over the DP shelf life. In-use stability data in support of 8 hrs post-reconstitution shelf-life at 2-8C was provided in the stability section of the BLA.

WFI sterility is ensured via validated manufacture per GMP in controlled environment, validated cleaning / sterilization of the equipment, (b) (4)

demonstrated over the DP shelf life.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

1. (b) (4)

   MMR: Formulation, filling, lyophilization, visual inspection, labeling and packaging; release testing (final bulk, final container, final product); warehousing operations

   WFI: Labeling and packaging, release testing (final product); warehousing operations

2. GlaxoSmithKline Biologicals (b) (4)
   (b) (4)
   MMR: Release and stability testing (final bulk and final container); warehousing operations
   WFI: Stability testing; warehousing operations

3. (b) (4)
   MMR, WFI: warehousing and distribution

4. (b) (4)
   WFI: Production and filling, release and stability testing

5. (b) (4)
   FEI# NA
   WFI: Warehousing operations

6. (b) (4)
   FEI# NA
   WFI: Warehousing operations

7. (b) (4)
   FEI# NA
   WFI: Warehousing operations

3.2.P.3.3 Description of Manufacturing Process

MMR: The vaccine is manufactured on a campaign basis in a fully aseptic manner. Production consists of the following steps:

(b) (4)

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

(b) (4)

3.2.P.3.5 Process Validation and/or Evaluation

MMR: Validation studies in support of DP production in (b) (4) included lyophilizer characterization studies, APV and PPQ.

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

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)

MMR: Release specifications within DMPQ purview include:

- Description (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. Acceptance criterion is per (b) (4) "Measles Mumps, and Rubella Vaccine (Live)"
- Absence of growth (final bulk and final container) as determined by (b) (4) sterility tests using (b) (4) Acceptance criterion is per (b) (4)

- Water content by (b) (4) (final container). Acceptance criterion is per (b) (4) , which requires water content of (b) (4) determined by (b) (4)

Reviewer Comment: *An information request was sent to the firm on 11/09/2021 and the response was received 12/17/2021 in STN 125748/0.16. The firm provided a justification for not performing* (b) (4) *routine testing per* (b) (4) *for* (b) (4) *in reconstituted product:*

- (b) (4)

Reviewer Comment: *Response appears acceptable.*

(b) (4)

- (b) (4)

3.2.P.5.4 Batch Analyses

MMR: The firm provided analyses for (b) (4) MMR final container lots manufactured from August 2008 and June 2020, including:

- (b) (4) lots of Phase 2 clinical material manufactured in 2008 at Rixensart. Lot size was (b) (4) 3ml vials closed with bromobutyl D/12 rubber stopper.
- (b) (4) lots of Phase 3 clinical material manufactured in 2011-2013 at Rixensart. Lot size was (b) (4) 3 mL vials closed with bromobutyl (b) (4) stopper.
- (b) (4) Phase 3/PPQ lots manufactured in 2012 at (b) (4) . Lot size was (b) (4) 3mL vials closed with bromobutyl (b) (4) stopper.
- (b) (4) commercial lots manufactured in 2020 at (b) (4) . Lot size was (b) (4) 3mL vials closed with bromobutyl (b) (4) stopper.

Sterility, description, and water content release specifications were met for all lots. Actual water content was (b) (4) (clinical lots), (b) (4) (PPQ lots), and (b) (4) (commercial lots).

WFI: The firm provided analyses for (b) (4) WFI diluent lots manufactured from August 2008 and June 2011, including:

- (b) (4) Phase 2 lot manufactured in 2008 at Rixensart. Lot size was (b) (4) prefilled glass syringes, USP (b) (4).
- (b) (4) Phase 3 lots manufactured in 2011 at Rixensart. Lot size was (b) (4) 3mL glass vials, (b) (4) , with butyl rubber stopper.
- (b) (4) PPQ lots manufactured in 2011 at (b) (4) . Lot size was (b) (4) prefilled glass syringes, (b) (4) .

Sterility, endotoxin, particle count release specifications were met for all lots. Actual endotoxin was (b) (4) (clinical lots) and NMT (b) (4) (PPQ lots); conductivity (b) (4) (clinical lots; NMT (b) (4) specification was in effect at the time of release) and (b) (4) extractable volume (b) (4) (clinical lots) and (b) (4) (PPQ lots).

Additionally, a reconstitution test (pass/fail) was performed for clinical lots; all lots passed. The details of such test were not provided.

3.2.P.7 Container Closure System

MMR: The formulation is filled and lyophilized in 3 ml vial containers, sealed with 13 mm ready to sterilize (RTS) stoppers for lyophilized formulations and secured with flip-off caps:

- 3mL vial container, uncolored (b) (4) glass that meets (b) (4) and (b) (4) requirements. The vials are (b) (4)

The vials are tested per GSK (b) (4), which includes the following testing:

- (b) (4)

- (b) (4)

In response received 05/06/2022 as amendment STN 125748/0.39, the firm clarified the vendors that supply the primary packaging specifically, the vials are supplied by (b) (4), the stoppers are supplied by (b) (4) and the caps are supplied by (b) (4). This information was not located in the original submission.

CCIT for Vials

The firm performs 100% (b) (4) CCIT (b) (4) on vials filled at the DP manufacturer using a (b) (4)

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

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

MMR: The firm performed (b) (4) stability studies using clinical (b) (4) PPQ (b) (4) and commercial (b) (4) lots of DP. Long-term (24 months at 2-8°C),(b) (4) 24 months at 2-8°C), accelerated (30 days at (b) (4) and in-use (reconstituted vaccine at 2-8°C up to (b) (4) hrs) studies were performed on PPQ (studies completed) and commercial lots (3 months of data available). Historical stability data from (b) (4) clinical lots spit between similarly designed studies (all completed) was also provided.

Stability tests within DMPQ purview included description (before and after reconstitution), water content, sterility (b) (4) and CCIT by (b) (4). All tests were performed at (b) (4) of the study, except for CCIT which for some clinical lots was performed at the end of the study; none of these tests were performed for in-use studies. I reviewed the provided results: all acceptance criteria were met except accelerated stability studies (b) (4) where a retracted cake was observed at (b) (4) days and/or later time points for lots (b) (4) (PPQ).

CCIT on stability was performed by (b) (4)

(b) (4)

.
(b) (4)

WFI stability was assessed via long term stability (60 months at (b) (4)) and MMR compatibility studies. PPQ lots manufactured at (b) (4) were used in long-term stability study and were tested for sterility (b) (4) and endotoxin at release, 12, 24, 36, 48, and 60 months. (b) (4) tests were performed at the same timepoints and additionally at 3, 6, 9, and 18 months. All results met the release specification. MMR compatibility studies were designed as in-use studies where (b) (4) lot of MMR was reconstituted with (b) (4) different lots of diluent. No tests within DMPQ purview were included in this study.

Reviewer Comment: *The information provided under the purview of DMPQ appears acceptable.*

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

MMR: The firm has committed to complete ongoing long-term, cumulative, accelerated, and in-use stability studies on the first (b) (4) commercial lots of MMR vaccine (b) (4) described above and to put at least (b) (4) lot of MMR vaccine (b) (4) on long term (24 months at 2-8°C) stability post approval. Annual stability studies will include testing for description and water content at 12 and 24 months and sterility (b) (4) and CCIT at 24 months.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

GlaxoSmithKline Biologicals submitted information about GlaxoSmithKline Biologicals (b) (4), GSK Vaccines (b) (4) GlaxoSmithKline Vaccines. This review is limited to these sites.

GlaxoSmithKline Biologicals (b) (4) Drug Substance Manufacturer

The information included in the BLA is limited to the following:

• Facility overview (building description and flows)
• Facility systems (HVAC, EM and facility classification, utilities and process gases, computer systems)
• Equipment
• Contamination and cross-contamination controls
• Facility floor plans (air classification, HVAC zoning; personnel, product, waste, and raw material flows)

The inspection for this facility was waived on the basis that the firm was determined to have an acceptable compliance history. The basis for waiving inspection is documented in the inspection wavier memo under STN 125748/0 in CBER Connect.

Description

(b) (4)

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

(b) (4)

***Reviewer Comments**: Information provided regarding mitigation of contamination and cross-contamination appears acceptable. Additionally, the firm has an acceptable compliance history for which contamination and cross-contamination procedures are evaluated in routine surveillance inspections.*

GSK Vaccines (b) (4) **-Drug Substance Manufacturer**

The information included in the BLA is limited to the following:

• Facility overview (building description and flows)
• Facility systems (HVAC, EM and facility classification, utilities and process gases, computer systems)
• Equipment
• Contamination and cross-contamination controls
• Facility floor plans (air classification, HVAC zoning; personnel, product, waste, and raw material flows)

The inspection for this facility was waived on the basis that the firm was determined to have an acceptable compliance history. The basis for waiving inspection is documented in the inspection wavier memo under STN 125748/0 in CBER Connect.

(b) (4)

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

(b) (4)

Reviewer Comment*: The firm's cross-contamination controls appear acceptable. Additionally, this firm has an acceptable compliance history; contamination and cross-contamination procedures were previously evaluated during surveillance inspections.*

(b) (4) **GlaxoSmithKline Vaccines- Drug Product Manufacturer**

The information included in the BLA is limited to the following:

• Facility overview (building description and flows)
• Facility systems (HVAC, EM and facility classification, utilities and process gases, computer systems)
• Equipment
• Contamination and cross-contamination controls
• Facility floor plans (air classification, HVAC zoning; personnel, product, waste, and raw material flows)

In addition to the review of the information submitted, a Pre-License Inspection (PLI) of this facility was performed (b) (4) and documented in an Establishment Inspection Report.

Description

MMR drug product manufacturing process occurs within the (b) (4) building and performs the following manufacturing steps: aseptic formulation, aseptic filling, freeze drying, and visual inspection. The (b) (4) building is a multi-product facility.

Building (b) (4) contains (b) (4) levels as follows:

(b) (4)

(b) (4)

(b) (4)

Flows

Product and Process Flow

Production steps of MMR take place in the following areas:

(b) (4)

(b) (4)

[redacted]

Personnel Flow

Personnel flow was covered during the PLI. Personnel will enter Building (b) (4)

[redacted]

(b) (4)

Incoming Materials Flow

(b) (4)

Waste Flow

Waste flow was covered during PLI. Waste materials are sealed in waste containers. The waste from Building (b) (4)

Media and Buffer Flow

Dilution media is stored at (b) (4) and is transferred to Building (b) (4)

Single Use Equipment and Materials Flow

Single use equipment and material flow was covered during PLI.

(b) (4)

(b) (4)

HVAC

The HVAC system was covered during PLI. The HVAC system includes separate Air Handling Units that supply air to the process areas including the formulation suite and RABS, filling suite and RABS, and non-process areas including personnel and material airlocks, and storage rooms.

(b) (4)

(b) (4)

Environmental Monitoring (EM)

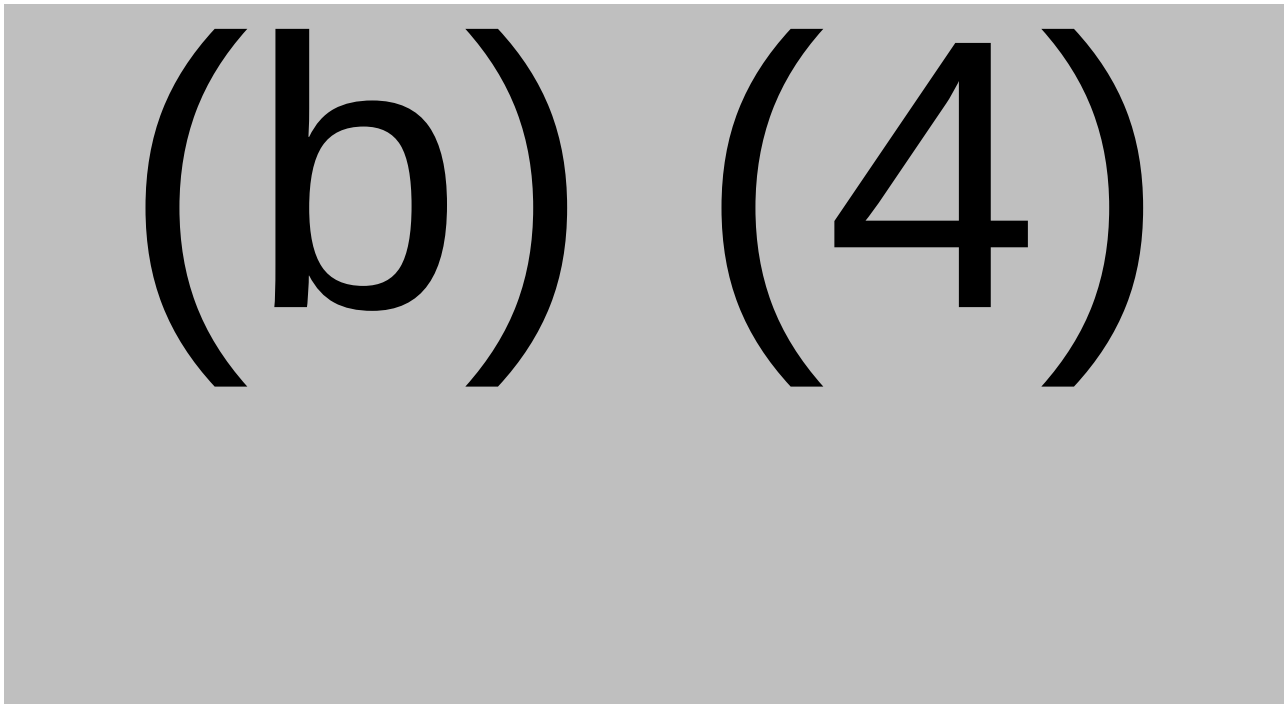
Environmental monitoring was covered during the PLI. Sampling plan qualification occurred over (b) (4) days of production activities under (b) (4) conditions. (b) (4) was performed at the same time as the (b) (4). Critical points for monitoring were selected based on a risk analysis and the monitoring locations are those defined in the protocol. Viable tests collected included active air sampling, passive air sampling, surface monitoring and finger touch. The monitoring methods applied during the qualification period are stated to be identical to those used during routine monitoring.

(b) (4)

(b) (4)

(b) (4)

(b) (4)



(b) (4)

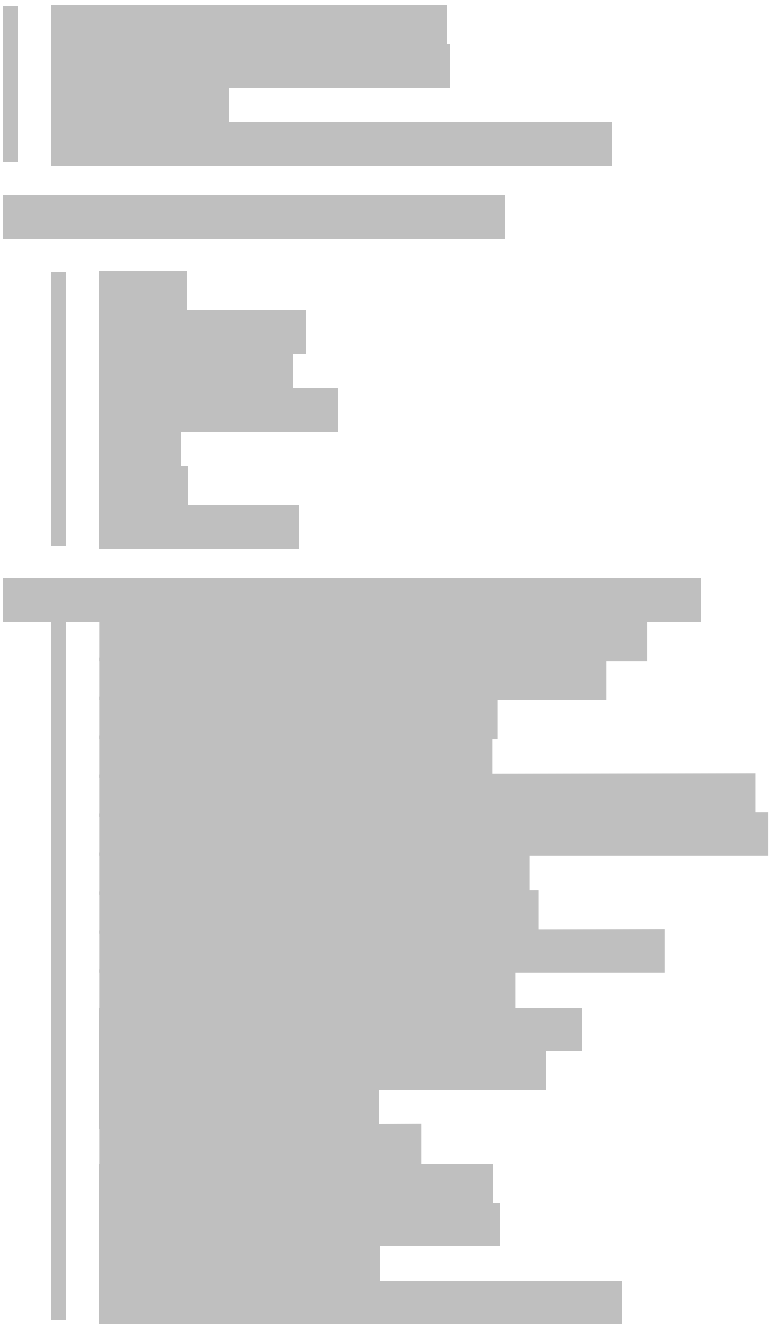
The trend analyses of routine EM monitoring data were reviewed during the PLI.

Facility Cleaning and Sanitization

(b) (4) and WFI are utilized to clean product contact surfaces. (b) (4) are utilized to clean non-product contact equipment and surfaces. (b) (4) are applied as disinfection agents in the bulk formulation and filling areas. (b) (4) are also used as a viricidal agents in the cleaning of non-product contact surfaces.

Several disinfectant effectiveness summary reports testing various disinfectants on all facility surfaces and against different microorganisms were provided in the submission and are described below. The validation conformed to the acceptance criteria if, for (b) (4) the tests on bacteria, fungi and viruses (challenge microorganisms) showed a (b) (4) reduction rate for a defined contact time and 2) the tests on spores showed a (b) (4) reduction rate for a defined contact time.

(b) (4)



The disinfectant efficacy studies adequately support the current cleaning approach at the facility. Selected disinfectants and sporicidals when applied with the validated exposure times adequately disinfect the facility's surfaces. Facility cleaning and sanitization was further evaluated during the PLI.

Water Systems

The water system was evaluated during the PLI. Source water is (b) (4) to create Purified Water. The purified water pre-treatment system distributes feed water to the Water for Injection (WFI) distillation units. WFI is generated by (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Water monitoring data are regularly evaluated and trended. Routine monitoring data (trends analysis) of the WFI system were evaluated during the PLI.

(b) (4)

.

(b) (4)

[redacted]

Computer Systems

The following process control systems are used in Building (b) (4) for vaccine production: Supervisory Control and Data Acquisition (SCADA) and DMg – Data Management tool. SCADA is used to supervise and monitor the system and production parameters and provide information for different equipment and processes of production activities in the building. SCADA is also used to maintain, archive and retrieve electronic records related to the production activities. All records are recorded in a database.

The Data Management tool DMg provides central reporting functionalities on the data coming from the different data sources i.e. real-time process control systems, equipment, field devices or short-term databases. DMg solution is deployed on one central server for the entire site. Clients are standard GSK workstations. The DMg server is connected to the SPN network.

Process automation systems are used for monitoring purposes such as environmental

monitoring and alarms, data management and scales management. Process automation systems used in Building (b) (4) are Particles and Environmental Monitoring System (PEMS) and Alarm Management System (AMS).

PEMS is a Client/Server solution used to monitor environmental conditions in clean rooms and to raise alarm signals (including local visual indications) when physical measures exceed predefined limits. AMS (Alarm Management System) is a site Client/Server solution used to ensure the collection, distribution and treatment of alarms collected from plant installations.

Equipment

Equipment was covered during the PLI. Product Contact Equipment used for MMR vaccine in (b) (4) facility is presented on the table below:

MMR Dedicated Equipment	(b) (4)
Shared Equipment	
Single-Use Equipment	

(b) (4)

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

(b) (4)

All acceptance criteria were met and equipment will be requalified per the firm's policy.

Contamination and Cross Contamination Controls

The following measures to prevent contamination and cross-contamination are in place:

(b) (4)

(b) (4)

(b) (4) **-WFI Diluent**

The information included in the BLA is limited to the following:

• Facility overview (building description and flows)
• Facility systems (HVAC, EM and facility classification, utilities and process gases, computer systems)
• Equipment
• Contamination and cross-contamination controls
• Facility floor plans (air classification, HVAC zoning; personnel, product, waste, and raw material flows)

The inspection for this facility was waived on the basis that the firm was determined to have an acceptable compliance history. The basis for waiving inspection is documented in the inspection wavier memo under STN 125748/0 in CBER Connect.

Aseptic filling, terminal sterilization and labelling of WFI diluent in syringes takes place at the (b) (4) site which is a multi-product commercial manufacturer.

Description

The (b) (4) building is a (b) (4) building, containing the following areas.

(b) (4)

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