### Part 1 | General information

#### Manufacturers details

#### Company information

<table>
<thead>
<tr>
<th>Name of manufacturer</th>
<th>Serum Institute of India Pvt. Ltd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corporate address and address of manufacturer</td>
<td>212/2, Hadapsar, Pune 411 028, India</td>
</tr>
<tr>
<td>Contact person</td>
<td>Dr. Suresh Jadhav, Executive Director</td>
</tr>
</tbody>
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#### Unit / block

**Regarding Rotavirus vaccine:**
- Rotavirus Bulk;
- Rotavirus vaccine Filling, Lyophilization, Sealing, Screening & Packing;
- Rotavirus vaccine testing;
- Raw material testing;
- Microbiological testing;
- Mycoplasma testing lab;
- Raw material & Packaging material storage;
- Diluent (Citric acid & Sodium bicarbonate – 2.5 ml – single dose & 5 ml – 2 dose) blending, filling, screening;
- Diluent labelling & packing.

**Regarding Rabies vaccine:**
- Rabies Bulk;
- Rabies vaccine Filling, Lyophilization, Sealing;
- Rabies vaccine Screening & Packing;
- Rabies vaccine testing;
- Raw material testing;
- Microbiological testing;
- Mycoplasma testing lab;
- Raw material & Packaging material storage;
- General safety / Abnormal toxicity / Innocuity / Undue toxicity, Pyrogen & Potency (NIH) testing.
## Inspection details

<table>
<thead>
<tr>
<th>Dates of inspection</th>
<th>29 January – 2 February 2018</th>
</tr>
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<tbody>
<tr>
<td>Type of inspection</td>
<td>Initial inspection for Rotavirus and Vero-Rabies inactivated (Freeze-Dried) Vaccines.</td>
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</table>

### Introduction

<table>
<thead>
<tr>
<th>General information about the company and site</th>
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<tbody>
<tr>
<td>Serum Institute of India Pvt. Ltd. (SIIPL) is a producer of Sera, Vaccines and other Biologicals in India. It is located in the extensive Poonawalla Estates of pollution free countryside in Pune.</td>
</tr>
<tr>
<td>Serum Institute was founded in 1966 by the Poonawalla Family with Dr. Jal Mehta and commenced production in October, 1967.</td>
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<tr>
<td>Starting with Tetanus Antitoxin, Serum Institute progressively launched DTP group of Vaccine; Polyvalent Anti-Snake Venom Serum; Measles Vaccine; Measles, Mumps and Rubella Vaccine; Hepatitis B Vaccine; Polysaccharide conjugate Vaccines (Men A Vaccine, Hib vaccine); Pandemic Influenza Vaccine (Human Live attenuated); Influenza Vaccine, Live Attenuated (Human) Seasonal, Trivalent; Oral Polio Vaccine; Inactivated Polio Vaccine; Erythropoietin Injection, Rabies Human Monoclonal Antibody, Rabies Vaccine, Rotavirus vaccine and several other products.</td>
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<tr>
<td>Since March 1994 SIIPL has started exporting Viral Vaccines and Bacterial Vaccines to WHO / PAHO / UNICEF.</td>
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<table>
<thead>
<tr>
<th>And brief summary of the manufacturing activities</th>
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<tbody>
<tr>
<td>The company provided the list of the regulatory authorities inspections carried out since 2015.</td>
</tr>
<tr>
<td>The last WHO onsite inspection was conducted in May 2015 and covered the Influenza and IPV / Polio vaccines manufacturing units.</td>
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</table>

### Brief report of inspection activities undertaken

#### Scope and limitations

<table>
<thead>
<tr>
<th>Areas inspected</th>
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<tbody>
<tr>
<td>The inspection focused on the production and control of Rotavirus and Vero-Rabies inactivated (Freeze-Dried) Vaccines. The inspection covered all the sections of the WHO GMP text, including quality assurance, sanitization and hygiene, qualification and validation, complaints and recalls, self-inspection, personnel, training, personal hygiene, premises and equipment, materials, documentation, materials, production and quality control and utilities.</td>
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<table>
<thead>
<tr>
<th>Restrictions</th>
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<tr>
<td>None</td>
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<tr>
<th>Out of scope</th>
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<tr>
<td>Products and vaccines other than Rotavirus and Vero-Rabies inactivated (Freeze-Dried) vaccines were not inspected during this inspection.</td>
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<tr>
<th>WHO product numbers</th>
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<tbody>
<tr>
<td>1. Live attenuated Rotavirus vaccine, oral freeze dried, provided in vials as 1 dose 2.5 ml</td>
</tr>
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</table>
and 2 doses 5.0 ml, with diluent, citrate bicarbonate buffer (single dose in vials).

2. Rabies Vaccine Human I.P (Freeze Dried): sterile, purified inactivated rabies vaccine provided in vials as 1 dose of lyophilized powder in vial with diluent (SWFI – 0.5 ml single dose in ampoules) from contract manufacturing unit - Sovereign Pharma, Daman.

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>AHU</td>
<td>Air Handling Unit</td>
</tr>
<tr>
<td>ALCOA</td>
<td>Attributable, Legible, Contemporaneous, Original and Accurate</td>
</tr>
<tr>
<td>APR</td>
<td>Annual Product Review</td>
</tr>
<tr>
<td>APS</td>
<td>Aseptic Process Simulation</td>
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<tr>
<td>BMR</td>
<td>Batch Manufacturing Record</td>
</tr>
<tr>
<td>BPR</td>
<td>Batch Production Record</td>
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<tr>
<td>CA</td>
<td>Compressed Air</td>
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<tr>
<td>CAPA</td>
<td>Corrective Actions and Preventive Actions</td>
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<tr>
<td>CC</td>
<td>Change Control</td>
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<tr>
<td>CFU</td>
<td>Colony-Forming Unit</td>
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<tr>
<td>CIP</td>
<td>Cleaning In Place</td>
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<tr>
<td>CoA</td>
<td>Certificate of Analysis</td>
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<tr>
<td>CpK</td>
<td>Process capability</td>
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<tr>
<td>DQ</td>
<td>Design Qualification</td>
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<tr>
<td>EDI</td>
<td>Electronic DeIonization</td>
</tr>
<tr>
<td>EM</td>
<td>Environmental Monitoring</td>
</tr>
<tr>
<td>FMEA</td>
<td>Failure Modes and Effects Analysis</td>
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<tr>
<td>FTA</td>
<td>Fault Tree Analysis</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practices</td>
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<tr>
<td>GPT</td>
<td>Growth Promotion Test</td>
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<tr>
<td>HEPA</td>
<td>High Efficiency Particulate Air</td>
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<tr>
<td>HVAC</td>
<td>Heating, Ventilation and Air Conditioning</td>
</tr>
<tr>
<td>IP</td>
<td>Indian Pharmacopoeia</td>
</tr>
<tr>
<td>IQ</td>
<td>Installation Qualification</td>
</tr>
<tr>
<td>LAF</td>
<td>Laminar Air Flow</td>
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<tr>
<td>LIMS</td>
<td>Laboratory Information Management System</td>
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<tr>
<td>MB</td>
<td>Microbiology</td>
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<tr>
<td>MBL</td>
<td>Microbiology Laboratory</td>
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<tr>
<td>MF</td>
<td>Master Formulae</td>
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<tr>
<td>MFT</td>
<td>Media Fill Test</td>
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<tr>
<td>MR</td>
<td>Management Review</td>
</tr>
<tr>
<td>NCA</td>
<td>National Control Authority</td>
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<tr>
<td>NCL</td>
<td>National Control Laboratory</td>
</tr>
<tr>
<td>NRA</td>
<td>National Regulatory Agency</td>
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<tr>
<td>OQ</td>
<td>Operational Qualification</td>
</tr>
<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
</tr>
<tr>
<td>PHA</td>
<td>Process Hazard Analysis</td>
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<tr>
<td>pH</td>
<td>(-ve) logarithm of H+ concentration</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>PLC</td>
<td>Programmable Logic Controller</td>
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<tr>
<td>PM</td>
<td>Preventive Maintenance</td>
</tr>
<tr>
<td>PQ</td>
<td>Performance Qualification</td>
</tr>
<tr>
<td>PQR</td>
<td>Product Quality Review</td>
</tr>
<tr>
<td>PQS</td>
<td>Pharmaceutical Quality System</td>
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<tr>
<td>PW</td>
<td>Purified Water</td>
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<tr>
<td>QA</td>
<td>Quality Assurance</td>
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<tr>
<td>QC</td>
<td>Quality Control</td>
</tr>
<tr>
<td>QCL</td>
<td>Quality Control Laboratory</td>
</tr>
<tr>
<td>QMS</td>
<td>Quality Management System</td>
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<tr>
<td>QRM</td>
<td>Quality Risk Management</td>
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<tr>
<td>RA</td>
<td>Risk Assessment</td>
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<tr>
<td>RCA</td>
<td>Root Cause Analysis</td>
</tr>
<tr>
<td>RO</td>
<td>Reverse Osmosis</td>
</tr>
<tr>
<td>SIP</td>
<td>Sterilization In Place</td>
</tr>
<tr>
<td>SMF</td>
<td>Site Master File</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SWFI</td>
<td>Sterile Water for Injection</td>
</tr>
<tr>
<td>UN</td>
<td>United Nations</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children's Fund</td>
</tr>
<tr>
<td>URS</td>
<td>User Requirements Specifications</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet-Visible Spectrophotometer</td>
</tr>
<tr>
<td>VVM</td>
<td>Vaccine Vial Monitor</td>
</tr>
<tr>
<td>WFI</td>
<td>Water for Injection</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
Part 2: Brief summary of the findings and comments

1. Pharmaceutical quality system
There generally appeared to be adequate resources available for the management of the implemented QMS. Quality assurance and quality control activities were functioning with independence from the production unit. Managerial responsibilities were specified in job-descriptions. Production and control operations were specified in written form and GMP requirements were generally followed. Product and processes were monitored and the results taken into account in batch release; regular reviews of the quality of vaccines were conducted.

Product quality review
The product quality review was performed as per the procedure in place. Annual product review shall be prepared product wise for the commercial products manufactured during the calendar year and shall be prepared within three months. Provisions were in place for trend reviews.

Product Quality Review includes:
- Batch Manufacturing Records (BMRs) are reviewed for critical in-process controls to ensure that the process is within the established yield range at each stage and product meets quality standards (specifications).
- Critical deviations and recommendations are reviewed to ensure that deviations are assessed for its quality impact.
- The trends of environmental monitoring are evaluated to check any adverse trend observed or any Out of Trend (OOT) results are reported and investigated to check any variation that could adversely affect the product quality.
- The trends of the quality parameters for in-process and finished product tests are reviewed for compliance with specifications, consistency and compared with trends of previous year batches.
- Out of Specification (OOS) results, if any, are investigated to identify root cause and to ensure proper corrective and preventive actions are taken to avoid re-occurrence.
- The results of stability studies of the products kept for stability study are evaluated.
- Review of product complaints and adverse drug events, if any, are evaluated and investigated.
- Review of products returned, if any, during the year and summary report for the same is prepared.
- Review of compliance to all recommendations made by local or international regulatory authorities.
- Validation activities are performed as per the validation master plan.
- Review of change control proposals for its impact on quality attributes of the product.
- Review of corrective actions, post marketing commitments and technical agreements.
- Qualification status of relevant equipment and utilities.
- Retained samples of all products are checked for any change in physical appearance and to ensure that the product remains as it is throughout the shelf life.

- **PQR of live attenuated Rotavirus vaccine:**
PQR related to 2017 was available at the time of inspection.
Rotavirus bulk vaccine production started in March 2017, while manufacturing of rotavirus vaccine started in August 2017. In this period of time the following batches of DS were produced: 11 batches of G1, 11 batches of G2, 6 batches of G3, 9 batches of G4 and 4 batches of G9.
60 batches of rotavirus vaccine were manufactured by blending different amounts of DS, 13 of which were for single dose presentation (all stored at <25°C) and 47 lots for the 2 doses presentation (3 stored at <25°C and 44 kept at 2-8°C).

It should be highlighted that for rotavirus vaccine intended for storage at <25°C, a higher overage was foreseen which takes into account an expected higher decrease in potency at the end of shelf-life. Accordingly, rotavirus vaccine intended for storage at 2-8°C cannot be moved for storage at <25°C. No OOS was observed and only one lot of DS was rejected, because of erroneous addition of stabilizing solutions that caused precipitate formation.

- **PQR of Rabies vaccine:**  
The product quality review of Rabies vaccine (inactivated freeze dried, 1 dose) for the year 2017 was spot-checked. 12 final batches were produced at different batch sizes. A scaling up of the batch size was introduced without an adequate change control. In the submitted product summary file, only one batch size was validated.

- **PQR of Diluent:**  
The annual product quality review of the diluent water for injection from the third party subcontractor for the year 2017 was available.

Deficiencies regarding the management of the PQRs were raised and adequately addressed by the company through the provided CAPA.

**Quality risk management:**  
Procedure for QRM was in place. The procedure discuss only the FMEA model, however any other suitable model including FMECA, PHA, FTA, HACCP, HAZOP could also be used with justification. The following risk assessment reports were spot checked.

The risk assessment report of “fill and finish”.
- The transfer of stoppered vials from the lyophilizers to the capping area was performed through grade B area.
- The non-viable monitoring during the aseptic process of manual transfer of vials in trays to the lyophilizer was limited to one sample during 10 minutes.

The risk assessment report of “Vero-Rabies bulk vaccine production”.
- There was no risk assessment for the environmental monitoring for Vero-rabies bulk building in place.
- The risk assessment for the lyophilizers use was unacceptable and several risks were not identified and analysed with regard to the compliance and the sterility assurance of the products.
  There was no cleaning in place of the lyophilizers. The trays of the lyophilizers were manually cleaned, sterilised in the autoclave and transferred to the aseptic filling room for further processing. The sterilisation of the lyophilizers was performed weekly. The air vent/nitrogen input filter was integrity tested in-situ once a month. The stoppering of the half stoppered vials was performed under vacuum conditions.

The process validation protocol “Process validation of Vero-Rabies bulk manufacturing process” was available. The process flow chart and its mapping were available. A gap analysis between initial and currently validated Vero-Rabies vaccines was available however not detailing the critical parameters and the extent of the validation work to be undertaken.

There was no formal risk assessment of the current process validation including all the changes that occurred since the initial process from which the clinical batches were produced and drawn.
Deficiencies regarding the QRM were raised and adequately addressed and/or committed to be addressed by
the company through the provided CAPA.

Deviation management:
Procedure for deviations handling was in place. Deviations are categorized as critical, major and minor
according to the impact to the quality safety and efficacy of the product. Timelines and recurrences of
deviation were considered in the procedure.
The lists of deviations for Vero-Rabies vaccine and Rotavirus vaccine were spot-checked.

Management review:
Provisions for management review were in place.

Change control:
Change control management was in place. According to the product impact, the changes were categorised as
major, moderate and minor. Appropriate review of each proposal, as well as the qualifications/validations/training/regulatory actions needed, were considered.
There was statistics for total number of changes, closed and open changes. An effectiveness check of
implemented changes was mentioned in the procedure.
There was no trending for cumulative changes in place.
The list of change controls related to Rotavirus vaccine and Vero-Rabies vaccine were spot-checked.
There was no CC initiated for the validation work regarding the scale up of filling volume of Vero-Rabies
vaccines that has already started.
The company was reminded that any significant change to the process, even if found to be acceptably
validated through this inspection, needs to be submitted as per WHO variation guideline.

CAPA management:
Procedure for CAPA system management was in place. The procedure covered the internal and external
observations, corrective and preventive action from deviation, OOS, OOT, system, product complaint product
recall. The effectiveness check was mentioned in procedure.
CAPA from external audit conducted in October/November 2017 was spot-checked.
WHO audit performed in May 2015 gave rise to 42 observations. 42 CAPAs were raised to address the non-
conformities. At the time of this inspection, 5 CAPA were still open with the deadline for completion in April
2018.

Documentation:
Manufacturing activities are supported by product wise standard operating procedures and master formula. SOPs
are reviewed annually and records are maintained in the form of History sheets. These documents are authorized
by Head of Quality Assurance. During the inspection, the assessment of the documentation system was
performed by checking procedures, instructions, trend analysis, protocols and reports.
Batch numbering systems for products, intermediates, media, buffers and other materials were in place.
There was no discrimination between commercial and non-commercial (developmental and experimental products) numbering systems: 8 engineering (non-commercial) batches were rejected because of OOS/OOT, but the manufacturing details and the associated incidents were not presented and discussed in the APQR 2017.

Deficiencies regarding the documentation management were raised and adequately addressed by the company through the provided CAPA.

**Complaints:**
The systems in place for quality complaint management has been previously checked at on-site inspection and was not further reviewed during this inspection. No quality complaints have been received regarding Rotavirus vaccine or Rabies vaccine.

**Pharmacovigilance (PV):**
At SIIPL the Pharmacovigilance group had 5 people from Operations and 5 from QA. A contract has been established with a third party company for pharmacovigilance monitoring.
Under Indian government requirements, all AEFIs should be reported [The non-serious within 30 days and serious within 15 days]. The third party contracted company was responsible for categorization, for maintaining a database and for reporting to the Indian authorities. This included events reported to them by SII and also based on their review of the published literature. A toll free number indicated by SII for reporting of AEFIs was directly to the third party contracted company. The contractor also prepared the Periodic Safety Update Reports (PSURs). Since January 2016, India has introduced a PSUR format based on ICH guidelines. The Indian guidelines require additional breakdown of Indian cases. Indian rules indicate that after 4 years of manufacture no PSUR is required. However, SIIPL still prepares PSURs for submission to WHO/PQT as part of the annual report for each vaccine. The SIIPL reporting of the AEFIs to WHO was described in the relevant procedure. The procedure indicated reporting to WHO within 48 hours of fatal cases. Other AEFIs were indicated to be reported to WHO through Uppsala Monitoring centre.
There have been no serious AEFIs reported for Rotavirus or Rabies vaccines.

New Indian PV guidelines were introduced in January 2018. Indian authorities upload reported AEFIs to the Uppsala monitoring centre. One issue identified by the company was that their level of access to Uppsala data gave them the possibility to look at AEFIs only by vaccine type, but not by manufacturer source. In accordance with Indian regulations, the company must demonstrate that their PV system has been audited. To achieve this goal, the company performed self-assessments and also received yearly an external contracted review.

SIIPL developed a PV Master File in 2016 (revised in 2017), in accordance with EMA, WHO and ICH guidance, for each vaccine. Version 2 of the SSIPL Risk Management Plan was prepared in January 2018, in accordance with European Guidelines and was indicated to cover all approved vaccines.

For Rotavirus vaccine, Indian clinical studies in support of Indian licensure had of the order of 10K participants. Since licensure, there have been 200,000 doses distributed. With regards to potential intussusception risk, in the risk management plan there was an indication of the need for active post-marketing safety surveillance in a “large” population, but that size was not yet indicated. The protocol for this active surveillance study was scheduled for finalization in 2 months from the time of inspection.

**Product recalls:**
The procedure for recall has been updated since the last inspection. Mock recalls were performed annually to test the system. The SAP system at SIIPL had information on batch distribution and capability to identify and issue notifications. SAP system could select mock or actual recall, identifies level of recall, input of reason for recall and could cover multiple products and/or batches of a product.

The last exercise was performed in September 2017 with a batch of TT vaccine. This vaccine was chosen because of its level of distribution in seven countries in multiple continents. Currently, there was capacity for system advice on message delivery failure but there was no delivery notification receipt enabled in the system. The procedure described telephone contact in the event of delivery failure or if there was no email contact. In the report of the last exercise, responses were received from all seven first level distributors (SII in-country agents) within 24 hours indicating nil vaccine in stock. However, within the mock recall exercise there was no information requested or supplied to show that the distributor had forwarded the letter from SIIPL to the customers or sought feedback. The quality agreement with the agent doesn’t specifically indicate the need to have systems in place to manage recalls, including the further distribution of SIIPL notification, nor reporting to SIIPL.

Self-inspection:

Procedure to conduct self-inspection was in place. The document covered all areas of interest including production, Quality Control laboratories, Quality Assurance and warehouse.

Provisions were in place to identify and train auditors from different departments. A list of 66 qualified auditors was available. 34 out of 66 were identified as team leaders all belonging to the QA department. The lists of audits planned and performed in 2017 and 2018 were reviewed and found appropriate.

The QA department was assessed by specific auditors invited from external parties.

Yearly, all departments are visited at least once by internal auditors. In addition, during the year 2017, 24 national regulatory inspections were conducted at SIIPL and were considered among the activities in place to review, inspect and audit the quality system.

Quality audits and suppliers’ audits and approval:

Vendor qualification was managed through relevant procedure. Each supplier was categorized as critical or non-critical depending on the materials/service provided. The current version of the procedure has recently introduced a number of improvements including a more stringent frequency of re-auditing (2 years for critical suppliers and 3 years for non-critical) and a thorough review of all existing Quality Agreements (QAs). For this reason, most of the quality agreements checked during the visit, even if still valid, were in the process of being re-issued to comply with new provisions.

All suppliers have been subjected to a pre-evaluation based on a questionnaire, eventually followed by audit on site. Quarterly and annually the vendor list was updated. The last approved vendor list for rotavirus vaccine was dated 08/2017 and for rabies vaccine, the most recent update was in 11/2017.

The vast majority of incoming materials have been subjected to testing, even if they were not considered critical.

The qualification of the vendors was spot-checked:

- Supplier of glycine. It was recently approved also for rotavirus vaccine production. It was already approved for other vaccines. 61 batches of the same products have been used in other productions with no
objection. Next audit planned in April 2018.

- Supplier of sucrose for production. It was already approved for other products (13 lots already purchased from the same vendor).
- Supplier of BPL, used in the inactivation of rabies vaccine. It was requalified in January 2018. It was already approved for other vaccines. 11 batches already purchased in the past 2 years. The issuance of a quality agreement was ongoing.
- Supplier of FBS for both rotavirus and Vero-Rabies vaccines. The vendor was already qualified and in June 2016 its qualification status was confirmed by providing a new questionnaire. The Quality Agreement in place was dated 2012 and was still considered valid, however according to the new procedure it should be updated every 2 years. As the product is considered highly critical, an additional suitability testing is foreseen to verify functionality in cell cultures.
- Supplier of trypsin in bulk manufacturing areas. The vendor was requalified in 2017 and an additional audit was planned in June 2018. A Quality Agreement dated 2012 was in place. Trypsin was considered a highly critical reagent, a suitability test was performed on each consignment, thus the qualification of the vendor was considered continuously monitored.

**Personnel:**

An overall organizational chart indicating key personnel involved in manufacturing, quality control, quality assurance, warehouse, engineering and department wise organogram was available. Individual responsibilities were defined, described and accepted by personnel in job descriptions. All departments at the site had sufficient number of personnel with appropriate qualifications with respect to education, experience and training to perform their functions.

**Training:**

Procedure for training all employees was in place. Each Head of Department (HOD) had the responsibility of identifying initial training needs of each operator. Regular theoretical training was provided each year on the procedures in place in each department (Plan related to 2017 and 2018 reviewed). On the job training was only foreseen as initial qualification and was claimed to be performed up to the satisfaction of the HOD; routine manual operations were considered sufficient to maintain the qualification status of each staff unit.

For aseptic operators, three consecutive aseptic gowning must be performed before having access to manufacturing areas and a confirmation of proper gowning was repeated every 6 months.

Deficiencies regarding the training of personnel were raised and adequately addressed by the company through the provided CAPA.

**Personal hygiene:**

Nine different SOPs were in place to detail and identify medical tests for each employee. Monthly check-up by an internal physician was foreseen; eye-test for visual inspection operators was done every 6 months; records of medical check-ups were maintained in specific files. The vaccination status of each employee was defined in relevant procedure and people at risk were subjected to repeated boosts.

**2. Production system**

Resources were available, including qualified and trained personnel, premises, equipment and services,
materials, containers and labels, procedures and instructions, laboratories and equipment for in-process and other controls. Procedures for qualification and validation of equipment, manufacturing processes and quality control testing methods were in place. Qualifications and validations were performed. Systems were in place for handling complaints and recalling batches of product from sale or supply.

The premises were generally maintained at an acceptable level of cleanliness. The company had provisions for personal hygiene and sanitation in its production facility. Manufacturing areas were provided with airlocks for personnel and materials entries and exits. Gowning procedures for access to the classified manufacturing areas were in place. Cleaning, disinfecting and decontaminating procedures along with the environmental monitoring program were in place to control the non-viable and viable contamination levels in the production areas.

**Waste management:**
Specific provisions were foreseen for each type of vaccine, based on different inactivation studies.

**Rotavirus manufacturing:**
Waste management of rotavirus contaminated materials was performed according to the relevant procedures in the bulk manufacturing area and in the fill-finish area respectively.
A dedicated autoclave for decontamination was present in the bulk manufacturing area, where high titre virus and permissive cell substrates were manipulated. A treatment by temperature at defined period of time has been demonstrated to properly inactivate the virus; to assure effectiveness of inactivation, a standard autoclave cycle was routinely applied for decontamination purposes.

**Vero-Rabies bulk manufacturing:**
The assessment of virucidal activity of various disinfectants against rabies vaccine virus was discussed through the protocol “Assessment of virucidal activity of disinfectants against rabies virus”. The study was aimed at identifying the highest concentration of disinfectants which was non-toxic to Vero cells and at verifying the efficacy of the disinfectants against rabies virus.

There was no spill kit in place in case of spillage of infectious material in the manufacturing facility.

**Production of Rotavirus and Vero-Rabies vaccines:**

- **Rotavirus vaccine:**
  Process validation of rotavirus vaccine has been performed in 2017 for prequalification purposes and it was foreseen to be repeated whenever changes with possible impact on product quality were introduced.

  The specification for CMVP (Clarified Monovalent Pooled Harvest) titre, expressed in CCDI$_{50}$ was set at the time of development of the product, when clinical lots were obtained. It was stated that in case of low yield, the final blended product (with defined target specification) would have been adjusted by mixing higher titre CMVPs. However, by analysing data related to about 300 CMVPs/strain manufactured in 2017 for commercial purposes, a much higher titre was always achieved, without any correction of the specification, as low virus contents were only considered Out of Trend results.
  - It was reminded that to ensure consistency of production, CQA as well as CPP need to be properly identified and eventually adjusted in order to keep under control the process and the product.
  - In addition, and given that the same specification was applied for suitability tests used for approving critical reagents including Fetal Bovine Serum and trypsin, the impact of such inappropriate specification was considered significant and not acceptable.
To confirm that the above mentioned higher yield had not affected the viral sequence, genetic stability was also investigated during inspection. Indeed, a specific study was conducted by SII in October 2017, by sequencing full length VP7 gene in 3 consecutive commercial lots and comparing results to parental strain, master and working seeds. 100% identity was demonstrated in all cases.

- However, it was recommended to extend virus replication by at least one additional passage, to confirm genetic stability at the End of Production.

The manufacturing date was assigned to the finished product based on the last available potency test, which could be performed up to 1 year after the actual manufacturing, with an intermediate storage at -20°C. Data were available indicating no significant loss of potency following storage for two years at -20°C.

- However, cumulative stability data after 4 years of storage (1 year at -20°C and 3 years at <25°C or 2-8°C) were not available, neither for potency nor for sterility.

**Upstream process of Rotavirus vaccine:**

Manufacturing process of rotavirus vaccine bulks was carried out in a dedicated building. The process was standardized in terms of volumes and time requested for each activity, thus routinely one lot of one single strain was produced per week, followed by 2 days dedicated to clean up procedure.

Overall, three steps of cell passaging using Vero-cells were performed, followed by inoculum with working seed virus of 5 different strains (G1, G2, G3, G4 and G9) at different MOIs depending on the strain. Uninfected control cell cultures were taken at this stage for subsequent QC tests. After incubation at 36°C to promote virus replication, roller bottles were subjected to one cycle of freeze-thaw; harvests were collected and immediately mixed with the stabilizer solution, containing sucrose and glycine. Clarification was achieved through 30 µm filtration (Clarified Monovalent Harvest Pool) and CMVPs could be stored for up to 5 years at -20°C.

Antibiotics were not used during production; culture medium was supplemented with fetal bovine serum; viral infection was promoted by the addition of low amount of porcine trypsin, the same used to split cells.

During inspection, manufacturing activities related to cell splitting were observed and some weaknesses identified, as detailed below.

Four operators were present in a wide cubicle dedicated to cell cultivation: two of them operating in class A and two for supporting activities (transfer of flasks/roller bottles from and to the incubation room). Cells were manipulated under an extended LAF with four adjacent working stations; operators moved from one working station to the adjacent one to perform different steps (trypsin addition, splitting).

- Manual pouring of medium containing cells, from flask to flask or from roller bottle to roller bottle was foreseen during manufacturing process. This practice was considered of high risk of i) spillage and ii) residual medium on the neck of containers, which might provide a vehicle for contamination.
- In fact, a Bunsen burner was used under the laminar flow to flame flasks/bottles, with the aim of drying bottle necks and eventually eliminating microorganisms; this practice clearly creates turbulence (smoke test reviewed) by disturbing the LAF.

During the observed operations, only limited environmental monitoring was performed.

**Downstream process of Rotavirus vaccine:**

The building for filling rotavirus was originally built for rotavirus production in 2010, and at that time it was also used for the production of three consecutive validation batches of Hib and MenA vaccines (so called PCV vaccines).

In 2012, this building was readapted for OPV filling operations, in order to meet a global emergency, and then used for measles. In 2016 it was dedicated to rotavirus filling (live attenuated vaccine) and, for
commercial reasons (not enough rotavirus vaccine to justify the exclusive use of one filling area for this product), it was also used for MenA and Hib vaccines (inactivated).

A general change over procedure was in place in the facility. Seven consecutive days of standard cleaning (see below), alternated by the fumigation at night as per relevant procedure, were foreseen by the changeover procedure. Several foggers were used in pre-specified positions in classified areas, to cover all rooms where the product was exposed, as well as immediate surrounding areas. During the fogging process, the HVAC was fully operational. Moreover, all product contact equipment was dedicated (gasket of tank, filling groups with pipes and needles, vessels). Lyophilizers were cleaned and sterilized in place (SIP) following the standard procedure.

Two preliminary and not complete studies were performed in 2009 and 2015 to validate some aspects of the changeover procedure applied for measles; in January 2018 some additional elements were evaluated specifically applicable in the rotavirus area. Overall the three studies were not conclusive and do not fully support the use of live and inactivated viruses in the same facility.

- The report related to rotavirus facility was issued on 25/01/2018, when filling of Hib had been already performed.
- The effectiveness study did not use all the contact materials used in the aseptic processing area, but was limited to plastic of Petri dishes.
- Positions of Petri dishes in the study were not detailed, thus it was not possible to evaluate whether all the areas were properly reached by the defined concentration of the fumigant.
- The concentration of decontaminating agent was not measured throughout the facility to demonstrate the effectiveness of decontamination process.

The report related to the last changeover performed in the concerned building was reviewed and the following deficiencies have been found:

- Pumps dedicated to different vaccines (Rota vs. Hib) were not properly traced by reporting the unique ID codes, thus a thorough control of the changeover procedure could not be performed, even by QA. The sterilization cycle of Lyophilizer, performed prior to starting filling operations of Hib vaccine, was not complete in that only one steam injection was performed instead of two, but the area was released for subsequent production. Following this observation, during the inspection, SII reported that the correct sterilization cycle was indeed performed in time, even if its absence had not been properly identified nor assessed by QA before releasing the area for production. Indeed, several “forcing” activities were traced by the system, in all lyophilizer sterilization cycles, whose extent and impact could not be evaluated.

Deficiencies regarding the manufacturing of Rotavirus vaccine were raised and adequately addressed and/or committed to be addressed by the company through the provided CAPA.

**Visual inspection:**

Visual inspection of active component vials was semi-automatic. There was conveyor feed to a machine where the operator manually checked the vials. If a fault was identified, conveyor was stopped and rejected vials were transferred to a reject box. Passed vial trays were also inverted to check for small particle contamination. At the end of the shift, there was reconciliation of rejected vials with identification of fault type. There was an overall defined rejection limit. Limits for individual fault types were also set. Operators dedicated to visual inspection underwent regular six-monthly eye-check. The initial and ongoing qualification records of an operator selected from a batch record were reviewed. Three runs were performed. Criteria set for critical were 100%; major (A) 90%; major (B) (80%) and minor defects (70%); also <5% false positive.
rejections were identified. Routinely, operators read vials for 30 min with 5min rest intervals. AQL sampling of passed vials for inspection was also performed with limits set for rejection rate.

**Diluent:**
The filling of diluent can be performed in two buildings, where two different filling lines could be used. One filling line was visited during inspection. The line was in use for filling the pentavalent vaccine. The same filling capacity was used for all products. Vials were inspected online by 8 laser stations. A verification run with 50 vials (40 defects and 10 good) was performed daily and the Knapp test was repeated annually. Once filled, vials were stored up to a request from the market, which routinely triggers labelling.

- **Vero-Rabies vaccine:**
The flow chart of the manufacturing and control test of Vero-Rabies vaccine was presented and discussed with the company.

**Upstream Process of Vero-Rabies vaccine:**
Process validation report and raw data for manufacture of the inactivated purified rabies antigen bulk were made available during inspection.

Process validation was based on data from 3 commercial production batches. According to the batch records, all batches were produced using cube systems for cell propagation followed by virus infection. One harvest resulted in one concentrate. Up to 7 harvests were further processed. The inactivation kinetic studies were conducted with harvests 1 through 7 for 24 hours at 2-6°C using BPL at a concentration. As regards purification a specified column followed by TFF system was used.

The data indicated that the commercial process was acceptably validated and capable to manufacture consistently inactivated, purified rabies antigen. Studies on removal of process and product related impurities such as neomycin, host cell protein and DNA were performed and the results showed that these contaminants were reduced to acceptable levels in the bulk material.

Qualification, cleaning and process validation of columns was spot-checked.

The cleaning validation was executed according to an approved protocol. Report and raw data were available. Five batches were included in the study. The following parameters were applied: pH, bioburden and BET. All established criteria were fulfilled.

A life span study for the column was planned to be performed concurrently. A study protocol was approved. Change control for the use of a new column with higher capacity in antigen purification of Rabies bulk vaccine production along with a risk assessment was made available.

The following concerns regarding the validation were raised:

- It was understood that any rabies vaccine provided to UN agencies was produced according to the process found to be acceptably validated through WHO PQ assessment, i.e. any change to the process found to be acceptably validated through this inspection needs to be submitted to WHO for preapproval assessment.
- As regards the life-span validation of the columns, an approved protocol on the reuse assessment was made available. The protocol covered only the reuse assessment for the initially used column. As it was planned to employ the initially used column for purification of 1st and 2nd harvest and the second column with higher capacity for purification of the 3rd to 7th harvest due to higher antigen content, a reuse assessment should be performed for all currently used and all column sizes intended for use in future routine production. The proposed assessment for BET and MLT (bioburden) should be changed.
to be performed on every run to ensure absence of any contamination. Assessment of antigen loss overtime should be based on calculation of total antigen yields per run.

Qualification, cleaning and process validation of the TFF system was made available. The cleaning validation was executed according to an approved protocol. Report and raw data were available. Three batches were included in the study. The following parameters were applied: pH, bioburden, conductivity, TOC and BET. All criteria were fulfilled.

A life span study for the TFF system was planned to be performed concurrently to assess the number of usage cycles. The protocol of this study was approved by QA. The study was considered appropriately designed however it was recommended to assess BET and bioburden after every run.

Extractables and leachables testing results/validation report from the supplier of EVA bags were available. It was certified that the EVA bags comply with compendial requirements for parenteral (EP 1.3.7). Validation data of extractables and leachables of EVA bags were provided by the supplier. These bags could be used for storage of monovalent rotavirus bulks for up to four years at -20°C. These bags were also used for storage of other bulks at the company. There was no physical check of container integrity performed, although technology was provided by the bag supplier to perform such tests. The company argued that maintenance of sterility and conservation of titre were indirect evidence of closure integrity. This was not considered acceptable.

No commercial process validation data were available on the harvest, inactivation and purification of rabies antigen from the 7th consecutive virus harvest onwards. The BMR still included the possibility to produce 1-15 consecutive harvests from one infected cell culture system during routine production.

- The BMR should be amended to reflect the currently validated state of the commercial manufacturing process, i.e. only up to 7 consecutive harvests were assessed in the PV.

**Downstream process of Vero-Rabies vaccine:**

Process validation of blending, filling and lyophilisation was executed on four batches of Rabies vaccine. The batch sizes of blended vaccine and of filled vials were defined.

The lyophilisation cycle was defined based on previous process experience for MRC-5 rabies vaccine. Samples were drawn for residual moisture and antigen content from different positions on the shelf (right, middle, left) and different shelves (top, middle, bottom or all shelves). All predefined criteria were fulfilled for all parameters set.

In conclusion, based on the data provided, the commercial blending, filling and lyophilisation process indicated consistent performance with regard to the batch size evaluated.

Deficiencies regarding the manufacturing of Rabies vaccine were raised and adequately addressed and/or committed to be addressed by the company through the provided CAPA.

### 3. Facilities and equipment system

The building under the scope of this inspection covering Rotavirus and Rabies vaccines were visited.

The sterile product manufacturing areas of Rotavirus and Vero-Rabies vaccines were access controlled. They were provided with anterooms, change rooms and air locks. Sterile products manufacturing areas were under positive/negative air pressure with pressure differentials to prevent risk of cross contamination. Dedicated
facilities were used for handling highly toxic and hazardous material. Pressure differential of 10 to 15 Pascal was maintained between adjacent areas of two different classes. Pass box/hatch or material transfer ports were installed for transfer of materials across the rooms when appropriate. Facilities were equipped with suitable utility supplies in respective process areas.

Overall, the manufacturing facilities for Rotavirus and Vero-Rabies vaccines were found in appropriate conditions of cleanliness and were organized in a logical order. A separation between infected and non-infected area was in place and there was no observed cross flows of personnel and materials. The temperature of critical storage rooms and critical equipment including the deep freezers, cold rooms, incubators, liquid nitrogen containers and the differential pressure were monitored through the building management system.

The filling machine for rotavirus vaccine had the capability for online periodic checking of volume by weight. However, there was an open issue related to an electrical problem preventing use of this capability. The filling machine supplier has been unable to determine the cause of this problem. The same model of this filling machine was not used elsewhere in the company. The company has reverted to manual checking of volume each 30 minutes.

After lyophilisation, trays of vials were transferred manually to the capping room. There was no on-line automatic check for misplaced or missing stoppers. It was stated that there was manual check when loading the machine.

Four different buildings could be used for storage of materials and reagents, some of them being dedicated for export products. The warehouse was visited: ground floor was dedicated mainly to packaging material and 1st floor to reagents. Cold rooms at 2-8°C and -20/-30°C were present for storage of temperature sensitive materials, as well as areas dedicated to 15-25°C storage. Facilities were adequately organized, separate quarantine areas were identified for materials under tests. Rejected materials were also adequately separated and identified.

Incoming and outgoing materials were managed through the SAP system, which was challenged during the inspection through spot check for traceability of FBS and trypsin lots currently in use. Upon receipt of materials, relevant procedure was followed to identify storage locations and temperatures. Specific provisions were present for bulk vaccines purchased from outside sources, which were dispatched directly to the building in which they would have been formulated and filled.

The premises and equipment were considered adequately designed and maintained however deficiencies were raised and adequately addressed and/or committed to be addressed by the company through the provided CAPA.

➢ Qualification and validation:
Provisions for qualification and validation were in place and covered premises, equipment, utilities and systems, processes and procedures at periodic intervals and when changes have been made. Preventive maintenance programme and calibration plan were in place.

The validation master plan was in place. Annual validation plan shall be prepared for existing production facility to track various validation activities to be carried out in the facility in a calendar year. The validation plan for the years 2017 and 2018 for the rota and Vero-Rabies bulk vaccine production facility was spot-checked.

The qualification and validation of the following equipment was spot-checked.
Validation of aseptic process (Media simulations):
The procedure for media fill process simulation was in place.
Soybean casein digest media powder was used. Filled vials were incubated at 20 – 25 °C for 7 days and 30 – 35 °C for 7 days. Growth promotion test was performed at the end of incubation.

- Aseptic simulation for upstream process of Vero-Rabies bulk:
Aseptic simulation report for Rabies bulk process was spot-checked. The initial aseptic simulation was performed through only one run and not three runs as expected. In addition, only one unit of cell cube system was considered during this aseptic simulation instead of four cell cube systems used during the manufacturing process. The aseptic simulation was performed on yearly basis and not biannually without adequate justification and documentation.

- Media fill simulation for downstream process of Vero-Rabies vaccine:
The MFT for the filling line with regards to the manual aseptic activities for loading of the lyophilizer was performed annually and not biannually as expected. The initial MFT validation of lyophilized Vero-Rabies vaccine was performed through 3 runs performed. The last MFT for the filling line including the manual aseptic activities for loading of the lyophilizer was performed in 2017 with full capacity of the lyophiliser. The sterilisation of the lyophiliser was intimated during this MFT. The last MFT performed in December was limited to the liquid vaccines and not including the manual aseptic activities for loading of the lyophilizer. The MFT test results for 2016 and 2017 were all presented as conclusive by the company.

- Aseptic simulation for upstream process of Rotavirus vaccine bulk:
As for Vero-Rabies bulk, the aseptic simulation was performed yearly and not biannually. The last simulation performed in 2017 was spot-checked. This covered roller bottle seeding, decanting, stabilizer addition, filling of intermediate bulk bags and blending.

- Media fill simulation for downstream process of Rotavirus vaccine:
Media fill test were performed according to the relevant procedure. Three runs were initially performed to release the area. MFT were repeated twice per year. The fill volume of 1ml was used; being representative of both monodose and 2 doses presentation of the vaccine. The full batch size was always used. A rotation of the four identical lyophilizers was foreseen to include each once per year in the media fill tests.

Lyophilizer:
Requalification of the sterilisation cycle (SIP) was spot-checked. Thermocouples coupled with biological indicators were used. Routine sterilisation cycle was used for the qualification. The worst case conditions were not considered.

Requalification of lyophilizer was spot-checked. During requalification the following was checked: the calibration status, alarm/safety checks, power failure-emergency stop test, separating valve leak test, shelf cooling time, chamber evacuation time, pressure rise test and shelf heating time.
The initial and only thermo-mapping of the chamber of the lyophilizer was performed in 2006. There was no thermo-mapping performed since the initial qualification of the equipment.

Production department was in charge of performing integrity test of the vent and nitrogen filters on a monthly basis. Filters were changed every 6 months. The SIP was performed on weekly basis and not before each manual load of the lyophilizer.

Depyrogenation Tunnel:
Requalification of depyrogenation tunnels (rabies facility) was spot-checked. The integrity test of the HEPA filters was performed every 6 months. 3, 4 and 5 ml vials were considered during the annual qualification. The test results were satisfactory including the temperature and bacterial log reduction. It was not the current
practice of the company to sanitize the internal surfaces of the cooling zone of the depyrogenation tunnel after the interventions of the qualification operators.

**Autoclaves:**
The building dedicated to the manufacturing of Vero-Rabies bulk was equipped with three autoclaves, two for sterilisation and one for decontamination purposes. Leak test was performed daily and Bowie Dick test monthly.

Requalification of autoclaves was spot-checked. One run for heat distribution using thermocouples and BIs was performed.

A viral decontamination study (rabies bulk vaccine) was performed. The report of decontamination of rabies virus by heat treatment was spot-checked. The company stated that based on the evaluation of the results, it was recommended that the autoclave cycle used for inactivation of rabies virus at 121°C for 60 minutes completely inactivate the live rabies virus from working seed, wash spent and concentrated rabies harvest.

However, the load pattern used for the viral decontamination study through the three runs was not matching with the load pattern used in routine decontamination cycle. More items and materials were used during the routine decontamination cycle than the load pattern used for the validation of rabies virus decontamination, without any documentation or justification.

**Vial washing machine:**
Vial washing machine qualification in rotavirus filling facility was performed last time in July 2016. Both vial capacities were challenged with the following tests:
- Presence of large particles;
- Sub-visible particles;
- NaCl residues after spiking;
- Protein residues after spiking with Human Serum Albumin;
- Bioburden of recycled WFI.

Daily tests were performed by adding WFI and checking visible particles.

**Capping machine:**
The capping machine was not provided with a probe or sensor to reject displaced rubber stoppers.

**Air Handling Units:**
The classification of the manufacturing areas was performed initially at rest and in dynamic conditions. The annual classification of the classified manufacturing areas was performed only at rest.
- There was no classification at dynamic conditions in place.

The last qualification of the Laminar Air Flow hood for cell passaging was reviewed. It was performed in November 2017 and it was repeated every 6 months.

Video records of the air flow visualisation studies in the blending and filling areas were reviewed and showed appropriate air flow pattern. Smoke test studies for air flow pattern were conducted every two years.

**Water systems:**
Details of the water system production, capacity and sanitization were provided in the site master file.

- **Water for injection**
Specific loops per each facility were present in the plant. In case of different facilities in the same floor of the same building, 2 dedicated loops have been established.

During inspection, the loop of rotavirus bulk manufacturing area at first floor, was spot-checked. WFI was obtained by multicolonm distillation of PW and circulated at a temperature >70°C. Five points of use were provided in the facility, three in the washing area, one for media preparation and the last one for GS vessel. In addition, a sampling point at the generation and one at the return loop were also provided.

The initial qualification took place in 2014 with Phase I, Phase II and Phase III studies; routinely WFI was sampled as per the relevant procedure, which foresees sampling of all user points once/week and a daily sampling at the generation and returns points.

Data related to March-April 2017 were reviewed and no excursions were observed. Trend analysis was performed once/year.

5 Laboratory control system
Entry to all QC buildings/areas and rooms was restricted to specific personnel (list of authorized personnel was given at entrance) and was controlled by access code. Visitors and guests had to sign in before entering the QC area or animal housing.

The QC laboratories carried out testing of rabies vaccine in different buildings (e.g. description, BSA content, particulate matter, container/closure integrity, antigen content by SRID), (e.g. sterility test, BET), (e.g. residual moisture), (e.g. mycoplasma), viral vaccine block (e.g. residual host cell DNA) and animal housing labs (e.g. general safety/innocuity, NIH potency, pyrogen, test on effective inactivation).

QC buildings had dedicated areas/labs for QC testing of rabies, rotavirus, HepB, and BCG vaccine, diluent and a common QC testing area (instrumental lab for e.g. preservative content, container/closure, aluminium content, BSA content).

During the audit the conduct of the following in-process tests were observed:

- Test for effective inactivation in mice on inactivated rabies antigen samples in the animal housing building, ground floor.
- SRID testing of purified rabies antigen samples.

The procedure of sampling at different stages in the process of rabies vaccine production was in place (last change due to request of WHO to do mycoplasma testing on every harvest).

Samples receipts in QC labs were managed through inward sample and analytical registries specific for each product; the samples codes, number and size of samples, date of delivery, are recorded and signed off.

QC samples were delivered by QA (collected in production and delivered to QC lab) accompanied by test request form; IPC samples were delivered to QC by production personnel.

If samples were not directly tested by the respective QC lab, they were kept either in cold storage (dedicated shelves) or freezer. All spot-checked equipment was in calibrated state according to labels.

The performance of the SRID test for determination of the rabies antigen content was showed for samples of purified rabies antigen. Specifically, addition of diluted test samples to punched wells and documentation of test conduct was observed. Reading of plates was done manually by measuring the rings using a Vernier caliper (calibrated once a year, was in calibrated state). The radius of the diffusion zone for each sample and reference dilution was measured 2-times independently, then the mean of the two measures was determined and transferred to a validated excel sheet for calculation of the antigen content. The calculation by excel was verified prior use. Performance of the reference standard was monitored through a control chart as described.
in the document Preparation, Calibration and Handling of in-house reference standard for rabies vaccine and its intermediates.

**Management of OOS test results**

OOS test results were reported and processed according to procedure in place. If test result did not comply with the specification defined for a specific sample, the analyst reported this result to the supervisor/head of QC. Subsequently an intimation form was filled out covering the product, batch number, date, test result and specification, analyst name and signature. The form was then signed off by the head of QC and send to QA. Further information including the status of calibration of used equipment might be requested. Based on the results and the additional information provided a decision on the repetition of the test on stand-by samples or on the confirmation of an OOS result was made by management group (QC&QA).

**Qualification of in-house reference standard:**

The general policy and the management of biological reference standards and in house reference standards were laid down in relevant procedure.

The preparation, calibration and handling of in-house reference standard for rabies vaccine and its intermediates were described in relevant procedure.

The in-house reference material was derived from a vaccine lot, manufactured and controlled according to approved procedures.

The procedure for calibration of the reference material was in place and relied on the availability of an international or national (secondary) standard. In general six independent assays were conducted. Based on the results, a value was assigned to the in-house reference. The reference material was monitored by established control charts. The control charts were independently evaluated quarterly for any trending. Reference data of the control chart and trending was reported annually in the PQR.

**Method Validation:**

- **Test for complete inactivation by cell amplification (rabies)**
  Validation of the test for complete inactivation by cell amplification on MRC-5 and Vero cells was validated for sensitivity, specificity and robustness. Test was performed for 21 days. Positive and negative controls were included in each run of the assay. According to the company the test was planned to be revalidated for amplification on Vero cells following start of commercial scale production.

  Samples were diluted and then spiked into inactivated material. Dilution corresponding to specific titer gave positive results. From the report, it was not clear that three independent runs were conducted to determine the limit of detection.

- **Determination of the rabies antigen content by SRID:**
  The SRID test was revalidated after a modification of the assay and change in the sheep anti-glycoprotein serum. The validation was executed in 2010 according to a preapproved protocol. The SRID assay was validated for specificity, range and linearity, precision, accuracy and robustness. The validation report was approved in 2010. The data demonstrated that the assay was properly validated for the intended purpose. The execution and reporting of the method validation was of adequate quality.

  - Based on the observation that method validation reports were of varying quality, it was recommended to provide a harmonised template for method validation reports reflecting the actual execution (e.g. number of runs, validation conducted from to, identification of batches/samples used) and results of the validation activities.

**Preparation and validation of working rabies challenge virus standard**
The rabies challenge virus standard (CVS) was prepared according to relevant procedure. The CVS was delivered to SSI through the CDL Kasauli, India and originates from the Pasteur Institute. CVS stocks were made following intracerebral injection into mice. The mice brain was harvested, grinded and clarified. After preparation, the virus titre of the CVS stock was determined by 6 independent tests in mice. The assigned titre of the currently used CVS was determined. Documentation on the consumption of the latest CVS stocks initially prepared in 2017 was made available.

**Preparation of anti-rabies glycoprotein sheep antiserum (AGPS):**
AGPS was used for the conduct of SRID and GP-ELISA. A new AGPS was raised according to relevant procedure. The immunizing antigen was derived from the PM strain. The inactivated antigen was prepared as described in the SOP in 5 steps including sucrose gradient purification. The qualification, standardization and calibration of the new AGPS Batch (in vials, lyophilized and stored at -20°C) was performed by evaluation against NIBSC anti-rabies GP-serum.

**Animal testing:**
For rabies, the NIH potency assay, pyrogenicity test and the test of effective inactivation were performed in animals. During the visit, the test for complete inactivation by intracerebral injection into mice was observed. Restriction of entry to animal house was through access codes; appropriate procedures and recording were in place for staff entering the animal housing. Procedures for disinfection and gowning were in place for animal breeding and testing facilities. Third floor of the animal housing was used for animal breeding (i.e. mice, guinea pigs, rabbits). Second floor was divided into breeding and testing. First floor was dedicated to animal testing (e.g. rabies NIH potency and test for effective inactivation).

For rabies test area and laboratories, additional gowning/shoe protection was required. Dedicated room was provided for inactivated rabies antigen and NIH potency tests. All waste material was autoclaved before exiting the building. Residual sample of potentially active material was heat treated before autoclaving. Available equipment was in calibrated status. The animal testing was spot-checked.

**Rotavirus diluent testing:**
For rotavirus vaccine diluent, the claimed label content was 9.6mg/mL citric acid and 25.6 mg/mL bicarbonate. However, to date, there was no verification of citric acid and bicarbonate content performed neither for lot release nor during product development. An identity test only was considered for release. A protocol and report of assay of 11 commercial batches was presented. It was indicated that a change control had been initiated for introduction of limits of 80-120% of labelled content. Internal review by QA indicated a requirement for method validation prior to application of the specifications to the final product. No explanation could be provided as to why method validation was not performed prior to analysis of commercial batches.

**Stability Studies (rotavirus vaccine):**
At -20°C storage, studies showed no significant difference between initial titre and titre after 24 months. At 25°C storage, data at 36 months in specification were shown. Based on this study, the statistically extrapolated expiry time was 53 months. The label claim was for 30 month storage at 25°C. For storage at 2-8°C a 0.1 log titre loss was observed over 36 months and it was not possible to extrapolate an expiry time at that temperature.

At 40°C, the statistical analysis predicted vaccine could be stored for 9 months, before reconstitution.

The company has conducted a stability study, following reconstitution, of seven clinical batches after storage at 2-8°C. To date, there have not been similar reconstitution studies after storage at NMT 25°C. Data from some batches were reviewed. For reconstituted vaccine stored at 2-8°C or NMT 25°C, there was little or no titre
reduction over 48h. However at 40°C, for the batch starting at 6 log, titre went below release limit (5.6) after about 4h at 40°C. All serotypes had similar behavior.

Batches that had been stored for 36 months at 25°C were no longer available for conducting reconstitution stability studies. Further studies were planned when samples would have been available.

Environmental monitoring:
Summary report for 2017 was Spot-checked. All test results were within specification and established limits except one OOL for aseptic operator at forehead location on date of exposure. The trend of the EM data was limited to a monthly basis.
Summary report for 2017 Vero-Rabies bulk vaccine was spot-checked. All test results were within specification and established limits.

6 Materials system

- **Materials/Reagents:**
  Each consignment of materials after receipt by Warehouse department was initially inspected. Different batch materials were segregated.

Separate areas have been allocated for storage of raw materials, packing materials. Materials were stored at controlled temperature depending on the storage requirement of the materials.

Standard operating procedures for sampling of the raw material and packaging materials were in place. The raw materials were approved or rejected by QC Department based on the results of analysis.

- **Finished products**
  Rotavirus finished products were stored in the same building where they were filled. A cold room at -20°C was foreseen for storage of naked vials of rotavirus vaccine, which were found properly identified. The batch number code was indeed able to distinguish mono and double dose products, as well as temperature of storage.

The same storage room was also used for other already labelled finished products, like Oral Polio Vaccine. Labelled vaccines ready for shipping were stored in a dedicated 2-8°C cold room.

7 Packaging and labelling system

Printed packaging materials like labels and cartons were stored under lock and key with restricted entry for authorized personnel. VVMs stored appropriately and density checks were performed before use. Spot check of packing BMR indicated hourly in process control performed for label content. Carton labelling and PI were also checked at beginning, middle and end of packaging run.

Rotavirus vaccine packaging was performed in adequate manufacturing building.

Rotavirus vaccine could be presented either in a kit with one vial of vaccine, one of diluent, and one syringe with its adapter, or in larger boxes containing 50 vials of vaccines, with diluent packaged in separate cartons and syringes and adaptors also supplied.

8 Distribution and shipping

For lyophilized vaccines, the packaging for insulated shipment internationally was the same as that used for other lyophilized vaccines from SIIPL. The same packaging configuration was used for rotavirus vaccine whether it was intended for labelling with VVM30 (for planned Indian EPI usage -from March 2018- and UNICEF shipments once prequalified, where storage at 2-8°C was indicated) or without a VVM (currently for
Indian private market, where storage below 25°C was indicated). Twenty-four cartons (1200 vials) were packed with 12 coolant packs conditioned to -20°C. The company provided a 2012 approval from WHO of the validation of this configuration against WHO international shipping guidelines. The study indicated that all monitoring points were less than 30°C at 75 hours. Diluent was shipped in the same insulated box but without cooling packs.

For single dose combination packs (where the carton contains, active, diluent and a syringe) a different insulated packing configuration was used to avoid diluent freezing. However, that presentation had not been submitted for prequalification, as it was not intended for UN supply. Therefore, that packaging validation was not considered further.
Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as the Corrective Actions taken and planned, and committed to be implemented, Serum Institute of India Pvt. Ltd. was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

All the non-conformances observed during the inspection that were listed in the full inspection report as well as those reflected in the WHO Public Inspection Report (WHOPIR), were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.