World Health Organization

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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the Vaccine manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**Sanofi Healthcare Private Limited**, previously known as *Shantha Biotechnics Private Limited.*
Registered Office address of manufacturer	Sanofi House, CTS No. 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai 400072, Maharashtra, India Tel.: +91 22 28032000, Fax.: +91 22 28032939, E-mail: shipl@sanofi.com
Contact person	Dr Rahul Kulkarni Rahul.Kulkarni@sanofi.com Tel.: +91(8418) 220922, 220693/94/95 Fax.: +91(8418)220656
Inspected site	
Address of inspected manufacturing site	• Industrial Park, Survey No. 354, Muppireddipalli Village, Manoharabad Mandal, Medak District – 502236, Telangana, India D-U-N-S number: 860037243 GPS: Latitude 17.646190 / Longitude 78.494681 • S. No. 274, Athavelli Village, Medchal, Medchal-Malkajgiri District 501401, Telangana, India D-U-N-S number: 915076104 GPS: Latitude 17.740576 / Longitude 78.483877
Manufacturing license number	Medchal Site: Manufacturing License No. 01/RR/AP/97/V/R, granted by the Drugs Control Administration (DCA), Government of Telangana. MRP Site: Manufacturing License No. 01/MD/TS/2015/V/G, granted by the Drugs Control Administration (DCA), Government of Telangana.
Inspected site	
Dates of inspection	09 to 13 December 2019
Type of inspection	Routine inspection

Representative from the National Regulatory Authority	The national regulatory authority (NRA) of the country CDSCO, where the inspection took place was informed and their officials participated to the inspection.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Muppireddipalli (MRP) site: Quality laboratory, Suite 2A for filling, sealing, visual inspection, labelling, storing and shipping of vaccines Medchal site: Suite J Hep B, Quality control, Suite D and Suite F
Restrictions	Not applicable
Out of scope	MRP site: Suite 2C (TT bulk), Insulin Plant Medchal site: Suite H (FF) and, Suite G (FF)
WHO product numbers covered by the inspection	• Tetanus Toxoid Vaccine (10 and 20 dose) • Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-*Haemophilus influenzae* type b Vaccine (1 and 10 dose) • Cholera Vaccine: inactivated oral (1 dose) • Polio Vaccine - Inactivated (IPV) (5 dose)
Introduction	
General information about the company and site And brief summary of the manufacturing activities	Shantha Biotechnics Limited was established in 1993 and is now Sanofi Healthcare India Private Limited, acquired by Sanofi Company in 2009. Sanofi Healthcare India Private Limited is specialized in vaccines manufacturing, formulation, filling, visual inspection, labelling, packaging, Quality Control and distribution. Sanofi Healthcare India Private Limited commercializes ShanTT®, Shanchol®, Shan5® and ShanIPV®. The products in pipeline are Shan6®, Hepatitis A vaccines and Insulin therapeutics. The main activities in MRP site are related to the filling of the vaccines in Suite 2A, visual inspection and packaging activities as well as the quality control tests limited to the environmental monitoring and water testing. The TT bulk antigen manufacturing in Suite 2C was stopped in 2017. The main activities in Medchal site are related to the formulation and filling of vaccines, the manufacturing of drug substances of the cholera, whole cell pertussis, diphtheria,

	tetanus toxoids and Hepatitis B and PRP-T. The main changes since the last WHO inspection are: - shutdown in suite 2A (MRP Site) in November 2018 for open active RABS implementation. Commercial batches were initiated with Shan5 mono-dose presentation from 14 October 2019. No recall from the market has been recorded since 2009.
History of the regulatory inspections	The last WHO onsite inspection to Medchal and MRP site took place in 2017. The company has adequately implemented and committed to implement the corrective and preventive actions (CAPAs) to the raised deficiencies. The company has also provided the list of the regulatory authorities' inspections carried out since 2015.

Abbreviations

AHU	Air Handling Unit
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
APR	Annual Product Review
APS	Aseptic Process Simulation
BET	Bacterial Endotoxins
BMR	Batch Manufacturing Record
BPR	Batch Production Record
CA	Compressed Air
CAPA	Corrective Actions and Preventive Actions
CC	Change Control
CFU	Colony-Forming Unit
CIP	Cleaning In Place
CoA	Certificate of Analysis
CpK	Process capability
D	Diphtheria
DQ	Design Qualification
EDI	Electronic DeIonization
EM	Environmental Monitoring
FMEA	Failure Modes and Effects Analysis
FTA	Fault Tree Analysis
GMP	Good Manufacturing Practices
GPT	Growth Promotion Test
HEPA	High Efficiency Particulate Air
HepB	Hepatitis B
Hib	*Haemophilus influenzae* type B
HVAC	Heating, Ventilation and Air Conditioning
IQ	Installation Qualification

LAF	Laminar Air Flow
LIMS	Laboratory Information Management System
MB	Microbiology
MBL	Microbiology Laboratory
MF	Master Formulae
MFT	Media Fill Test
MR	Management Review
MRV	Measles Rubella vaccine
NCA	National Control Authority
NCL	National Control Laboratory
NRA	National Regulatory Authority
OQ	Operational Qualification
PHA	Process Hazard Analysis
pH	(-ve) logarithm of H^+ concentration
PLC	Programmable Logic Controller
PM	Preventive Maintenance
PQ	Performance Qualification
PQR	Product Quality Review
PQS	Pharmaceutical Quality System
PW	Purified Water
QA	Quality Assurance
QC	Quality Control
QCL	Quality Control Laboratory
QMS	Quality Management System
QRM	Quality Risk Management
RA	Risk Assessment
RCA	Root Cause Analysis
RO	Reverse Osmosis
SH	Single Harvest
SIP	Sterilization In Place
SMF	Site Master File
SOP	Standard Operating Procedure
T	Tetanus
UN	United Nations
UNICEF	United Nations Children's Fund
URS	User Requirements Specifications
UV	Ultraviolet-Visible Spectrophotometer
VVM	Vaccine Vial Monitor
WcP	Whole cell pertussis
WFI	Water for Injection
WHO	World Health Organization

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.

Some elements of the QMS were found deficient during this inspection. The company has provided the CAPA plan adequately addressing the deficiencies raised.

✓ ***Annual product quality review:***

Procedures for APR were in place. APR for Shan5, Shanchol, ShanIPV and ShanTT vaccines manufactured in 2017 and 2018 were spot checked.

APR of Shan5 vaccine:

APR for Shan5 vaccine (inactivated), manufactured in 2018 was spot checked.
Review of critical in-process controls and finished product results showed there was no change to the critical in-process controls and Shan5 final product results. No out of specification were observed. No batches failed to meet the established specification/s during 2018. All the test results of batches of Shan5 filled in 2018 met the pre-determined specification limits. No OOS and no complaints recorded.

The internal limit of rejection rate for manual visual inspection was in place however not justified and documented. The trending for the type of defects as critical, major and others was in place but not for each individual defect. The established limits (action and alert) were not reflected to the individual type of defect. A high rejection rate was observed for container closure, capping and printing defects. The measures to correct and prevent the inconsistencies or mal functioning of the related processes and equipment were not considered appropriate and timely followed.

APR for Shanchol:

In 2017, several batches of blends were manufactured, of which 2 were rejected due to sterility failure of the blend. Two batches of the finished product were said to be "released to market/partially rejected" due to OOS observed in active air sampling (AAS). The corresponding deviations were reviewed and found adequately addressed.

In 2018, there were several formulation batches for Shanchol, of which three were rejected. Two rejections took place in 2018 (and are thus reported in this APR) whereas the third was reported later, and thus not part of the 2018 APR. These batches were rejected because of incorrect formulation or because of a pH OOS in bulk antigen stability. On the other hand, a filled batch has been aborted because of product loss during recirculation through vessel inlet line drain valve.

According to Sanofi procedures, a new capability verification tool for assessing consistency was implemented in 2018. CpK index for analytical parameters and/or the capability through control chart were found acceptable by the company. No trend on stability data was observed during the stability monitoring.

Although the APR for 2019 was not released yet, the following information could be gathered. Several Shanchol blends and Drug Product batches were filled and tested. Of these, only 1 batch was rejected due to a calculation error during formulation. In addition to this, several other batches were still undergoing testing procedure.

APR for ShanIPV:
In 2017, several batches of IPV blends were manufactured. Of these, one aborted, due to bulk leakage found at the Y junction of the C-flex tube. The rest of blends were filled to produce the drug product batches (all approved).

In 2018, several formulation batches and filled batches were manufactured, which were neither rejected nor aborted. CpK index for analytical parameters and capability through control chart were found acceptable by the company. Of note, only the 5-dose presentation has been prepared since there was no supply demand for the 10-dose in 2018.

Neither product recall, returned and salvaged batches nor AEFI were reported in 2018.
No critical deviations, three major deviations (e.g. inappropriate recipe selection in the filling machine) with no impact on quality and one OOS (related to BET testing procedure) were reported.

APR for ShanTT:
In 2018, several formulation batches and filled batches were manufactured. No rejection, no abortion reported. One OOS was observed relating to aluminum content, because an incorrect specification was applied. CpK index for analytical parameters and capability through control chart were found acceptable by the company. No AEFI and no complaint and recall were reported. No critical deviation was recorded. No ShanTT batches were produced in 2019.
On the basis of the reviewed APR, the conclusion of the company, that is "Product quality review for the year 2018 demonstrated that the manufacturing process is consistently producing quality product" is deemed endorsed.

Quality risk management:
Procedures for the QRM were in place. FMEA, FMECA, FTA, HACCP, HAZOP, PHA are used as tools. Low, medium, significant and high risks were used for the risk categorization. High risk category is considered as critical and therefore is escalated to Sanofi Pasteur Quality Operation (SPQO).

Some risk assessment reports were spot checked and included:

- The risk assessment for the formulation and filling of Shan5 in multiproduct facility for Shan 5 approved in March/May 2016.
- The risk assessment related to the handling of seed preparation activity in grade B area without aseptic operator qualification.

Some elements of the QRM and risk assessment were found deficient. The company has provided the CAPA plan adequately addressing the deficiencies raised.

✓ ***Deviation management:***

Procedures for deviations management were in place. In particular, the procedure "Management of deviations and investigations" is aimed to describe the process of reporting, documenting and investigating the deviations, evaluate the impact, to define the CAPA and batch disposition. This procedure applies to bulk antigen and drug products. The flow chart summarises the process as follows: when an event/awareness is identified, a deviation is created by the witness. The shop floor (responsible person of the area) is collecting data and decides whether or not an investigation should be launched ("Investigation is possible"). In the affirmative, the shop floor quality representative (a QA staff member specifically assigned to the process / area) will classify the deviation (critical, major, minor). Further investigation will be launched to identify the root cause analysis (RCA) and the product quality impact leaded by both the shop floor representative and the shop floor quality representative, possibly involving other persons/department (e.g. QC). Finally, when the investigation is completed, it will be successively reviewed and approved by the shop floor and the shop floor quality representative for final approval and eventually closed. CAPA might be then possibly launched (see below). Unexpected deviations are classified as critical, major and minor according to the quality impact of the product and GXP compliance. Critical classification regarding product impact is applied only for batches already on the market. Deviations are closed within defined number of calendar days otherwise documented and justified before the extension. Trending of deviations including recurrence was in place on a quarterly basis.

The list of deviations from 2017 was spot checked. The trend analysis report of deviations for the period from July 2019 to September 2019 for Medchal Site, approved on 16 October 2019 was reviewed.

Some elements of the deviation management were found deficient. The company has provided the CAPA plan adequately addressing the deficiencies raised.

✓ ***Management review:***

This topic was not inspected in detail during this inspection.
Procedures for the management review was in place to assure the quality reviews for continuous improvement and compliance with international and local regulatory requirements and Sanofi Global Quality
The senior management meets at least twice a year to discuss issues related to quality systems, operational quality and product quality topics.

The procedure "Management of quality performance indicators" and the global quality metrics report for October 2019 were spot checked. The total number of deviations, the assignable root causes, the timelines of closure of deviations and the timelines for resulting CAPA were taken into consideration.

Global quality metrics in June 2019 regarding the alignment to the global directives was also checked and showed that 100% of the global directives are in use for both Shantha sites.

✓ ***Change control:***

Procedures for change control management were in place. The procedure "Change control procedure" was reviewed. The list of change controls from 2017 was spot checked. A change control was issued regarding the implementation of a new LIMS system, which is planned in 2020 for commercial batches.

✓ ***CAPA management:***

Procedure for CAPA system management was in place. The procedure "CAPA system management" was reviewed. CAPA timeframe determination matrix was implemented in the SOP to define CAPA deadline according to technical complexity and resource availability. The procedure covered the internal and external observations, corrective and preventive action from deviation, OOS, OOT systems, product complaint and product recall. The effectiveness check was considered in the procedure.

WHO audit performed in February 2017 gave rise to 5 major deficiencies and 32 others. The company has implemented the corrective and preventive actions addressing the issues raised during this inspection. Some of the CAPA such as the implementation of the RABS at Medchal site in suite D was still not yet implemented. The company reported that filling Suite F will be dismantled in 2022.

Some elements of the management of the CAPA were found deficient. The company has provided the CAPA plan adequately addressing the deficiencies raised.

✓ ***Documentation:***

This section was not inspected in detail. Most of the documents reviewed during the inspection reflected an adequate documentation management system.

✓ ***Summary lot protocol (SLP):***

The procedure for SLP is described in the procedure "Procedure for Preparation, Review, Approval and Submission of Summary Lot Protocols to CDL". The SLP for production and testing of the vaccines is established as per WHO requirements.

✓ ***Batch release procedure for vaccines:***

The finished product is released or rejected as per approved written procedure.
The batch release is performed as per the procedure "Batch release / rejection". Production and QC department forward the BMRs and testing reports respectively to the QA Department, which will review the provided information for compliance with standards, including compendial requirements, WHO requirements and national control requirements. After completion of this review, batch shall be released for forwarding to NCL along with SLP and samples for obtaining batch release certificate. After receiving the batch release certificate from the NCL, the batch is released for dispatch. Complementary documented procedures include the procedure "Procedure for preparation review, approval and submission for SLP to CDL" and ''Product quality review".

✓ ***Complaints:***

Procedures for addressing complaints were in place. Complaints were addressed as per the procedure "Management of product complaints". Briefly, complaints are received, logged and further managed by the QA department. An initial assessment is performed, which may need a request for additional information. An investigation is performed (by QC and/or manufacturing department), an investigation report is issued, including CAPA. A reply is sent to the complainant and the complaint is eventually closed. Should there be a link with AEFI, an interaction will be in place with the pharmacovigilance department.

✓ ***Post Marketing Surveillance and Adverse Events***

Procedures for addressing AEFI were in place. Safety alerts were managed as per the procedure "Instruction document pharmacovigilance processes for Shantha products", under the responsibility of Shantha Global Safety Officer.

✓ ***Product recalls:***

Procedures were in place for handling recalling any batch of product from sale or supply. There was no recalled batch since the last WHO inspection in 2017. The last recall occurred in 2009 for Shan5 vaccine due to white sedimentation not easy to resuspend during physical reconstitution.

✓ ***Self-inspection:***

Self-inspection: SOP, Plans and summary reports

The procedure "Self-inspection" describing the self-inspection in all departments (i.e. manufacture, QC, Warehouse) was spot checked. A pre-schedule inspection plan based on risk assessment is prepared on yearly basis. An annual risk assessment is carried out so as to define self-inspection's frequency per topic to be covered. The category of finding can be classified as critical, major and minor. Auditors shall participate in one self-inspection under the supervision of the lead auditors. Self-inspection and CAPA system and CAPA follow up were in place.

The following documents were reviewed:

- Annual schedule for calendar year 2018 and 2019;
- Self-inspection program risk assessment for the review period of the year 2018;
- "Interim self-inspection annual review 2019";
- "Self-inspection observation report for QC" of the audit performed in 2019.

Quality audits and suppliers' audits and approval:

The company has a program of supplier audit and review. The vendors for the raw and packaging materials were approved as per the implemented procedures.

The schedule of the audit of suppliers for 2018 and 2019 were spot checked.

The following documents were spot checked:

- The procedure "Supplier qualification" was spot checked. An annual supplier performance review is carried out and is based on the following parameters: material rejections, material criticality, supplier complaints, supplier quality system, supplier compliance with respective to supplier audit. If any supplier is not found suitable (during routine audit or on performance review), QA initiates a deviation.
- The procedure "Quality audits";
- The list "Approved supplier list" for Tetanus, IPV, Pertussis, Hepatitis-B Antigen, Cholera, *Haemophilus Influenzae* type-B and Diphtheria products;
- "Packing material supplier performance review 2018";
- The audit report of the supplier of vials.

Some elements of the supplier qualification management were found deficient. The company has provided the CAPA plan adequately addressing the deficiencies raised.

✓ ***Personnel:***

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Specific duties were recorded in written job descriptions for responsible staff. Personnel met were aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. Steps were taken to prevent unauthorized people from entering production, storage and QC areas. The manufacturer had provided a breakdown of permanent and contractual employees in their site master file.

Organizational charts showing the relationships between different departments, including QA, Production and QC with identification of the key personnel were provided. Organogram for QC, QA and Production were reviewed and discussed. The list of temporary people was provided and discussed.

Training:

The implemented procedure describes the personnel training, qualification, education for GMP and GDP and to ensure the employees are qualified by appropriate training for all employees in both sites.

Training for visual inspection:

"Training and qualification of operators for visual inspection" was spot checked. Several steps were requested for the qualification:

- Training with training kits for each product and pack size containing good and defective units for each type of available defect listed;
- Evaluation with evaluation kits (including good and defective units);
- Operator qualification by inspection of commercial batch.

Training and evaluations kits were available for each product and adequately stored in cold room. Training and evaluations kits were spot checked.

Training package of a temporary employee in charge of visual inspection operations was reviewed.

Training of quality control analyst:

An analyst qualification report of LPS assay was spot-checked. The qualification and certification of the analyst was performed according to the relevant procedure.

A deficiency was found in the acceptance criterion of analyst qualification. The company has provided the CAPA plan adequately addressing the deficiencies raised.

Gowning procedure:

Gowning procedure for access to the classified manufacturing areas was spot checked.

Some elements of the personnel training and gowning were found deficient. The company has provided the CAPA plan adequately addressing the deficiencies raised.

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. In general production operations followed defined procedures and master formulas. Deviations from procedures were recorded and investigated. Qualifications and validations were performed. Systems were in place for handling complaints and recalling batches of product from sale or supply.

The validation of aseptic process simulation (APS) and reports were reviewed in detail. The validation of Time out of refrigeration (TOR) of vaccines was spot checked.

✓ ***Batch numbering:***

Batch numbering system was performed as per the procedure "Batch numbering system for bulk, blend and finished product". This procedure was applicable for bulk antigens, blend (formulated products), finished products, development and experimental products, seed lots and cell banks. The proposed batch numbering was governed by a rationale that permits unambiguous identification of each batch of active ingredient, finished product and intermediates.

✓ **Batch manufacturing record review**

The BMRs of the first batch of Shan5 manufactured in 2019 were spot-checked. Apart from some minor typos detected during the review, the BMRs were found to be satisfactory.

✓ **Visual inspection**

Visual Inspection room was visited in MRP site. The operators were performing inspection in a semi dark big room within individual light per booth (with white and black background). Each vial is inspected for at least 5 seconds against a white background and an additional 5 seconds against a black background. The vials are also slowly rotated to swirl up particles. The intensity specification of the illumination at the inspection point was ranging from 2000 to 3750 lux. The intensity of the illumination is checked before starting the activity. The SOP **"**Illumination intensity checking of optical lights by using lux meter" was spot checked.

AQL sampling is done by qualified operators who are not involved in 100% visual inspection of the respective batch. Evaluation and qualification are performed every 6 months for each operator in charge of visual inspection activities.

The following documents were spot checked:

- "Visual inspection of filled product" for MRP Site;
- "Visual inspection of filled product" for Medchal Site;
- "Sampling and visual inspection of finished product to determine acceptance quality limit".

Deficiencies related to the production system were found deficient. The company has provided the CAPA plan adequately addressing the deficiencies raised.

3. Facilities and equipment system

Access to production premises was restricted to authorized personnel. Overall, dedicated facilities were in place for manufacturing drug substances. Whole cell pertussis and Diphtheria drug substances were manufactured in the same facility on campaign basis. Seed lots were stored in qualified equipment with adequate temperature monitoring and inventory system. 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. A difference of 15 Pa between rooms of different grade is maintained. 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.

Qualification and validation:

Procedures 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. The validation master plan was in place. Preventive maintenance programme and calibration plan were in place.

Qualification protocols and reports were spot checked as presented below:

- Site Master Plan;
- Cleaning and Sanitization;
- Fumigation;
- Aseptic connections;
- Inactivation vessel for whole cell pertussis;
- Centrifuge;
- Autoclaves;
- Depyrogenation Tunnel;
- Vial washing machine;
- Capping machine;
- Visual inspection booths;
- Air Handling Units;
- Water systems.

Deficiencies related to facility and equipment were identified. The company has provided the CAPA plan adequately addressing the deficiencies raised.

4 Laboratory control system

The QC function was independent of other departments. QC performs testing of incoming raw materials, packing materials, intermediate products and final products, purified water, water for injection, pure steam, and the environmental monitoring and stability studies for intermediate / finished products. The products at intermediate/ final stages are tested against established specifications as per respective testing SOPs.

Adequate resources were available to ensure that all the QC arrangements were carried out. QC personnel had access to production areas for sampling and investigations as appropriate. Entry to all QC buildings/areas and rooms was restricted to authorised personnel (list of authorized personnel is given at entrance) and was controlled by access code. Visitors and guests must sign in before entering the QC area or animal housing.

In general terms provisions for calibration and validation of all equipment's are in place at periodic intervals and when major changes have been made.

The following laboratories were visited, and the associated activities and documentation spot checked as follows:

- Physico-chemical laboratories;
- Microbiology laboratory;
- Sterility testing;
- Biological tests;
- Stability Studies;
- Environmental monitoring;
- Water monitoring.

Deficiencies related to Quality Control systems were raised. The company has provided the CAPA plan adequately addressing the deficiencies raised.

5 Materials system

Each consignment of materials after receipt by Warehouse department is initially inspected. Different batch materials are segregated. Separate areas have been allocated for storage of raw materials, packing materials. Materials are 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 are approved or rejected by QC Department based on the results of analysis.

6 Packaging and labelling system

Printed packaging materials like labels and cartons are stored under lock and key with restricted entry for authorized personnel.

Labelled vials are inspected and inserted in either a foam base or in a carton box as relevant to the vaccine by an operator. A different operator is wrapping the foam base comprising the vials in a plastic pouch and inserting the literature insert (or including the literature insert in the filled carton box). A third operator is verifying the presence of literature insert in the plastic pouch and then seals the poach. If carton is used, this third operator is verifying the presence of the literature insert. A fourth operator is inserting the foam in its pouch and then in the burger packing (carton packing). Following that, secondary packaging is printed with relevant information (bar code, lot number, expiry date) by the barcode machine operator. Bar code is then visually verified by a different operator. The supervisor is randomly checking in process several printing bar code parameters such as expiry date bar code, printing legibility as well as packaging parameters. The security sticker is pasted. All containers are individually weighed for control. Cartons are wrap in a brick. 45 cartons of single dose or 12 cartons of multidose are merged per brick. This aggregation process is generating a label for each brick. A weight control is performed on the brick base on the above principle.
Finally, vials are sampled at initial, middle and end stage for QC testing.
The bricks are eventually transported to cold room and stored.
The batch record template used to record data of a batch of Shan5 vaccine was reviewed.

7 Distribution and shipping

This section was not reviewed during this inspection.

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, ***Sanofi Healthcare Private Limited., Telangana, India*** operating from the following manufacturing sites:

- ***Industrial Park, Survey No. 354, Muppireddipalli Village, Manoharabad Mandal, Medak District – 502236, Telangana, India***
- ***S. No. 274, Athavelli Village, Medchal, Medchal-Malkajgiri District 501401, Telangana, India***

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.

DEFINITIONS

Critical deficiency

A *critical* deficiency may be defined as an observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

Major deficiency

A *major* deficiency may be defined as a non-critical observation that:

- has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
- indicates a major deviation from the GMP guide;
- indicates a failure to carry out satisfactory procedures for release of batches;
- indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties;

- consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

Other deficiency

A deficiency may be classified as other if it cannot be classified as either critical or major but indicates a departure from GMP. A deficiency may be other either because it is judged as minor or because there is insufficient information to classify it as major or critical.

Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of another deficiency may be categorized as major.

PART 4

List of GMP guidelines referenced in the inspection report

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   Short name: WHO TRS No. 986, Annex 2

   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   Short name: WHO TRS No. 970, Annex 2

   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

3. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
   Short name: WHO TRS No. 929, Annex 4

   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

4. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
   Short name: WHO TRS No. 937, Annex 4

   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

5. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
   Short name: WHO TRS No. 961, 957), Annex 1

   http://www.who.int/medicines/publications/44threport/en/

6. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
   Short name: WHO TRS No. 957, Annex 2

   http://www.who.int/medicines/publications/44threport/en/

7. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
   Short name: WHO TRS No. 961, Annex 6

   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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