

**Prequalification Team Inspection services
WHO INSPECTION REPORT
Vaccine manufacturer**

Part 1	General information
Manufacturers Details	
Company information	
Name of manufacturer	Shantha Biotechnics Private Limited (A Sanofi Company)
Corporate address of manufacturer	Fateh Maidan Road, Basheerbagh, Hyderabad 500 004 Telangana, India
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	1. Industrial Park, Survey No. 354, Muppireddipalli Village, Toopran Mandal, Medak District – 502236, Telangana, India D-U-N-S number: 0 3 9 8 5 0 0 0 0 GPS: Latitude 17.646190 / Longitude 78.494681 2. S. No. 274, Athavelli Village, Medchal, RR District 501401, Telangana, INDIA D-U-N-S number: 0 3 9 8 5 0 2 3 2 GPS: Latitude 17.740576 / Longitude 78.483877
Manufacturing license number	Manufacturing License No.01/MD/TS/2015/V/G, granted by the Drugs Control Administration (DCA), Government of Telangana.
Inspection details	
Dates of inspection	6 to 10 February 2017
Type of inspection	Initial inspection to MRP site
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	- Suite 2A for filling, sealing, visual inspection, labelling, storing and shipping of vaccines at Muppireddipalli site - Suite B for the manufacturing of whole cell Pertussis and Diphtheria drug substances and the quality control laboratory for HepB at Medchal site
Restrictions	Not applicable
Out of scope	MRP site: Quality laboratory, Suite 2C, Insulin Plant Medchal site: Suite H(FF) and WH (GF), Suite G (FF) and Suite F (GF), Suite C, Distribution center, Suite A, Suite E and Suite D (GF), Suite S, AH.
WHO product numbers covered by the inspection	- Cholera: inactivated oral (Shanchol®) - Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae type b (Shan-5)

Introduction																																																																					
Brief summary of the manufacturing activities	Shantha Biotechnics Private Limited is specialized in vaccines drug substances manufacturing, formulation, filling, visual inspection, labelling, packaging, Quality Control and distribution of vaccines.																																																																				
General information about the company and site	Shantha Biotechnics Limited was established in 1993 and is now Shantha Biotechnics Private Limited, acquired by Sanofi Company in 2009. Shantha Biotechnics Private Limited commercializes Shanvac-B[®], ShanTT[®], Shanchol[®], Shan5[®] and ShanIPV[®]. The products in pipeline are Shan6[®], Hepatitis A vaccines and Lantus[®] as Insulin therapeutics. The main activities in MRP site are related to the filling of the vaccines in Suite 2A, the TT bulk antigen manufacturing in Suite 2C, the quality control tests limited to the environmental monitoring and water testing. A new Insulin plant was under construction during the inspection. The main activities in Medchal site are related to the formulation and filling of vaccines, the manufacturing of drug substances of the whole cell pertussis, diphtheria, tetanus toxoids and Hepatitis B and PRP-TT.																																																																				
History	This is the initial WHO onsite inspection of MRP site. The last WHO onsite inspection to Medchal site took place in September 2013. The company has adequately implemented the corrective and preventive actions (CAPAs) to the raised deficiencies. The main changes since the last WHO inspection is the addition of MRP site for the filling of Shan5 and Shanchol[®], and the manufacturing of the whole cell pertussis drug substance in Medchal suite B. A dedicated Insulin Plant was under the construction during the inspection. No recall from the market has been recorded in the past two years.																																																																				
Key persons met	<table><tr><th>Name</th><th>Designation</th><th>Department</th></tr><tr><td>Dr.Mahesh Bhalgat</td><td>Executive Director -COO</td><td>Management</td></tr><tr><td>Eric Auschitzky</td><td>Production Head</td><td>Manufacturing</td></tr><tr><td>Dr. A. Nagarjuna</td><td>Vice President</td><td>Quality Assurance</td></tr><tr><td>Dr. Partha Sarkar</td><td>Senior General Manager</td><td>Manufacturing</td></tr><tr><td>K. Venkateshwar Rao</td><td>Senior General Manager</td><td>Manufacturing</td></tr><tr><td>S. Muruganandham</td><td>Dy. General Manager</td><td>Quality Control</td></tr><tr><td>G. Ravi Kumar</td><td>Senior General Manager</td><td>Engineering</td></tr><tr><td>S. Sudhakar</td><td>Dy. General Manager</td><td>Supply chain</td></tr><tr><td>Dr.Rahul Kulkarni</td><td>Dy. General Manager</td><td>Regulatory Affair</td></tr><tr><td>Dr.Subhra Ranjan Chakrabarti</td><td>Dy. General Manager</td><td>R&D-MTECH CMC</td></tr><tr><td>Ravindra Dhanbhar</td><td>Assistant General Manager</td><td>Engineering</td></tr><tr><td>V.P Tiwari</td><td>Associate Vice President</td><td>Site Services</td></tr><tr><td>D. Madhavi</td><td>Dy. General Manager</td><td>HSE</td></tr><tr><td>M. Lachi Reddy</td><td>Senior General Manager</td><td>Human Resource</td></tr><tr><td>Pierre Lauer</td><td>Senior Director</td><td>International Quality Sanofi pasture</td></tr><tr><td>C. Mohan Ganesh</td><td>Dy. General Manager</td><td>Quality Assurance</td></tr><tr><td>CH. Suresh Kumar</td><td>Asst. General Manager</td><td>Quality Assurance</td></tr><tr><td>S. Shafi Ahmed</td><td>Senior Manager</td><td>Quality Assurance</td></tr><tr><td>K. Sivachytanya</td><td>Manager</td><td>Quality Assurance</td></tr><tr><td>G. Ravi kanth</td><td>Dy. Manager</td><td>Quality Assurance</td></tr><tr><td>Lavanya Kumar. P</td><td>Dy. Manager</td><td>Quality Assurance</td></tr></table>			Name	Designation	Department	Dr.Mahesh Bhalgat	Executive Director -COO	Management	Eric Auschitzky	Production Head	Manufacturing	Dr. A. Nagarjuna	Vice President	Quality Assurance	Dr. Partha Sarkar	Senior General Manager	Manufacturing	K. Venkateshwar Rao	Senior General Manager	Manufacturing	S. Muruganandham	Dy. General Manager	Quality Control	G. Ravi Kumar	Senior General Manager	Engineering	S. Sudhakar	Dy. General Manager	Supply chain	Dr.Rahul Kulkarni	Dy. General Manager	Regulatory Affair	Dr.Subhra Ranjan Chakrabarti	Dy. General Manager	R&D-MTECH CMC	Ravindra Dhanbhar	Assistant General Manager	Engineering	V.P Tiwari	Associate Vice President	Site Services	D. Madhavi	Dy. General Manager	HSE	M. Lachi Reddy	Senior General Manager	Human Resource	Pierre Lauer	Senior Director	International Quality Sanofi pasture	C. Mohan Ganesh	Dy. General Manager	Quality Assurance	CH. Suresh Kumar	Asst. General Manager	Quality Assurance	S. Shafi Ahmed	Senior Manager	Quality Assurance	K. Sivachytanya	Manager	Quality Assurance	G. Ravi kanth	Dy. Manager	Quality Assurance	Lavanya Kumar. P	Dy. Manager	Quality Assurance
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Abbreviations	AHU	Air Handling Unit	
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ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
APR	Annual Product Review
APS	Aseptic Process Simulation
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
DT	Diphtheria Toxoid
DTP	Diphtheria, Tetanus and Pertussis
DQ	Design Qualification
EDI	Electronic DeIonization
EM	Environmental Monitoring
eQMS	Electronic Quality Management System
FMEA	Failure Modes and Effects Analysis
FTA	Fault Tree Analysis
GMP	Good Manufacturing Practices
GPT	Growth Promotion Test
HEPA	High Efficiency Particulate Air
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
MRP	Muppireddipalli
NCA	National Control Authority
NCL	National Control Laboratory
NRA	National Regulatory Agency
OMCL	Official Medicines Control Laboratory
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
	SIP	Sterilization In Place
	SMF	Site Master File
	SOP	Standard Operating Procedure
	UF	Ultra Filtration
	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 QMS. Senior management demonstrated support to the system. Quality assurance and quality control activities were functioning with appropriate independence from the production unit.

Annual Product Review (APR):

Provisions for APR were in place.

APR for Shanchol[®] vaccine (inactivated), manufactured in 2016 was spot checked.

APR of Shan5[®] vaccine, manufactured in 2016 was spot checked.

No batches failed to meet the established specification/s for Shan5 during 2016.

Review of critical in-process controls, and finished product results:

There was no change to the critical in-process controls and Shan5[®] final product results.

No out of specification were observed. There was no fail. All the test results of batches of Shan5 filled in 2016 met the pre-determined specification limits.

Quality Risk Management (QRM):

Provisions 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).

Change Control Management:

Provisions for change control management were in place.

Deviation Management:

Provision for the deviation management was in place.

Planned deviations are dealt with through temporary change control. Unexpected deviations are classified as critical, major and minor deviations according to the quality impact of the product. Deviations are closed within 30 calendar days otherwise documented and justified before the extension. Recurrence and trending and of deviations are in place.

The list of deviations for MRP suite 2A and related facilities for 2016 was spot checked. The fourth quarter trend analysis of events October 2016 to December 2016 was spot checked.

CAPA management:

Provisions for the corrective and preventive actions (CAPA) plans were in place. The company has adequately implemented the corrective and preventive actions addressing the issues raised during WHO onsite inspection held in September 2013.

Management review:

Provision for the management review was in place in order to assure the quality reviews for continuous improvement and compliance with international and local regulatory requirements and Sanofi Global Quality

Documents. The senior top management meets at least twice a year to discuss issues related to quality systems, operational quality and product quality topics.

Batch release procedure for vaccines:

The finished product is released or rejected as per approved written procedure.

2. Good manufacturing practices for pharmaceutical products

Overall 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. Qualification and validation of equipment, manufacturing processes and quality control testing methods were in place. Manufacturing processes were defined and reviewed. Instructions and procedures were available. Operators were instructed to carry out procedures, and records were made for the production operations. Significant deviations were recorded and investigated, root causes were determined and corrective and preventive action were implemented. Systems were in place for handling complaints and recalling any batch of product from sale or supply.

3. Sanitation and hygiene

Most of 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 are 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. During the inspection the gowning procedures appeared to be complied with no dress code violations noted. The level of sanitation and hygiene for premises and manufacturing equipment are considered acceptable.

4. Qualification and validation

Overall, provisions for qualification and validation were in place and covers premises, equipment, utilities and systems, processes and procedures at periodic intervals and when changes have been made. Validation and qualification protocols and reports were spot checked as presented below.

- ✓ Inactivation process of whole cell Pertussis (wcP) at the Suite B Medchal Site:
- ✓ Process validation for Shan5[®] and Shanchol[®] vaccines
- ✓ Hold time studies
- ✓ Sterile filtration validation of Shan5[®].
- ✓ Cleaning validation
- ✓ Validation/revalidation of the autoclave
- ✓ Filling machine
- ✓ Sealing machine
- ✓ Container Closure Integrity Test (CCIT)
- ✓ Aseptic process simulation (APS)
- ✓ HVAC
- ✓ Washing machine
- ✓ Cleaning of the filling machine accessories

- ✓ Depyrogenation tunnel
- ✓ Temperature mapping
- ✓ Fumigation

Calibration policies, schedules and status:

The procedure for the calibration of measuring and testing instrument/equipment used for process control and testing was in place.

Preventative maintenance (PM) procedures:

The procedures involved in conducting and managing site's preventative maintenance (PM), breakdown predictive maintenance activities were implemented. The annual plan for PM of all equipment is initiated in the beginning of each year. The frequency of PM is in monthly, quarterly, half yearly and yearly basis according to the assigned criticality of the equipment (fermenter, autoclave), major equipment should be PM on quarterly, half yearly and yearly (balances, biosafety cabinet), and minor can be PM on yearly basis. Review maintenance performance and initiation of trend analysis is identified in the SOP and will be implemented from the year 2017.

5. Complaints

Provision for the complaints was in place.

The procedure for handling of adverse event following immunization (AEFI) describes the management of serious adverse event and management of investigational product (clinical trial before marketing) was spot checked. In case of serious event including fatal cases the Drugs Controller General of India (DCGI) should be informed within 14 days.

The procedure for handling of AEFI which describes the serious adverse event and management of post marketed products was spot checked. In case of any serious event including fatal cases received from any source, the PV team should inform DCGI within 15 days.

6. Product recalls

Provision for recall was implemented. Initiation of recall of class I shall be done immediately, within minimum possible time. For class II recall shall be done within 15 days of receipt of information. For class III recall shall be done within 30 days of receipt of information. According to the guidelines on recall and rapid alert system from drugs including biologicals and vaccines CDSCO/RRAS Ver.: 00 effective date 23/11/2012, class I within 24 to 72 hours, class II with 10 days and class III within 30 days are allowed.

The last recall recorded was registered in 2009 for Shan5[®] related to the appearance of the vaccine.

A mock recall (MR) was performed in 2015.

7. Contract production, analysis and other activities

The company has no subcontractor for manufacturing activities.

The aluminium phosphate gel is supplied ready to use. Testing including identification and sterility are performed on delegate samples delivered with each consignment. The last internal audit was performed in June 2016.

The list of material sent for external laboratory for testing and the quality technical agreement were available.

8. Self-inspection, quality audits and suppliers' audits and approval

✓ Self-inspection

Self-inspection: SOP, Plans and summary reports

The procedure is describing the self-inspection in all departmental section (i.e. manufacture, QC, Warehouse) was spot checked. A separate and independent system for internal inspection / audit is being in place for monitoring, evaluating and assessing the complaints for all manufacturing process, facilities, suits and quality system as per internal procedures, GMP and regulatory requirement. A pre schedule inspection plan is set every year in January which is based on risk assessment and complaints history. The self-inspection program consist of identifying the qualified auditors including team leaders, observation found during the inspection, report and critical findings in case of serious violation or deficiencies in the guidelines or quality documents/system. The category of finding can be classified 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 is in place. Archiving self-inspection report is in place. Self-inspection report from 27 December 2016 was spot checked for QC area. The team consisted of 1 audit leader and 2 auditors. The audit was focusing on equipment and employees, sample managements and raw materials, qualification/validation, requalification and microbiology lab.

✓ Vendor approval

The vendors for the raw and packaging materials are approved as per the implemented procedures

The schedule of the audit of supplier recorded for 2015 and 2016 was spot checked.

9. Personnel

Organizational charts showing the relationships between different departments, including QA, Production, QC, Warehouse and Engineering with identification of the key personnel are provided. Curriculum vitae and the job responsibilities for key personnel, with qualification, experience and responsibility are provided.

The employee job document describes the lay down the procedure for preparation and assigning the employee job description. The job description for the executive director was spot checked.

10. 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. Shantha is a member of the Sanofi Pasteur quality academy. The training is the responsibility of the senior management. Annual on job training is dedicated to all employees. Training is also provided for a new recruit and transfers from both sites. Training plan for QC department for the year of 2017 was spot checked. Employees training record was provided for January 2017. Training questionnaire and the evaluation report for individuals and the minimum qualifying marks is 80% provided.

11. Personal hygiene

The implemented procedure describes the procedure for monitoring the health care and hygiene of personnel before and after joining the service. Employee screening and vaccination prior joining the company is mandatory for all staff. Periodically health check schedule for employees is in place (i.e. yearly, biennial and triennially) for physical examination, chest X-ray and complete blood picture for contagious diseases. Other examination such as visual, skin, TB, respiratory and stool are examined once every 6 months. Vaccinations schedules for all employees have also been included in the SOP. Medical checks forms for all required examinations and employments are well described and included.

12. Premises and Equipment

Production areas: exposed surfaces were smooth, impervious and unbroken. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. Premises were cleaned and disinfected according to written procedures.

A difference of 15 Pa between rooms of different grade is maintained.

Suite 2A in MRP site is dedicated to the filling of the inactivated vaccines. The filling line is under grade A laminar air flow surrounded by grade B. The quality control tests limited to the environmental monitoring and water testing. Ventilation systems, details of AHUs with room-area identification, classification, differential pressures and environmental conditions in manufacturing facility were provided in the Site Master File.

Water system (PW and WFI) showing storage tanks, loops, point of use, sampling points, quality testing, sanitation procedures and schedules were spot checked.

Raw water is tested monthly. WFI and PW loops are sanitized monthly at 121 °C and over 85 °C respectively. Conductivity and temperature are monitored on line at return for WFI system.

Storage areas (Warehouse facility in MRP and Medchal sites consist of raw material storage, packing material storage, tertiary packaging material storage, consumables, rejected material room, bulk antigen storage,

Storage and distribution areas of finished products: material management transactions are carried out using SAP system and barcode labelling system. Hazardous storage areas are available to segregate materials including acids, solvents, alkaline. Hazardous collection samples carried on in identified room with two different entries to personnel and materials; samples are collected in a fume hood. Secondary packing materials are stored in identified area (glass vials, stoppers and aluminum seals), samples assigned a unique number with barcode. The labelling materials are stored in identified room equipped with temperature and humidity monitors. Appropriate storage for used and unused labels are identified and segregated. Identified and segregated area was assigned for rejected material.

Packaging facilities: the central packaging and labelling areas are located at the 2nd floor at MRP site. Cold room (2 to 8 °C) is used to store the fill finished vial of unlabeled Shanchol[®] vaccine. The cold room is well organized and there is enough spacing between boxes and shelves containing filled vials in Boxes.

Visual Inspection room was visited. Color coded boxes were used to distinguish between inspected (green) and uninspected (blue). The operators were performing inspection in a semi dark big room within individual light per booth.

VVM application room was visited. The labelling machine was inspected and preventative maintenance was performed on 20.01.2017 and due on 12.04.2017.

VVM14 is stored at -20°C Cold Room.

Quality control areas

Sufficient space was given to avoid mix ups and cross-contamination. Storage space was provided for samples, reference standards, solvents, reagents and records.

14. Materials

The reception, sampling, testing, storage and releasing or rejecting of starting materials, packaging materials, bulk and finished products is performed according to implemented specifications and SOPs.

Controls are in place at receipt, checking, sampling, storage, release, storage of approved materials in segregated areas (quarantine, approved and rejected) with adequate labeling.

15. Documentation

This section has not been inspected during this inspection.

16. Good practices in production

Access to production premises was restricted to authorized personnel.

Seed lots are stored in qualified equipment with adequate temperature monitoring and inventory system.

In general production operations followed defined procedures and master formulas. Deviations from procedures were recorded and investigated.

Overall, dedicated facilities were in place for manufacturing drug substances.

Suite B:

Diphtheria and wCP were manufactured in the same suite B on campaign basis. Changeover procedures were implemented with instructions and procedures for preventing the risk of cross contamination. Before resuming the production, EMP for specific organism is performed. Cleaning procedures and disinfection procedures were in place. Sterilizing and decontaminating autoclave with qualified cycle were in place. The contaminated liquid material was collected in collection tank and decontaminated in kill tank.

Premises and drains were disinfected using four types of disinfectants which were rotated.

Regarding the whole cell pertussis drug substances manufacturing the WSL are received from Sanofi Pasteur France. The whole cell pertussis process in Shantha was implemented through Tech transfer from Sanofi.

Waste Management in both sites MRP and Medchal:

Two procedure documents were available describing the management of liquid and solid waste disposal.

The procedure describes the responsibility of departments and personnel, source/category of wastes and treatment/disposal procedure of liquid waste. Liquid wastes collected from the manufacture are treated with 1% sodium hypochlorite and then transferred to the kill tanks (120°C treatment) before release to effluent treatment plan ETP (reverse cycling for internal use i.e. garden). The Health Safety and Environment (HSE) shall decide the disposal mechanism of liquid chemicals rejected/expired as per nature of chemical wastes. Final bulk disposal follows the implemented procedure instructions on destruction of bulk, blend and finished products.

The implemented procedure describes the procedures to be followed for segregation, collection, labelling, packaging, storage, transportation and disposal of solid waste disposal from production, QC including animal house, biological and chemical wastes. Colour coded containers have been used to distinguish between types of

wastes (yellow, white, blue and red containers). Biological waste materials should not be stored in the site for more than 48 hrs.

17. Good practices in quality control

The QC function was independent of other departments. 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.

- Stability testing program

Procedure for stability studies was in place. It describes the system to conduct stability studies on seeds banks, intermediates, drug substances (DS) and finished product (FP). Each stability study is performed based on per specific SOP. A specific design should be followed according to the purpose of the study (example of VVM study was spot checked). The preparation and numbering system of stability protocol and report is well explained. Labelling of stability samples during study period is explained. Summary sheet, data evaluation preparation of summary report and data archiving of filing is explained well.

- retention samples archive

Procedure for retention sample is in place. It describes the procedures for sampling, storage, handling, retention, and destruction of retention and reference samples of vaccines bulks/intermediates and FC and reference standards.

3 validation lots produced for Shan5[®] using wcP produced in Medchal. Vials of Shan5[®] filled containers (FC) have been retained for ongoing stability data (real time and accelerated), retention sample logbook was spot checked and found satisfactory.

The Out of Specification (OOS), out of trend (OOT) and out of limit (OOL) handling

Procedures handling OOS, OOT and OOL were in place. It describes the handling of OOS and OOTs and process for investigation, documentation, tracking and trending results and to take the corrective and preventative action in order to prevent the reoccurrence of the OOS and OOT. Procedures for management of sterility test failures were in place.

Stability studies

In MRP, 6 batches of Shan5[®] were produced in 2015 for initial process validation. All the 6 batches underwent Stability studies (Real time, Accelerated and Stress conditions).

The stability results for up to 18 months' time point were complying with the specifications as per the protocol (The testing of 24 month time point samples was initiated at the time of the onsite inspection).

Environmental monitoring:

The environmental monitoring program is performed according to the implemented procedure. Quarterly and annually trend review was in place.

Water monitoring:

PW loop is dedicated to suite 2A with 5 sampling points and only one user point in washing room.

The qualification of the water system was performed in 3 phases. The first two phases in 14 days each and the third phase in 52 weeks as per WHO recommendations. A monthly sanitization by temperature over 80°C is in place. The results of phase 1, 2 and 3 are in compliance with the specification for PW. Objectionable organisms were not detected.

WFI sub-loop is dedicated for suite 2A with 6 sampling points and 3 user points. The sanitization by steam is performed every 3 months. The results of the phase 1, 2 and 3 are conclusive. Objectionable organisms were not detected.

Compressed air:

Compressed air was used for the leak test of the C-Flex.

18. Distribution and dispatching

Shipping validation from Medchal to MRP sites:

Procedures for transporting of sterile bulks and product from site to site are described in relevant procedures. Protocol describes the validation process of cold truck for temperature transportation of blended bulks at 2 – 8°C. The validation is performed once every 3 years using 16 thermo-probes (15 internal and 1 representing the ambient temperature). The validation process was spot checked and the location of thermal sensors was checked as satisfactory for both loaded and empty truck.

The last validation performed was on 30.06.2016 on both empty and loaded truck with three rounds of temperature measurement. All temperatures were within the 2 to 8 °C requirement.

The temperature of last 2 transfers from Medchal to MRP was spot checked. The temperature was within 2 to 8°C for shipments delivered to MRP on 30.1.2017 and 03.2.2017

Shipping validation for international packaging of vaccines:

The data to support the shipping validation has been submitted.

PART 3: CONCLUSION

Based on the areas inspected, the personnel 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, Shantha Biotechnics Private Limited. was considered to be operating at an acceptable level for 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.