TMDA/DMC/MCIE/F/001

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

HUMAN BIOLOGICALS INSTITUTE (A DIVISION OF INDIAN IMMUNOLOGICALS LIMITED)

PUBLIC GMP INSPECTION REPORT

November, 2020

Part 1: General information about the company

Manufacturers details	
Name of manufacturer	Human Biologicals Institute
Corporate address of manufacturer	Kozhipannai, Pudumund Post, Dr. Basavaiah Nagar, Udhagamandalam-643007, Tamil Nadu, India.
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Same as above Human Biologicals Institute (HBI) is located in the campus of National Dairy Development Board (NDDB) at Kozhipanai, Pudumund Post, Dr. Basavaiah Nagar Udhagamandalam-643007.
Unit/ block/ workshop number	N/A
Inspection details	
Date of inspection	20th -21st June, 2019
Type of inspection	Renewal inspection
Introduction	
General information about the company and site	Human Biologicals Institute (HBI) is the division of Indian Immunologicals Limited and subsidiary of National Dairy Development Board (NDDB). The company and its manufacturing facility were established in the year 1998. Manufacturing facility is licensed by the office of Drugs Control General of India and Drugs Control Administration, Government of Tamil Nadu to manufacture human vaccines. The facility is dedicated for manufacturing of Rabies Vaccines with a separate dedicated and registered facility to conduct in vivo tests and other toxicological tests.
History	Manufacturing facility has been inspected and certified by a number of regulatory authorities including Tanzania, Ghana, Zimbabwe, Uganda, Kenya, Botswana and Egypt. It was first inspected by TMDA on 23rd July, 2011 and approved after it complied with the minimum GMP requirements for the manufacturing of human rabies vaccine.
Brief report of the activities undertaken	
Areas inspected	The inspection covered the following areas: external surroundings, materials receiving area, materials and

	finished goods warehouses, production areas, packaging areas, quality control laboratory and utilities. The inspection also verified the qualification of key personnel and training, premises layout, design, sanitation and hygiene, state of the buildings and equipment used in various manufacturing operations, laboratory instruments, complaints handling and recalls, self-inspection, documentation, qualification and validation as well as production and quality control practices.
Production lines inspected by TMDA	Human rabies vaccine production line
Restrictions	N/A
Out of scope	Products for which application for registration has not been submitted
Abbreviations	**Meaning**
AHUs	Air Handling Unit(s)
HVAC	Heating, Ventilation and Air Conditioning
SOP	Standard Operating Procedures
TMDA	Tanzania Medicines and Medical Devices Authority.

Part 2: Brief summary of the findings and comments

1. Personnel

There was sufficient number of personnel at all key sections of the facility. Key positions were occupied by fulltime, qualified and experienced persons with their job descriptions in line with the organogram. The organogram indicated that Head of Production and Head of Quality Control were independent from each other.

Review of training procedure, training program and records indicated that personnel were imparted with induction training immediately after employment and on-job training once per year and whenever the need arise. The training covered cGMP, safety, hygiene and relevant standard operating procedures.

Pre-employment and annual medical examinations were observed to be carried out as specified in the standard operating procedure for medical examinations. Personnel working and exposed to restricted production areas were further subjected to

vaccination against rabies antigens annually. Adequate measures were put in place for personnel hygiene.

2. Premises

The premises had adequate space and consisted of basement, ground floor and first floor. Finished goods warehouse and packaging area were located at the basement, packaging materials warehouse, raw materials warehouse and manufacturing area at the ground floor while quality control laboratory, retention sample room and stability chambers were located at the first floor. Dedicated and separate building was designed for animals of which animal breeding was at the ground floor and animal testing (in vivo and toxicity) at the first floor.

Layout and design

The facility was designed in such a way that it allowed for a unidirectional flow of materials and personnel to minimize the risk of cross contamination and mix up. The wall, ceiling, floors and corners were constructed with hard non-porous and non-shedding materials for easy cleaning of the facility. The door interlocking system was provided in all critical areas to avoid contamination.

Sanitation and Hygiene

Adequate measures were put in place to maintain the general cleanliness. Some of these measures were availability of change rooms equipped with necessary facilities such as wash area, cabinets, step over benches and sanitizing solutions; air locks, pictorial illustrations and procedures for gowning, de-gowning, entry and exit from production areas.

All personnel were provided with protective garments and those working in clean areas and direct in contact with products were further provided with secondary gowns so as to maintain their safety and of manufactured products. The facility had the system of decontamination for all used clothes. Generated wastes were treated before being sent out of the facility for disposal.

3. Production

Upon receiving, raw materials were cleaned and verified before being quarantined. Provision was in place for sampling and dispensing booths both equipped with laminar air flow. Sampling of starting materials and packaging materials was done in accordance with laid down procedures. Quarantined, under test, approved and

rejected materials were clearly identified, demarcated and arranged. Raw materials were maintained at temperatures of 23 ± 2^0C, 2^0C to 8^0C, -20±2^0C and -70 ± 10 ^{0}C depending on their nature.

Production area was divided into two sections; un restricted area consisting of media preparation area, cell culture area, purified area blending, filling and sealing area; and restricted area consisting of infection and harvest area, concentration and inactivation area. All production operations were carried out in accordance with written procedures and measures were observed to be taken to prevent cross contamination and mix up.

Line clearance and in process quality check were executed at appropriate manufacturing stages. Status labels were provided for each manufacturing activity and equipment. Details of all activities were updated in batch manufacturing records and batch packaging records of each manufactured batch for easier traceability.

4. Quality Control

The facility had quality control laboratory composed of chemical and biochemical laboratory for wet and biochemical testing; microbiology laboratory for microbiological and sterility testing and cell culture and virus laboratory for viral vaccine testing. Each , had sufficient number of qualified and experienced analysts and technicians to undertake the assigned responsibilities.

There were adequate equipment and instruments which were calibrated, qualified and subjected to scheduled preventive maintenance as verified in their respective user log books. Reagents and volumetric solutions were properly prepared, tested and documented according to written procedures. Reference books, monographs, standards and microorganisms required for analysis were available and suitably stored. Analytical records were reviewed and found in compliant with specifications.

Control samples of starting materials and finished products were kept in reserved samples room as reference samples to permit future examinations where necessary. Stability studies were performed in accordance to procedure. There were three types of stability studies conducted; accelerated stability study (25 ± 2˚C/60% ± 5%RH), thermal stability study (35 ± 2 ˚C) and real time stability study (2 ˚C to 8 ˚C). Stability studies data were reviewed and found in compliance with the prescribed requirements.

5. Equipment

The facility had sufficient number of production equipment which was designed, located, installed, qualified and maintained to suit the operations carried out.

Equipment design facilitated effective cleaning to prevent contamination and cross contamination.

6. Water Treatment System

The facility was equipped with two water treatment plants; one for generating purified water from municipal water through chemical treatment, reverse osmosis and UV sterilization and another for generating water for injection through multicolumn distillation of purified water.

Purified water was stored in a SS 316L tank and maintained in a loop. Water for injection was stored in a jacketed SS 316L tank whose internal surfaces were maintained at a temperature above 80^0C and continuously recirculated. Sanitization of both plants was carried out at regular intervals as per procedure. It was evidenced in the reviewed records that, generated water was checked regularly for their quality as per sampling plan according to documented procedures. Parameters monitored included TOC, conductivity and total microbial count.

7. Heating, Ventilation and Air Conditioning

The facility had a heating, ventilation and air conditioning (HVAC) system installed to supply filtered fresh air and maintain adequate temperature and relative humidity conditions to different areas. The HVAC system utilized 90% of recirculated air from the clean zone and 10% of fresh air from the atmosphere and consisted of clearly labelled air handling units (AHUs) indicating direction of air flows and rooms to which they supplied.

The system was designed such that, all sterile areas were maintained at Class A under LAF cabinet and Class B background clean rooms. External corridors were maintained at Class D environment. Differential air pressure was set between areas of different air classification to prevent cross contamination. Magnehelic gauges to monitor differential pressures were routinely calibrated and records were maintained.

Records indicated that all AHUs were qualified in accordance to written procedures and respective calibration and preventive maintenance schedule in which the air velocity and air changes, filter integrity, viable and non-viable particle count, air flow pattern, temperature and differential pressures were evaluated.

8. Document Review

A documentation system was in place to support quality management and quality assurance in the manufacturing facility. The documents were designed, prepared and reviewed as per GMP requirement. Traceability and availability of the documents was flawless and this was acceptable.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in of the inspection report, **Human Biologicals Institute (A division of Indian Immunologicals Ltd) located at Kozhipannai, Pudumund Post, Dr. Basavaiah Nagar, Udhagamandalam- 643007, Tamil Nadu, India** is considered to be operating at an acceptable level with the East African GMP Guidelines for the manufacturing of human rabies vaccines.

This report shall be valid for three (3) years from the date of approval unless forms and operations herewith are changed or the site is no longer considered to be in compliance with current GMP requirements

Part 4: References

1. EAC, (2014), Compendium of Good Manufacturing Practice Guidelines Technical Documents for Harmonization of Medicines Regulations, EAC Secretariat, Arusha, Tanzania.

2. TMDA Good Manufacturing Practices Regulations, Manual and SOPs, Tanzania Medicines and Medical Devices Authority, Dar es Salaam, Tanzania.

3. Tanzania Medicines and Medical Devices Act, Cap 219.

4. Human Biological Institute Site Master File: HO/SMF/OOl-15

5. Human Biological Institute Inspection Report