GOOD MANUFACTURING PRACTICES - GMP INSPECTION REPORT TO BHARAT SERUMS AND VACCINES LTD, IDENTIFIED WITH LICENSE FOR REGISTRATION AND RUNNING OF FACTORY No. 1681700218146

In Ambernath - India, on October 02nd to 06th of 2023, the GMP inspectors from the Colombia's National Institute of Food and Medicines surveillance (INVIMA)- designated by the Health and Social Protection Ministry of the Republic of Colombia, were at **BHARAT SERUMS AND VACCINES LTD.**, located at Unit I, Unit II, Biological Testing and R&D, K-27, K-27/PART, K-27-1, Anand Nagar, Next to Jubilant Life Sciences, Anand Nagar, Ambarnath, Thane, Maharashtra – 421506 – India; Phone: +91 251-262-7000, Fax number: +91 251-262-7008, identified with License for Registration and Running of Factory No 1681700218146 issued by Industrial Safety and Health, Maharashtra Government, The inspection was carried out to evaluate the compliance with the Good Manufacturing Practices for Biological products in order to respond the request received in this Institute with number 2017125861 of 01/09/2017. E. mail: sanjeeb.mishra@bsvgroup.ccm

The following people received the Inspection: **Dr. SANJEEB KUMAR MISHRA**, as President-Quality; **Mr. KALYAN S CHOWDHURY** General Manager (Head- Quality Assurance), **Mr. LAKHIRAM PETWAL** as President-Operations; **Mr. DEBASIS SAHU** as Dy. General Manager-Quality Assurance, among others who it was given the presentation letter.

MR. KALYAN S CHOWDHURY General Manager (Head- Quality Assurance), He is the Sanitary Responsible in front of the sanitary and regulatory authorities identify with a Bachelor of Pharmacy issued by Biju Patnaik University of Technology Rourkela University, email: kalyan.chowdhary@bsvgroup.com

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The activities which were programmed according to the inspection methodology were carrying out during the inspection visit. The Inspection methodology was based on WHO Technical Reports Series Number 908, annex 4°of 37th Report and WHO Technical Reports Series Number 961 annex 6 of 45th Report Good Manufacturing Practices for finished products, established in Colombia by Resolution 1160 of 2016, the Decree 335 of 2022, Resolution 3028 of 2008, Resolution 5402 of 2015 and Decree 2086 of 2010 of the Colombian Ministry of Social Protection.

I. METHODOLOGY

The inspection team performed a presentation of the inspection objective, its methodology and a brief historical summary of the Colombian Drug Regulatory Authority – **INVIMA** to the administrative and technical staffs of the company. After that, the inspection methodology was explained. Once the requirements were detected during the inspection, these requirements would be notified in order to implement the corrective actions immediately.

The inspection began with a general observation of the production facilities, packing, quality control, storage and technical – ancillary areas. Then, the Inspectors evaluated **RANDOMLY** by general methodology "areas to inspect" such as:

- Quality Assurance
- Quality Control
- Sanitation and Hygiene
- Validations
- Production
- Personnel and Organization
- Premises (Facilities)
- Equipment
- Instruments and critical support systems
- Storage Area
- Documentation

- Regulatory Affairs.

II. GENERAL INFORMATION OF THE COMPANY

BHARAT SERUMS AND VACCINES LTD., located at Plot No. K-27, K-27 Part and K-27 /1, Ananda Nagar, Jambivil Village, Additional M.I.D.C, Ambernath (East), Thane 421506, Maharashtra State, India, complies with the requirements of Good Manufacturing Practices for Pharmaceutical Products, according to GMP certificate number NEW-WHO-GMP/CERT/KD/107921/2022/11/39826 for Active pharmaceutical ingredient (bulk drug), Blood Products, synthesis, purification, packaging labeling, Quality Control, Quality Assurances, *and among others*. By Food and Drugs Administration M.S. of India on July 4th of 2022.

III. SCOPE

The scope of the inspection was defined in a letter issued on October 03rd of 2023 signed by **Mr. KALYAN S CHOWDHURY** as General Manager (Head- Quality Assurance) who mentioned "*we would like to offer you acceptance of audit from INVIMA for our manufacturing facility located at Plot No. K-27, K-27 Part and K-27 /1, Additional M.I.D.C, Anand Nagar, Ambernath (E), Pin 421506, for GMP Inspection. Following product is proposed to inspection.*

1.Unit-I (Production C)
1.1. Sterile Liquid Formulation and Filling
- *Normal Immunoglobulin for intravenous use B.P.*
- *Pack size: 100ml (clear vial)*
-

Product include cold chain (2-8°C)"

IV. ITEMS INSPECTED

1. QUALITY ASSURANCE

1.1 In **Bharat Company,** the quality management system is under the responsibility of the Head Quality (Pharmacist); who report directly to Managing Director and supports his activities with a team that include QA head, QC head, ATL (Animal Testing Laboratory Head) and all team for Quality Department. Responsibilities for Key personnel are documented and assigned.

1.2 Quality Assurance Department is responsible for Documentation, Validation, Deviation, Change Control, Recall/Return/Reject, complaints, validation, annual product review, Self-inspection, CAPA System, Batch Release, Quality Risk Management, review batch of Drug finish product (drug substances is purchased from a supplier).

1.3 Quality Manual is documented, which the quality management system is described with the responsibilities, policies, objectives of the quality. likewise the aims and the activities it comprise such as: document management, validations and qualifications, internal and external inspections, personnel training, sampling and testing materials, market complaints handling, quality control, change control, deviations, CAPA system, risk assessment, annual product review, out of specification, analysis of trends, product recall, vendor qualification, in process controls and sanitation and hygiene, among others, at the time of the auditor they presented the training records. Likewise, the yearly trend records were presented including market compliance, deviations, APQR, CAPA system and changes request. **however, the training manual was not provided to Bharat personnel and retraining has not been defined.**

1.4 The quality management review is documented with meetings of quality assurance system periodical according to the procedure, they also have the effectiveness evaluation of quality system, the 2023 records were presented.

1.5 Validation master plan was presented which the responsibilities, polices, the aims, and the topics it comprises such as personnel training, documentation, self-inspection, process validation, and qualification, sampling material, among other topics.

1.6 Under the Indian Government the Head Quality (Quality Person) is the authorized person, responsible

for product release.

1.7 There is procedure for internal and externa audit management, which define inspection team requirements (GMP training, experience, and qualification) and designations including the independence between auditor and auditee department, there are established check lists for internal inspections that are performed at twice per year, findings are classified as minor, majoror critical. After inspection each area prepares a compliance action plan and then action is implemented, and follow-up is done. Audits calendar and records were verified, including manufacturing, engineer, maintenance, quality control and quality assurance Departments.

1.8 The procedure for deviations control is documented. These are classified, reporting and investigation according to the procedure, while a deviation is detected, the corrective action is carried out, then, during the evaluation, the impact investigation on the product quality, as well as, the root cause are determined. The process includes the CAPA system, when applies, including identification (corrective and preventive action) and implementation of the action plan and follow-up, responsible for each step, records were verified, as well as, to describe and implement different investigation tools in order to strengthen the investigations and get properly root cause, the responsibilities are QA to Follow up and closed the action.

1.9 The procedure for the control investigation is documented, including the corrective action is carried out, the investigation of the impact on product quality, as well as the root cause, is determined, action and corrective action, and if necessary include deviation, change control or other tools established within the quality assurance system.

1.10 The Annual Product Quality Review procedure is performed taking into account different parameters such as, consistent manufacturing and quality parameters, including critical process deviations, stability studies, complaints received from the market, recall cases, CAPA system, validations, change control, performance of each stage, number of batches manufactured and rejected and released during the year, as well as a small trend analysis since during 2022 they only manufactured 4 batches and included the batches manufactured during the previous year, among others. The annual product report for the year 2022 was reviewed.

1.11 There is a documented procedure for change control management, which includes the initiation, review, approval and closure of each change that may be related to procedures, specifications, batch manufacturing/packaging records, processes, equipment, documents, facilities, among others, considering the evaluation of the impact (on product quality, current validated systems, marketing authorization, critical and major changes must be reported to regulatory affairs, among others). The head of the Quality department is responsible for the evaluation of changes, their authorization or rejection. The procedure ensures that changes with regulatory impact are communicated to authorities and customers located in other countries, for which records have been checked.

1.12 The company has a supplier's (vendor's) qualification and audit SOP (Qualification of Raw Materials Supplier, Packaging, Labels, among others). According to this SOP they select, approve, and evaluate all suppliers, including approval and qualifications for APIs, excipients, packaging materials and services. Some of the criteria that are evaluated are Government Certifications (for each type of business), quality system, and commercial information among others. Also, they perform audit to the quality system to the suppliers (frequency) where they evaluate the quality system using a checklist. During the audit the suppliers may comply or not comply. If the problems are critical the supplier does not comply, therefore Corporative stops buying from the specific supplier. This activity is carried out by the CQA, but in this side has all the support for initial evaluation and auditors' inspection. There is also a Master List of approved suppliers. **However, at the time of vendors qualifications have not been established:**

a) Recording and verification of continuous monitoring
b) Adopt an international guideline
c) Update the supplier's supports with respect to what is established in the current SOPs.

And at the time of reviewing the contract with NEUTRAL LABS, it was found that it did not include the 100mL vial size.

1.13 There is also a Master List of approved suppliers. Records of qualification and evaluations were observed randomly: API: immunoglobulin (GMP certificate of Government of India), excipient: maltose, Environment, primary packaging (vials), Leaflet (insert), Pest Control, among others. All the approved

suppliers (vendors) in the company are included in the approved list. For raw materials (API) or excipient or packaging or laboratory test, the vendors have GMP certification or approval by the government.

1.14 There are policy and SOP for handling complaints. Complaints can be received written, email, call, website or orally as those related with clinical usage as well those related with quality problems such as appearance of product, chemical, adverse event, biological problem. After reception these are logged in, classified according to the problem reported (critical, major, or minor), investigated, evaluated, and reporting product. When of the conclusion is one the adverse events shall be classified based on the investigation findings. QA Department sends the answer to complainer in writing. The records were checked.

1.15 There is a SOP for handling of return goods, which includes the motives of return, the location in a pre-designated area into the respective warehouse and then QA analyses them and decides the destination; they can be return to stock or rejected and destroyed. **The SOP for handling returned goods did not include verification of the storage conditions of the products, since some products require a cold chain, storage in a cool area, in a dark area, among other storage conditions, according to the specifications of the product.**

1.16 There is a procedure for Product Recall by forced or voluntary recall or as result of damage or market complaints. These have scope over real, mock, domestic and overseas recalls. The Recall Products from the market is coordinated by a quality department, and the SOP includes notifying the event to customers and regulatory agencies, the classification (three levels depending on the impact on the heath: I, II, III and IV), the reception, investigation of the cause, reconciliation between the manufactured, information to the sanitary agency, delivered and recovered quantities of products. Quality department performs evaluations of the recall procedure once per year. Record was checked and it was according to the procedure).

1.17 The potential risk is evaluated as per risk managements SOP based on national or international guidelines. It is to control, reduce and/or eliminate the reasonable risk that can affect all phases in the life cycle of the product from the initial development until product discontinuation, the SOP describes appropriate risk management tools. There are established the main risk assessment stages: risk identification analysis evaluation, control revision and quality risk evaluation monitoring, for each case critical control points are defined. Record was seen.

1.18 The batch release and approval of finished goods to the market is made by Head Quality and Qualified Person or his deputy, after inspection of finished products and review of the all the batch record and analysis certificate, investigation of deviation if any, release in SAP System, verification of all results a product release note, among others. Records were checked.

2. QUALITY CONTROL

2.1 The BHARAT SERUMS AND VACCINES LTD company has a 3-level building dedicated to perform physicochemical, biological, microbiological and toxicity quality control analyses of the products and materials subjects to certification. On the third level are located the physicochemical and microbiological quality control laboratories, on the second level are located the stability chamber and on the first level is the animal lab.

2.2 The physicochemical quality control laboratory is separated from the microbiology laboratory.

2.3 For the realization of the test for abnormal toxicity that required, there is an animal lab, which is located on the first level of the quality control building. For the analysis of pyrogens, the company did it with an externa supplier. The procedure for perform the toxicity test was presented, which is based on the recommendation of the BP pharmacopeia. Abnormal toxicity test reports of the product immunoglobulin for intravenous use BP 5.0 g were presented.

2.4 The animal lab has areas for the handling of mice, rabbits and guinea-pigs. This laboratory has the following areas for its management: Gowning room, observation room, breeding room, sampling preparation room, washing and sterilization room, toxicity test room, euthanasia room among others. It is defined to performance qualification of the autoclave six months. The qualification report was presented with maximum and minimum loads. These different areas were in good conditions of cleanliness, order and maintenance. These areas have ventilation system and the areas maintain controlled temperature (20 °C –

24 °C) and humidity (30 % - 70% RH.). The flow of process is unidirectional to prevent cross contamination. The areas of each animal species are independent.

2.5 The microbiology laboratory has the following areas: water generation and distribution room, change room, media/consumable storage room, sample material transfer, change room I, change room II, microbiological testing room, culture handling room, decontamination room, garment washing room, Walkin incubator, sterility testing room, media storage and preparation room, autoclave room, BET room among others, **however, it must be ensured that incubators do not located in corridor at microbiological laboratory.**

2.6 Validation protocols and reports for Qualification (IQ/OQ and PQ) of HVAC system were reviewed for the microbiology laboratory and the sampling room. The PQ study includes several parameters such as; temperature & relative humidity, differential air pressure, viable and non-viable particle count (at rest and dynamic conditions), integrity test for terminal HEPA filters, air changes per hour and recovery test. Records were checked. Results of all parameters were within their pre-established limits and according to the ISO 14644-1: 2015 guidelines. The sterility area is grade B, microbiological testing room is grade C and the other areas are grade D (media storage room/preparation room, autoclave media/dispensing room, decontamination room, garment washing room, sample material transfer, culture handling room and change room I), and sampling room is grade C according to the results presents from the particle counts. The protocols and report of performance qualification de laminar flow cabinets and biosafety cabinet of microbiology and sampling room were presented. Which are carried out every six months. The following test were performed: HEPA filter integrity, viable particle count, flow rate and smoke test. All previous test were within defined specifications.

2.7 The physicochemical laboratory has the following areas: Sample storage room and reception of samples, documentation room, TOC room, KF room, GC room, HPLC room, biological testing room, liquid reagent storage room, chemical test room, reference/working standards storage room, balance room, washing room, storage standard solution room, balance room, chemical and glassware store room among other.

2.8 In general, quality control laboratories and animal lab were found during the inspection in good conditions of cleaning, maintenance, and organization.

2.9 Quality control personnel have the appropriate protection and safety equipment, as aprons, mask and gloves; laboratories have fire extinguishers, biosafety cabins (in case of microbiology laboratory) among others.

2.10 Quality control laboratories have the necessary equipment and instruments to perform physicochemical test, microbiology test, biological test and animal test for raw materials, intermediate products, packaging materials, finished products, stability samples, environmental microbiological monitoring, water system monitoring and plasmas test. Those includes: two autoclaves (one autoclave to sterilizer clothes and tools and other autoclave to carried out materials decontamination), incubators, electronic balances, pH meter, conductivity meter, TOC, High Performance Liquid Chromatography, Gases Chromatography GC, Gas Generator for GC, microbalance, analytical balance, glassware washing machine, UV spectrophotometers, cyclomixer, heating block, stability chamber, laminar air flow, biosafety cabin, oven to dry glasses, conductivity meter, steritest, vertical electrophoresis, pH meter, polarimeter, UV cabinet, Elisa reader, colony counter, microscope, centrifuge, SDS PAGE instrument, osmometer, Fourier transform infrared spectrophotometer, liquid particle counter, muffle fumace, Mili -Q water system, particle size analyzer, hematology analyzer, air sampler among others. Instruments and equipment's were found calibrated and/or qualified according to their requirements, and labels are used to indicate their status. For electronic balances, it is used certified standard masses to verify them. Each of the electronic balances has its printer. Protocols and reports of qualification (URS, IQ, OQ and PQ) for some of them (GC, HPLCS, UV spectrophotometers, stability chamber and TOC) were observed. The computerized systems associated with such equipment was also presented.

2.11 There are documented procedures to operate maintenance and clean of each equipment or instruments, as well as use logbook. Usage logbook for some of them was observed with the respective traceability. Analysts are trained in the use of each equipment or instruments.

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2.13 The protocols and reports of the installation, operation and performance of the microbiology autoclave were presented. The following test were performed for this equipment: vacuum leak test, Bowie-dick test, empty chamber heat distribution study and heat penetration study, as well as the report of the chemical and biological indicator. Heat penetration studies were performed with maximum and minimum load and the Fo values obtained were within specification. For each of previous studies or tests, 3 run were made for each of the loads used in the laboratory, both solids and liquid.

2.14 The protocols and reports of the installation, operation and performance of the microbiology and physicochemical refrigerators used for the storage of samples for analysis, standards, culture media, solution among others were presented. The following test were performed for this equipmentmen: empty chamber heat distribution study, load chamber heat distribution study, and challenger test (Door opening and power failure study). The results were within specification.

2.15 For the analysis of pool, the gamma IV bulk, the company has a room independent in the physicochemical laboratory. In which the analysis of the different types of virus (screening) and the total protein of each pool the gamma IV bulk that is received from de supplier, as well as the finished product. In the laboratories of the sample units the following test are performed: HBsAg (By ELISA method), Anti-HCV (By ELISA method), Anti - HIV (By PCR method), HBV (By PCR method), HCV (By PCR method), Protein composition (By zone electrophoresis), Anti-D antibodies, immunoglobulin A (By immunochemical method) and total protein (By biuret method). Reports of the analyses carried out in pool gamma IV bulk and finished product were reviewed, finding them within specifications.

2.16 The specification of analysis of the normal immunoglobulin for intravenous use B.P – 5.0 g are available in vial of 100 ml which must be stored under refrigeration (2 °C – 8°C). The following test should be performed for the release of products: appearance, identification by immunoelectrophoresis (IgG), Ph, osmolality, total protein (By biuret method), protein composition, molecular size distributions (By size exclusion chromatography), prekalikrein activator, Anti -A and Anti -B Haemagglutinis, Anti-D antibodies, ,sterility test (By membrane filtration method), pyrogen (By biological method), abnormal toxicity, and virus (HBsAg (By ELISA method), Anti-HCV (By ELISA method), Anti - HIV (By PCR method), HBV (By PCR method), HCV (By PCR method). Analyses of release of finished product were presented in which it was evident that they complied with the established analyzes and were within the specification given in the BP pharmacopeia.

2.17 The specification of de excipients used in the formulation (glycine and maltose) area available. Reports ere presented where it is observed that they comply with the defined specification, **however it was evidenced that for glycine the test of related substance is not carried out as established by the BP pharmacopeia.**

2.18 Raw material is performed in the sampling rooms located at warehouse of the company. Sampling is performed by QA personnel; **however, the primary packaging material is not made in a controlled areas as established in numeral 14.19 of the resolution 1160 of 2016.**

2.19 The sampling procedure of raw material and primary packaging materials establishes the following aspects: responsible for sampling, precautions, control of the environmental conditions of the areas, control of pressure differentials, quantities of samples to be taken on the type of analysis (physicochemical, biological and microbiological), identification of the sample, sampling utensils to be used among other aspect.

2.20 For the storage of samples for analysis in quality control laboratories there are cabinets with restricted access and environmental conditions are recorded. Record was reviewed, which were found within the defined specifications. They also have refrigerator or freezer to store the raw materials that require it. They themselves were qualified. They also have the procedure for receiving, handling and storing samples for analysis and a label has been defined for their identification, which guarantees their traceability, **however samples were found for analysis without the established identification.**

2.21 There are specifications and methodology of analysis for WP and WFI, appearance, TOC, pH, conductivity, acidity, microbial limit, bacterial endotoxin, ammonium, chlorides, heavy metal, nitrate, calcium and magnesium, Escherichia coli, staphylococcus aureus, Salmonella specie, Pseudomona aeruginosa is carried out. Frequency of monitoring for sampling point and user point is documented. Microbiological and physicochemical test are done in user point according with the respective procedure and conclusion of the validation study. Trends analyses of 2022 and 2023 were checked and all of them are according with de specification.

2.22 The compressed air monitoring procedure is available, which establishes the following aspect: personnel responsible for sampling, sampling methodology, specification, frequency, analysis to be carried out (microbiology test) among other aspects. Trends analyses of 2022 to 2023 were checked and all of them are according with de specification.

2.23 There are cold chambers for retention samples storage, where temperature and relative humidity are monitored, record were checked into specifications. Raw materials samples (gamma pool, glycine and maltose) and finished products are stored one year after of this expiration date, as well as the quantity samples is enough to perform twice complete analyses.

2.24 The volumetric solution (VS), test solutions (TS) and mobile phase are prepared according to the procedure, preparation record have traceability (reagent used and standard used). They were found correctly identified.

2.25 There are procedures for culture media management: reception, storage, handling and final disposition. It is established to perform growth promotion test when it is received or preparations. Records were checking according to procedure. Culture media are purchased sterile. It has the procedure of management, storage and use of the strains. It used certified strains which are labeled and store in deep freezer or in a refrigerator, sub culturing is performed according with SOP and its used is limited no more than three passage. Record was checking according to procedure.

2.26 Protocol and report of the study of storage time of the 14 days given to the media soybean casein digest, that is stored at 20 °C 25 °C was presented. The following parameters were evaluated: appearance, pH and GPT.

2.27 Environmental microbiology is done within classified areas as well as on surface, personnel according to SOP. The limit and frequency are defined according to air classification of the area (A, B. C and D), program, records and trend analysis were verified within acceptance criteria for sterile vial lines (Unit I – Production C).

2.28 There are SOP and protocols for carry out the stability studies; those include the kind of studies (long term, accelerated and ongoing), stability sampling plan, storing time, number of samples, temperature conditions, as well as the tests to be done. The laboratory has qualified stability chamber and cold chamber, results of these qualifications performed were found into specifications. The qualification of said cold chamber and stability chamber was presented (IQ, OQ and PQ). The qualification of the cold chamber of the stability are carried out every year. In the annual qualification the following test are carried out: temperature distribution with load and challenge test (Door opening, power failure and alarm challenge). From the qualifications reviewed, the raw data, calibration certificate of the measuring instruments of the equipment and with which they performed the test were presented.

2.29 There is a procedure for out of specification management, which described the different phases of investigation.

3. SANITATION AND HYGIENE

3.1 The manufacturing areas of production C (Unit I), storage areas, QC and animal house were found in good conditions of order, maintenance, and cleanliness. **However, during walk around it was found some areas required maintenance as Labeling 1, 2 and 3 at secondary packing, Cold room No. CP/CR/G078 and cleaning of terminal sterilization area.**

3.2 Production areas and equipment were found identified according with the cleanliness status through tags, as well as, cleanliness areas are performed according to a written and approval SOP, its status is reflected on fixed labels. **Nevertheless, dispensing tools were found without cleaning label identification.**

3.3 There are procedures and records for cleaning areas, also for equipment and utilities used in those manufacturing process, all pipeline and others are dismountable and washed all mobile parts in washable rooms and sterilized by moist heat sterilization.

3.4 There is a cleaning procedure for cleaning the different types of areas (grade A, B, C and D) in which establish methodology, cleaning order, sanitizer to be user among others. The mops used to clean aseptic areas are of single-use, for other areas mops, **however, during walk around it was observed that cleaning utensils are handle in manufacturing area as well as vacuum and other cleaning equipment are storage on manufacturing personnel airlock.**

3.5 Disinfectant solutions are applied in manufacturing rooms in order to control the bioburden, those solution are rotated weekly, and prepared according to SOP instructions, the disinfectant solution used are: Imagrad

Plus (hydroxide Peroxide 12% and Silver Nitrate 0,01%), Imagrad IG Pro 40% (Alkyl Dimethyl Benzy Ammonium Chloride 8.19% and Didecyl Dimetil Amonium Chloride 8.7%), Imagrad IL 15 (Alkyl Ethyl Benzyl Ammonium Chloride Dimethyl 2,3%) and Imigrad Biguat Plus (Biguanida, Dimethyl Ammonium Chloride and Benzalkonium Chloride). It was verified records of this preparation and filtration.

3.6 Pest control is done by the third party according to specific SOPs (flies, ants, spiders, lizards) on monthly basis. Rodent station and insect cuter devices are monitored periodically the Alert limits and action limits are established for each kind of pest. Records were reviewed.

3.7 They have an effluent treatment plant, records regarding effluents testing were checked, parameters are within established specification, those analysis were done by a government entity. Periodically is sampling and analysing effluents; parameters such as pH, C.O.D, B.O.D., among other are evaluated, they were found within permitted limits.

3.8 The medical examination of personnel SOP establishes to perform pre-employment and annual check-ups; these include physical examination, eye examination, clinical exams, blood testing (pressure and chemistry), among others., Records were seen for personnel involved in manufacturing of sterile products. Records of different activities were verified.

3.9 There are documents about Environment that included the different related activities such as waste management, hazardous wastes. Records of different activities were verified. They count with the HSE Department that is responsible to waste management. Records of different activities were verified.

3.10 The emergency evacuation route is identified.

3.11 The fire extinguishers were seen loaded according to needs. The expiry date was checked.

3.12 There is a laundry for the laundering of garments used in clean areas. There is a SOP for cleaning work clothes and footwear used in grade D and common areas. Washing is done with liquid detergent and purified water; they are then folded. The records of the different activities were verified. inside the production area are sterilized.

3.13 The manufacturing is in charge for the qualification yearly of personnel in the visual inspection, they have a retention for different sample for the defect. they have the reports and records for each people qualification, the qualification Kit, they also include the review of the training of the personnel in all aspects related to this activity, they include the verification of the visual examination, which is carried out twice a year, rest times of the personnel, Luxes of the lamps according to USP, among other aspects.

3.14 The manufacturing is in charge for the qualification yearly of personnel in the sterility areas in sterility gowning, **however the qualification report for the use of gowns did not include the medical examination and full training in accordance with the standard operating procedure (QA:6N:050/R10).**

4. VALIDATIONS

4.1 Validations are performed based on validation master plan – VMP/EV/008- that include the policy, purpose, responsibilities, organizational structure for validation, type of validations (prospective, current and verification continue), scope over facilities, summary of facilities, processes (cleaning and manufacturing), holding time, utilities (Water systems, HVAC, compressed air, pure steam), schematic layout of critical support system, qualification equipment, analytical method validation, computerized system, temperature and mapping validation and transportation qualification, trends analysis, transfer analytical methods, aseptic process simulation, validation of container closure seal integrity, cold chain validation, hold time study among others; as well, revalidation or requalification criteria and schedules are defined. It is established that if there is any change in equipment, areas quality control equipment or major changes they apply change control and re-validation. The validation of the analytical methods include mainly: validation of analytical methods of raw material, final bulk and finish products, microbiological and sterility test methods, cleaning residues test methods and stability test methods among others. The validation master plan for 2023 was also presented.

4.2 Whitin the validation management procedure it has been defined that the validation of analytical methods must have the following test: system suitability, accuracy, precision (Reproducibility and intermediate precision), specificity, LOD, LOQ, linearity, robustness and hold time study.

4.3 It has been defined that the qualification of the equipment must include the following aspect: FAT, SAT, URS, QRM, DQ, IQ, OQ, PQ and re-qualification.

4.4 For the unit I – Production C, there are one system for generation de purified water and a system for obtaining water for injection, which is obtained by distillation. The protocols and reports de URS, DQ, IQ, OQ and PQ were presented.

4.5 All sampling point and use points of the different water system are monitored with the following parameter: appearance. Nitrate, conductivity, Flow rate, pH, TOC, microbial limit test and endotoxin (for WFI points). It was checked trends of analyses for TOC, conductivity, microbial limit test, pH, endotoxin test for 2022 and 2023 and all of them are according to current specification. For pure steam, the following test are performed: non condensable gas, superheat, and dryness). Maintenance routines are established. Record for prevent maintenance, cleaning process and sanitization for storage tank, reverse osmosis and loop distribution was checked. Sanitization of the system is also performed by heat at: ≥ 85 °C for 60 minutes, every monthly. In the case of WFI sanitization is performed by heat at: ≥ 95 °C for 60 minutes. Records were checked according to the procedure and between the established frequencies.

4.6 The respective protocols and cleaning validation report were presented for each of the equipment used (Unit 1 -production C) in the following process: formulation, transfer product, finished products filling and sealing. The validation was performed with 3 consecutive batches (A03323008, A03323009 y A03323010) of the product (normal immunoglobulin for intravenous use B.P – 5.O g, considered the work case). The matrix of the evaluation of the worst case was presented, based on the solubility, of least therapeutic dose and toxicity of the products.

4.7 The protocols clearly defined the following aspects: equipment sampling points, sampling method (swab and rinse), sampling methodology, specifications, calculation of the limits for the acceptance criteria, and the test performed on each sample: pH, conductivity, BET, TOC and microbial limit test, HNIG content and teepol content. The cleaning process of the equipment is carried out with is WP, followed by WFI and addition of sodium hydroxide 1 % and sanitized with 70% IPA.

4.8 The corresponding supports of the studies and raw date of the validation of the analytical technique for determination of traces of the active ingredient (by HPLC) and detergent (by UV spectrophotometric method) were presents.

4.9 The sterilization process of the product subject to certification are by filtration sterilization and aseptic filling. The company has defined as a policy to perform the initial validation or re-validation with three successful process simulation tests and monitoring every six months with a single simulation process for each production line. It was checked protocols, report and raw data for the monitoring for media fill (simulation aseptic operations) for unit I - production C. The simulation media fill test is done every six months were include different vial size (work case 100 ml), microbiology monitoring, on the personnel and environmental, were include as well as routine and non-routine intervention. TSB liquid media was used, and GPT (grow promotion test) report were checked (before and after incubation of vials). Incubation took place to 7 days at 20 °C ± 25 °C following for 30 °C ± 35 °C for 7 days consecutively. The filling time was performed for 8 HRS. The result of the inspection of the vials (2953 unit) after incubation for 14 days was found into specification. The simulation process incorporates all manufacturing step, such as formulation, connection, transfer filling, aseptic filling, stoppering and sealing process. Support of depyrogenation of vials, sterilization rubber stoppers, part of equipment's, count of non-viable and viable particle, inspection visual of the filled vials among other. Protocols, reports, batch record and raw data for the validation of aseptic fillings corresponding to sterile solutions of small volumes manufactured in Unit I -production C object of the audit were also presented. All data presented were within the defined specifications. (Result show no growth in one single unit). Standard lot size is 2473 vials.

4.10 Routine interventions included the following: aseptic assembly and volume checking, overcrowding in filling area, speed alteration, addition of rubber stopper, changeover of filling vessels, microbial air sample/plate exposure, removal of empty vial from turntable, adjustment of rubber bung from stopper chute among other.

4.11 Non-routine intervention included the following: lunch break, filling machine maintenance, spillage of media, jamming of vial at infeed of filling station, LAF shutdown for 05 minutes, power shutdown for 15 minutes among others.

4.12 The protocol and report of the transport shipment of cold chain products from Mumbai to Philippines was presented. In the following aspects were contemplated: Time and temperature of freezing of gel pack, material of the transport boxes (thermocool box), their capacity, configuration, and quantities of the gel packs among other. 2 sensors were included in each box and 1 shipment was made to Philippines with 3

boxes of the same capacity and the same configuration and with a capacity of 1800 vials each. According to the reported results, temperature conditions from 2 °C to 8 °C were maintained for 9 days in each of the boxes.

4.13 The protocol and report of the validation of the endotoxin (by gel clot method) and sterility test (by membrane filtration) for the product and raw material were presented.

4.14 or requalification criteria and schedules are defined. It is established that if there is any change in equipment, areas quality control equipment or major changes they apply risk assessment and re-validation.

4.15 Qualification of equipment for new equipment describe has to performance following steps: URS, FAT, SAT, Installation Qualification, Operational Qualification and Performance Qualification, Periodic Performance Qualification is done per equipment and systems.

4.16 HVAC revalidation is according with Validation Master Plan with six-monthly for areas located in grade b and A and yearly areas Grade C and D; following test are carried out: air changes per hour, integrity test for HEPA filter, non-viable particles (at rest and in-operation), viable particle count (settle plates and air bone), flow visualization, differential pressure, temperature and humidity and recovery test. As international guideline follows ISO 14644. Report done of 2023 were verified, found all result within specification.

4.17 Differential pressure is designed that cleaner zones on the manufacturing areas maintain relatively higher pressure compared to the less clean area. During the inspection, pressure difference and air direction were found according to design for all manufacturing areas. This record is done by BMS system, differential pressure of areas as well temperature and relative humidity.

4.18 There is some process that have laminar flow boots such as dispensing, sampling areas, filling, sealing, among others, performance test are done: air changes per hour, air flow, integrity test of HEPA filter, viable and non-viable particle count, qualification report was verified (2023).

4.19 Compressed air system is generated in the utilities building and piped directly into the manufacturing area. Compressed air is generated by three oil free compressors, then 2 receiver tanks, filters (1 µm, 0,01µm and 0,01µm), then desiccant dryers, and connect to distribution line where a 0.2µm filter is located at user points, compressed air is distributed by piping system.

4.20 According with Validation Master Plan, revalidation of compress air is done once in a year. It was presented revalidation report done on 2023 where is checked results of following parameters: non-viable particle, viable particle, dew point and oil content and impurities as CO, CO_2 and SO_2, found all tests within specification, the quality of the air is classified according with the area classification and according to the guidelines ISO 8573, trends were checked within specifications.

4.21 Revalidation frequency for nitrogen system validation is done once in a year, and it is evaluated following parameters as non-viable particles, viable particle, dew point and oil content and impurities as O_2, it was verified protocol and report done 2023 where all parameters were found within specifications.

4.22 For the passage of materials in the different areas (drugs substance and finished product) there is pass box dynamic. These are carried out the following test: air velocity, air changes per hour, integrity test for HEPA filter and non-viable particles and microbiological test according to the defined frequency. Records were checked. Results of all parameters were within their pre-established limits.

4.23 Manufacturing equipment are qualified according describe in Master Plan new one with URS, FAT, SAT, installation, operational and performance qualification and there are two frequencies for drug products equipment re-qualification are done every year and for drug substance and warehouse, every two years. It was verified last qualification protocol and report for some equipment as autoclave, depyrogenation tunnel, manufacturing vessels 100L, bioreactor, cold room, freezer room, biosafety cabinet, among others.

4.24 It was verified autoclave OQ and PQ protocol and report (PC/SS/G129) done in June 2023, where was verified some parameters such as: vacuum test, Bowie Dick test, empty heat distribution, heat penetration of each load pattern as garments, stoppers, seals in minimum and maximum load where three were carried. Concludes all parameters were found in specification. **however, it was not present verification of users of PLC in vial washing and autoclave.**

4.25 It was present protocol and result of depyrogenation tunnel (PC/DT/G130) where was carried out verification empty heat distribution, air velocity, non-viable particle count, HEPA integrity test, heat penetration different size of vial minimum and maximum (2mL and 100mL) and endotoxin test found all results in specifications.

4.26 There was present protocol and report of installation, operational and performance qualification of manufacturing vessel 600L done in 2014 located in manufacturing area, where was mention main

components, verification functionality speed verification, found all parameters in specifications. **However, it is not carried out a verification of qualification of maintenance status of equipment which are requalified.**

4.27 It was verified cold room No. PL/CR/G032 and PL/CR/G079 where a verification of temperature over 07 days, and door open, recovery and power outage were verified, found all parameters in specifications.

4.28 It was verified protocol and report of vial washing (PC/VW/G021), filling (PC/VF/G131) and caping machine (PC/VS/G132) which is done once in a year (06/2023). Vial washing machine were verified washing cycle, differential pressure of filters and verified washing cycle with removal of vial spike with riboflavin, sodium chloride an charcoal, where were found in specifications. Filling machine was verified filling volume at different speed and capping machine were verified crimping and integrity of seal.

4.29 It was present protocol and report of sterile filter validation of Normal Human Immunoglobulin done in September 2023 where was evaluated compatibility test, integrity test, adsorption, viability test, bacterial challenge test, extractables test and leachable found all parameters complies within specifications. **However, it was not present raw data of filters certificate, B. Diminuta certificate, integrity test results and incubation results support of bacterial challenge test.**

4.30 Company has a Process Validation SOP, where mentions two types of validation: prospective and concurrent, as well as mentions scope, responsibilities, activities regarding to protocols and reports, sampling strategy for each unit operation, critical process parameters and critical quality attributes to be monitored, activities in case there are changes, it was mentioned follow lifecycle of product (design, qualification, continuous process validation), among other activities.

4.31 Master Formula Records are issued per product in which is captured all information related to product details, quantitative formula, primary and secondary materials, manufacturing instruction. **However, it is not including batch size, equipment and instrument required, instructions, sterile filter catalog number, among others.**

4.32 It was checked the protocol and report of process validation of the Normal Human Immunoglobulin 5,0gm (100 mL), which are validate with three consecutive commercial batches were manufactured for process validation. The validation indicated and evaluated process parameter of manufacturing process and evaluate some critical attributes, manufacturing process, sterile filtration (online, 0,22 µm), filling, stoppering, sealing, critical process parameters such as times, pressure, among other were checked are found in specification, as well as, critical quality attributes such as bioburden, pH, BET, sterility tests, protein concentration, fill volume, among others, were performed in order to demonstrate that the product is homogenous during the whole process. **Nevertheless, it was not included it was not considering a representative sample during formulation, it was not included and analyze filling process in the report, it was not present statistical analysis and it was not including speed in report and BMR.**

4.33 In Validation Plan is document Continuous process verification is done once in a year, therefore was present through CPV of Normal Human Immunoglobulin 5,0gm of period January to December 2022 where was compiled data of 13 batches for CPP and CQA and get trend graphics of those data. **However, all CPP and CQA define and verified in process validation it was not include in CPV report, as well any statistical analysis was done.**

5. PRODUCTION

5.1. Facilities and equipment to manufacture the products included in the scope of this inspection are drug product (formulation and filling) of biological products Human Normal Immunoglobulin liquid small parenteral solution manufacture in Unit I at production C areas.

5.2. Dispensing and sampling of excipients and Bulk is carried out under laminar flow cabinet surrounded by area classified as grade C located in production C and the environmental conditions (Temperature and relative humidity) and differential pressure is checked by BMS. **However, it was observed that in usage balance logbook is not describe each material dispensed per batch and also, close blank spaces as well as there is not a properly place to wash and keep dispense utensilies.**

5.3. Formulation process of Normal Human Immunoglobulin is carried out at manufacturing area of Production C, where Bulk first is pooled and a sample is sent to QC to verify protein content; then this pooled bulk is mixed with excipients, verified pH or adjust if required, after that bioburden, protein content, pH and description is verify sent sample to QC.

5.4. Solution is transfer from manufacturing area to filling area through pressure pipeline use nitrogen, then if receive in three 100L vessel (previous sterilized by autoclave) and connect to filling machine.

5.5. Vials are washed in a vial washing machine and sterilized in a depyrogenation tunnel, all the process is continuing with the filling process, before start washing and in process there are checked pressure of different filters of compress air; also in the sterilization are checked differential pressure of filters in tunnel those records are include in the Batch Record.

5.6. Rubber stoppers are sterilized in autoclave, this equipment has a double door that´s mean that rubber stopper clean and sterilized are collected in grade A and transport to filling machine where before going inside laminar flow is remove one bag.

5.7. Filters used in primary and secondary (online) sterile filtration are checked its integrity every manufacturing batch before and after of filling process and those are rejected when the manufacturing process is over. Records prints are attached to the Batch Record.

5.8. Filling, sealing and capping process is carried out under aseptic conditions and the volume is checked as in process control; Environmental conditions are recorded. **However, aseptic critical process (filtration and filling) cannot be observed from outside at production C.**

5.9. Viable and non-viable particle are count during all the manufacturing process, likewise environmental conditions (temperature, relative humidity and pressure) results are recorded and be part of the BMR.

5.10. In-process controls are recorded and checked by manufacturing and Quality Assurance personnel, data are input in the respective batch record; yield calculation is done for each step during manufacturing and packaging process. The reconciliation activity is recorded as well.

5.11. Vials are carried to visual inspection room where are inspected all of them (100%) manually, there are established defects than can appear such as foreign matter, cap sealing, robber stopper status, aluminum caps, printing, material defects, foreign substance glass, material shines, foreign substance metal. For visual inspector there are prepared a training kit; visual inspectors to be qualified should check and found 100% of vial with foreign matter. Quality inspector is in charge to perform quality accept level where according with a representative sample defect are evaluated.

5.12. There are cold rooms in production C area in order to keep cold condition after filling process; then those vials area transfer to cold chamber in packing area to visual inspection and then in quarantine cold chamber; in BMR are record excursion time in each step of the secondary packing.

5.13. Secondary packing process since visual inspection, labeling, printing, cartooning, shipping are carried out in ground floor at Unit I.

5.14. There was checked the batch record for product scope of the inspection, batch number A03323011 and batch record used in process validation where it was observed that are composed for the following documents request order, weighting records, areas and equipment cleaning records, manufacturing instructions, and cleaning records, in process controls for each manufacturing process, releasing sheet, Certificates of Analysis (CoA), sample labels, sterility records (autoclave, tunnel), visual inspections records, reconciliation and yield calculations, and, among others.

5.15. There is a SOP regarding to assigning batch numbering system, manufacturing date and expire date, intended market designation for each batch number is defined by prefixes to the batch numbers, compose by a product code, manufacturing number (sequence), month and year of the manufacture, there is a logbook in order to record assignation activities.

6. PERSONNEL

6.1. The organizational chart shows the positions and the different departments with the hierarchical levels of

6.2. The organizational chart shows the positions and the different departments with the hierarchical levels of the organization. The general organization is composed mainly of the following positions: Managing Director, Qualify Person & head Quality, head Production, head QA, head QC, workers, among others.

6.3. The organization counts with qualified personnel. The key personnel have more than 2 years of experience. The organization chart shows the designation and the respective departments with the hierarchical levels of the organization.

6.4. The Sanitary Responsibility is the personal: Qualify Person & head Quality. He is Pharmacy.

6.5. The heads of Production and Quality Control are independent of each other. Their responsibilities are well defined in the job descriptions, they report to the head operation.

6.6. The personnel recruitment and selection are done according to SOP. The area Head must do a

requirement of manpower to Human Resources, then the selection is responsibility of Human Resources (HR) Department.

6.7. The new recruited personnel receive a general induction and a specific induction related to their work post. Records were checked.

6.8. The selection and involvement of staff is carried out according to professional profile. It if existent workers can apply for a new position, or if the recruitments are only applied for external people, also if interview is done, and how is selected the candidate. This process includes medical test.

6.9. There are job responsibilities for each position that describe basic information of position, purpose, responsibilities, and deputies for key personnel. Their compliance was reviewed.

6.10. The laboratory has sufficient personnel with the necessary education, training, technical knowledge, and experience for their assigned functions.

6.11. There is a training management procedure, which includes initial training of employees, training in general information about company, GMP system, documentation system, safety rules and personal Hygiene, among others. Technical, job responsibilities and the specific training is done according to the annual training plan. All the activities are registered. Likewise, this procedure includes training evaluation. The periodical training done according to the schedule, which includes GMP topics, quality control and analytical techniques; among others, the personnel is evaluated. Those records, including training evaluation report were checked. Likewise, the procedure includes training in particular aspects like handling of hazardous and highly sensitive substances. The records were checked.

6.12. The company has documented the procedure for personnel hygiene, which includes the rules regarding personal cleanliness and restrictions to enter the QC lab such as is not allowed jewellery, eat or drink; also, if people are suffering any diseases, they are not permitted to work in sterile areas, among others.

6.13. Each head of department is responsible for detects if any employee needs to be retrained.

7. PREMISES (FACILITIES)

7.1. **BHARAT SERUMS AND VACCINES LTD** is composed by several buildings of which all building is related to manufacturing of products scope of this inspection is Production C at Unit I, QC building, Animal and utilities are included in the scope of this inspection.

7.2. Production C is located in ground floor of Unit I, where are conform following areas: dispensing area, manufacturing area, filling, sealing area, capping area, vial washing, depyrogenation, autoclave materials area. **However, washing and depyrogenation area are used for different process such as: storage clean vessel (100L/200L) and tools, cleaning dispensing tools, preparation of autoclave tools, garments, among others.**

7.3. In same Unit I is located manual visual inspection, and secondary areas as three labeling areas two manual lines where these activities are carried out.

7.4. QC laboratory is located at first floor of building "Quality Control Unit", where is located physicochemical and microbiological areas. At ground floor on this building is located animal house.

7.5. Utilities require for this process as purified water, water for injection, compress air system, and nitrogen system (by nitrogen liquid) is located in another's buildings.

7.6. The changing rooms and bathrooms used to enter to manufactures areas are separated for gender and there is another for visitors, it was found in good conditions of cleaning, maintenance.

7.7. Pressure, temperature, and relative humidity is permanently monitored by BMS twice a day and record in the batch record of each process.

7.8. The rest and eating areas are located outside of productive areas.

7.9. There are airlocks for personnel and materials to enter to manufacture areas, raw and packaging material enter in pass box, which are provide of air flow.

7.10. Manufacturing areas have ceilings, walls and doors, smooth and easy to clean and suitable designed, it was found in good condition of cleaning and maintenance.

7.11. Personnel, material, and finish product flows are designed in a logical way to avoid cross-contamination and confusion, **however, workflow should be designed and arranged to allow for a logical flow of material and products, because it was observed manufacturing areas used as passageways to other working areas (e.g. unloading terminal sterilization to visual inspection/secondary packing areas), which is not complies with numerals 5.3 of annex 1 and 3.8. of annex 2 of Resolution 5402 of 2015.**

8. EQUIPMENT AND CRITICAL SUPPORT SYSTEMS

8.1 The equipment used in the manufacturing process related with the scope of this inspection are built of suitable material, which do not affect the quality of the processed products in the areas, as well as the pipeline some are made in SS and there another in silicon.

8.2 Equipment installation and operational qualification where appropriate, adequacy of equipment design, size, and location.

8.3 For Drug Product manufacturing in Production C at Unit I, the company has the following equipment: washing vial and depyrogenation tunnel, vial filling machine, autoclave, sealing and capping machine, vial inspection cabinet, manufacturing vessels, among others, in general all the equipment were found in good maintenance and cleaning conditions. **Nevertheless, leak test equipment is located at lyophilized technical area.**

8.4 The equipment is cleaned according to SOP where there is a cleaning and sanitization procedure for each part of the equipment, which define the frequency for sanitation and how to perform it, as well as every equipment has its SOP of operation, usage logbook and cleaning logbook, records were checked.

8.5 The dispensation and sampling of API´s and excipient are carried out in separate area there are one area for dispensing API´s. All activities are carried out under laminar cabinet flow where it provided of balances to performance this activity, every time before use the balances are verified. SOP and records were cheeked.

8.6 The temperature, humidity, and pressure differential of the air conditioning system are record online by BMS and those conditions are record in the batch manufacture records.

8.7 The conformation of the bank filters of air handling units (AHU) for sterile areas (grade B/C/D) are defined as follow: one pre-filter 10+5µm, 3µm, 0,3µm in the Air Handle Unit, and HEPA filters located in manufacturing areas.

8.8 Drug product manufacturing process present following grade classifications: filling, stoppering, sealing and capping process are performance under laminar flow (class A) with a background class B, formulation is carried out in grade C, washing tools, washing and depyrogenation of vials, are carried out in area grade C; visual inspection and secondary packaging process is done at non-classified area. The classification of these areas is related in the layouts.

8.9 Air flow for Drug product areas is in cascade from the more critical (class B) to less critical area (non-clean areas).

8.10 Temperature, humidity and pressure differential using in manufacture areas are controlled by BMS and recorded according with the SOP. Record was found inside the specifications.

8.11 There is a calibration annual plan for different measuring instrument such as: gauges, pressure gauges, temperature indicator, sensors, manometers, balance, among others have a define classification as critical or not critical according with a QRM, it was verified SOP, schedule and calibration certificates of measure cylinders, balances, standard weight, thermohydrometers, among others.

8.12 The Unit I – Production C is equipped with one water system which is composed of: soft water tank (capacity 20KL liters), SMBS dosing system, ADS dosing system, auto pH system, filter (10 micron), filter (5 micron), EDI unit, 2- RO system, EDI hot water, UV lamp and 2 -storage tank for WP and distribution loop. The WFI is obtained by a distillation system consisting for distillation columns and the feed water is WP. It has two storage tanks for WFI and 13 points of use.

8.13 Maintenance routines are established. Record for prevent maintenance, cleaning process and sanitization for system and loop distribution was checked.

8.14 Sanitization of the system of WP is performed by heat at: ≥ 85 °C for 60 minutes, every monthly. In the case of WFI sanitization is performed by heat at: ≥ 95 °C for 60 minutes. Records were checked according to the procedure and between the established frequencies.

8.15 Water system (WP and WFI) construction material of storage tank and distribution loop is stainless steel 316L.

8.16 Sampling point and user points of water purification are defined and identified.

8.17 The water production system has the following in-line measuring instruments: conductive-meter, flow-meter, pressure meters, TOC among others, which found with current calibration.

9. STORAGE

9.1 The reception and cold storage of pool the gamma IV bulk, raw material, primary packeting material, secondary packeting materials, elements used in production (filters among other) and the finished products is located in the warehouse; as well as the sampling areas. For the storage of gamma IV bulk cold chamber and finished products, they have dedicated cold chamber for the storage of quarantined, rejected and approved. All cold chamber is monitored online through the ICDAS system and qualification each year.

9.2 The company has independent areas for the storage of raw materials, primary packaging material, label and finished products. **However, the identification of each location of quarantine primary packaging must be guaranteed, as well, guarantee free access to all area.**

9.3 The areas of reception of materials and storage of raw materials, secondary packaging materials and finished product were in good condition of order, maintenance and cleanliness.

9.4 They have a warehouse for storage raw materials, primary and secondary packaging material, rejected products, returned, recall and finished products. It also has an area to carry out the sampling process of raw materials and for sampling of secondary packaging material.

9.5 There are procedure and pictograms of restrictions and type of clothing to be used to enter the storage areas.

9.6 When raw material arrival at company, material is de-dusted, they area then identified with a quarantine label and then sampled to define the status of approved or rejected.

9.7 During the inspection by the warehouses all raw materials and secondary packaging materials were identified according to their quality status.

9.8 Rejected materials and re-call products are stored in located zones with restricted access.

9.9 The quality control status for raw materials, packaging materials and finish products location are done manually. Materials rotation is controlled by FIFO rules.

9.10 Calibrated instruments are available for monitoring the environmental condition de raw materials storage and finished product. Temperature and relative humidity conditions are monitored in each of the storage areas. The records reviewed were found to be within established specification.

9.11 In general, the procedures for receiving, storing and dispatching materials and finished products are available.

9.12 The protocol and report of the temperature and humidity mapping of the warehouse were presented.

9.13 The warehouses have rooms for the storage of pool the gamma IV bulk, raw materials and finished products that require storage condition between 2 °C to 8 °C. The protocols and reports of qualifications were presented.

9.14 The protocols and reports of the validation of cold chain transport were presented.

10. DOCUMENTATION

10.1. The document administration and control are responsibility of Quality Assurance Team. The main documents are Quality Manual, Quality Policy, Standard Operation Procedures, Logbook and records, among others.

10.2. All official documents are in English.

10.3. Documents are prepared as per Preparation of document and record SOP which describes format, content, code, or serial number, written, and those criteria for review, approval, revision, distribution, modifications, obsolete handling, training and disposal. Quality Assurances department keeps the master Copy.

10.4. To date, they are implementing the Ampleologic software, where the request starts through the change control and the system keeps a record of the documentation approval flow. Some documents are already controlled in the software. Likewise, eLearning Software has the records of dissemination and training of the same.

10.5. At once documents are approved, to concerned people training is given, always previous effective date; then documents are released to use. Human resource and each Department are in charge for all training: GMP, SOP, Induction, among others.

10.6. The controlled copies and obsoletes (older documents) are identified with a stamp or Ampleologic software. In the distribution of the documents there is an adequate control of the obsolete versions, they are identified as supersedes. Also, retention time is defined, after retention time completion, documents are destroyed.

10.7. Retention time for batch record is one year beyond its useful life.

10.8. Also is documented the good documentation practices that include the guidelines about use ink in records, how to correct errors, how to fill in dates, such as clarity, exactly, completely, no erasable, blank spaces are not permitted in any record, under no circumstances use artificial correction tool and using ball point pens, among others. It was evidence supports of divulgations to all personnel.

10.9. Quality Department has the master list of all documents per area for their control.

10.10. Changes Control are recorded and each document at the end has a table that describes the revision history.

10.11. All of documents must be reviewed with a frequency (every three years) from its effective date or early if required.

10.12. **However, at the time of the review of the plans during the first day, it became evident that: the animal house layout did not adequately include the control and identification in the documentation system and the flow of material and personnel in the layout of this area was not present.**

10.13. Each copy of a document that is distributed has a stamp on it that specifies that is a copy.

10.14. The master formulas for the product involved in this inspection were reviewed and the production process and the control of each stage of the processes are documented.

10.15. There are contracts for the different services suppliers such as raw material (API and excipient), packaging, waste dispositions, pest controlled, amount others.

10.16. The SOP numbering system guarantees that there will not be more than one document with the same code; it includes the abbreviation of the department name and a consecutive number and version (e.i. SOP: QA:6N:050/R10). It is established that documents should be reviewed and when that happens the version number is updated.

11. REGULATORY AFFAIRS

11.1 **BHARAT SERUMS AND VACCINES LTD,** has not sent the scope product in this auditor to Colombia.

11.2 The product normal immunoglobulin for intravenous BP possesses the authorization of the authority FDA India.

11.3 **BHARAT SERUMS AND VACCINES LTD.,** located at Plot No. K-27, K-27 Part and K-27 /1, Ananda Nagar, Jambivil Village, Additional M.I.D.C, Ambernath (East), Thane 421506, Maharashtra State, India, complies with the requirements of Good Manufacturing Practices for Pharmaceutical Products, according to GMP certificate number NEW-WHO-GMP/CERT/KD/107921/2022/11/39826 for Active pharmaceutical ingredient (bulk drug), Blood Products, synthesis, purification, packaging labeling, Quality Control, Quality Assurances, and among others. By Food and Drugs Administration M.S. of India on July 4th of 2022.

11.4 It was presented the Quality agreement between BHARAT SERUMS AND VACCINES LTD and Pharmalab PHL Laboratories, which establishes the responsibilities between the parties, the compliance with GMP, the products to be marketed, **however it did not include: the responsibilities of maintaining the cold chain preserving the shipping and marketing conditions and did not include the product that was the object of this inspection.**

12. ACTIVE PHARMACEUTICAL INGREDIENTS AND MANUCTURING DRUGS FOR CLINICAL TRIAL

12.1 **BHARAT SERUMS AND VACCINES LTD** manufactured in this site at Unit II Recombinant Follicle stimulating hormone which are currently used in a clinical trial

13. NON-CONFORMITIES

NON CONFORMITIES	CRITICITY (CRITICAL, MAJOR, MINOR)	CHECKING
1. To guarantee animal house layout include properly control and identification in documentation system and to present material and personal flow layout of this area.	Minor	FULFILLED
2. To guarantee in usage balance logbook should be describe in format each material dispensed per batch and close blank spaces.	Minor	FULFILLED

NON CONFORMITIES	CRITICITY (CRITICAL, MAJOR, MINOR)	CHECKING
3. To guarantee a properly area to wash and store dispensing tools used in dispensing area (production C).	Major	FULFILLED
4. To give maintenance of follow areas, because was found bad conditions of cleaning and maintenance: a. Labeling 1, 2 and 3 at secondary packing b. Cold room No. CP/SR/60/78. c. Cleaning of terminal sterilization area	Major	FULFILLED
5. To guarantee that aseptic critical process (filtration and filling) could be observed from outside at production C	Major	FULFILLED
6. To give compliance to numerals 5.3 of annex 1 and 3.8. of annex 2 of Resolution 5402 of 2015 regarding to workflow should be designed and arranged to allow for a logical flow of material and products, because it was observed manufacturing areas used as passageways to other working areas (e.g. unloading terminal sterilization to visual inspection/secondary packing areas).	Major	FULFILLED
7. To clarify and take actions because washing and depyrogenation area are used for different process such as: storage clean vessel (100L/200L) and tools, cleaning dispensing tools, preparation of autoclave tools, garments, among others	Major	FULFILLED
8. To clarify and take corrective action because in manufacturing area at production C, it was observed cleaning tools handle on the wall and as well vacuum and another cleaning equipment storage in personal airlock. As well as, it was observed several manufacturing vessel storage in this area blocking which return grill of HAVC system.	Major	FULFILLED
9. To guarantee that disinfectant containers do not transport from unclassified to classified areas because as it was observed containers from secondary packing to manufacturing area (where disinfectant solution are prepared)	Major	FULFILLED
10. To guarantee that in process control of leak test should be carried out in properly area because this activity is done at lyophilizer technical area	Minor	FULFILLED
11. To guarantee sampling of primary packing should be done in classified area according with numeral 14.19 of Resolution 1160 of 2016.	Major	FULFILLED
12. To guarantee identification of each location at quarantine primary packing area at warehouse. As well, guarantee free access to all area	Minor	FULFILLED
13. To include in sampling reception records biological and stability tests	Minor	FULFILLED

NON CONFORMITIES	CRITICITY (CRITICAL, MAJOR, MINOR)	CHECKING
14. To clarify and take corrective action because it was found samples storage at cold conditions without sampling identification label (Leuprolide 22,5mg and 3,75mg); and it was not present reception record of those samples	Major	FULFILLED
15. To guarantee that incubators do not locate in corridor at microbiological laboratory.	Major	FULFILLED
16. To clarify and take corrective action because in process validation of Human Normal Immunoglobulin for Intravenous was found: a. It was not considering a representative sample during formulation. b. It was not included and analyze filling process in the report. c. It was not present statistical analysis. d. It was not including speed in report and BMR	Major	FULFILLED
17. To clarify and take corrective action because in Continues process verification report done at 2023 of Human Normal Immunoglobulin it was not evaluated same CPP and CQA stablished in process validation. As well as to guarantee carried out statistical analysis	Major	FULFILLED
18. To complete the master formula of Human Normal Immunoglobulin: a. Batch size b. Production line and equipment c. CPP and CQA d. Catalog sterile filter number use in sterile filtration	Minor	FULFILLED
19. To guarantee training in Quality Manual to all Bharat Serum and vaccine personnel, as well as define this retraining frequency	Minor	FULFILLED
20. To include in the Quality agreement following items: a. Responsibility of keep cold chain conditions of shipping and marketing. b. Mentioned product scope of this inspection	Minor	FULFILLED
21. To guarantee periodic monitoring of traces of Human Normal Immunoglobulin	Minor	FULFILLED
22. To adjust in Handling Return Goods SOP to include the verification of storage condition of products	Minor	FULFILLED
23. To present raw data of bacterial challenge test as: filter certificated, B. Diminuta certificate, integrity test results, incubation results	Major	FULFILLED
24. To guarantee carried out verification of qualified status of equipment qualified more than one year	Minor	FULFILLED
25. To complete access verification of users of PLC in	Minor	FULFILLED

NON CONFORMITIES	CRITICITY (CRITICAL, MAJOR, MINOR)	CHECKING
vial washing and autoclave		
26. To guarantee carried out related substance analysis for glycine according with mentioned in British Pharmacopeia	**Major**	FULFILLED
27. To guarantee in vendors qualifications a. Record and verification of continuous monitoring b. To adopt an international guideline c. To update the vendors supports regarding which is stablished in current SOP d. To present annex of NEUTRAL LABS where include the vial size of 100mL	**Major**	FULFILLED
28. To guarantee that gowning qualification report include medical examination and complete training according with SOP (QA:6N:050/R10)	**Minor**	FULFILLED

V. TECHNICAL CONCEPT

In accordance with the WHO Technical Reports No. 908, annex 4 of 37th Report and Technical Report Series No. 961, annex 6 of 45th Report of Resolution 1160 of 2016, Decree 335 of 2022, Resolution 3028 of 2008, Resolution 5402 of 2015 and Decree 2086 of 2010 of the Colombian Ministry of Social Protection, the inspection team of the National Institute for the Surveillance of Food and Drugs - **INVIMA** concludes that **UNIT I** belong to the establishment **BHARAT SERUMS AND VACCINES LTD.,** located at Unit I, Unit II, Biological Testing and R&D, K-27, K-27/PART, K-27-1, Anand Nagar, Next to Jubilant Life Sciences, Anand Nagar, Ambarnath, Thane, Maharashtra - 421506 - India, **COMPLIES,** with the **GOOD MANUFACTURING PRACTICES,** for **PRODUCTION OF DRUG PRODUCT** with the active pharmaceutical ingredient and the pharmaceutical dosage form described below:

STERILE		
ACTIVE PHARMACEUTICAL INGREDIENT	**PHARMACEUTICAL DOSAGE FORMS**	
BIOLOGICAL PRODUCT HUMAN PLASMA DERIVATES PRODUCT (NORMAL HUMAN INMUNOGLOBULIN)	Liquids	Small volume parenteral solutions (vials)

REMARKS:

1. Biologic products are manufactured in special manufacturing areas, defined as, separate physical facilities in other areas of production, including equipment, air handling systems and independent airlocks, personnel access and separate materials, garment handling and appropriated training that includes rules, procedures and precautions to be taken for personnel who enter to those areas, with the propose to avoid contamination risk from and to above areas.
2. The solutions in small volume for injection are sterilized by filtration and the filling and sealing are performed under aseptic condition.
3. Small volume parenteral solution includes up to 100mL.
4. The manufacturing process (formulation and filling) of Normal Human Immunoglobulin is carried out in production C line at Unit I.
5. The above technical concept authorizes exclusively the manufacturing of the products with active

pharmaceutical ingredients and the pharmaceutical dosage forms that were described which required cold chain.

6. Any critical change made to inspected and certified conditions during the current inspection, regarding equipment, areas, manufacturing process, main technical personnel (Sanitary Responsible), or third parties contracted to carry out critical activities of production or Quality Control, must be reported to INVIMA in order to evaluate whether a new visit or technical concept verification is required, according to disposition on Sanitary Normative, in case of not compliance of this statement, sanctions could be taken.

Spanish translation of the above technical concept

CONCEPTO TÉCNICO

Una vez evaluado el cumplimiento de los requerimientos previstos en la en el Anexos Técnico de la Resolución Nro. 1160 de 2016, Serie de Informes Técnicos 908 de la OMS, Informe Técnico Nro. 37 anexo 4 y Serie de informes Técnicos 961, Informe Técnico Nro. 45 anexo 6, Decreto 335 del 2022, Resolución 3028 de 2008, Resolución 5402 de 2015 y Decreto 2086 de 2010 del Ministerio de la Protección Social, el grupo de inspección del Instituto Nacional de Vigilancia de Medicamentos –**INVIMA** concluye que la **UNIDAD I** perteneciente a la sociedad **BHARAT SERUMS AND VACCINES LTD.,** ubicado en Unit I, Unit II, Biological Testing and R&D, K-27, K-27/PART, K-27-1, Anand Nagar, Next to Jubilant Life Sciences, Anand Nagar, Ambarnath, Thane, Maharashtra – 421506 - India, **CUMPLE** con las **BUENAS PRÁCTICAS DE MANUFACTURA,** para la **FABRICACIÓN DEL PRODUCTO BIOLÓGICO** en la forma farmacéutica que se relaciona a continuación:

ESTÉRILES		
PRINCIPIOS ACTIVOS	**FORMAS FARMACÉUTICAS**	
PRODUCTO BIOLÓGICO PRODUCTOS DERIVADO DE PLASMA HUMANO (INMUNOGLOBULINA NORMAL HUMANA)	Líquidos	Soluciones parenterales de pequeño volumen (viales)

NOTAS ACLARATORIAS:

1. Los productos biológicos se manufacturan en áreas especiales para su elaboración, entendiéndose por tal, instalaciones físicas independientes de otras áreas de producción, incluidos equipos, sistemas y manejo de aire independiente, esclusas, acceso de personal y de materiales independientes, manejo de vestimenta y entrenamiento apropiado que incluya normas, procedimientos y precauciones a tomar para el personal que ingresa en dichas áreas, con el fin de evitar riesgos de contaminación desde y hacia dichas áreas.
2. Las soluciones estériles de pequeño volumen son esterilizadas por filtración esterilizante con posterior llenado aséptico.
3. Las soluciones parenterales de pequeño volumen incluyen hasta 100mL.
4. La fabricación (formulación y llenado) de proceso de Inmunoglobulina Normal Humana se realiza en la línea de Producción C en la Unidad I.
5. El anterior concepto técnico, autoriza únicamente la fabricación de los productos con los principios activos y las formas farmacéuticas descrita que requieran cadena de frio
6. Todo cambio crítico que se haga y afecte las condiciones evaluadas y certificadas durante la presente auditoria, respecto a equipos, áreas, procesos productivos, personal técnico principal (Director Técnico) o de las empresas con las que se contrató la realización de actividades de producción y control de calidad, deberán ser notificados al Invima con el fin de que éste evalúe y verifique si se requiere una visita de ampliación o verificación del concepto técnico emitido, de acuerdo con las disposiciones de la Normatividad Sanitaria correspondiente, so pena de las acciones a que haya lugar.

NOTE: The personnel designated by the legal representative of **BHARAT SERUMS AND VACCINES LTD,** informed that according with the article 9° of the Decree 355 of 2022, in the next 15 calendar days will be issue the Invima's Resolution that adopts the GMP certification, for which it is indicated that from the week of October 23th of this year, the notification of the respective resolution will be executed using the telematic media enabled for

this purpose. As well as it is submit the data of the contact person to confirm the assistance, besides they answer will be in charge OLGA LUCIA TORRES MARIN, mobile phone: +57 3156011316, +51 9777268452 and email: olgaluciatorres@arunasesores.com, cesar.batens@bsvgroup.com

This inspection was carried out by following professionals, according to the current sanitary regulation without extra limitation of their duties, this report has been read and signed on October 06th of 2023. The inspected company **BHARAT SERUMS AND VACCINES LTD.**, keeps an original Inspection report.

By **INVIMA:**

LILIANA SILVIA ALVAREZ ESPEJO
University Professional, Pharmacist

SANDRA EYICED OYUELA MORENO
University Professional, Chemical Engineer

MANUEL BECERRA MOJICA
University Professional, Pharmacist

By **BHARAT SERUMS AND VACCINES LTD.:**

06/10/2023

Dr. SANJEEB KUMAR MISHRA,
President-Quality

06/10/2023

Mr. KALYAN S CHOWDHURY
General Manager (Head- Quality Assurance)

06/10/2023

Mr. LAKHIRAM PETWAL
President-Operations