

**Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
Vaccine Manufacturer**

Part 1	General information
Manufacturers details	
<i>Company information</i>	
Name of manufacturer	Biological E. Limited
Corporate address of manufacturer	Biological E. Limited Road No. 35, Jubilee Hills, Hyderabad, 500033 Telangana, India.
Contact person	Srinivas Kosaraju, Sr. Vice President Quality & Regulatory Affairs, Srinivas.Kosaraju@biologicale.com
Inspected sites	
Address of inspected manufacturing site if different from that given above	BE Shameerpur Site, Kolthur Village, Shameerpur Mandal, Medchal-Malkajgiri District – 500 078, Telangana, India. - Site for manufacturing and testing of Rubella Virus Bulk; Blending, Filling, Testing, Packing and Distribution of Measles and Rubella Vaccine (Live) (Attenuated, Freeze dried): Plot No. 1, Biotech Park, Phase II, Geo location: Latitude: 17.6650900, 78.6193950 Longitude: 17° 39' 54.32'' N, 78° 37' 9.82'' E BE Azamabad Site, 18/1&3 Azamabad, Telangana Hyderabad – 500020. - Site for manufacturing and testing of Japanese Encephalitis Vaccine
Activities at Unit / block	Azamabad site: - Japanese Encephalitis Vaccine Antigen & Final Bulk Shameerpur site: - Primary Manufacturing: - Recombinant Vaccine Block: Hepatitis B and CRM₁₉₇ - Bacterial Vaccine Block: Whole Cell Pertussis, Diphtheria, <i>Haemophilus influenzae type b</i> (Hib) - Conjugate Block: Hib Conjugate - Secondary Manufacturing: - Blending suites: TT, Td, DTP, Hep B, LPV and MR Vaccines - Filling Lines: LPV, TT, Td, DTP, Hep-B, JEEV & MR - Packaging

	• Warehouse • Animal house • QC Block
Inspection details	
Dates of inspection	04 - 08 February 2019
Type of inspection	Routine inspection for: • Liquid Pentavalent Vaccine (LPV - Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae type b) • Japanese Encephalitis Vaccine (JEV). Initial inspection for: • HepB vaccine • Measles and Rubella (MR) vaccine (<i>follow up of previous inspection</i>).
Representative from the National Regulatory Authority	The national regulatory authority (DCG(I), CDSCO) of the country where the inspection took place was informed and participated in the inspection:
Introduction	
Brief summary of the manufacturing activities	Biological E. Limited (BE) manufactures a range of childhood and adult vaccines, pharmaceuticals (specifically anti-coagulants and anti-infective) and Active Pharmaceutical Ingredients (API). BE has been producing Tetanus Toxoid (TT) Vaccine since late 1960's, Diphtheria and Tetanus (DT) and Diphtheria, Tetanus and Pertussis (DTP) vaccines since mid-1970's. It has been supplying vaccines to the Extended Program of Immunization (EPI), ever since EPI commenced in India in the late 1970's. In later years, the company has introduced other vaccines like Hepatitis B Vaccine, <i>Haemophilus influenza type-b</i> Vaccine (Hib), Tetravalent Vaccine (DTP-HepB), IPV (Inactivated poliomyelitis Vaccine), Pentavalent Vaccine and Japanese Encephalitis (JE) Vaccine.
General information about the company and site	BE was established in 1953. Manufacturing site at Shameerpet is about 40Km away from Hyderabad city centre in the suburbs towards North. JEV manufacturing is established at Azamabad site. An additional manufacturing site is present at Gaganpahad, about 25Km from the city centre towards South (not visited during the present inspection). BE is approved by WHO for various vaccines to supply Single and Multiple Dosage presentations. It is estimated that approximately 4.8 billion doses of vaccines (TT, DTP DT, Hep-B, DTPH, IPV, JE, Reconstituted Pentavalent and Liquid Pentavalent Vaccines) have been distributed by BE upto February 2019.

Brief report of inspection activities undertaken

Scope and limitations

Areas inspected	The inspection focused on the production and control of Liquid Pentavalent, HepB, JEV and Measles/Rubella (MR) vaccines. The inspection covered the sections of the WHO GMP text, including quality assurance, sanitization and hygiene, complaints and recalls, self-inspection, personnel, training, personal hygiene, premises and equipment, materials, documentation, qualification and validation, production, quality control and utilities.
Restrictions	None
Out of scope	Products and vaccines other than those listed in the scope were not inspected during this site visit.
Vaccines covered by the inspection	- Measles Rubella Vaccine - Japanese Encephalitis Vaccine (Inactivated) - Hep B Vaccine - Liquid Pentavalent vaccine: Diphtheria, Tetanus, Pertussis (whole cell), Hepatitis B, <i>Haemophilus influenzae</i> Type B (fully liquid)

Abbreviations	AHU	Air Handling Unit
	ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
	APR	Annual Product Review
	APS	Aseptic Process Simulation
	BET	Bacterial Endotoxins
	BMR	Batch Manufacturing Record
	BPR	Batch Production Record
	CA	Compressed Air
	CAPA	Corrective Actions and Preventive Actions
	CC	Change Control
	CFU	Colony-Forming Unit
	CIP	Cleaning In Place
	CoA	Certificate of Analysis
	CpK	Process capability
	D	Diphtheria
	DQ	Design Qualification
	EDI	Electronic Deionization
	EM	Environmental Monitoring
	FMEA	Failure Modes and Effects Analysis
	FTA	Fault Tree Analysis
	GMP	Good Manufacturing Practices
	GPT	Growth Promotion Test

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

	WHO	World Health Organization
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Part 2	Summary of the findings and comments
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The present report is related to the visits of two independent sites of Biologicals E Limited (BE):

- Azamabad site, where manufacturing and quality control of JEV bulk take place,
- Shameerpet site, where bulk manufacturing of HepB, Hib, Diphtheria, WcP and Rubella are carried out, as well as the formulation/filling and QC tests of all vaccines (including JEV).

Tetanus bulks are produced at Gaganpahad site (not visited during this inspection) and then transferred to Shameerpet, to be used either i) in formulation/filling of TT, Td, DTP, DTPH and Liquid Pentavalent Vaccine (LPV), or ii) as critical reagent in Hib conjugation.

Since the general structure of the Pharmaceutical Quality System and the Quality Management System was applicable to both sites, similar weaknesses were identified.

It is also underlined that recurrent observations were raised in previous WHO reports (2016 and 2018), particularly those related to APQRs, QRM, EM, MFT and good documentation practices (as discussed in this report). It is reported that the company is in the process of implementing the corrective actions.

Where applicable, each of the following sections of the report has been split to highlight the relevant findings.

1. Pharmaceutical quality system

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

Deficiencies were raised regarding the weaknesses of the implementation of the quality management system through the organisation at the two manufacturing sites located at Shameerpet and Azamabad. The company has adequately addressed the issues raised through the provided CAPA.

1.1 Product Quality Review

Product Quality Reviews (PQR) are finalized and approved by April each year. Separate documents are prepared for bulks and finished products.

APQRs related to all bulk antigens and finished products covered by this inspection were reviewed and several common observations were raised. On the other hand, significant discrepancies in the approach used to evaluate the performance of each manufacturing process were also found, thus highlighting the lack of harmonized management, as detailed below.

PQR-JE, bulk and finished product

Since the prequalification of JE vaccine in 2012, there was no supply to UNICEF.

There was no commercial batch of JE vaccine manufactured in 2018.

There were no JE vaccine filled in vials in 2016.

So far, no commercial batches of JE multidose vaccine were manufactured except the three PV batches that were used for the process validation.

The PQR 2017 of JE vaccine inactivated (Adsorbed, human), covering the manufacturing period from January to December 2017, was approved in April 2018. Several doses of the vaccine have been supplied in 2017. All the batches were exclusively for domestic market. No OOS, rejection, recall or return was recorded.

There was no trend analysis in the PQR since only limited batches were produced. The company stated that for Nelsons rules, there should be at least the test results from several batches for statistical analysis. Water data were stated as within the established limits however the trend was not discussed.

The annual product quality review reports related to purified inactivated vaccine (bulk adsorbed on aluminium hydroxide) were spot checked.

PQR-Recombinant Hepatitis B, bulk

Even if HepB as a single component vaccine has not yet been prequalified, HepB bulks have been manufactured for several years to be formulated in the LPV, thus a PQR was available.

Hepatitis B was manufactured in “Recombinant Vaccine Block” on a campaign basis, with respect to the manufacturing of CRM₁₉₇ (recombinant diphtheria toxin used as carrier protein in vaccines under development): the last production was stopped in April 2017 and a new campaign restarted in October 2018. The last PQR available related to lots manufactured in 2016, was reviewed and results related to lots manufactured in 2018 were spot checked.

PQR-Tetanus, bulk

Even if this bulk antigen was manufactured at Gaganpahad site, it was a component of the Liquid Pentavalent Vaccine and the APQR related to 2017 was reviewed.

PQR-Diphtheria, bulk

Diphtheria manufacturing is carried out in the Bacterial Vaccine Block (BVB), in the same facility used to produce Hib.

No fermentation batches were manufactured in 2017, thus APQR related to 2016 was reviewed and results obtained in 2018 were spot-checked.

PQR-Pertussis, bulk

A dedicated facility is used for manufacturing Pertussis and, due to the increasing market demand, a new dedicated expansion block has been recently constructed; a specific request of approval will be submitted in the next months.

APQR related to 2017 was reviewed and results related to 2018 were spot checked.

PQR-Haemophilus influenzae type b, bulk

APQR related to 2017 was reviewed.

PQR-MR, finished product

PQR of MR vaccine was not investigated in detail, since it was reviewed in the previous inspection (2018). No batches were rejected since 2017.

PQR-LPV, finished product

PQR related to 2017 was reviewed and results related to 2018 were spot checked.

1.2 Quality risk management

Procedure for QRM was in place.

The plan of risk assessments performed in 2018 and 2019 was reviewed.

Deficiencies were raised regarding the understanding, the adequate use, the level of maturity and the implementation of the QRM at the company.

1.3 Management review

Provisions for management review were in place.

The management board meets regularly once every three months.

The last meetings were held on 25/10/2018 and 24/01/2019 and reports were spot-checked.

1.4 Change control management

Management of change controls was in place.

Changes are classified as critical, major, minor and other.

List of changes annexed to all PQRs were reviewed and some of them were spot checked.

1.5 Deviation management

Procedure for deviation handling was in place.

The list of deviation was provided, and some deviations were reviewed as spot check.

Some weaknesses were identified in the deviation management for which BE proposed CAPAs.

1.6 CAPA management

Procedure for CAPA management was in place.

CAPAs resulting from the last two WHO inspections carried out in October 2016 and February 2018 were spot checked during inspection.

1.7 Documentation

Procedures for the documentation management were in place. The production activities are recorded in respective records in forms of batch manufacturing records, equipment logbook and/or general control records according to the procedure in place.

Procedures, operating conditions and specifications related to the manufacturing processes were established. The quality control activities were recorded in respective records including laboratory control records, equipment logbooks and general control records. Procedures, operating conditions and specifications related to the quality control activities were established.

Documentation management was found inadequate i.e. ALCOA principles (data to be Attributable, Legible, Contemporaneous, Original and Accurate) were not respected, both in production and in QC.

Batch Release Process

Procedures were in place to review BPR and BR of bulks, final bulk and final lot, finished product manufactured at BE. The procedures were to provide documented evidence to ensuring that the vaccines were being thoroughly reviewed throughout the production procedures, quality control reports and related document for release of bulks to the finished product.

Batch manufacturing record review (BMR)

BMRs were spot-checked as detailed in relevant paragraphs.

Manufacturing data from hepatitis B concentrated bulk (HBCB) through hepatitis B purified bulk (HBPB), final bulk (FB) and final product (FP), for the latest standalone Hepatitis B vaccine production were reviewed. Relationship between production steps with specific numbers and production scale was present. No issues were identified during review.

1.8 Quality audits and suppliers' audits and approval

Written specifications were available for the raw/packing materials and critical process consumables used in the production. The materials required for manufacturing were procured from qualified vendors. The vendors and contracted testing service providers were qualified. Vendor qualification involves site visits and testing of representative samples, wherever applicable. Periodic assessment of the vendors was carried out for evaluating their performance. The accepting and/or rejecting of suppliers as per criteria stated in the SOP.

Deficiencies were raised regarding the qualification of the supplier of some critical materials, such as Flexboy plastic bags: no evaluation was performed of the sterilization procedure, nor of the capability of these containers to preserve sterility of JE through the whole manufacturing processes and storage up the filling point.

Quality agreements

The procedure dealing with quality agreements, stated under section 5.4.3 that: *"The approved version of quality agreements shall remain valid and effective for at least 6 months after its due date for revision/until the next version of the agreement is signed off by both parties and becomes effective"*, but this clause was not reported into the agreements thus generating potential gaps.

Quality agreements with one subcontractor for testing was reviewed and it was observed a gap of six months in the quality agreements between previous version and current version.

1.9 Personnel**Training****➤ Azamabad site**

For aseptic operations, each employee must undergo 3 successful runs of gowning according to the procedure. The gowning qualification was checked biannually. The microbial test limits of grade B were established for the qualification of aseptic operators including the interventions within the manufacturing areas of grade A and where the product was exposed to the immediate environment. The records for the gowning qualification of QC, production, engineering, and QA staff were spot checked and found within the established specification. There were some contaminations within the established limits for grade B area however there were no identification in place. There was a specification of <1cfu for fungal contamination in place.

➤ ***Shameerpet site***

Training was performed in the plant according to several procedures.

Each new employee was firstly subjected to theoretical training on general manufacturing and GMP aspects and then assigned duties outlined in the relevant job description. Based on the duties assigned, a specific initial on the job training was planned by the respective head of department.

The study report related to manual optical inspection (liquid forms) was reviewed as well as the personal file related to one operator and no issues were identified.

For aseptic operations, each employee must undergo 3 successful runs of gowning and should participate to 3 Media Simulation tests for initial qualification and biannually to confirm qualification. Certifications of individual personnel were spot-checked.

Personal hygiene

➤ ***Azamabad site***

There was an access control to the manufacturing areas. The personnel were not dedicated to live or non-live areas.

Personnel entry and exit to non-infected area was governed by the relevant procedure.

The procedure indicated under section 5.1.2 that: “*Only the personnel authorized to work in non-infected area can access/enter the area*”. And under section 5.1.3 that: “*The personnel worked in infected area are not allowed to enter the non-infected area on the same working day, thereby reducing the risk of cross contamination of area*”.

No control was in place to make sure that operators could not access non-infected area coming from infected zone, and no provision was in place for the movement of QC staff with access to both infected and non-infected areas, with risk of cross contamination.

➤ ***Shameerpet site***

Procedures for health requirements of personnel working in production areas were in place. Medical checks were carried out for the new hired employees and afterward on annual basis. Operators employed in manual visual inspection of filled vials/containers were tested for their vision as per implemented procedure.

Based on the requirement and risk of infection, all the concerned employees were immunized, and titers of personnel were checked when needed to ensure adequate protection.

2. Production system

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

➤ **Azamabad site**

JEV production

The manufacturing at Azamabad site included the manufacturing of the drug substance up to the final sterile filtration and the formulation of JEV.

The JE virus strain and Vero Cells were currently used for JE vaccine manufacturing. Master and working seeds and cell banks were adequately stored and maintained in two different locations.

All raw materials used for JE vaccine production at Azamabad site were released and provided from Shameerpur site. The shelf life of JE vaccine was based on the potency test on the formulated bulk in the Flexboy bags.

Validation of aseptic process through media simulations

The media simulation of the aseptic process of JE vaccine including the drug substance and the final bulk was performed twice a year. The aseptic media simulation was performed with SCDM and not with the maximum batch size as per routine process, thus underestimating the aseptic process activities carried out during the formulation and the downstream the aseptic filling process.

The prepared media of the aseptic simulation was sent to Shameerpur site for incubation and growth promotion tests. The GPT was performed using the strains *A. brasiliensis*, *C. albicans*, *B. subtilis*, *S. hominis* and an in-house isolate.

Validation of sterile filtration of JE vaccine

The validation of the sterile filtration of JE vaccine was initially conducted in September 2005. This included the microbial challenge with *Brevibacterium diminuta*. There was no up to date validation report of the sterile filtration of the actual JE vaccine. There was no up to date assessment/review report of the validation of the sterile filtration of JE vaccine and the adequacy of the sterile filtration of JE vaccine.

Leachable and extractable

Protocol and final report related to the “Analysis of extractable and leachable from container/closure systems” dated May 2006 were spot checked.

The extractable and leachable studies were not considered acceptable since they were not covering the actual prequalified vaccines with the actual processing and storing of the formulated finished bulk, with the actual used plastic bags.

Moreover, the Flexboy plastic bags were labelled with stickers containing adhesive. There were no studies on the nature of the adhesive and the possible risks for JE vaccine, deriving from additional leachable of the adhesive stickers, attached to the porous Flexboy bags.

Transfer of JEV in Flexboy bag from Azamabad to Shameerpur site:

Transport validation for the transfer of JE bulk was performed in year 2012.

➤ **Shameerpur site**

✓ **Primary manufacturing**

No significant changes have been introduced in the manufacturing processes of all bulk antigens, including HepB which has been manufactured for several years as a component of LPV.

A seed lot system was properly established for all antigens, Master and Working Cell Banks were stored in two separate locations and all WCBs were sampled and tested once/year for Critical Quality Attributes.

Manufacturing process steps, In Process Controls and release tests, as well as holding times, storage times and temperatures related to all bulk antigens were reviewed; process validations, method validations and qualifications were spot-checked, and deficiencies raised as outlined below.

All bulks were sterilized by filtration at last step before long term storage, except for Pertussis which consisted of whole cells. Manufacturing areas were mainly classified C and open operations were performed under Biosafety Cabinets (BSC) or Laminar Air Flow Units (LAFU), which were maintained in grade B according to WHO document dated 2012 “*Environmental monitoring of clean rooms in vaccine manufacturing facilities – Points to consider for manufacturers of human vaccines*”. Only sterile filtrations were performed in class A with B surrounding.

Common deficiencies were found, which were applicable to all manufacturing processes of bulk antigens, mainly related to inadequate control measures to minimize the risks of contamination.

Additional risks of contamination and cross-contamination were observed in Pertussis bulk manufacturing as two different strains of *B. pertussis* are produced concomitantly in the same fermentation area. However, the identification is performed to evaluate eventual cross-contaminations by different agglutinogens present in the strains. Inadequate holding time studies were also found, however BE has committed to conduct the hold time studies.

In Diphtheria upstream manufacturing, the detoxification kinetics was performed in 2013 and it was never repeated; the actual process consisted of three consecutive additions of formalin and lysine and sequential incubation.

Inadequate holding time studies were performed to monitor Hib conjugate before sterile filtration, however BE has committed to conduct the hold time studies.

Validation of aseptic process through media simulations

Protocols for media simulations applicable to bulk antigens were spot checked and found overall reflective of the manufacturing steps, except for multiple opening of screw capped bottles.

✓ **Conjugation**

The following manufacturing steps of Hib Conjugation are performed in class C at the Conjugation Block: concentrated PRP stock solution preparation, alkaline degradation, activation, modification, PRP-ADH concentration and diafiltration, PRP-ADH & TTd conjugation, PRP-TTd concentration and diafiltration with PBS, PRP-TTd purification, PRP-TTd concentration and diafiltration with PBS, pre-filtration. Sterile filtration was held in class A with B surrounding.

Batch Manufacturing Record for HiB bulk conjugation in PRS was reviewed and no objections were raised.

✓ ***Secondary Manufacturing***

Filling line

Sterile vaccine bulks were aseptically transferred from vessels into the filling machine. The control of weight vials was carried out manually on balance.

During production (machine set up, filling and sealing), monitoring of non-viable particles as well as microbiological monitoring was performed. Initial vials were routinely rejected.

Batch Manufacturing Record Pentavalent vaccine was reviewed.

Deficiencies were identified related to control of fill volume in both filling lines.

Production of Pentavalent vaccine 0.5 mL, 1.0 mL, 2.5 mL, 5.0 mL was carried out in accordance with relevant procedure. Batch Manufacturing Record of Pentavalent vaccine was reviewed.

Time out of Refrigeration (ToR) was established and controlled according to relevant procedure.

During the whole production period, all starting materials, packaging materials, containers, main equipment and rooms used were marked with identification and status labels.

Validation of aseptic processes through media fills

MFT was held every 6 months; protocol and report related to «Aseptic process simulation of liquid Pentavalent vaccine filling process» were reviewed and it was verified that repeated filling interruptions and holdings of final bulks in the blending vessels were never simulated.

3. Facilities and equipment system

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

Nonetheless, some deficiencies were identified and highlighted below.

➤ ***Azamabad site***

The manufacturing building for JEV was dedicated. Dedicated areas for cell culture and viral culture were provided. Viral culture area was provided with dedicated AHU. There were dedicated airlocks and pass boxes for entry and exit from the area. Air returns in live areas were through HEPA filters. Pressure Differential was set to be maintained between the rooms of different classification. A positive pressure was maintained between the rooms of same classification, but air-flow patterns were not set up to achieve proper containment.

The list of critical equipment included BSC, centrifuges, TFF System, Flexboy bags and the filters. The live viral area was equipped with decontamination autoclave and collection tank for liquid waste. The solution of the collection tank was transferred to kill tank for decontamination purpose.

There was an aseptic room where the final sterile filtration and the formulation of JE vaccine takes place. There was no autoclave for transfer of material to the aseptic room. All the material was transferred through pass boxes. There was an autoclave for the sterilization of the material used in the manufacturing process including the equipment used for aseptic processes and sterile filtration. The unloading zone provided with LAFU of this autoclave was in grade C area.

There were unidentified and unmitigated risks of cross contamination of the live virus to the non-live viral manufacturing areas.

Additional deficiencies were raised with respect to risk of cross contamination due to material transfer from live to non-live area, poor design and maintenance of facility and equipment, qualification of HVAC, management of water system, qualification of autoclave and management of pure steam.

The quality control laboratories at Azamabad site were consisting of biochemical and cell culture testing rooms as well as microbiology and environmental monitoring rooms. The testing in charge at Azamabad site covered the intermediates up to the formulated bulk. The testing of the starting material, the finished products and the animal testing of JEV vaccine were performed at Shameerpet site.

Water system production description

Details of the water system production, capacity and sanitization were provided in the site master file. JE vaccine block was equipped with dedicated water system providing PW, WFI and pure steam. User points available for PW and WFI. PW is sanitized weekly during two hours with a temperature over 85°C. WFI was sanitized on monthly basis by pure procedure.

Distribution skid of WFI loop was changed in December 2018 and the qualification through three phases as per WHO guideline recommendation was initiated. Phase 3 qualification was ongoing. Return loop was tested daily and the other user points sampled weekly on rotation basis. The trend report of WFI and pure steam for 2017 was spot checked. The test results were within the established specification. The microbial specification for pure steam was nmt 10 cfu/100mL. Contamination of pure steam were recorded. Although within the established limits, this is not considered acceptable as the pure steam is used for the sterilization of some vessel and the material used in the final formulation of JEV.

The same water loops were used for both infected and non-infected areas. There was no risk assessment in place for the risk of cross contamination between infected and non-infected areas. The viral area in QC laboratory was supplied with PW from Biological E Pharma. There was no risk assessment in place for the risk of contamination of the purified water used at Biological E Pharma.

Sanitation

Manufacturing, supporting and other areas, as well as equipment were cleaned according to approved cleaning procedures. The concentration, method and frequency were included in the respective facility SOPs. Major cleaning procedures were listed as follows:

- SOP for “Preparation and Filtration of Disinfectant used in Clean Room”.
- SOP for “Cleaning and sanitization of Clean Rooms and General Area”.
- SOP for “Operation and cleaning of Tangential Flow Filtration (TFF) System with Feed tank (Make: Millipore)”.
- SOP for cleaning and sanitization of JE Quality control laboratory.

Major equipment/instruments had separate cleaning and operating procedures.

Disinfectants solutions were used for cleaning floors, ceilings and walls and 70% v/v IPA was used for cleaning door surfaces, door handles and surfaces of equipment.

Equipment cleaning procedures were validated by using rinse samples/swab samples. Visual examination, chemical residue testing, microbial counts and endotoxins testing were the attributes used for assessing the effectiveness of cleaning.

Fumigation was done using freshly prepared Bacillocid solution. The fogger was operated up to the required time as per the standard operating procedure. The area had to be closed for an hour for effective fumigation. After fumigation, areas were cleaned using lint free cloth /wipe.

Deficiencies were raised with respect to the demonstration of effectiveness of Bacillocid on JE virus.

In case of spillage inside Bio-safety cabinet or laminar air flow unit, the equipment was kept in running condition.

70% v/v IPA solution was applied on the walls, work surfaces and allowed the 70% v/v IPA solution to contact with the spill area.

Excess IPA was removed by wiping or absorbed using lint free wipe in autoclave bag.

In case of liquid spill in catch basin, 2% v/v Bacillocid solution was applied and left for defined minutes before cleaning the spilled materials using lint free wipes and further wiped using 70% v/v IPA solution.

All materials to be used in BSC/LAFU were disinfected using lint free wipe cloth soaked in 70% v/v IPA solution before transferring into the BSC / LAFUs.

After cleaning, all waste was collected in autoclavable bags before decontamination.

Handling of Spillage in the Aseptic Area was spot checked and no objections were raised.

Qualification and validation

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

The qualification and validation of equipment were spot checked.

➤ ***Shameerpet site***

Production of bulk antigens took place in different buildings at Shameerpet site.

Recombinant Vaccine Block

Production of Hepatitis B and CRM₁₉₇ (non-toxic variant of Diphtheria) was carried out in RVB, which was dedicated to recombinant vaccines on a campaign basis.

Manufacturing of CRM₁₉₇ was firstly introduced in the facility in April 2017 and the production was continued up to September 2018, when production Hepatitis B was restarted.

A submission through Form 29 to CDSCO was in place.

The changeover procedure applied when Hepatitis B was reintroduced in the facility in September 2018 was checked. Fumigation, decontamination and cleaning procedures were applied in the facility, followed by sampling to specifically detect the presence Diphtheria, used in the previous campaign.

Bacterial Vaccine Block

Production of Diphtheria and Hib were carried out in a segregated area of BVB. Production in fermentation area was conducted on a campaign basis, being alternatively used for manufacturing of Hib and Diphtheria; detoxification/purification steps of Diphtheria and conjugation/purification steps of Hib were instead performed in dedicated areas with dedicated equipment.

The general design of the facility was considered adequate except for the area in which detoxification of Diphtheria was carried out. Cross-flows of toxic and nontoxic materials as well as of personnel, were foreseen in the normal practice. Even if the issue was already identified in the previous inspection (2016), a systematic review of all possible sources of cross-contaminations and a thorough analysis of mitigation measures were not available.

Pertussis manufacturing took place in the same BVB building but in a segregated area with different access for materials and personnel. The same fermentation area could be concomitantly used for the preparation of two different strains of *B. pertussis*.

Blending and Filling Facility

One filling line consisted of washing machine, hot air circulation sterilization tunnel, filling and sealing machine. Washing and sterilization were in class C, while filling and sealing in class B, inside LAF classified as grade A.

Process equipment were selected, positioned, operated and maintained in a proper manner according to the intended use. The structures and materials of the working surfaces allowed proper cleaning. Equipment (vessel) were fitted with cleaning/sterilization-in-place systems; parts of the filling machine were manually cleaned and sterilized in autoclave.

Number of personnel required in clean areas was confirmed by MF test.

Filling and sealing machine were not equipped with gloves and all interventions were carried out with opening of the doors.

Washing machine used circulating water, WFI and clean compressed air. The sterilization tunnel adopted the principle of hot air laminar flow and high temperature sterilization process to preheat, dry, sterilize, remove heat.

The incoming dry vials (sterilized) were fed through the distribution table and suitably guided on the moving conveyor belt to filling machine. The sterilized and siliconized rubber stoppers stored in the vibrator bowl moved to the rubber stopper chute. Loading rubber stoppers into the filling machine was carried out with the opening of doors. Bulks were aseptically transferred from vessels into the filling machine. The control of weight vials was carried out automatically by the machine.

Another filling line consisted of washing machine, hot air circulation sterilization tunnel, filling and sealing machine. Washing and sterilization were class C. Filling and sealing in class B, inside LAF class A. Filling and sealing machines were equipped with gloves port. Gloves were tested for integrity test after each batch. The equipment (vessel) was fitted with cleaning/sterilization-in-place systems, parts of filling machine were manually cleaned and sterilized in autoclave. Process equipment were selected, positioned, operated and maintained in a proper manner according to the intended use. The structures and materials of the working surfaces allowed proper for cleaning.

All materials and equipment parts were cleaned and sterilized in accordance with the procedure «Preparation of materials for sterilization in filling lines».

Microbiological QC Department

The following activities were performed in the area:

- monitoring of ambient conditions in clean rooms;
- assessment of bioburden before sterilization;
- microbiological analysis of starting materials;
- analysis of intermediate products, bulk products, solutions, finished products;
- detection of microorganisms;
- validation of analytical methods.

Microbiological testing (sterility) was performed in two rooms (class B), inside LAF class A.

Each batch of media was controlled by growth promotion test.

Internal specifications for starting materials, intermediates and finished products were available.

Waste management

Procedures for decontamination and disposal of used contaminated materials and waste management were spot checked. Procedures instruct the safety precautions and measures to be followed for handling of live microorganisms. The decontaminated liquids were to be disposed into the Effluent Treatment Plant (ETP). Hard disposable, reusable and garments contaminated materials were to be decontaminated by autoclave.

Qualification and validation

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

The qualification and validation of equipment were spot checked.

The list of computerized critical systems was reviewed.

Security management of computerized systems was performed according to the procedure in place.

Periodic evaluation of computerized systems was performed according to the procedure in place.

Validation plan of computerized systems was spot checked.

5 Laboratory control system

In both facilities Quality Control is an independent department, separate from the Production. QC performs testing of incoming raw materials, packing materials, intermediate products and final products, purified water, water for injection, pure steam, and the environmental monitoring and stability studies for intermediate / finished products. Animal testing is also carried out by Quality Control Department. The products at intermediate/ final stages are tested against established specifications as per respective testing SOPs.

Handling of out of specification (OOS) results was conducted according to specific procedures. Two levels of investigation are in place. The first level covers the assessment of the laboratory data. If the root cause of the OOS cannot be defined, a detailed investigation including production process review and/or additional laboratory work is undertaken. Both levels result in CAPA plan. A trending of the OOS is in place every six months.

➤ Azamabad site

The quality control laboratories in Azamabad site oversaw the following testing:

Bioburden, antigen content, PRNT, appearance, pH, degree of adsorption/non-adsorption, environmental monitoring. Biological E Pharma department performed water testing. FBS was supplied from Shameerpet site. The immunization of mice and collection of serum was performed in Shameerpet site.

The procedure for ELISA for determination of Antigen content in JEV drug product was spot checked.

The procedure for plaque reduction neutralization test PRNT for enumeration of Anti JE virus antibodies in serum samples from JEV immunized mice was spot checked.

Deficiencies were identified related to documentation management.

Environmental monitoring

The procedure “Microbiological monitoring of classified areas by Settle plate method, volumetric air sampling and contact plates/surface swabs” was in place. There was a risk assessment for the location of the sampling points for microbial monitoring. The contact plates in the “drug substance/drug product room” was limited to three locations. One under BSC and two in the room. This was not drawn from the aseptic processes carried out in this room. Several equipment contact surfaces in the room were not considered for microbial monitoring. The LAFU in grade C and in grade D were classified with the microbial limits of grade B. LAFU were used cell culture, inoculation, filtration and sampling.

The trend report for 2017 was spot checked. No microbial counts were observed for grade A areas. Few counts within the established limits were recorded in grade B area.

There was no identification for microbial counts detected in the aseptic room of grade B area. The monitoring of the data was limited to representing the test results as within the specification however no evaluation of recurrence of counts with respect to the locations and according to the process was in place.

Procedures for NVP in the manufacturing areas were in place.

➤ ***Shameerpit site***

Qualification of QC equipment

Calibration reports of the following equipment were checked:

- *Incubator;*
- *Micropipettes;*
- *Plate reader;*
- *Densitometer;*
- *Distilled water production system;*
- *pH meter;*
- *TOC reader;*
- *Sterilisation autoclave.*

No issues were found during review.

Qualification of in-house reference standard

Validation of ELISA reference standard was reviewed. New references were established against a primary standard. This standard was a lot with proven efficacy during clinical trials. Moreover, several parameters were to be considered for the acceptability of this lot as primary standard: source, quantity, characterisation, potency and stability. If validation of new reference was considered satisfactory, a 3-year shelf life was established. Aside from reaching its expiry date, a current reference might be replaced if a downward trend in potency was observed or if availability was below 500 vials. Current in-house reference standard was satisfactorily established in October 2018.

Method Validation

HBPB potency determination by ELISA

It was performed as per ICH Q2(R1) guidance. Accuracy, precision (repeatability/intermediate precision), specificity, linearity and range were envisaged, even if limit of detection and limit of quantification were not. Outcome of method and software validation was satisfactory.

Characterization of MCB and WCB

Report on history, preparation, testing and characterisation of cell banks used for HepB antigen manufacturing was reviewed.

Stability studies

Different stability or ongoing stability studies were reviewed:

Recombinant HepB vaccine

No issues were found.

MR vaccines

Several issues at documentation level (issuance of report without final potency results, no traceability of report versions) were found. Outcome of studies were satisfactory otherwise.

Computerised systems

Caliber LIMS

The laboratory information management system in place was reviewed. Access is username and password controlled and each registered user had his own unique credentials. 2 different user profiles, user and administrator, co-existed with strictly separated privileges. Traceability of one batch was followed from reception to final report. Results encoded by analyst were reviewed by the supervisor, then the laboratory manager. The latter could ask the analyst to amend the encoding if any error was found. The possible change was tracked through audit trail, if there is any change in the encoded data (user) or the software environment (administrator).

HPLC software

Data integrity on the software controlling HPLC devices was checked. Access is username and password controlled and each registered user had his own unique credentials. 2 different user profile, user and administrator, co-existed with strictly separated privileges. Change in raw data was not possible as these were generated by the chromatography device and therefore non-corruptible. All downstream modifications were tracked through audit trail.

Trending activities

A new review of trending mechanisms was performed.

- ***Positive control for mycoplasma kit***

Quantification cycle (Cq) values of positive control were plotted since October 2016. The graphs showed no trend over the observation period. Since the test was qualitative and no trend was observed and the decision to stop plotting was endorsed.

- ***RK13 and Vero cell counting***

Counting of cells at cells seeding, middle of cell culture and end of cell culture over the lifespan of RK13 and Vero cryovials used in quality control was plotted and found satisfactory. No limits were applied.

- ***MR vaccine reference***

Results of 2018 of titration for both measles and rubella antigens were plotted on separate charts. A minimum of 200 results were available for both antigens and standard deviation was small. Neither alert nor action limits were shown but maximum titration precision allowed was used as validity limits. Comprehensively, no periodic evaluation of the limits was made but a regular analysis of the chart was performed to check limits overruns.

- ***HepB vaccine reference***

This reference is used for potency estimation by ELISA and antigen content by ELISA. As a relative potency is automatically calculated by calculation software, no potency for the reference is available. Instead, optical density values are plotted on a full control chart with alert and action limits. No trend is observed.

- ***HBPB HBsAg antigen content***

Antigen content values were plotted on a chart with limits calculated based on average content plus or minus 3 standard deviations. These limits were fixed for once and not periodically revised. No evaluation of LoD and LoQ was foreseen.

The excel sheet was checked for validation and data protection and was found not satisfactory on these 2 points.

Additional deficiencies were identified related to inconsistent approach on limit establishment and management of critical QC reagents.

Environmental monitoring

Upstream EM

Media for environmental monitoring of the manufacturing areas were supplied from external vendors. Media were supplied containing polysorbate and lecithin as neutralizers.

Environmental monitoring of viable particles in the plant is performed according to 4 different procedures: for settle plates, for active air, for surfaces and for operators. The plan of EM was run independently of activities, with a specific frequency established on different classifications. Additionally, critical areas were monitored whenever an activity was performed. BSCs and LAFUs were always classified B. EM results were collected and analyzed quarterly and annually.

Raw data and trends related to different areas of bulk manufacturing were spot checked.

From the data provided, it was shown that the plant was generally under control in terms of microbiological contamination, even if area classification and frequency of sampling was kept to the minimum acceptable levels, according to WHO document dated 2012 “*Environmental monitoring of clean rooms in vaccine manufacturing facilities – Points to consider for manufacturers of human vaccines*”. Indeed, data related to critical BSCs and LAFUs (classified B), where inoculation and open manufacturing steps were performed, showed a level of contamination not compatible with higher classification (Grade A).

Even if the same deficiency was raised in the previous inspection, operators were never monitored in classified areas of bulk manufacturing.

In the CAPA submitted to fix the previously identified deficiency, BE stated that a risk assessment had been performed and operators were included in regular testing, but this was applied only to rubella manufacturing. Similarly, Non-Viable Particle Counting was performed according to the procedure in place, which did not detail whether BSCs and LAFUs were considered as grade A, B or C in terms of acceptable limits, what was the air sample to be taken for each measurement and which sampling frequency was to be applied. This was mainly linked to inaccurate definition of critical areas and activities.

Downstream EM

Non-viable as well as viable particles were monitored. The risk assessment for selection of NVPC locations in filling Line №1, №3 and PFS was reviewed, as well as EMP Trends, summary report related to filling areas in Q4 2019.

Differently from what foreseen in the relevant SOPs, several deficiencies were witnessed in routine Environmental Monitoring practice.

6 Materials system

Previously identified deficiencies related to warehousing were solved. A new building named Warehouse II was built and dedicated to storage of packaging materials in order to decrease the level of congestion found in the old Warehouse.

Tracking of materials entry/exit and dispatch to different buildings was spot checked and no issues were identified.

Control of new trypsin batches and WCB was addressed properly. Control of new batches of foetal calf serum however was still not addressed adequately as suitability of new batches with influence on MR vaccine titres was not implemented.

7 Packaging and labelling system

After capping, vials were visually inspected, labeled, and packaged.

Visual inspection of vials was performed manually. Vials were inspected for particles, fill volume, quality of sealing and availability defects. BMR for optical inspection of Pentavalent vaccine was reviewed.

Packaging was carried out manually. Inspection and packaging operations were conducted in controlled but not classified (CNC) rooms. After completion of each step (inspection and package), the intermediate product was transferred to storage area (2-8°C).

8 Distribution and international shipping

Distribution and international shipping was not covered during this inspection as it was reviewed during previous inspection in February 2018.

Part 3: Conclusion

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

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

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

DEFINITIONS

Critical deficiency

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

Major deficiency

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

- has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
- indicates a major deviation from the GMP guide;
- indicates a failure to carry out satisfactory procedures for release of batches;
- indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties;
- consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

Other deficiency

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

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

PART 4***List of GMP guidelines referenced in the inspection report***

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
Short name: WHO TRS No. 986, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
2. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-Sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
Short name: WHO TRS No. 970, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
3. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-Ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
Short name: WHO TRS No. 929, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1
4. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
Short name: WHO TRS No. 937, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1
5. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 1
Short name: WHO TRS No. 961, 957, Annex 1
<http://www.who.int/medicines/publications/44threport/en/>
6. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
Short name: WHO TRS No. 957, Annex 2
<http://www.who.int/medicines/publications/44threport/en/>
7. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
Short name: WHO TRS No. 961, Annex 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

8. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
Short name: WHO TRS No. 961, Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
9. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
Short name: WHO TRS No. 961, Annex 9
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
10. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
Short name: WHO TRS No. 943, Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1
11. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
Short name: WHO TRS No. 961, Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
12. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
Short name: WHO TRS No. 981, Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
13. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
Short name: WHO TRS No. 981, Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
14. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
Short name: WHO TRS No. 961, Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

15. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
Short name: WHO TRS No. 992, Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
16. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
Short name: WHO TRS No. 992, Annex 5
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
17. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
Short name: WHO TRS No. 996, Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf
18. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
Short name: WHO TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
19. Requirements for measles, mumps and rubella vaccines and combined vaccine (live).
Short name: WHO TRS No. 840, Annex 3
http://www.who.int/biologicals/publications/trs/areas/vaccines/mmr/WHO_TRS_840_A3.pdf?ua=1