World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)

Finished Product Manufacturer
(VACCINES)

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Chengdu Institute of Biological Products Co., Ltd. (CDIBP)**
Inspected site	
Name & address of inspected manufacturing site	379, 3rd Section, Jinhua Road, Jinjiang District, Chengdu, 610023, Sichuan Province, P. R. China.
Unit / block / workshop number	Japanese Encephalitis Vaccine production, filling & packaging (Building 208) QC (Building 209) Raw Material and Finished Product Warehouse (Building 218)
Inspection details	
Dates of inspection	20 – 24 November 2023
Type of inspection	Routine inspection
Introduction	
Brief description of the manufacturing activities and general information about the company and site	The Chengdu Institute of Biological Products Co., Ltd. (CDIBP) was founded in 1958. The company is affiliated with Sinopharm China National Biotech Group (CNBG), one of the six biological product institutes in China. The major products in production are the following: • Japanese Encephalitis Vaccine, live (freeze-dried) and respective diluent (PBS). • 23-Valent Pneumococcal Polysaccharide Vaccine. • BCG Series of Products. • Diphtheria, Tetanus and Acellular Pertussis Combined Vaccine, Absorbed. • In addition, the company has about 20 other products not routinely manufactured, such as Hib and typhoid vaccine. Japanese Encephalitis Vaccine (JEV), the focus of this inspection, was developed collaboratively by CDIBP and the National Institute for Food and Drug Control (NIFDC). The vaccine is for active immunization of healthy children older than 8 months of age, as well as children and adults who intend to enter the endemic areas from non-endemic areas. The vaccine was prequalified in October 2013.

	JE vaccine was licensed in China in 1990 and millions of doses have been administered in China and to other Asian children. Till the end of 2022, total exportation of JEV reached over 530 million doses, supplying Thailand, South Korea, India, Nepal, Sri Lanka, Vietnam, Indonesia, etc. From 2015 to 2022, CDIBP supplied nearly 36 million doses of 5-dose-vial JEV to UNICEF for use in Laos, Nepal, Cambodia, the Philippines, and Myanmar.
History	The initial on-site WHO GMP inspection took place in May 2013. After that, CDIBP was inspected by WHO in 2016 and 2018. Since the last WHO inspection, the company has received regular inspections from Sichuan Provincial Drug Administration and National Medical Products Administration (NMPA).
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	The inspection focused on the main changes made since the last WHO inspection: • Additional filling and lyophilization line (named Area B) for JE vaccine in Building 208, approved by WHO on 17th, December 2021. • Implementation of terminal sterilization of the PBS Diluent for the JE vaccine. • A new warehouse (Building 218) was constructed and put into use in 2022.
Restrictions	Due to time constraints and the time spent on interpretation, the production of bulk drug substance and the packaging and labelling system were not covered during this inspection.
Out of scope	Products and vaccines other than the Japanese Encephalitis vaccine (live, attenuated) were not inspected during this inspection.
WHO products covered by the inspection	Japanese Encephalitis Vaccine (live, attenuated) 1 dose/vial and 5-doses/vial. Lyophilized active component to be reconstituted with an excipient diluent before use. Two vial set (active + excipient). Diluent for 1 dose JE Vaccine: 0.5 mL/ampoule, steam sterilized WFI. Purchased from Jiangsu Desano Pharmaceutical Co., Ltd. (not subjected to this inspection). Diluent for 5-dose JE Vaccine: PBS 2.5mL/vial, terminal sterilized, manufactured by CDIBP.
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CCS	Contamination Control Strategy
CFU	Colony-forming unit

CIP	Cleaning in place
CoA	Certificate of analysis
Cpk	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HAZOP	Hazard Operability Analysis
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
JEV	Japanese Encephalitis Vaccine
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
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
RABS	Restricted Access Barrier System
RCA	Root cause analysis
RO	Reverse osmosis
SIP	Sterilization in place

SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	**Summary of the findings and comments**

1. Pharmaceutical quality system

From the review of the quality system, it appeared that adequate resources were made available for the management of the implemented Quality Management System (QMS). Quality assurance and quality control activities operate independently 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 were taken into account in the batch release; regular reviews of the quality of vaccines were conducted.

Management review:

The Management Review (MR) was performed at least once per year following the SOP for management review. The purpose of the MR was to demonstrate the effectiveness of the quality management system and to meet the customer requirements. The procedure applied to the assessment and management of the entire system. The agenda was prepared by the management representative and circulated three days in advance wherein the meeting was attended by the senior management, heads of the modules as well as the department heads. The last MR meeting minutes were spot-checked.

Quality risk management

Quality risk management guideline provided a policy for product quality risk management and applied to the whole life cycle of products manufactured on-site. A high-level overview was provided in the guideline whereas a separate SOP "quality risk management" was also available. The guideline provided a list of tools (e.g., FMEA, HAZOP, FTA, etc.) to be used for assessing risks. The SOP provided instructions for carrying out the QRM and gave reference to various regulatory guidelines.

Contamination Control Strategy (CCS)

The contamination control strategy report included process and facility design, facility and equipment, personnel, utility, raw materials and process controls, product container closure system, vendor management, contract services, process risk assessment and process control, process validation, preventive maintenance, cleaning and disinfection and monitoring system, quality management system, biosafety and continuous improvement.

Product quality review:

A procedure for Product Quality Review (PQR) was in place. The review period was correspondent to the production year. Some reports were presented and discussed.

Trend Analysis was in place. The company used control charts, histograms, and Cpk index for evaluating trends and consistency. Alert limits and action limits were defined.

Deviation management:

The deviation control procedure was reviewed and it provided instructions for the identification, documentation, investigation, analysis, reporting and disposition of non-conformities. Some deviation records were reviewed and discussed.

Change control:

The procedure for change control management was in place. Change controls were categorized as critical, major, and minor. Critical changes had a significant impact on product quality, safety, and efficacy. Major changes had a moderate impact on product quality, safety, and efficacy. Minor changes may have little or no impact on the product quality, safety, and efficacy. Regulatory notification impact was assessed by Regulatory Affairs personnel. The procedure referred to WHO guidance on variations to the PQ vaccines. The impact on validation was evaluated through Risk Assessment. The list of changes since 2020 was presented and some change control records were discussed.

Documentation:

Overall, the production activities were recorded in the form of batch manufacturing records, equipment logbooks and/or general control records. Procedures, operating conditions, and specifications related to the manufacturing processes are established. The quality control activities were recorded in the respective documents of record including laboratory control records, equipment logbooks and general control records. Procedures, operating conditions and specifications related to the quality control activities were established.

A data integrity (DI) guideline was prepared by the company's QA based on WHO TRS 1033, Annex-4, PIC/S, and other guidelines. It described the purpose, responsibilities, definition, and procedure related to the management of DI. The focus was given to management responsibility and how DI issues would be handled.

Complaints

The complaints handling procedure was not covered during this inspection.

Product recalls:

The product recall procedure delineated instructions for recalling the product if the finished product was found defective after distribution. There had not been any recalls in the past 5 years. A mock recall was performed in April 2022.

Self-inspection:

The SOP for internal audit management was reviewed. The internal audit was performed at least once per year. An internal audit schedule was presented. A separate procedure was available for the qualification of internal auditors. The internal auditors were qualified on the GMP regulations by one of the experienced staff of the company.

Quality audits and suppliers' audits and approval:

The SOP for supplier qualification was reviewed. It was noted that suppliers were assessed based on a review of various documents such as business certificates, drug manufacture licenses, industry product licenses, hygiene licenses, manufacture licenses for hazardous materials, ISO certificates, list of materials used in the manufacture of the product in question, quality specification, test methods and so on. The material in question was then tested and used in the trial production before an on-site audit was performed. The material was then qualified through a change control procedure and listed in the approved supplier list.

Contract production, analysis and other activities and quality agreements:

The company uses contracted laboratories for the gene sequencing of drug substances whenever there was a change of working seed lot. In addition, environmental isolates and raw materials were tested by the contracted labs. A list of the contracted labs was maintained.

Personnel:

Organizational charts showing the relationships between different areas, including quality assurance, production, and quality control, with identification by name and title of key personnel, were presented. CDIBP was considered sufficiently staffed with qualified personnel.

Training:

Personal qualification for aseptic operators provided training requirements for Grades A, B and C. The operators were qualified through three steps, namely training, qualification for gowning and participation in the APS. The training included topics such as cleanroom behaviour, gowning, air visualization study, GMP basic knowledge and regulations and knowledge about microbiology. In addition, on-the-job training on the use of RABS, isolators and other areas was provided. The gowning qualification was also described in the same procedure. In addition, participation in the APS was required for three successful participations (whereas for the routine one participation per year). During the gowning qualification stage, microbiological samples were taken from the operators from different locations. A booklet or certificate was issued following the successful qualification of the operators. In general, the training requirements for the aseptic operators appeared adequate.

Batch Release Process:

A presentation was made by the QA Manager on the batch release. A review of the batch records was performed by both the production and QC teams before the issuance of the product review sheet. The NIFDC decided who would pick up the sample and perform the testing for batch release. It would either be the Sichuan Institute for Drug Control (SIDC) or NIFDC performing the sampling and testing. The presentation provided perquisite for the issuance and release of a batch. The same prerequisite had been covered in the SOP for finished product batch release management. The presentation also provided QA on-site supervision and management for upstream production, filling and freeze drying, inspection, labelling and packaging, sampling, testing and release. This was governed through several SOPs including a procedure on product batch review audit. It was confirmed that no batch had been rejected by either NIFDC or SIDC.

2. Production system

In general, 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 the qualification and validation of equipment, manufacturing processes and quality control testing methods were in place. Qualifications and validations were performed.

The present inspection focused on the JEV fill and finishing activities conducted in the additional line (Area B) and the new process for the PBS diluent (terminal sterilization).

100% manual inspection was performed for the JE vaccine. This was followed by an AQL sampling for critical and minor defects. The eye test was performed once every 6 months. Several workstations were being provided for the inspection.

Some batch records were reviewed during the inspection.

Aseptic process simulation (APS)

A procedure was in place for APS. APS was performed as part of the initial validation, with at least three consecutive satisfactory simulations, and repeated every 6 months.

The APS protocol and reports were spot-checked. The list of interventions was reviewed. Lyophilization was simulated without a decrease in the temperature, the use of compressed air instead of nitrogen, and a partial vacuum was applied. All personnel working in the aseptic process needed to participate at least once a year in the APS. The media growth promotion test was checked. Qualification of visual inspectors for media fill was in place. No contaminated unit was observed.

3. Facilities and equipment system

JEV was produced in a dedicated workshop (Building 208). The production workshop was constructed in July 2007 and completed at the end of 2008. The facilities and equipment of the premises were validated in July 2010, followed by the process validation. All the validation of the company was completed in March 2011, and the workshop was put into use after the GMP certificate was obtained in November 2011. The building consisted of 3 floors, with a total floor area of 12,303 m^2, an area of clean area of 3,672 m^2 and a maximum annual production capacity of 50 million vials.

The second floor was mainly used for sterilization filtration, filling, lyophilization and capping of the final bulk of Japanese Encephalitis Vaccine, Live and preparation, filling and capping of supporting diluent. In addition, visual inspection was also carried out in this layer. Its clean area covers 1,054 m^2, and the non-clean area covers 2,915 m^2.

The two filling areas (Area A and Area B) on 2F, Area B were reconstructed in 2019, and all the validation of the reconstructed area was completed in July 2020. It was approved by NMPA in August 2021 and put into use in January 2022. In August 2021, the upgrading and reconstruction of Area A were started, and the validation of facilities, equipment, and processes was completed in 2022. Area A has restored production in May 2023. The PBS diluent was filled, and the terminal sterilization happened in Area C on the Second floor.

The inclusion of filling and lyophilization area B for JEV was approved by WHO in 2021. Area B was similar to area A, with the difference that this area had 2 lyophilizers, whereas area A had 4 lyophilizers. Filling and loading/unloading of the lyophilizer were performed in open and passive restricted access barrier systems (RABS). Capping was common for both lines (A and B).

The layout plans of the cleanroom classification, differential pressure, personnel flow diagram, material flow diagram and product flow diagram were provided and followed the GMP requirements for biological and sterile products.

Qualification and validation:

2023 Revalidation master plan for live attenuated Japanese Encephalitis Vaccine (JEV) was reviewed. This document provided guidance on requalification frequency for HVAC, utilities, equipment, media fill, sterile filtration validation, cleaning validation, CIP, transport validation and other validation activities. The revalidation master plan also contained the list of equipment and instruments, building/floor number and their planned revalidation date. A list of planned validation activities was maintained in the spreadsheet. Also, a validation policy was in place guiding the validation activities. A separate guideline for the revalidation was available.

HVAC system

AHU's initial qualification of a new area B was performed by an external service provider whereas routine PQ was performed by the company. For Grade A and B areas, requalification was performed once every 6 months for temperature, relative humidity, differential pressure, HEPA integrity and air velocity whereas for Grade C and D, it was performed once every 12 months. Some protocols and reports were spot-checked.

Sterilization in place (SIP)

Revalidation of SIP cycles was conducted once a year. The validation of the SIP of the filter line and the revalidation of the SIP system for the Freeze Dryer were spot-checked.

Depyrogenation Tunnel

The Area B depyrogenation tunnel requalification planned twice a year as per the VMP was spot-checked.

Autoclaves

Autoclave requalification was reviewed. Three (3) runs were conducted for each load related to a change control. Bowie dick test was performed daily while the leak test was performed weekly. Biological indicators were verified before use for the population, purity and identity.

The revalidation of the sterilization of PBS diluent was conducted with 1 run once a year. In the event of a change, revalidation had to be conducted with three runs.

Disinfectant validation

General guidance on disinfectant validation was in place. Verification of disinfectant validation was stated to be performed every 5 years. When a new isolate of EM was not representative, unscheduled validation would be conducted.

The protocols and reports for disinfectant validation were spot-checked.

Gowning laundry and sterilization

A protocol and a report demonstrated the number of cycles that gowning can be used, laundered, and sterilized.

4 Laboratory control system

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

The chemical laboratory was located in a separate building, mainly responsible for the testing of incoming, in-process, and finished products. The laboratory was spread over three floors for testing of various tests and products. The laboratory was well equipped with the latest equipment and instruments. At the time of the visit to the laboratory, no testing activity was being carried out.

The micro lab testing (virus titration, sterility, mycoplasma, adventitious agent, identity, EM incubation) was also visited during this inspection.

Management of OOS test results:

Out-of-specification and out of trending procedure was reviewed and applied to raw materials, primary packaging materials, process water, solutions used in production, animal quality, intermediate product, bulk, final bulk, finished product testing and EMP. The procedure was common for both chemistry and microbiology data deviation.

Environmental and Personnel Monitoring

The environmental monitoring (EM) program was in place. The risk assessment was used for defining the sampling locations. Personnel were also monitored. RABS Gloves were sampled after each batch.

The trend analysis report was spot-checked. Alert limits and action limits were defined. All microorganisms found in grades A and B were identified.

The protocol and the report for the recovery study for settle plates and active air sampling was reviewed.

5 Materials system

A visit to the new warehouse (storage and shipment department on building 218) was conducted. The new warehouse was found to be spacious, clean and tidy. It was spread over four floors for the storage of incoming materials and finished products. The first floor was used for the receipt of the incoming materials as well as for the dispatch of the finished product. A separate receiving and dispatch bays were provided. The company used a barcode system to determine the status of materials stored in the warehouse. In addition, a manual green colour label was used to assist production personnel.

The construction work of the new warehouse started in June 2021 and was completed within a year. The NMPA inspected the new warehouse in July 2022 and it was put the use in October 2022. The new warehouse was used for the storage of materials and finished products. A change control was raised and three action items were identified covering the construction of the new warehouse, revision of the procedures and training and qualification of the equipment and facility.

Initial IQ/OQ covered verification of areas such as P&ID, utility connection, power failure, access control, alarm and deviation and other aspects. The PQ protocol covered verification and tests for operation parameters, location for the probes for routine monitoring, precooling, temperature holding, temperature holding when power off, layout of the data logger, temperature and humidity distribution

empty load, assessment criteria and summary of the non-conformance. The temperature mapping (empty and full load) for the cold storage area was reviewed and noted that hot/cold spots were identified and found to be within the limit.

Provisions for incoming materials, intermediates and finished products were in place for reception, quarantine and release processes. Appropriate storage conditions were provided. Rejected and returned material procedures were in place.

The SOP on the sampling management for raw materials and primary packaging materials was discussed. The SOP on the identity test for raw materials was reviewed.

6 Packaging and labelling system

The labelling and packaging system areas were not inspected during this inspection due to time constraints.

Part 3	Conclusion – Inspection outcome

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, the **Chengdu Institute of Biological Products Co., Ltd. (CDIBP)**, located at **379, 3rd Section, Jinhua Road, Jinjiang District, Chengdu, 610023, Sichuan Province, P. R. China** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the 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.

Part 4	List of WHO 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***

2. WHO good manufacturing practices for biological products. WHO Expert Committee on Biological Standardization. Sixty-sixth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 999), Annex 2. ***Short name: WHO TRS No. 999, Annex 2***

3. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 2. ***Short name: WHO TRS No. 1044, Annex 2***

4. WHO good manufacturing practices for active pharmaceutical ingredients (bulk drug 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***

5. 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***

6. Good manufacturing practices: guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third report. Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3. ***Short name: WHO TRS No. 1019, Annex 3***

7. 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***

8. 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. 957, Annex 1

9. 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 3.
Short name: WHO TRS No. 957, Annex 3

10. 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***

11. 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***

12. 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***

13. 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***

14. 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***

15. 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***

16. 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***

17. 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***

18. WHO general guidance on variations to multisource pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10. ***Short name: WHO Multisource guidance*** or ***WHO TRS No. 996, Annex 10***

19. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10. ***Short name: WHO TRS No. 1010, Annex 10***

20. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3. ***Short name: WHO TRS No. 1025, Annex 3***

21. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4. ***Short name: WHO TRS No. 1025, Annex 4***

22. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6. ***Short name: WHO TRS No. 1025, Annex 6***

23. WHO Recommendations, Guidelines and other documents related to the manufacture, quality control and evaluation of biological products. WHO Expert Committee on Biological Standardization. Seventy-first Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1028), Annex 1. ***Short name: WHO TRS 1028, Annex 1***

24. New and replacement WHO international reference standards for biological products. WHO Expert Committee on Biological Standardization. Seventy-first Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1028), Annex 4. ***Short name: WHO TRS 1028, Annex 4***

25. Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. ***Short name: WHO TRS 1033, Annex 2***

26. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3. ***Short name: WHO TRS 1033, Annex 3***

27. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS 1033, Annex 4***

28. Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. WHO Expert Committee on Biological Standardization. Sixty-first report. Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 978), Annex 6. ***Short name: WHO TRS No. 978, Annex 6***

29. Guidelines for independent lot release of vaccines by regulatory authorities. WHO Expert Committee on Biological Standardization. Sixty-first report. Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 978), Annex 2. ***Short name: WHO TRS No. 978, Annex 2***