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Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer
(VACCINES)

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Yuxi Zerun Biotechnology Co., Ltd.**
Corporate and inspected manufacturing site address	No.83 South Dongfeng Road, High-tech Zone, Yuxi, Yunnan Province, P. R. China GPS: N24°19′36.01″ E102°31′31.37″
Inspection details	
Dates of inspection	13 to 17 November 2023
Type of inspection	Initial inspection for Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (Pichia pastoris)
Introduction	
Brief description of the manufacturing activities	Yuxi Zerun only carries out the manufacturing activities of preventive biological products authorized by the National Medical Products Administration (NMPA). It is not involved in the production of non-pharmaceutical products. Yuxi Zerun is licensed by Yunnan MPA (License No. 20170422).
General information about the company and site	Founded in 2016, Yuxi Zerun Biotechnology Co., Ltd. is a wholly owned subsidiary of Shanghai Zerun Biotechnology. Shanghai Zerun is a majority-owned subsidiary of Walvax. Walvax is an innovative biotechnology company dedicated to the development, manufacturing and distribution of human vaccines, with 8 products launched on the market. Walvax has exported over 300M doses of vaccine products to 18 countries. Yuxi Zerun is the Marketing Authorization Holder of the Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (Pichia pastoris) in two presentations, pre-filled syringes (PFS) and vials. On March 22, 2022, the company obtained the Certificate of Drug Registration issued by the NMPA. The site located at No.83 South Dongfeng Road, High-tech Zone, Yuxi, Yunnan Province, China construction was completed in February 2018, occupying an area of 4334.58 m^2 with a construction area of 18005.03 m^2.
History	Yuxi Zerun has undergone regular inspections by the Chinese regulatory authorities (CFDI of NMPA and Yunnan MPA). This was the first WHO Prequalification inspection for the site.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Bulk Production Suite: Lines 1 and 2; Fill and Finish Suite: Line 1 (Vial line); Quality Control Laboratory including microbiology lab, and physical & chemical lab; Warehouse.

Restrictions	Due to the time spent in interpretation, several topics of the inspection plan (including Packaging and Labelling system, and Animal House) were not covered in detail during this inspection.
Out of scope	Other vaccines than bivalent HPV vaccine (vial presentation). The PFS line was not covered during this inspection.
WHO products covered by the inspection	Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine (Pichia pastoris) - Single-dose (0.5 mL) vial
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
AMAB	Adsorbed Monovalent Antigen Bulk
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
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
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography
HPV	Human Papillomavirus
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
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification

oRABS	open restricted access barrier system
PFS	Pre-Filled Syringe
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PMAB	Purified Monovalent Antigen Bulk
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PUPSIT	Pre-Use Post-Sterilization Integrity Test
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
VLP	Virus-Like Particle
VVM	Vaccine Vial Monitor
WFI	Water for injection

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

1. Pharmaceutical quality system (PQS)

The elements of the PQS appeared to be adequately implemented and compiled in the Quality Manual, which described the quality policy and quality objectives of Yuxi Zerun, as well as the basic requirements of its quality management system. The company, through the issuance of quality policy and quality objectives, required all departments to implement the quality objectives and regularly measure the completion of quality objectives to achieve the effective operation of the quality management system.

The quality management system included organization and personnel, premises and facilities, equipment, materials and products, qualification and validation, documentation management, manufacturing management, quality control, quality assurance, product shipment, recall, and self-inspection, etc. The Quality Department consists of Regulatory Affairs Department, Quality Assurance (QA) Department, Quality Control (QC) Laboratory, and Validation and Calibration Department.

Management review (MR):

A SOP was in place for Quality Management Review, performed quarterly and annually, with the presence of the legal representative (chairman of the board) and the quality management committee, which was composed of the head of relevant departments (Production, QC, Regulatory Affairs, Validation, QA, logistics, etc.).

The contents of the annual management review included but were not limited to the following: Operation status of the quality system: self-inspection and external audits results and respective CAPA, quantity and classification of deviation, completion and delay of investigation, recurring deviation; completion and delay of change, implementation and effectiveness of CAPA, status and effectiveness of extensions, quality risk review, complaints, recalls, completion of audit of suppliers, outsourced service providers; Impact of changes or updates of laws and regulations; Pharmacovigilance; Production status; OOS/OOT/OOE; Rejection and release; Delay in qualification, validation, re-validation, calibration, EM; Maintenance; and Data integrity. KPIs were established. Minutes of the last meetings were spot-checked.

Product quality review:

The procedure for management of Quality Annual Review was presented. Annual retrospective analysis was conducted by Yuxi Zerun on the production process control, quality of intermediate products and finished products, stability investigation of the commercial batches of Recombinant Human Papillomavirus (HPV) Bivalent (Types 16, 18) Vaccine (Pichia pastoris), quality of raw materials and excipients, packaging materials, deviations and changes that occurred during production and testing processes, facility and equipment conditions, as well as product complaints and recalls.

The annual product quality review (APQR) report for Recombinant HPV Bivalent (Types 16, 18) Vaccine (Pichia pastoris) for lots produced during 12 months from 1 Jan 2022 to 31 Dec 2022 was spot-checked. The trend analysis of test parameters related to the batches produced in 2021-2022 was spot-checked. The test results were in compliance with the set of specifications.

Quality risk management:

The SOP for quality risk management was reviewed. The procedure was essentially based on the ICH Q9 and several tools were stated in the procedure to assess the risks. The FMEA was used to calculate RPN, and acceptance criteria were stated in the procedure. Some risk assessments were spot-checked during the inspection.

Contamination control strategy (CCS)

The SOP for management of contamination control strategy was reviewed. The SOP provided a high-level overview of the contamination control strategy covering areas such as facility design, product design, personnel, equipment, repairs & maintenance and materials etc. The CCS for the bulk production process of recombinant HPV bivalent vaccine covered the manufacturing process of bivalent vaccine (fermentation and purification processes), utilities (cleanroom, purified water, WFI, pure steam, compressed air, HVAC), equipment, personnel, supplier management, contracted activities and monitoring systems (environmental, water system and personnel monitoring). A separate CCS for the vial filling line in the production process of recombinant HPV bivalent vaccine was presented. It covered areas such as process description, buffer/adjuvant formulation, monovalent bulk dilution and

sterile filtration (PUPSIT), monovalent bulk adsorption, aseptic filling, manual visual inspection, aseptic process simulation, personnel, equipment and other areas.

Deviation and CAPA management:

The company had established the Standard Operating Procedure for Deviation Handling to provide standardized procedures for handling deviations, including deviation identification, deviation reporting, deviation numbering, preliminary risk assessment of deviations, root cause investigation, and impact assessment, deviation classification, corrective/preventive action formulation and tracking, and deviation closure. Deviations were classified as minor deviations, major deviations, and critical deviations. The deviation procedure was applied to all deviations related to company facilities, equipment, products, materials, procedures, processes, standards, methods, environmental controls, document implementation, and GxP implementation processes that are relevant to quality.

The root cause analysis tools included but were not limited to FTA, 5Why, fishbone diagram, and brainstorming. The supervisors/heads of the department where the deviation occurred, and the quality operations formulate specific CAPA based on the root cause and impact assessment of the deviation investigation.

Trends were assessed quarterly. The last report for Q1-Q3, 2023, was spot-checked. Some deviations records were selected for review

Change control (CC):

The company had established a SOP for Change Control to manage the change control process, ensuring that the proposal, impact assessment (including validation and regulatory), classification, approval, formulation of implementation plan, implementation, effect evaluation, and final review of changes were compliant with relevant requirements. Changes were classified as minor changes, moderate changes, and major changes. The change control process applied to change management throughout the product lifecycle (development, technology transfer, commercial production, product discontinuation), including company facilities, equipment, products, materials, procedures, processes, standards, methods, environmental controls, and all aspects related to product quality, including GxP and newly introduced products. The list of changes control for 2023 was presented and some changes were spot-checked.

Complaints:

The SOP for quality complaints was reviewed and noted that QA was responsible for the management of quality complaints. The complaints were classified into service complaints, invalid complaints, quality complaints, and medical complaints. Service complaints were handled by the marketing department, medical complaints were handled by pharmacovigilance department, and complaints related to product quality (including recurrent quality complaints) were handled by QA. Complaints were investigated using the 6M (Fish-bone diagram), 5-Why, FTA etc. The quality complaints were further categorized into Levels 1 to 4 based on the severity of the complaints.

Some complaints records and investigation reports were reviewed during the inspection.

Product recalls:

The SOP for recall management was reviewed and noted that recall was categorized into levels 1 to 3. Based on the criticality of the issue, recall (e.g., level 1 within a day) would be initiated. A mock recall was performed in 2022 for the domestic market.

Self-inspection:

The SOP for self-inspection guided to monitoring of the implementation of GMP and continued improvement of the QA system. The self-inspection was carried out across the entire year due to the ongoing production activities. A schedule for 2023 was available confirming that the self-inspection was performed as planned.

Quality audits and suppliers' audits and approval:

The list of key materials and approved suppliers was reviewed and some supplier qualification records were selected for review.

Contract production, analysis and other activities and Quality agreements:

The company confirmed that no production activity of bivalent vaccine was contracted out or outsourced. The company uses external laboratories for some of the in-process testing, finished product testing and material testing. The SOP for management of entrusted testing was reviewed which provided a procedure for the qualification of the outsourced laboratories.

Personnel

At the moment of the inspection, the company had 300 employees, including 177 production personnel and 87 quality personnel.

Organization, organogram, independence of production from quality control:

The company organogram was presented. Quality unit was independent from production department. The qualified person (QP) who had a concurrent post of head of quality management was overall responsible for QA, QC, RA, validation and calibration reports. Pharmacovigilance department was independent from the quality system.

Training:

The SOP for training management was reviewed and noted that an annual training plan was prepared based on the need analysis. Training was provided by the SMEs, trainers, and consultants. The trainees were assessed based on questions and on-the-job demonstrations. An assessment criterion was described in the procedure. The training plan identified several topics for the training. This included but was not limited to APS, EHS, validation, EU GMP Annex-1, Documentation System, HBEL, Good Chromatography Practices and other topics.

The training records and qualification of operators working in the aseptic area were reviewed.

The SOP for training and assessment of visual inspection personnel was discussed. The procedure included the scope, responsibilities, and methodology for training visual inspectors. To qualify the visual inspectors, defective samples were used which were classified into critical, major and minor defects. The examples of critical and other defects were described. A library of defective samples was

maintained by the fill and finish suite. The routine eyesight/vision check was carried out once every year at the hospital and the requalification of the visual inspector was performed annually as well.

Batch Release Process and Lot Summary Protocol:

The procedure for lot release vaccine product by the company to be released for domestic and international markets was spot-checked. Procedures indicated the responsibility of QA, QC and QP for the release of the vaccine lots. A template for lot summary protocol (LSP) for the domestic market was provided. As part of PQ CMC's assessment, an updated English version of LSP was provided to include all test parameters as per WHO TRS 999, Annex 4, Appendix 1 requirement.

2. Production system

The active ingredient of Drug Product (DP) (0.5 ml per dose) contained 40μg of HPV type 16 L1 protein and 20μg of HPV type 18 L1 protein adjuvanted with aluminium phosphate and formulated with excipients including histidine, sodium chloride, polysorbate 80, water for injection (no preservatives and antibiotics). The presentation for WHO prequalification was in vial (0.5 ml per vial) while the prefilled syringes (PFS) presentation was only for domestic marketing. The Batch size and the approximate filling output of each lot of DP was about 100,000 ~ 200,000 doses.

The production process of the Bivalent Human Papillomavirus Vaccine is divided into fermentation, purification, absorption, filling, and packaging.

The L1 proteins were produced by separate fermentations using recombinant *Pichia pastoris*, and self-assembled into VLPs. The purified VLPs are adsorbed on aluminium phosphate adjuvant. Each bulk serotype was subjected to sterilizing filtration and adsorbed on aluminium phosphate separately. PUPSIT was in place. Aluminium phosphate adjuvant was sterilized by autoclave.

Seed lots and cell banks

Shanghai Zerun Biotechnology Co., Ltd. (Shanghai Zerun), was responsible for establishing the seed lots and manufacturing the clinical trial material for the Phase I, II and III/IIIb trials. Yuxi Zerun Biotechnology Co., Ltd. (Yuxi Zerun) performs commercial production and QC testing.

The working seed preparation procedures were spot-checked. The inventory of Primary, Master and Working seeds was provided. The certificates of analysis (CoA) for Master and Working Seeds were reviewed. Most tests on MSL and WSL are performed in-house, except for gene sequencing, which was a contracted out. The previous seed lots were tested by Yuxi Zerun and Shanghai Zerun. All in-house test methods have been transferred from Shanghai Zerun to Yuxi Zerun which will be responsible for the testing on future seed lots.

Visual inspection:

The SOP for the physical appearance inspection of vials was discussed which guided the inspection as well as sampling using the AQL sampling plan. The defects were classified into three categories namely critical, major and minor and acceptance criteria were described in the procedure. Visual inspection was conducted for 100% of the vials and alert limit were described in the procedure for all three types of defects. The eyesight check was performed once per year. Each station was equipped with a white/black background and prior to the start of the inspection activity, the light intensity was checked from three different locations. The inspectors take a break after 45 minutes. The library of

defective vials was stored in a locked PMMA (acrylic) box and was placed in a cold storage room (2-8ºC). The defective samples were categorized into critical, major and minor.

Batch numbering:

Procedures for batch numbering were spot checked. The documents describe the requirement for numbering of all batches for solution, water, seed banks, intermediate, purified and adsorbed bulks and finished product, air, compressed air, and sterile product.

Process Validation

The list of lots used in the PPQ and CPV and associated batches produced from the WSB was presented. The process validation of 3 out of 6 finished product lots (3 vial and 3 PFS presentations) of bivalent HPV vaccine were spot checked. The holding time at different manufacturing steps was provided.

The Filter validation was also presented.

Aseptic process simulations (APS):

The SOP for Aseptic Process Simulation (APS) was presented. The initial APS protocol and report for vial filling line were spot checked. No contamination was found. APS was required to be conducted every 6 months. Personnel were required to participate in at least one APS every 12 months. The list of qualified personnel was presented.

Batch manufacturing record review (BMR):

Some BMRs were spot-checked during the inspection

3. Facilities and equipment system

The manufacturing facilities were completed and put into operation in February 2018 with an area of 4,334.58 m^2 and a construction area of 18,005.03 m^2 for HPV vaccine production. The production area was located in Building 1 and the QC laboratory on the 2nd and 3rd floor of building 2. Experimental Animal House was located in an independent building (building N).

The first floor of building 1 was for storage and utilities systems, including a water production room, refrigeration units and air compressors and nitrogen plants, a biological inactivation area, etc. The second-floor workshop was the main production area, including fermentation, centrifugation, purification, adsorbed monovalent antigen bulk (AMAB) preparation, final bulk preparation and filling processes area. The third floor was the packaging and auxiliary area, including the solution preparation area, visual inspection and packaging area, intermediate warehouse and air-conditioning room.

The bulk production area had two independent production lines to produce 16L1 and 18L1 purified monovalent adsorbed bulks (PMAB), respectively. Each production line was divided into active and inactive areas to minimize contamination and cross-contamination.

There was an independent adjuvant preparation and adsorption preparation area in the fill and finish workshop for the preparation of each AMAB, and two filling lines for aseptic filling of the vial and prefilled syringe (PFS) respectively. The filling was conducted in an open restricted access barrier system (oRABS).

Waste management:

The waste disposal at the upstream production suites was described during the interview with the production management team. The procedures for sewage treatment and waste management were reviewed. The daily logbook record of the sewage treatment system was spot-checked.

Qualification and validation:

The validation master plan for the recombinant HPV (Types 16, 18) vaccine was reviewed. The VMP provided a high-level overview of the validation philosophy covering process validation, cleaning validation, APS, equipment qualification (including utilities), packaging validation, shipping validation, warehouse validation, etc. The risk assessment or impact assessment was part of the VMP before qualification and validation activities were performed. For the computerized systems, direct impact systems were considered to be validated.

HVAC

The Layout for the AHUs of the production area was presented. Separate AHUs were provided for different activities.

An SOP was in place for the management of facilities and equipment qualification. Grade C and D clean HVAC systems were qualified once a year, and Grades A and B clean air conditioning systems were qualified once every 6 months. RABS technology with unidirectional flow was adopted in the area of grade A cleanliness level to effectively control contamination and ensure the cleanliness of the operation area. For key grade A and B areas, continuous particle measuring system (PMS) was in place.

The protocols and reports for the requalification of the grade A and B areas were spot-checked.

SIP

SIP revalidation of adsorption vessels was spot-checked.

Cleaning validation:

The risk assessment report on cleaning validation of the new cervical cancer vaccine production workshop was reviewed. The assessment was performed to determine hard-to-clean areas, sampling methods and analytical methods used to analyse test items as part of the cleaning validation.

The SOP for the cleaning validation, which guided the cleaning validation, was reviewed. Three batches of bivalent vaccine were taken for the cleaning validation covering various equipment. The sampling points and sampling methods (swab and rinse sampling) were identified, and testing was performed.

Computerized Systems

The SOP for management of computerized system safety guided user permission management. The access privileges were defined.

Incubators

Qualification of the QC micro incubators were spot-checked. The coldest and hottest spots defined.

4. Laboratory control system

The Quality Control laboratory was independent from the production area. The quality control laboratory was located on the 2nd and 3rd floor of Building A. The physical and chemical testing was performed on the 2nd floor whereas microbiology testing was carried out on the 3rd floor. The 3rd floor also occupied stability chambers and retention samples. A separate area was designated for the storage of incoming samples providing different storage conditions based on the type of the samples. Separate cabinets were provided for the storage of samples to be tested and samples of packaging materials.

Out-of-specification (OOS) management:

The SOP for investigation and treatment of OOS, OOT and out-of-expectation (OOE) results in the laboratory was presented. In addition, separate procedures were in place for the handling of laboratory incidents and laboratory deviations. A separate procedure was available for the handling of OOS related to microbiology tests. In general, the SOP appeared to be adequate. Some OOS records were reviewed.

Potency

Procedures for In Vivo Potency of Recombinant Human Papillomavirus Bivalent (Types 16, 18) Vaccine was in place and was briefly explained. Due to the time limitation, the procedure was not thoroughly reviewed.

Reference Standards

The in-house reference standards of HPV PMAB 16L1 and 18L1 were managed using documented procedures. All the reference materials for purified monovalent antigen bulk (PMAB) and final product were manufactured in-house with the same production scale, equipment and processes of commercial lots. The working references were tested and calibrated in the QC lab, and then issued and released by the QA department in accordance with the SOP. The reference materials were verified/calibrated every year. In cases of any quality decline, insufficient inventory or closing expiry date, a new lot of reference material will be manufactured and calibrated as per approved procedures.

Stability:

Stability protocol stated for collection of one lot to be tested annually at 2-8°C. Completed and ongoing stability studies were spot-checked and results were within the acceptable criteria of release specifications.

Environmental monitoring results:

The environmental monitoring (EM) of cleanrooms was documented in an SOP. The risk assessment report on the layout of EM points in clean areas was used for defining the EM locations. Trends were evaluated quarterly and annually. The last available EM quality trend report was spot checked. Alert and action limits were defined based on historical data. Any microorganism found in grades A and B was identified.

Grade A total particle monitoring was performed according to a respective SOP. Continuous NVPCs were located in grade A filling/capping and alert level was defined. The alarms were linked to the PMS system (validated).

5. Materials management

The warehouse at Yuxi Zerun had a storage area of 2010 m^2, which is divided into raw material/excipient storage, packaging material storage, label storage, consumable storage, strain storage, quarantine area, rejected product storage, highly toxic material storage, hazardous chemical storage, cool warehouse (for special materials), finished product cold storage and others.

The warehouse was found to be clean, tidy, and well-maintained. The incoming materials were classified into different categories and were stored in the raw material warehouse. Appropriate controls were in place for the storage of incoming materials.

Some of the materials were verified and noted that these materials were sampled according to the pre-established sampling plan. The containers of these materials bear the status as the date of sampling. The warehouse management system (WMS) was used for maintaining the inventory of the materials. The sampling area was equipped with MAL and PAL and a biosafety cabinet was used for the sampling of raw materials.

The VVM labels were stored inside a medical load temperature preservation box maintained at -30°C. These VVMs were bearing an approved green label. The preservation box was validated.

International shipping

This service was contracted with a third party for carrying out the international cold chain shipment of the HPV-2 vaccine. Contract details between were spot-checked. The validation protocol and study report were reviewed.

6. Packaging and labelling system

The labelling and packaging areas on the 3rd floor were inspected. VVM applicator was not installed at the moment of the inspection. It was notified that the purchase order for the VVM applicator was already initiated. The company further presented in the CAPA evidence that the installation and commissioning were completed, the qualifications have been completed according to the protocols and the equipment qualification report has been issued.

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, **Yuxi Zerun Biotechnology Co., Ltd.**, located at **No.83 South Dongfeng Road, High-tech Zone, Yuxi, Yunnan Province, 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***

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***

30. Recommendations to assure the quality, safety and efficacy of recombinant human papillomavirus virus-like particle vaccines. WHO Expert Committee on Biological Standardization. Sixty-sixth Report. Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 999), Annex 4. ***Short name: WHO TRS No. 999, Annex 4***