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Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Vaccine Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Instituto Butantan (IB)**
Inspected site	
Address of inspected manufacturing site	Avenida Vital Brasil, 1500 – Butantã, São Paulo – SP, Brazil.
Inspection details	
Dates of inspection	19 to 23 February 2024
Type of inspection	Joint inspection with ANVISA (Brazilian NRA) for Influenza trivalent vaccine (split virion, inactivated).
Introduction	
Brief description of the manufacturing activities	The Instituto Butantan (IB) is one of the largest producers of vaccines, antivenoms and antitoxins in Brazil and Latin America. IB is responsible for manufacturing most of the hyperimmune sera used in Brazil, including antivenoms, antitoxins, and anti-rabies. It also answers for a considerable amount of the national production of vaccine antigens and produces 100% of the flu vaccines used in the Brazilian national influenza vaccination campaign. The IB is authorized by the Brazilian Health Regulatory Agency (ANVISA) to manufacture, purify, package, store in its facilities, ship, distribute, export and import, for its own use, drug substances and to manufacture, store in its facilities, distribute, pack, ship, export, import and transport antivenoms, antitoxins and finished vaccines (small volume parenteral suspensions and solutions, and lyophilized powders).
General information about the company and site	The Instituto Butantan is located in the western region of the city of São Paulo in the neighborhood of Butantã. It has a total area of 711,080.73 m^2, containing parks, museums, research sites, and the industrial complex. The Foundation Butantan was established on May 31, 1989, to support the Institute in its activities and is a nonprofit legal entity governed by private law. The Institute is responsible for scientific, technological, cultural and educational activities and the production of biologics supplied to the Ministry of Health. In 2023, approximately 9 million vials of influenza vaccine were produced. In total the manufacturer supplied 80 million doses of influenza vaccine for the Brazilian National Influenza Campaign and 5.8 million doses for other countries. According to the manufacturer, the annual production capacity is

	140 million doses of influenza vaccine, including southern and northern hemispheres campaigns.
History	The Influenza trivalent vaccine (split virion, inactivated) was prequalified in April 2021. Due to the pandemic situation, a GMP inspection was not conducted at that time and the GMP compliance was based on reliance on the ANVISA inspection. The site is regularly inspected by ANVISA (Brazilian NRA), a PIC/S member.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	- Building 32 (Seeds production and QC) - Building 59 (Influenza Monovalent manufacturing) - Building 41 (Formulation, Filling and Packaging) - Warehouse, Quality Control Labs and related Utilities
Restrictions	The scope of the inspection was restricted to the Influenza trivalent vaccine (split virion, inactivated)
Out of scope	Facilities used for other products were out of the inspection scope.
WHO products covered by the inspection	Influenza trivalent vaccine (split virion, inactivated) – 10-Doses Vial
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
CAPA	Corrective Actions and Preventive Action
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
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning

IB	Instituto Butantan
INCQS	National Institute for Health Quality Control
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
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
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
RCA	Root cause analysis
RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
TIV	Trivalent Influenza Vaccine
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
VVM	Vaccine Vial Monitor
WFI	Water for injection

Part 2	Summary of the findings and comments

1. Pharmaceutical quality system

The Quality Manual \ defined the Quality Policy and the Quality Management System of the Instituto Butantan (IB). In general terms, the pharmaceutical quality system (PQS) and all of its elements were in place. The production was independent of the quality control department.

The deficiencies noted in this section were adequately addressed and will be verified during future PQ inspections.

Management review (MR):

The Management review procedure was in place. Every six months the management review meetings took place, with the participation of senior management representatives. The meetings aimed to improve the IB Quality System and generate independent action plans managed by the SQF area (Quality Systems). The minutes of the last meetings were presented.

Product quality review:

The SOP for Product Quality Annual Report was reviewed. The APQR report for the influenza monovalent bulks (review period 23/09/2022 to 14/09/2023) was spot-checked. The APQR Report for formulation and filling of the seasonal trivalent vaccine (inactivated, split virion) was also spot-checked. The period covered by the Report included information on the total number of batches manufactured from 01 July 2022 to 30 June 2023. There were no rejected batches during this period.

Quality risk management:

A SOP was in place for Quality Risk Management, referring to ICH Q9 (R1) and WHO TRS 981 Annex 2. A contamination control strategy (CCS) was in place.

Deviation management:

There was a system in place for recording and investigating deviations from procedures and processes. The list of deviations raised in the last and current Influenza campaign was presented and several records were selected for assessment. The following aspects of deviation investigations were reviewed: responsibilities for initiating & recording deviations, root cause analysis, trending of deviations and determination of recurrence, application of Quality Risk Management (QRM) tools & methodologies, assessment of product quality impact, identification and implementation of CAPAs.

CAPA management:

The work process for managing actions and action plans was described in an SOP. This procedure managed the plans in the computerized system for actions resulting from Immediate Action Plans, "CAPA" Action Plans from deviation records, or independent Action Plans originating from qualification, validation, RPP, and audits. Several CAPA records were spot-checked.

Change control (CC):

The procedure for Change Control Management was presented. Changes were classified as Critical, Major, Minor, , Temporary or Permanent at the opening of the CC, being changed if necessary during the execution and completion. A committee (CMU) was created with the participation from all areas that assessed impact. Some CCs were selected for review by the inspection team.

Complaints:

The procedure for product complaint management was spot-checked. It described the receipt, registration, forwarding, monitoring and archiving of occurrences regarding product complaints. The List of market complaints – Influenza Vaccine from 2021 to 2023 was requested and some records were reviewed.

Product recalls:

The procedure for Product Recall and Return established guidelines for communicating to Health Authorities and consumers about recall actions. The QA assessed whether there was a possibility of health risk, and if so, it activated the Recall Committee (CR). At the first CR meeting, the risk of the recall was assessed, which could be classified as class I, II or III. The procedure provided for the mock recall in the case there was no recall.

Self-inspection:

An Internal Audit Program was in place. The audit process, as well as the preparation of the Risk Matrix, Schedule, and conduct of Internal audits, were described in the respective SOP. The risk matrix for determining the frequency of internal audits and the internal audit schedule were spot-checked.

Quality audits and suppliers' audits and approval:

A program for the qualification of manufacturers, suppliers, service providers and partners was in place. Suppliers of raw and packaging materials were classified according to risk, and qualification could be performed by desktop assessment, remote audit or onsite audit. The company carried out annual monitoring of suppliers and qualification could be valid for 2, 3 or 4 years, depending on the criticality. A Risk Analysis methodology to determine the Classification of Audits and Frequency of Audits for Suppliers and Service Providers was presented along with the list of raw and packaging materials, with all suppliers being qualified.

Personnel

Organization, organogram, independence of production from quality control:

At the time of the inspection, the manufacturer informed to have around 2800 employees, with 1036 dedicated to Production and 397 to Quality Operations. The Quality Department was independent from the Production Department.

- ***Training:***

The General Training Guidelines and the Annual Training Plan were presented.

- ***Qualification of aseptic operators in Grade B areas:***

The procedure for qualification in aseptic operations was reviewed. Overall, the program defined the minimum steps and requirements in aseptic technique and behaviour in clean rooms, while also providing the rationale for initial qualification and periodic requalification in order to cover the full qualification cycle of an employee. The requirements and process for staff qualification were documented with satisfactory results in relevant procedures and results and records were maintained and updated for each employee as checked on site.

Documentation:

The Guidelines for Issuing Quality Systems Documents were presented. Types of documents, creation, elaboration, review, distribution, frequency of revaluation, and archival were defined. A specific document for Data Integrity was in place, establishing the guidelines to maintain the data integrity throughout the entire life cycle of data, from generation, processing, reporting, verification, use for decision making, storage and disposal, according to ALCOA+ (attributable, legible, contemporary, original, accurate, complete, consistent, available and traceable) principles. It described organizational policy; addressed specific considerations for integrity such as document management and control, record completion; record controls located at the point of use, and integrity considerations in computerized systems: validation, data transfer and electronic signatures.

Batch Release Process:

The procedure for the release of the products was spot-checked. This was an internal procedure that set the steps for the release of any product. In the case of the influenza trivalent vaccine (inactivated, split virion), QA prepared the Lot Summary Protocol (LSP) accompanied by an analytical certificate. A template of the vaccine batch was presented, as well as a release certificate issued by the Brazilian National Control Laboratory (INCQS). This certificate served as evidence that the format and content of the protocol were accepted by the INCQS. These documents were generated through a computerized system and therefore identified with the information of the staff that generated it. Protocols were signed by defined responsible persons that were identified in the respective document (Activity delegation for Finished Product Release). This documentation was sent to INCQS, with lot samples (when required). Protocols were not destroyed but scanned and archived.

2. Production

Seed lots and cell banks

The viral strains were received from WHO reference laboratories. Building 32 was an area dedicated to the production of viral seeds and the release of working seed lots.

Drug Substance

The production of monovalent bulks takes place in Building 59 (LIN), including storage. Among others, the following documents were reviewed: Product development report – monovalent influenza virus, containing the flowchart of the production process; SOP of Filtration of the viral suspension, Sampling and storage of the monovalent influenza virus (strain) ultra-concentrated.

Fill and finishing operations:

Formulation, filling and packaging took place in Building 41, on the first floor.

Formulation of the influenza trivalent vaccine was performed in a grade A/B environment. The vaccine bulk is prepared in a stainless-steel vessel and sterile filtered to a second sterilized mobile vessel in a closed system. PUPSIT was in place. The mobile vessel was transferred to filling, and during filling, it was kept in the grade C room adjacent to the filling room.

Two filling lines (line I and line II) were used for the influenza vaccine, grade A/B. A second sterilized filtration (with PUPSIT) was performed in the filling room. Capping was performed in adjacent rooms, also grade A/B. Volume checks were performed.

Visual inspection:

Visual inspection was conducted automatically. Qualification of the equipment was reviewed. Rejects from the machine were manually re-inspected and the defects were classified. AQL sampling was performed for both automated and manual inspection.

Process Validation

The process validation was described as a lifecycle approach in 3 phases: Process design, Validation, and Continued Process Verification (CPV).

For the monovalent bulks, splitting and inactivation were validated every time the strain changed. Otherwise, they remained validated. This was done using three consecutive batches for each new strain.

Process validation was conducted by the validation group of IB. In the case of the inactivation process, the exercise included the determination of the log reduction during this phase.

Reprocessing

Reprocessing of Trivalent influenza vaccine may occur according to defined internal procedures. A formal QA authorization is mandatory for reprocessing. Any reprocessing operations performed at IB were limited to the repeat of a filtration step. All refiltration operations were performed as per SOP, only in exceptional cases where the quality of the product would not be impacted. Re-filtrations were validated and were approved in the marketing authorization applications.

Batch manufacturing record review (BMR):

Some batch records were reviewed during the inspection. The approach to the execution and documentation of the BMR was generally considered to be compliant with GMP.

3. Facilities and equipment system:

The following facilities were inspected:

- Filling and packaging of influenza vaccine (SEA), Building 41 - First floor
- Formulation of serums and vaccines (FOR), Building 41 - First floor
- Production of Influenza Seeds (PBI), Building 32
- Monovalent Influenza Bulk Production (LIN), Building 59
- Quality Control (CDQ) Building 41 – Ground floor
- Quality Control (CDQ) Building 32
- Quality Control (CDQ) Building 54
- Related Warehouse Building

The equipment used in the manufacturing processes generally met the specifications required for its correct operation and undergone qualification processes (when applicable), maintenance and calibration. There were internal procedures that provided guidelines for carrying out these activities. Qualification activities considered all stages of the equipment's life cycle, starting with the elaboration of the specification of user requirements, going through the final use of the equipment and monitoring them through a continuous monitoring program, which was based on a periodic review, with previously defined frequencies and evaluation criteria.

The equipment was maintained in a qualified/validated state. Any changes made to equipment were managed through the change management process. The impact of changes to qualification/validation status was assessed based on risk management principles. Instruments calibration, equipment qualification and maintenance management were planned via computerized systems.

Deficiencies related to facilities and equipment were identified. The company has provided the CAPA plan, adequately addressing the deficiencies raised.

Qualification and validation:

A Validation Master Plan was in place. The general guidelines for conducting qualification activities for all life cycles of equipment, utilities, electronic spreadsheets, and computerized systems were presented. The list of qualified manufacturing equipment was provided. The maintenance of the validation status of equipment, utilities, and instruments was carried out per the guidelines in the procedure, describing the program and the periodicity for carrying out requalification and validation activities. Some (re)qualification plans and their associated periodic reports were randomly selected and reviewed.

Calibration

The Equipment and Instrument Calibration Program was presented. It Specified that calibration management was performed through software. Certificates issued by the metrology sector and certificates issued by external laboratories must be entered and stored electronically in the software. Some certificates were spot-checked.

Maintenance

The preventive maintenance plan for the year 2024 was reviewed. The plan included, among others, the following data: description of the technical object, number of equipment, plant, functional location, maintenance plan and frequency. Some records were spot checked.

Water and Pure Steam systems:

The Purified Water (PW), Water for Injection (WFI) and Pure Steam (PS) systems related to the influenza vaccine were inspected. A procedure for issuing periodic review of clean utilities was presented. It specified that the review must be carried out every 6 months. It was stated that microbiological and physicochemical trends of all points must be presented to the committee in monthly meetings. In situations where, during committee meetings, the need to implement preventive or corrective actions was identified, action plans were issued. Several reports were spot-checked during the inspection. For all reports evaluated, it was noted that the systems were statistically stable and maintained the Qualified/Validated status. Monitoring of water systems consisted of controlling the system's operational parameters (such as pressure, temperature and flow) and quality in relation to physical-chemical and microbiological conditions.

Trends were evaluated during Systems Periodic Reviews. Alert and action limits were defined. The procedure for Management of Out-of-Trend Results for Water and Pure Steam was presented. The raw data related to the last 3 months were spot-checked.

HVAC

The Area Classification and Pressure Cascade Layout (HVAC) for Influenza Vaccine Production Laboratory (LIN) and for Building 41 Formulation and Filling areas were presented.

Differential pressure monitoring at critical locations was performed continuously by a supervisory system. According to the procedure, the differential pressure between rooms of the same grade should be at least 5 Pa and 10 Pa between different grades.

A procedure established guidelines for the qualification of HVAC (Heating, Ventilation, and Air Conditioning) systems and clean air equipment directly related to the manufacturing of products at Instituto Butantan.

The last qualification report for the Building 41 (Formulation and Filling) HVAC was spot-checked as well as for the Sampling and Weighing areas (Building 45).

Gases and vacuum systems

Description of the system for supplying compressed air was presented. Before feeding the points (supply), it passed through a 0.22µm terminal filter. The Qualification and Requalification Schedule for Compressed Air referring to the year 2024 was reviewed. A procedure described the general guidelines for compressed air qualification. The Performance Qualification Report - Compressed air distribution system – influenza – building 59 was reviewed. The monitoring for grade A and B areas was performed every four months. Other points in areas grade C, D and non-classified areas were monitored annually. The Trend Analysis Report – Compressed air system – Filling and Packaging – Line II – Building 41, was spot-checked.

Aseptic process simulations (APS):

A procedure was in place for Aseptic Process Simulations (Media Fill / Media Hold). Initially, 3 runs were conducted, repeated every 6 months ± 2 months. The APS took into account risk-based aseptic manipulations and interventions known to occur during normal production, as well as worst-case situations. The validation schedule for 2024 was presented.

Campaign Changeover

Campaign changeover procedures were conducted between each campaign to prevent cross-contamination. The Product changeover was accomplished through procedural controls to ensure that the risk of cross-contamination between products is minimized. Equipment which was used for multiple products has undergone product changeover prior to use in a subsequent campaign or has a validated cleaning protocol which has demonstrated adequate removal of residues. When a new strain is introduced into the facility, appropriate cleaning validation for equipment/area was performed.

Disinfectant Validation:

The List of disinfectant agents used on the materials and surfaces of the clean areas was presented. The list defined the approved agents, with their respective fungicidal, virucidal and bacterial actions and respective contact times for each kind of material. Disinfectant efficacy testing was reviewed as part of a facility contamination control strategy. The program included the selection of the appropriate disinfectants, an assessment of their capability to inactivate or kill vegetative cells, plus bacterial spores and fungal spores, as applicable and their proper rotational application and use. Some reports were spot-checked.

Cleaning validation:

The cleaning validation strategy was presented and reviewed. Overall, the document provided sufficient detailed technical guidelines for developing cleaning validation rationales included in the validation plans specific to each production area and operational instructions to conduct cleaning validation studies on equipment/tools. Cleaning procedures were validated including dirty and clean hold times. Other GMP-relevant documents related to cleaning validation were also checked.

Storage Equipment

Performance Qualification Protocol and Report for the cold chamber located in building 45, used for storing the influenza vaccine and for a refrigerator used to store samples in the QC lab were reviewed. The Calibration Certificate for the temperature monitoring device used for that cold room was also spot-checked.

Computerized Systems

The Computer Systems Validation (CSV) Plan was reviewed. The document described the strategies, methodologies, guidelines and responsibilities for computerized systems validation activities. The need for qualification of outsourced services was provided in the procedure. The general guidelines for validating computerized systems were presented.

The Computerized Systems Validation Schedule and Criticality Matrix presented the allocated systems, installation area, version, category, status of qualification, criticality assessment, validation completion dates and date of planned requalification or qualification.

The procedure for Backup and Restore established the criteria for the entire IB plant for data availability in the event of equipment failures.

Qualification reports for some selected computerized systems were reviewed during the inspection.

The deficiencies noted in this section were adequately addressed and will be verified during future PQ inspections.

4. Laboratory control system

Samples were received in the Sample Document Reception Unit – Central Quality Sector (CQC), which directed the samples to the respective laboratories, microbiological or physical-chemical, in accordance with the procedures for Reception, Registration, Distribution and Traceability. Access to the rooms was performed with facial recognition (access restriction). Samples were received and recorded in a hybrid manner.

For the analysis, requests were generated, which were specific per sample, such as one checked during the inspection.

Test reports were completed manually by the analyst. After the batch tests were completed, the results were entered into the computerized system by a dedicated team for registration in the documentation room. After the conference, the Supervisor signed the tests and released the results to the CQC Team.

During the inspection of the physical-chemical and micro laboratories, it was possible to note that the manufacturer had proper traceability of the analyses carried out, from entry into the laboratory, records in the logbooks, and records of the analyses carried out. Receiving samples was unique for the three laboratories, and there was a specific logbook for water samples, products and environmental monitoring upon receipt, a request number (NR) was generated, which accompanies all tests to be carried out.

Logbooks for recording usage, calibration and maintenance activities for each piece of equipment were available.

The procedure for Storage and Management of reference and retention samples was presented. Reference samples were available for raw materials, monovalent bulks and finished products. They were kept under appropriate storage conditions.

Out-of-specification (OOS) management:

OOS results were investigated and recorded as per respective SOP. OOT and OOL were investigated following the workflow documented in another SOP. The list of laboratory investigation reports raised in the last Flu campaign was presented. Several records were selected for review.

Analytical method validation

The specifications of the finished product were checked. Validation reports for some methods were reviewed and the methodologies can be considered validated.

Reference Standards

The Management of Reference Standards (Chemical and Biological), Antibodies and Kits in Quality Control were defined in a specific SOP describing the receipt, recording, handling, storage, control and disposal of QC standards, antibodies, solutions, kits and reagents. The Inventory Summary was requested and presented. The expiration dates of the prepared solutions were defined, and the management of working standards took place in a computerized system.

Stability:

The stability programme and respective stability chambers were checked during the inspection. The chambers were controlled for temperature and humidity and these parameters were automatically monitored and controlled by a supervisory system and by manual recordings. The vaccine batches included in the on-going stability programme were checked. Batches were properly identified and stored.

Environmental monitoring:

An Environmental Monitoring (EM) Program was in place. It described the procedures for carrying out environmental monitoring of viable particles (air sampling - volumetric and settle plates, surface monitoring - Rodac and Swab) and total particle counts of classified areas. Alert and action levels were defined based on historical data. EM locations were defined based on a risk assessment. The last trend report for the filling area (SEA) was spot-checked. All microorganisms isolated in grades A and B were identified to species level. For grades C and D microorganism identification was conducted when out of alert limit. Recovery study for the settle plates were conducted.

The deficiencies noted in this section were adequately addressed and will be verified during future PQ inspections.

5 Materials management:

An inspection was carried out in the storage areas of Building 45, and at the time the areas were properly organized. Controls were in place at receipt, checking, sampling, storage, release, and storage of materials.

Starting materials were purchased from approved suppliers. Incoming materials and finished products were quarantined after receipt or processing until they were released for use or distribution. Materials and products were stored under the appropriate conditions and in an orderly fashion. Material status was controlled by an ERP system. The procedure for changing material/product status was verified.

The temperature monitoring registration form for cold chambers, antechambers, and refrigerators was spot-checked. The inspection team reviewed temperature data from the last 12 months for the Cold Chamber used for storing the influenza vaccine.

The procedure for Raw Material Weighing Operations was also reviewed.

The deficiencies noted in this section were adequately addressed and will be verified during future PQ inspections.

6 Packaging and labeling system:

Labelling and packaging were performed in building 41. Online sensors were available for checking 100% of labelling variable data. VVM, when required, was placed manually. Packaging variable data was checked visually and at defined intervals. Time out of the refrigerator (TOR) was defined and controlled during these operations.

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, **Instituto Butantan**, located at **Avenida Vital Brasil, 1500 – Butantã, São Paulo – SP, Brazil** 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 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***

4. 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***

5. 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***

6. 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***

7. 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***

8. 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***

9. 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***

10. 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***

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***

12. 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***

13. 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***

14. 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***

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***

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***

17. 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***

18. 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***

19. 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***

20. 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***

21. 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***

22. 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***

23. 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***

24. 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***

25. 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***

26. 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***

27. WHO Guidelines for the International Packaging and Shipping of Vaccines, 6th edition. Geneva, World Health Organization, 2020.

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