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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	**Instituto Latinoamericano de Biotecnologia Mechnikov SA**
Corporate and inspected manufacturing site address	Km 6, Carretera Norte, Managua, 11018, Nicaragua
Inspection details	
Dates of inspection	24 to 28 April 2023
Type of inspection	Initial WHO inspection for: - Trivalent Inactivated Split Influenza Vaccine - FLU-M® - Influenza vaccine (split virion, inactivated)
Introduction	
Brief description of the manufacturing activities	The Instituto Latinoamericano de Biotecnologia Mechnikov S.A. is licensed in Nicaragua for activities to import raw materials, to commercialize, distribute, and manufacture pharmaceutical products. The company is authorized to manufacture Flu vaccines in monodose and multidose presentations. Currently, the company is responsible for filling, packaging and quality control release of Flu vaccines for the Federal State Unitary Enterprise "Saint Petersburg Scientific Research Institute of Vaccines and Sera and Enterprise for the Production of Bacterial Preparations" of the Federal Medical and Biologic Agency (FSUE SPbSRIVS FMBA of Russia)
General information about the company and site	Mechnikov Instituto facility located in Managua, was designed to perform production activities, quality control, as well as the generation of critical support services. The building covers a total area of 9011 m2, organized into four levels as follows: - On the ground floor, production areas, support systems and warehouses are located. The production area has a total area of 1327 m^2 with cleanrooms representing 330 m^2. - At the mezzanine, air handling units, reverse osmosis unit, and BMS (*Building Management System*) are located. - On the first floor, quality control laboratories are located. - On the terrace, chillers, compressors and drinking water tanks are installed. The company has one filling line installed. The production capacity is 30 million doses per season (northern and southern hemisphere).
History	The manufacturer has received regular inspections from CECMED/Cuba and MINPROMTORG/Russia. This was the first WHO Inspection of the site.

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	- Filling, visual inspection, labeling and packaging areas. - Warehouses and shipping areas. - Quality control laboratories. - Utilities.
Restrictions	None
Out of scope	The inspection was limited to Fill/Finish activities of Trivalent Inactivated Split Influenza Vaccine and FLU-M® [Influenza vaccine (split virion, inactivated)]
WHO products covered by the inspection	- Trivalent Inactivated Split Influenza Vaccine - FLU-M® - Influenza vaccine (split virion, inactivated)
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
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
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

The Instituto Latinonamericano de Biotecnologia MECHNIKOV, S.A. had established a Pharmaceutical Quality System (PQS) based on the ICH Q10 and WHO GMP guidelines. The Quality Department was independent of production and is composed of 4 divisions: Quality Assurance (QA), Validation (VD), Quality Control (QC) and Training (TD).

Management review (MR):

The verification of the adoption and improvement of the PQS was reviewed semi-annually according to the specific procedure for Analysis of the PQS. The presentation for the last analysis was spot checked.

Product quality review:

Product Quality Reviews were conducted according to the a established SOP. The objective of the review was to verify the consistency of existing processes, adequacy of raw material, and finished product specifications as established in the marketing authorization dossier, to detect any trend and to identify

opportunities for product and process improvement. The review content included the topics defined in the WHO GMP Guide. The last PQR approved available for the Trivalent Inactivated Split Influenza Vaccine was reviewed.

Quality risk management:

Provisions for Quality Risk Management (QRM) were in place according to a documented procedure for assessment, control, communication and review of risks to the quality of the vaccine. The procedure was based on WHO TRS 981 Annex 2 and ICH Q9. Risk management tools were described in the procedure. The Risk Management Logbook was presented and some risk assessments were spot checked.

Deviation management:

The deviation handling SOP was presented. Deviations were recorded in a paper-based system. Deviations were classified as critical, major and minor according to the risk. The root cause was investigated using defined tools. Based on the criticality classification, the timelines for investigation were set. Product impact assessment was included in the SOP. Reoccurrence was checked during the investigation. CAPA provisions were established. Some deviations reports were discussed.

CAPA management:

The CAPA Management SOP was discussed. The system was manual and linked to each of the other systems related (deviations, complaints, audits, etc). For deviations, the CAPAs were attached to each deviation. Tracking was performed manually, and record by record. Effectiveness checks were conducted.

Change control (CC):

The SOP on Change Control was discussed. Changes were evaluated by a QA specialist and a multidisciplinary team. Change approval was the responsibility of the chief of quality. Changes were classified as minor, moderate, and major based on quality impact. The system was manual, and tracking was performed in a logbook. The current logbook was spot checked. Some change control records were selected for review.

Complaints:

Provisions were in place for investigations of complaints. Complaints were classified as Mild, Moderate and Severe. The need to consider a recall, in the case of a complaint concerning a possible product defect, and communication with competent authorities were described in the procedure. No complaints related to quality were received so far.

Product recalls:

The procedure for the handling of recall was reviewed. The Authorized Person was responsible for leading the recall process. Three classes of recall and timelines were defined in the procedure:

- Class I (Emergency): 24h
- Class II (Urgent): 48h
- Class III (No urgent): 5 days

Provisions for communication with competent authorities were defined in the procedure.

The company had never had a recall.

The effectiveness of the arrangements for recalls was tested annually by the Mock Recall procedure. The report for the last simulation performed was spot checked.

Self-inspection:

An SOP was in place for quality audits, including internal and supplier audits. A risk assessment was performed to define the frequency of quality audits. The minimum frequency for internal audit was once a year, but for some departments, such as production, technical department and QC it was performed twice a year. Internal auditors were certified according to ISO standards and received training on ICH Q10. CAPAs were followed by a QA expert. The internal audit annual plan was checked.

Quality audits and suppliers' audits and approval:

The activities related to suppliers and service providers, including subcontractors for laboratories, were governed by a defined procedure. Overall, the material was categorized into critical, important and non-critical. Some supplier qualification records were selected for review.

Contract production, analysis and other activities and Quality agreements:

There was no production subcontracted. However, some quality control tests were outsourced to a third-party QC laboratory. An onsite audit of the lab was conducted. The service contract and the quality agreement between both parties were presented.

Personnel

Organization, organogram, independence of production from quality control:

The organization chart was presented, and it was observed that the Quality Department was independent from the Production Department. Responsibilities were described in job descriptions.

- ***Training:***

Planning, organization, conduction evaluation and follow-up of the training, qualification and development of human resources was described in a SOP. Training efficacy evaluation was performed.

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

An SOP was in place for the gowning qualification. Cleanroom operators should undergo annual medical exams. Periodic reassessment was annually and required participation in a successful APS. Rules for disqualifying personnel from working in aseptic areas were established. The list of authorized personnel to aseptic areas was presented, and the qualification of one operator was reviewed.

- ***Qualification of visual inspectors:***

The qualification of manual visual inspectors was conducted as per the respective procedure. A qualified kit was used for the qualification of the visual inspectors. For the initial qualification, each visual inspector performs three runs. For the annual qualification, the test is repeated once. The eye checks were conducted before the initial qualification and on an annual basis.

- ***Qualification of sterility tests operators:***

The qualification of the operators for the gowning and sterility test at the microbiology laboratory was briefly discussed. No sterility test failure was recorded.

Documentation:

The Documentation Management SOP was spot checked. The procedure outlined how documents should be prepared, reviewed, approved, or authorized. It was established that records should be performed according to ALCOA principles.

Batch Release Process and Lot Summary Protocol

The procedure for batch release of finished product was spot-checked along with the release certificate of one batch. The Lot Summary Protocol was in line with WHO TRS 923 Annex 3. The conformity certificate for the concerned batch lot number was signed off by the qualified person of the company.

2. Production system

The drug product was manufactured as 10 multi-dose vials. Each vial contains 5.0 mL (10 doses of 0.5 mL each) and was presented as glass vials.

The list of batches of trivalent and tetravalent inactivated influenza vaccines produced from 2020 to the date of the inspection (2023) was provided. The list included batches for both the Northern and Southern hemispheres. Since the start of production in 2019, no single batch has been rejected.

The final (trivalent) sterile bulk in a sterile single-use bag is sent from the St Petersburg manufacturing site to the manufacturing site at Instituto MECHNIKOV, S.A., Nicaragua. The manufacturing operations at Instituto MECHNIKOV, S.A., Nicaragua site started from the receipt of the final formulated bulk for filling, stoppering, capping, visual inspection, labeling, packaging, storing, and shipping operations.

The master formulae for the filling and packaging was presented. During the filling, representative samples were taken at the periodic interval for QC tests. The fill volume was controlled over the filling process as an IPC.

The filling of the final (trivalent) bulk was performed using a filling and sealing machine for vials, followed by final sterilizing filtration through a 0.45 µm + 0.2 µm sterilizing capsule membrane filter.

The vessels were cleaned and sterilized in place.A bioburden sample was collected before sterilizing filtration.

The vials were washed and depyrogenated. The rubber stoppers used could be ready to use or ready to sterilize (autoclave).

Manual 100% visual inspection was conducted with AQL in place.

After the visual inspection, the vials were labeled and packaged. The variable mentions, including the lot number and its expiry date, were set on the printer display. At the beginning of labeling and after changing a roll, the printing of variable data was checked for correctness.

After the labeling, the vials were placed in a blister package (PVC) (10 vials per blister package) and subsequently packaged in a cardboard box.

Overall, each box (package) contained 10 vials (1 vial – 10 doses of 0.5 mL) in 1 PVC blister package and a package insert. During the packaging process, secondary packaging was checked for completeness. The packed product was placed into a corrugated box and then transferred to the cold room at the quarantine warehouse, where it was stored at 2 – 8 °C.

A line clearance and identification of the batch, equipment, and status were in place. There were verification and checks of a roll of labels, the printing of variable data over the labeling and packaging process, and there was a 100% check of the labels with variable mentions. Reconciliation was in place.

The time out of refrigerator (TOR) was defined.

One executed batch record was reviewed.

Process Validation

The validation protocol and reports were presented. The test results as per the sampling plan mentioned above were presented and found within the established specification. The validation of the sterile filtration of the vaccine was also reviewed.

Aseptic process simulations (APS):

According to the VMP, APS should be performed every 6 months. The Annual Plan was presented. A procedure was in place. Initial validation was conducted with 3 runs. Periodic revalidation was performed with 1 run every 6 months. Each aseptic operator should participate in the APS at least once a year.

The last available Protocol and Report of APS was reviewed. No growth was detected.

3. Facilities and equipment system:

The facilities were located in one building. The building's total area was 9011 m^2, organized into four levels as following:

- On the ground floor, production areas, support systems, and warehouses for raw materials and finished products were located. The production area was 1327 m^2 (clean area 330 m^2).
- At the mezzanine, four air handling units and the reverse osmosis unit were installed.
- On the first floor, quality control laboratories were located.
- The terrace was a technical area with chillers, compressors and drinking water tanks.

The company had one filling line, composed of a vial washing machine, a depyrogenation tunnel, a filling/stoppering machine and a capping machine. Access to classified areas was performed by dedicated material and personnel airlocks. Personnel access to the grade B area is performed by a sequence of 3 airlocks (grades D, C and B respectively).

Qualification and validation:

The Validation Master Plan (VMP) defined the key elements of the qualification and validation programme of the company.

Water and Pure Steam systems:

Details of Purified Water (PW), Water for Injection (WFI), and Pure Steam (PS) systems were provided in the SMF and spot checked on site. Some qualification protocols and reports were reviewed.

The water monitoring plan was defined in the respective procedure. The Periodic Review of Critical Systems was spot-checked. Alert and action levels were defined. Pure steam non-condensable gases, superheat, and dryness were tested once a year. The last test report was checked.

HVAC

The Classification Area Layout for the Ground Floor was presented.

The Validation Master Plan (VMP) and a specific procedure were in place for qualification and requalification of cleanrooms. Some selected HVAC qualification protocols and reports were spot checked.

Autoclave:

The qualification report of the autoclave used for the steam sterilization of the material used for the aseptic filling process, was spot-checked. A vacuum leak test was conducted on a daily basis if used. The same for Bowie Dick. The load pattern for the filling machine assembly was spot-checked.

Depyrogenation Tunnel:

The depyrogenation tunnel was qualified annually for the depyrogenation cycle and every six months for the HEPA filters. The annual qualification of the tunnel was spot checked. The qualification was performed using temperature sensors and bacterial endotoxin challenges.

Vial washing machine:

Vial washing machines were performed once a year. The last one executed was reviewed. Compressed air filters were changed at the start of each campaign (Northern and Southern Hemisphere) and tested for integrity.

Compressed Air

Compressed air was tested once a week according to the respective SOP.

Disinfectant Validation:

The disinfectants were prepared in-house, and sterilized by filtration. The disinfectant efficacy validation protocols and reports were spot-checked.

4. Laboratory control system

Overall, Quality Control was an independent department, separate from Production. QC performs testing of incoming raw materials, packing materials, final bulks and final products, purified water, water for injection, pure steam, and environmental monitoring and stability studies for finished products.

Out-of-specification (OOS) management:

Provisions for OOS investigation were in place. The list of OOS from was spot-checked and some selected records were spot-checked.

Analytical method validation

The list of analytical methods for the raw materials, packaging materials, final bulk, and finished product, as per the specifications of the vaccines, was in place.

The following test methods were spot-checked:

- Sterility test: The sterility test was performed according to the respective procedure. The sterility test verification for the multidose vaccine with thimerosal was conducted.

- Potency: The identification and specific activity were performed as per the procedure. The method was validated. The reference standards and antiserum used for the identification and activity test are provided by WHO centers. The test result for one batch was spot-checked.

Stability studies:

The stability protocol and report were presented. In the three batches at 2 to 8°C, all the test results were found within the established specifications for up to the claimed shelf life of 12 months.

For each season, three batches of each vaccine are put in stability studies for 12 months at 2 to 8°C. The stability report, for the last season was presented and the test results were found within the specifications.

The accelerated stability studies report was also available.

Environmental monitoring:

A Environmental monitoring programme was in place. Sampling locations were based on a risk assessments. Action and action limits were established. Trend reports were prepared every 3 months. The lasts trend reports were spot-checked. Microorganisms were identified according to the respective SOP. For grades A and B all microorganisms were identified.

5. Materials management:

Overall, the materials and formulated bulk were stored under the appropriate conditions in an orderly fashion to permit segregation according to the status (quarantine, released, rejected, etc.). Storage areas were cleaned and well-maintained. In general, adequate space was provided for the storage of raw materials, in-process materials and finished products.

The finished product, labeled and packaged (100 boxes of 10 vials per blister) were stored in cold rooms at 2 to 8°C which were found in general in good state of cleanliness and order. There was continuous temperature monitoring through two temperature sensors placed at the hot and cold spots as defined during the biannual thermo-mapping of cold rooms.

The international shipping was prepared as per the respective procedure. 1 sensor was placed inside the box and 1 external sensor for 10 boxes. Corrugated boxes with 100 boxes of 10 vials 6R were added with the internal sensor in the middle and closed the box. The validation report of the temperature mapping of the corrugate boxes and the temperature mapping study of the actual load to be shipped with one internal and one external WHO prequalified temperature probes were presented.**6. Packaging and labeling system:**

The packaging and labeling material was provided by approved suppliers, received, verified, sampled, and tested as per the implemented procedures and stored in relevant storage conditions.

Line clearance procedures for labeling and packaging lines were in place. The rolls of labels were released for production, verified, and checked before use and the remaining non-printed labels can be returned to warehouse storage. The variable mentions were printed on labels during the labeling process and subjected to 100% checks for absence or presence and for the quality of variable mentions. Specimen of labels were annexed to the batch records.

The secondary packaging material and the package inserts had similar levels of control and checks before use and during the packaging process.

The labeling and packaging area was visited and in general, found in a good state of cleanliness and order.

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 Latinoamericano de Biotecnologia Mechnikov SA**, located at **Km 6, Carretera Norte, Managua, 11018, Nicaragua** 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. Recommendations for the production and control of influenza vaccine (inactivated). WHO Expert Committee on Biological Standardization. Twenty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 927), Annex 3. ***Short name: WHO TRS 927, Annex 3.***