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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Pharco B International (2) for Chemicals (PBIC)**
Corporate address of manufacturer	New Borg El-Arab City-Second Industrial Zone-Part No. 5- Block No. 22, Alexandria, Egypt
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Same as above
Synthetic unit /Block/ Workshop	N/A
Inspection details	
Dates of inspection	9-10 & 13 November 2022
Type of inspection	Follow-up inspection
Introduction	
Brief description of the manufacturing activities	Pharco B International (2) for Chemicals (PBIC) is involved in the manufacturing, packaging, labelling, testing, and storage of intermediates and Active Pharmaceutical Ingredients (APIs).
General information about the company and site	Pharco-B international (2) for Chemicals (PBIC) was established in 2015 focusing on the production of Active Pharmaceutical Ingredients (APIs) and their intermediates. The site became operational in April 2016. The facilities are located in Borg El-Arab City, Second Industrial Zone; Alexandria, approximately 20Km from Borg El Arab International Airport. The site was certified for ISO 9001:2015, ISO 14001:2015 and ISO 45001-2018 and was operating under an integrated quality management system.
History	This was the second WHO inspection. The site was periodically inspected by the Egyptian Drug Authority

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Documents reviewed including but not limited: - Job descriptions for key personnel - Training - Product Quality Review - Quality Risk Management - Management Review - Complaints and Recalls - Deviation control - Change Control - OOS/OOT and investigations - Batch Release - Validation/ Qualification/ Calibration - Sampling and testing of materials - Batch processing records - Materials Management System - Purified Water System - HVAC System <u>Areas inspected</u> - Production operations with focus on Sofosbuvir API - QC laboratory - Warehouses (raw /packaging materials, intermediate/finished product, solvent store, rejected products)
Restrictions	Only the API submitted to WHO Prequalification was covered.
Out of scope	APIs not submitted to WHO for Prequalification. The new processing area under construction was not covered during this inspection.
WHO APIs covered by the inspection	APIMF403 Sofosbuvir
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
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
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
KF	Karl Fisher
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
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
RCA	Root cause analysis
RO	Reverse osmosis
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer

Part 2	Summary of the findings and comments

1. Quality management

PBIC indicated in the SMF that they had established an integrated quality management system based on GMP and ISO 9001:2015, ISO 14001:2015 and ISO 45001:2018 standards.

In general, a Pharmaceutical Quality System was established, documented and implemented, with written procedures covering essential quality elements being in place. Several procedures had been amended according to the CAPAs for the deficiencies made following the last WHO inspection and the changes were found adequate. The procedures that were reviewed and discussed during the inspection were generally of an acceptable standard.

Production and quality control operations were independently managed and specified in written form. GMP requirements were essentially being met. The minutes of the most recent Management Review meeting, conducted in October 2022, were reviewed.

Product Quality Review (PQR)

PQRs were performed according to a written procedure. The PQR was performed for batches manufactured in a period of 12 months. PQRs had to be compiled and approved within 90 days after the end of the evaluation period. The APQR schedule along with the Sofosbuvir PQR (evaluation period 01.01.2021 to 31.12.2021) were reviewed.

Deviations

A procedure for handling deviations (non-conformity control) was presented. The procedure defined responsibilities to ensure that non-conformities were identified, documented, controlled, investigated, evaluated, and prevented from reoccurring. Once an event was identified, a non-conformance report (NCR) was generated, and an investigation had to be conducted within 3 working days for major or minor deviations and within one day for critical deviations. The deviations were registered in the NCR Index.

The last non-conformity trend analysis along with examples of deviations were reviewed

Corrective and Preventive Actions

The SOP on Management of CAPAs was reviewed. The implementation was verified through review of some examples.

Internal audit

The SOP on Internal Audit describing the method of internal audit and its associated activities, processes and documentation system was in place and was reviewed. Based on the results of the assessment, internal audit could be conducted once or twice per year focusing on different departments and activities.

Regarding internal audit the following documentation was reviewed:

- List of Lead auditors
- Audit plan interval assessment
- New auditor qualification
- Notification to internal audit and the internal audit reports for the warehouse audit on 24.04.2022, for the QA department audit on 19.06.2022 and for the QC department audit on 29.03.2022.

Batch Numbering System

A procedure for issuance and numbering of batch manufacturing records and batch cleaning records was in place. It described the process for issuance, control and retrieval of a unique batch number for each material and product. Unique batch numbers for materials and products were generated by the Oracle system.

Batch Release

A system for reviewing and documenting that a batch has been manufactured in accordance with GMP and the product specifications was established. The production manager was responsible for reviewing the BMR and assigning the BMR/BPR in oracle software to be assessed and released by QA. Similarly, the QC responsible had to review the analytical records and assign these records to QA for release. QA was responsible for reviewing and assessing the BMR and relevant analytical records prior to batch certification and release in the database. QA was also responsible for completing the Certificate of Compliance for the batch.

Quality Risk Management

There was a procedure in place describing the principles of QRM applied on the site. The objective of the SOP was to provide appropriate instructions for the identification, assessment, control, communication, review and mitigation of risks and it was applicable to all processes and systems on site. Examples of risk assessments were reviewed.

2. Personnel

There were approximately 150 staff working on-site with appropriate qualifications, experience and training. The quality assurance function was independent of all other plant functions. The Quality Assurance Head reported directly to the site director. All site managers / directors were reporting to the Site Director who in turn reports to the CEO. Responsibilities of key personnel were described in job descriptions.

The job description cards, of the Preparation leader and the Service leader in PHARCO B2 including training records were reviewed.

Induction and continuous training were provided in accordance with written procedures. These procedures were applicable to all personnel whose activities may impact the compliance with regulatory requirements and the quality of products. The training coordinator was responsible for managing the training programme. Corporate training plans were prepared quarterly, and their implementation was monitored.

3. Buildings and facilities

There were separate stores for raw and packaging materials, solvents, and intermediate/finished products. Temperature was monitored. Production operations were conducted in one building, divided in the chemical processing area (reactor's area) and the finishing production area (clean area). The finishing production area consisted of two separate areas namely the centrifuge suite and the finished product suite.

Utilities

Purified Water System (PWS)

The PWS Daily Shift Reading Circulation Mode along with the WTP Daily Shift Reading Working Mode were reviewed.

4. Process equipment

There were 13 SS and 3 glass-lined reactors installed in the processing area. In the clean areas, 3 centrifuges, two vacuum tray dryers and one milling machine were installed.

Preventive maintenance of the glass and SS reactors was carried out according to a written procedure. The Engineering department was responsible for performing the relevant work. Preventive maintenance was performed monthly and annually, and records were maintained. Records were signed by the technician performing the maintenance and verified and approved by the supervisor and the Engineering manager. In case of maintenance by an external contractor or use of replacement parts, the remark section of the preventive maintenance form was used. Examples of maintenance records were reviewed.

In addition, the SOP on maintenance of flexible reinforced rubber hoses was reviewed along with the maintenance record for the hose used for the transfer of Sofosbuvir from the reactor 5 to the centrifuge.

The SOP on maintenance of static dryers and the SOP on maintenance of nitrogen filters in production along with the records for dryer 01 and nitrogen filter for Dryer 01 were reviewed.

5. Documentation and records

In general, documents were designed, prepared, reviewed, and distributed according to a documented procedure. Quality system documents were regularly reviewed and kept up to date. Approved specifications and testing procedures were available for raw materials, packaging materials, intermediates and APIs. Batch manufacturing records (BMRs) were retained for each batch produced.

The following documentation were reviewed:

- The SOP on "How to write a standard operating procedure and a method of analysis" providing the steps on how to prepare and format all SOPs and Methods of Analysis.
- The Document Coding System
- The Document Control System.
- The logbook for issuing and controlling documents.

6. Materials management Incoming raw materials/packaging materials were unloaded on the receiving bay. Materials received were checked against the delivery note and a checklist was completed. The raw material receiving check list for Methanol Batch M025078-22 was reviewed. The list of approved suppliers was available at the warehouse. Quarantine labels were placed on all containers and the receipt note was forwarded to Quality control department for sampling.

Sampling and dispensing of materials were done under LAF. The sampling and dispensing room included separate material and personnel entries. Sampling and dispensing of solvents were performed in the solvent storage area. Regarding sampling and dispensing the following documentation was reviewed:

- The SOP for dispensing and sampling of material in the central weighing area
- The Logbook for pre-use checks of the weighing booth
- The SOP for cleaning of production areas
- The SOP for tools usage in production
- The Working Instructions on issue of released raw materials
- The Calibration certificate of the balance installed in the solvent warehouse
- The Balance usage and cleaning checklist

7. Production and in-process controls Production operations followed defined procedures.
Sofosbuvir production was performed according to instructions in the BMR. The Sofosbuvir production comprised of the following three stages:

- Stage I: Manufacturing process of SOFO-C1-MAC (Enzymatic reaction) starting from SOFO-C2
- Stage II: Manufacture of Sofosbuvir crude (First reaction: Manufacturing process of SOFO Acetate; Second reaction: Manufacturing process of SOFO Crude)
- Stage III: Manufacturing process of Sofosbuvir polymorph-alpha (Crystallization step)
  Final centrifugation step, drying, milling and packaging were performed in Grade D clean area.

8. Packaging and identification labelling of APIs and intermediates
Sofosbuvir API was packed in double antistatic low-density polyethylene LDPE plastic bags, using a Nitrogen blanket. Each bag was sealed using a plastic zip tie. Then the bags were placed in HDPE plastic drums and secured with appropriate seals.

Packaging materials and labels were subject to quality control before release and use. Packaging and labelling operations were described in batch packaging records.

9. Storage and distribution
There was a storage area for raw/packaging materials (quarantine and release), including a dedicated and locked area for rejected materials. Solvents were stored in drums in a dedicated solvent warehouse. There was no separation between flammable and non-flammable solvents. Finally, there was a cold room for temperature sensitive materials and an Intermediate/Finished Products warehouse (quarantine and release). Temperature records were maintained.

10. Laboratory controls
Quality Control (QC) operations were independent from production. The QC laboratory was designed and equipped with chemical, instrumental, and microbiological testing facilities. The analytical laboratory was equipped with instruments like Karl Fischer Titration, pH meter, Gas Chromatography, Conductivity meter, High Performance Liquid Chromatography, Potentiometer, Analytical balance, Moisture Analyzer, Melting point, Heating bath, and Rotary evaporator distiller.

During the visit in the analytical laboratory the following logbooks and documentation were reviewed:

- The logbook for receiving QC (packaging materials) samples
- The SOP on Sampling of Received Packaging Materials
- The method of testing Anti-static low density polyethylene bags and the certificate of testing of LDPE bag B.N.2838-197908.
- The method of testing black polyethylene bag
- The logbook for receiving raw materials
- The analytical method of Sofo-1
- The logbook for HPLC column LC-14
- The logbook of mobile phase preparation record
- The certificate of analysis for Palladium
- The certificate of analysis for Isopropyl Alcohol
- The method of analysis of Sofosbuvir crude and the certificate of analysis
- The calibration certificate of melting point apparatus
- The calibration certificate of pH meter

Reference/Working standards

Reference/Working standards were provided, maintained, and stored. The following documentation was reviewed with regards to standards:

- The SOP for handling of Reference and Working Standards
- The reference standards control sheet.
- The standardization report of Sofosbuvir Working Standard.

11. Validation

There was a procedure in place describing the principles of establishing the VMP and providing an overview of the validation operations, activities, organizational structure, and planning. All validation activities were planned by the Validation/Qualification Team and were approved by the relevant department managers. The QA manager was responsible for final review and approval of all validation/qualification activities and documentation. A series of SOPs describing validation activities in different GMP areas were available. The following were reviewed:

- Computer System Validation
- Cleaning Validation
- Process Validation
- Design Qualification
- Installation Qualification
- Operational Qualification
- Performance Qualification

The 2022 validation/qualification schedule matrix was spot-checked. A list of unplanned/triggered validations/qualifications was also available.

Process Validation

The process validation procedure described the steps for verifying the manufacturing process was robust, reproducible and it consistently produced the API within the established specifications. Three types of validation were defined in the procedure (prospective, concurrent and revalidation). The QA manager was responsible for the final approval of process validation protocols and reports. The following PV reports were reviewed:

- Sofosbuvir NPP Stage I SOFO-C1-MAC
- Sofosbuvir NPP Stage II Sofosbuvir Crude
- Sofosbuvir NPP Stage III Sofosbuvir Pure

With regards to Stage I SOFO-C1-MAC, following comparison of the three validation campaigns during 2017-2020, yields for the first batch in the manufacturing campaign and the three remaining batches in the campaign were established.

In relation to Sofosbuvir Crude PV, it is noted that based on the results appropriate yields were established for the manufacturing process and time limits were set for the 1st and 2nd reaction as well as centrifugation.

Cleaning validation

Cleaning validation was managed according to a written procedure. The scope was to verify the effectiveness of the cleaning procedure for removal of API and intermediates residues, cleaning agents & microbial contamination.

With regards to cleaning validation the following documentation was reviewed:

- The PDE determination strategy for Sofosbuvir.
- The quality agreement for providing toxicological services
- The worst-case study for equipment train 1
- The list of manufacturing train equipment and its shared products, selecting the worst case based on solubility, strength, toxicity, formulation (difficult to clean).
- The cleaning validation protocol for equipment train 01
- The cleaning validation report for equipment train 01
- The cleaning validation report for Molnupiravir
- The analytical method validation summary report for determination of traces of Ravidasvir in swab and rinse samples

Equipment qualification

The cone mill qualification was performed in 2017. IQ and OQ protocols and reports were made available. Qualification of other key equipment (centrifuges and reactors) was covered in detail during the previous inspection.

Calibration

With regards to calibration of the instruments, the following were reviewed:

- Calibration certificate for differential pressure gauge of prefilter of supply unit AHU01
- Calibration certificate for differential pressure gauge of prefilters & bag filters of exhaust unit AHU01

12. Change control

A change management procedure was available. The SOP was applicable to any alteration, abolishment, addition or replacement of an established standard, a validated system or process. Changes were classified as temporary and permanent. The change initiator had to register the proposed change in the CCR system (software). The change had to be approved by the department lead and QA. An impact assessment was carried out and each department lead was responsible for the implementation of the relevant parts of the change. As a final step, QA was responsible for evaluating and closing out the change. The following changes were reviewed:

- Introduction of electronic change control system (CCR)
- Introduction of electronic deviation handling system (NCR) – ongoing at the time of the inspection
- Extension of manufacture campaign from 3 to 7 batches for Sofosbuvir Stage III
- Validation of manufacturing process of SOFO-C1-MAC (Stage I)
- Validation of manufacturing process (Stage II) of Sofosbuvir crude
- Validation of manufacturing process (Stage III) of Sofosbuvir α-polymorph.

13. Rejection and re-use of materials

Reprocessing and reworking were managed according to a written procedure. Production or R&D department could initiate the reprocessing/reworking request. QA was responsible to assign a new batch number.

An example of reprocessing for Sofosbuvir was reviewed.

14. Complaints and recalls

The SOP on Management of Customer Complaint was discussed. Complaints were received by QA, who recorded them and initiated investigations. Complaints were recorded in the Complaint Index Form. Investigation for critical complaints had to be concluded within 5 working days, while for major/minor complaints within 30 working days. Complaint trending and assessment was performed annually according to the procedure.

In total, one complaint had been received in 2021 and one in 2022.

There was a procedure in place for effectively recalling defective APIs from the customers. Details and decisions concerning product recall were defined in the Recall SOP. The QA Department was responsible for coordinating the recall process. No batch recall of APIs had been recorded. The most recent mock recall was carried out in January 2022.

15. Contract manufacturers (including laboratories)

There was no contract production of Sofosbuvir API. The storage of samples in stability chambers for the stability studies and the particle size distribution were contracted to a company within the same group of companies. The relative quality agreement between the two companies was reviewed. The transportation conditions for stability study samples were monitored with data loggers.

The quality agreement between PBIC and an external contract laboratory for FTIR testing was reviewed.

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, ***Pharco B International (2) for Chemicals (PBIC)***, located at ***New Borg El-Arab City-Second Industrial Zone-Part No. 5- Block No. 22, Alexandria, Egypt*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines for APIs.

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 GMP Guidelines referenced in the inspection report

1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO TRS No. 957, Annex 2***
   http://www.who.int/medicines/publications/44threport/en/

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

4. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4.
   Short name: WHO TRS No. 937, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

5. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3. ***Short name: WHO TRS No. 943, Annex 3***
   http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

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
   http://www.who.int/medicines/publications/44threport/en/

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
   http://www.who.int/medicines/publications/44threport/en/

8. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6.
   Short name: WHO TRS No. 961, Annex 6
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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 9***
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2.
    Short name: WHO TRS No. 961, Annex 2
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14. ***Short name: WHO TRS No. 961, Annex 14***
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

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***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3. ***Short name: WHO TRS No. 992, Annex 3***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

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***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

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***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

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***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

19. Guidelines on heating, ventilation and air-conditioning systems for non-sterile 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 8. **Short name: WHO TRS No. 1010, Annex 8**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

20. 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
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

21. 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
https://www.who.int/publications-detail/978-92-4-000182-4

22. 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
https://www.who.int/publications-detail/978-92-4-000182-4

23. 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
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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
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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***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

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***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations