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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the Vaccine manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**Hualan Biological Bacterin Inc.**
Inspected site	
Address of inspected manufacturing site	No. 1-1, Hualan Avenue, Xinxiang 453003, Henan People's Republic of China. GPS coordinates in WGS 84: *35°17'0" north latitude, 113°54'7" east longitude*. DUNS number: 421166107
Inspection details	
Dates of inspection	18-22 October 2021
Type of inspection	This inspection covered the following: 1. Follow up inspection for previous inspection performed by WHO on 16-20 July 2018. 2. Routine for Seasonal Influenza Vaccine.
Introduction	
Brief summary of the manufacturing activities	Production of the trivalent influenza vaccine (TIV) at the site. The manufacturing and quality control of the product was divided into four manufacturing stages, as follows: • Strains establishment and maintenance • Drug substance production; production of monovalent bulks • The monovalent bulks preparation • Drug product production (Formulation, filling, visual inspection and packaging areas • Warehouses and shipping • Quality control
General information about the company and site	Hualan Biological Bacterin Inc. was founded in 2005 and located in Xinxiang, Henan province. Hualan Biological Bacterin Co., Ltd is a subsidiary company of Hualan Biological Engineering Inc. It is mainly specialized in research, development and manufacturing of vaccines. Currently, the site is authorized for Preventative biologics (Influenza Vaccine (Split Virion), Inactivated; Influenza Vaccine (Split Virion), Inactivated Quadrivalent; Group ACY and W135 Meningococcal Polysaccharide Vaccine; Group A and C Meningococcal Polysaccharide Vaccine; Recombinant Hepatitis B Vaccine (Hansenula Polymorpha); Influenza A (H1N1) Vaccine, (Split, Inactivated); Absorbed Tetanus Vaccine; Rabies Vaccine (Vero Cell) for Human Use, Freeze-dried; H7N9 Influenza Vaccine, (Split Virion), Inactivated; H7N9 Influenza Vaccine, Inactivated; Pandemic Influenza Vaccine for Human Use (Split); Meningococcal Group ACY and W135 Conjugate Vaccine; Meningococcal Group A and C Conjugate Vaccine; Diphtheria, Tetanus and Acellular Pertussis Combined Vaccine, Absorbed; Acellular Diphtheria, Tetanus Pertussis, and Haemophilus Influenza Type b Combined Vaccine; Haemophilus Influenza Type b Conjugate Vaccine; Purified JE Vaccine (Vero Cell); HFMD (CA16) Vaccine (Vero Cell), Inactivated, Absorbed; HFMD (EV71) Vaccine (Vero Cell), Inactivated, Absorbed; HFMD (EV71, CA16) Vaccine (Vero Cell), Inactivated, Bivalent; Pneumococcal Vaccine Polyvalent; Pneumococcal Conjugate Vaccine Polyvalent; Measles Vaccine, Live; Rubella Vaccine, Live; Mumps Vaccine, Live; Varicella Virus Vaccine, Live;); Therapeutic biologics (Therapeutic Botulinum Toxin)

	were manufactured by the company. The Company currently has 6 products marketed, which are: the Influenza Vaccine (Split Virion), Inactivated, the Influenza Vaccine (Split Virion), Inactivated, the Quadrivalent; Group ACY and W135 Meningococcal Polysaccharide Vaccine, the Group A and C Meningococcal Polysaccharide Vaccine, the Recombinant Hepatitis B Vaccine (Hansenula Polymorpha), and the Influenza A (H1N1) Vaccine, (Split, Inactivated). Three products were applied for production, they were the Rabies Vaccine (Vero Cell) for Human Use, Freeze-dried, the Tetanus Vaccine, Absorbed and the Influenza Vaccine (Split Virion), Inactivated, the Quadrivalent. While the Group A and C Meningococcal Polysaccharide Vaccine, the Diphtheria Tetanus and Acellular Pertussis Combined Vaccine, Absorbed, etc. were under development. Influenza vaccine (Split virion, inactivated, 1 dose of 0.5ml, vial) is listed in WHO list of prequalified vaccines.
History	The history of the regulatory inspections at the site was provided in the SMF. This was a follow up inspection to deficiencies identified in 2018 when the production of Men ACYW135 vaccine was inspected for WHO prequalification. Since April 2016, the Company has received a total of 49 on-site inspections by the domestic pharmaceutical regulatory authorities of provincial and above levels and by foreign pharmaceutical regulatory authorities, which were: 27 inspections by the domestic provincial pharmaceutical regulatory authorities, 15 inspections by the national pharmaceutical regulatory authority, 3 inspections by WHO, and 4 inspections by other foreign authorities. In August 2020, the Henan Institute for Food and Drug Control conducted 4 sampling inspections against the Influenza Vaccine (Split Virion), Inactivated and the Influenza Vaccine (Split Virion), Inactivated, Quadrivalent, of which one is of the Influenza Vaccine (Split Virion), Inactivated, and 3 were of the Influenza Vaccine (Split Virion), Inactivated, Quadrivalent. All sampling inspections were qualified. A full list of inspections was provided during the inspection.
Brief report of inspection activities undertaken	
Scope and limitations	

Areas inspected	The inspection was restricted to the follow up and confirmation of CAPA submitted following the previous inspection performed in 2018 related to the manufacture of seasonal flu vaccine. During the CAPA review additionally limited aspects of the following activities were reviewed.
	• Quality system elements including;
	  o Data integrity systems and policies
	  o Change Control
	  o Investigations and deviations
	  o CAPA management and closure
	  o QRM and the contamination control strategy (CCS)
	• Production process from virus seeds preparation to final bulk preparation of Influenza Vaccine (Split Virion), Inactivated
	• Sterile filtration, filling, visual inspection, and packaging of final bulk
	• Recent aseptic process validations including MFTs, sterilizer and tunnel re-validations
	• Testing of raw materials, packaging materials and finished products and quality control of some intermediate products.

	• Quality control of Influenza Vaccine (Split Virion), Inactivated from virus seeds to final bulk, raw materials and excipients, packaging material acceptance and sampling of raw materials and excipients, delivery of finished products.
Restrictions	There was no commercial lot manufacturing or filling activity for Influenza vaccine in vial presentation during the inspection week, the seasonal filling having been completed for the year. The manufacturing activities were therefore, limited to the filling of a demonstration engineering run of water in vials. Only limited buildings and associated activities directly related to CAPA review and Flu production were therefore inspected. The supported utilities were not physically visited. The animal house was not inspected. The QC laboratory was not physical inspected, and inspection of QC activities was restricted only to data review reports and trending present in the PQR. The production of Men ACYW135 vaccine was not inspected as the company had withdrawn its application for PQ of this vaccine following the previous inspection.
Out of scope	The inspection was limited to Trivalent Influenza Vaccine (Split Virion), Inactivated vaccine in 1 dose vial presentation and did not include any other presentation or other vaccine or other activity.
Vaccines covered by the inspection	Influenza Vaccine (Split Virion), Inactivated:

Abbreviations

AHU	Air Handling Unit
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
APR	Annual Product Review
APS	Aseptic Process Simulation
BMR	Batch Manufacturing Record
BPR	Batch Production Record
CA	Compressed Air
CAPA	Corrective Actions and Preventive Actions
CC	Change Control
CFU	Colony-Forming Unit
CIP	Cleaning In Place
CoA	Certificate of Analysis
CpK	Process capability
DQ	Design Qualification
D-U-N-S	Data Universal Numbering System
EDI	Electronic De-Ionization
EM	Environmental Monitoring
FMEA	Failure Modes and Effects Analysis
FTA	Fault Tree Analysis
GMP	Good Manufacturing Practices
GPS	Global Positioning System
GPT	Growth Promotion Test
H	Hour(s)
HEPA	High Efficiency Particulate Air
HVAC	Heating, Ventilation and Air Conditioning
IQ	Installation Qualification
LAF	Laminar Air Flow
LIMS	Laboratory Information Management System
MB	Microbiology

MBL	Microbiology Laboratory
MEN	Meningococcal
MF	Master Formulae
MFT	Media Fill Test
MR	Management Review
MSL	Master Seed Lot
NCA	National Control Authority
NCL	National Control Laboratory
NRA	National Regulatory Agency
OQ	Operational Qualification
PHA	Process Hazard Analysis
pH	(-ve) logarithm of H^+ concentration
PIVI	Program for Influenza Vaccine Initiative
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
SH	Single Harvest
SIP	Sterilization In Place
SMF	Site Master File
SOP	Standard Operating Procedure
UN	United Nations
UNICEF	United Nations Children's Fund
URS	User Requirements Specifications
UV	Ultraviolet-Visible Spectrophotometer
VVM	Vaccine Vial Monitor
WFI	Water for Injection
WGS	World Geodetic System
WHO	World Health Organization
WSL	Working Seed Lot

Part 2	*Brief summary of the findings and comments*

Introductory section on the inspection process and approach used.

The inspection began with an opening meeting on the 18th of October. Prior to the meeting the company was sent a detailed agenda for the inspection and was requested to provide documentation (site master file, product quality reviews (2019 and 2020), list of batches produced since the start of the year and their status, procedures for recall, complaints, change control, deviations, etc.) for desk review.

The inspection was completed on Friday, 22nd October with a close-out meeting with the staff of the company.

The inspection covered limited parts of the following systems relevant to the review of critical and major deficiencies reported at the previous inspection:

- Pharmaceutical quality system
- Production system
- Facilities and equipment system
- Laboratory control system
- Materials,
- Packaging and labelling system

The following list of documents were reviewed during the inspection:

- Quality management system of Hualan PPT
- Layout Diagram of personnel Material Production Waste Flow in Filling Area II
- Layout Diagram of Production Equipment in Filling Area II
- CAPA for 2018 WHO Inspection
- Management Procedure for Paper Data
- Management Procedure for Electronic Data
- Management Procedure for Filling out Record
- Batch Production Record of Formulation of Filling Line X and Y
- Training PPT of Data Integrity
- Training Record (SOP for Computerized System and Equipment)
- Examination Papers of New Employees – Production
- Pictures of Signature Wall of Quality Awareness Week
- Publicity Pictures of Quality Awareness Week
- Management Procedure for Deviation Management
- Standard Operating Procedure for Deviation Handling
- Validation Protocol of APS for Influenza Vaccine (Split, Virion), Inactivated, Quadrivalent of Filling Line X
- Standard Operating Procedure for Incident Handling
- List of Incident in 2020 and 2021
- Specification of WFI
- Specification of Pure Steam
- SOP of Water Sampling
- SOP of Pure Steam Testing
- Contamination Control Strategy of Influenza Vaccine
- Risk Assessment Report on Contamination Control Strategy of Influenza Vaccine (Split Virion), Inactivated
- Risk Assessment of Particle Contamination in Production Line X of Influenza Monovalent Bulk
- SOP of Materials in and out of Production Area of Vaccine Section X Workshop Y
- Pharmacopoeia of the People's Republic of China Volume II (2020 Edition)
- SOP for Use and Maintenance of EMS of HVAC System in Filling Area X

- Manufacturing process flow chart
- Specification of In-Process Control of Influenza Vaccine (Split Virion), Inactivated
- Qualification Protocol of Vial Visual Inspection Machine
- Qualification Report of Vial Visual Inspection Machine
- SOP for Visual Inspection Accuracy Test
- Management Procedure of Rejected Reference Standards for Visual Inspection
- Guidance of GMP for Drug-Sterile Products
- Qualification Report of Personnel Qualification for Visual Inspection
- SOP for Sampling and Testing for AQL of Product Visual Inspection
- Re-qualification Report of Tunnel Oven
- SOP for Use and Maintenance of Vial Washing Machine and Tunnel Oven
- Equipment (Instrument) Log (Tunnel Oven)
- Batch Production Record of Filling of Filling Line X (Vial Washing)
- Qualification Report for Visual Inspection Personnel Qualification of Media Fill Test
- Management Procedure for Validation Document
- SOP for Air Pattern Test
- SOP for Aseptic Process Simulation Test (Preparation
- SOP for Cleaning and Disinfection of Cleaning Area in Vaccine Section X During the Period of Shutdown and Changeover
- SOP for Cleaning and Disinfection of Grade A/B Cleaning Area
- SOP for Cleaning and Disinfection of Shutdown and Campaign Production in Filling & Packaging Center
- Video for the Air Pattern when Opening the Door of Autoclave in Post-sterilization Room
- SOP for Use and Maintenance of Autoclave in Filling Area X
- SOP for Use and Maintenance of Vials Washer and Tunnel Oven
- SOP for Using and Testing of Filter Materials
- Equipment Log of Integrity Tester
- Management Procedure for Filter Materials
- Analysis Report of Failure Rate of Filter Element Test
- Review Record for Audit Trail of Integrity Tester by QA Department
- Release Form of Finished Products
- Statistical Analysis Report for Integrity Test Data of Filter Element in Production Department
- List of Brief Information on Deviation and CAPA
- PPT of Moist Heat Sterilization
- Performance Qualification Report of Pulsating Vacuum Sterilizer in Vaccine Section X and Workshop Y
- Batch Production Record of Packaging Line X (Labelling）
- Standard Operating Procedure for Product Release
- Management Procedure for Record Review
- Product Quality Review and Analysis Report of Influenza Vaccine (Split Virion), Inactivated in 2020
- Management Procedure for Review and Analysis
- CAPA for the improvement and preventive measures proposed in “Product Quality Review and Analysis Report in 2019” of the QA Department on influenza vaccines
- Secondary Packaging Material Release Sheet
- Materials Inspection Receipt
- Standard Operating Procedure for Rubber Plug Test
- Specification of Rubber Stopper
- Material Release Sheet
- Factory inspection report of Hubei Huaqiang, brominated butyl rubber stopper

The following buildings, manufacturing and testing rooms were observed either directly or remotely during the inspection:

- Vaccine Department
- Filling and Packaging Department
- Quality Assurance

1. Quality management system

An overall structure of quality management system was in place with adequate resources. The Quality assurance and quality control activities were independent from the production unit. Managerial responsibilities were specified in job descriptions. Production and control operations were specified in master formula, SOPs, batch records etc. Broadly the elements of the pharmaceutical quality system were of an acceptable level of maturity however some aspects still varied in their maturity and need further attention and improvement.

Deviation and Investigation management:

The company has established Management Procedure for Deviation Management and SOP for Deviation Handling. Both procedures had been revised and reissued shortly before the inspection. There was also a related document entitled Standard Operating Procedure for Incident Handling. These together with the summary lists of deviations and incidents for 2020 and 2021 to date were provided for review.

A number of deviation documentation was reviewed.

CAPA:

SOP and CAPA register for 2020 and 2021 were provided and checked.

Product Quality Review:

PQRs for TIV for 2019 and 2020 were provided prior to the inspection and Product Quality Review and Analysis Report of Influenza Vaccine (Split Virion), Inactivated in 2020 was reviewed off-site. These were generally of a good standard and had critique of the process performance and identified potential opportunities.

Quality risk management QRM and the Contamination Control Strategy (CCS):

The company was in the process of more fully implementing Quality Risk Management principles into its GMP system and process development of operations. The implementation was moderately mature. The following tools were considered for the QRM flow diagram - fishbone diagram, failure mode and effects analysis (FMEA), failure mode effects and criticality analysis (FMECA), hazard analysis and critical control point (HACCP).

A number of QRM documentation was reviewed.

Management review:

Quality management review was in place as per Management Procedure for Record Review. The procedures included the plan, protocol, report, team and the frequency of management review meeting.
In addition, CAPA for the improvement and preventive measures proposed in “Product Quality Review and Analysis Report in 2019” of the QA Department on influenza vaccines was available and spot checked.

Data Integrity:

Updated policies and systems were in place.

Documentation:
Procedures for the documentation management were in place. The production activities were recorded in respective records in forms of batch manufacturing records, equipment logbook and/or general control records. Procedures, operating conditions and specifications related to the manufacturing processes were established. The quality control activities were recorded in respective records including laboratory control records, equipment logbooks and general control records. Procedures, operating conditions and specifications related to the quality control activities were established.

The procedures and work instructions could be revised at any time if needed but the review process was five years which was found to be long period. The reasons for review or revisions of the procedures and documents have to be clearly incorporated in the relevant SOPs and management procedure.

Batch release process:
The QA representatives review the batch production records, batch packaging records, batch test records and verify the lot release certificate (issued by the NIFDC). The company submits samples and a summary manufacturing protocol to NIFDC for the official batch release. The qualified person (QP) reviews, sign and release the final products.

Contract production, analysis and other activities And Quality agreements:
There was no contract manufacturing for vaccines. Provisions for contract testing were in place. The National Institutes for Food and Drug Control (NIFDC) was subcontracted by Hualan to carry out the tests for adventitious avian leukosis virus and avian adenovirus of the master seed lot used for the manufacturing of Influenza Vaccine (Split virion), Inactivated.

Personnel:
Organizational charts showing the relationships between different departments, including QA, Production, QC, Warehouse and Engineering with identification of the key personnel were provided. Curricula vitae and the job responsibilities for key personnel, with qualification, experience and responsibility were provided.

Training:
The procedures for the personnel training and qualification were in place. The training procedures with the records of induction and annual training were spot checked for production operators.
Training records for aseptic operators in charge of aseptic filling operations and the inspection qualification were spot checked.

Response and CAPA Implementation to the 2018 inspection:
CAPA for 2018 WHO Inspection version was reviewed and spot checked.

2. Production system
In general terms, resources were available, including qualified and trained personnel, premises, equipment and services, materials, containers and labels, procedures and instructions, laboratories and equipment for in-process and other controls. Manufacturing processes were generally defined and reviewed. Instructions and procedures were generally available. Qualification and validation of equipment, manufacturing processes and quality control testing methods were in place. Operators were instructed to carry out procedures, and records were made for the production operations.

Harvest & manufacture of monovalent bulks:
This process was only spot checked during this inspection primarily using the PQR records.
The upstream manufacturing process from harvesting of the embryos to production of monovalent bulks of each viral strain has been validated and the process description in company documents (validation report and batch manufacturing records) essentially corresponds to that in the Product Summary File (PSF) submitted to WHO.
In-process controls have been implemented at each stage, which ensure that the manufacturing process produce intermediates and monovalent bulks of consistent quality.

Holding periods have been defined for intermediate products that were isolated

Manufacture of Final Bulk Product:
The final bulk was made up of a mixture of the three monovalent bulks diluted with PBS. The monovalent bulks, after removal from storage, were transferred to a preparation tank by means of a peristaltic pump, diluted with PBS and mixed.

Filling:
Batch Production Record of Formulation of Filling was provided and reviewed offline. The process was compared with that in Validation Protocol of APS for Influenza Vaccine (Split, Virion), Inactivated, Quadrivalent.

The media simulation records, automatic and manual inspection systems as well as the operation SOP for Use and Maintenance of Vials Washer and Tunnel Oven and associated validation of the Bosch washing and hot air sterilisation tunnel were reviewed.
After vials were filled, they were stoppered with rubber stoppers. A camera checks whether stoppers were correctly positioned on the vials were in place.

Automatic visual inspection:
The company used Automatic Inspection machine for Influenza Vaccine (Split Virion), Inactivated, where they were subjected to a 100% automatic inspection.

Manual visual inspection:
An AQL procedure was in place for manual inspection of qualified vials A sample of vials, which passed automatic inspection, will be manually inspected to confirm the proper functioning of the automatic inspection machine. It was stated that size of the sample was determined by the National Standards Table (GB/T 2828.1 – 2003). The validation of both the automatic and manual inspection and the allocation of quality factors to the test vials was discussed at length.

3. Facilities and equipment system
The premises were generally maintained at an acceptable level of cleanliness. The company had provisions for personal hygiene and sanitation in its production facility. Manufacturing areas were provided with airlocks for personnel and materials entries and exits. Gowning procedures for access to the classified manufacturing areas were in place. Cleaning, disinfecting and decontaminating procedures along with the environmental monitoring program were in place to control the non-viable and viable contamination levels in the production areas.
The layout of the premises and the flow charts of the manufacturing areas (including personnel, products and material flows) were provided in the Site Master File and presented during the briefing meeting the first day of the inspection.
There were X buildings in the site, used as vaccine production workshop, warehouse and administration offices.

Qualification and validation:
Overall, provisions for qualification and validation were in place and covers premises, equipment, utilities and systems, processes and procedures at periodic intervals and when changes have been made. Validation and qualification protocols and reports were spot checked.

Depyrogenation tunnel:
Vial Washing Machine and Tunnel Oven of the filling line PQ was carried out yearly. HEPA filter integrity and particle monitoring were performed every 6 months.
The validation report and the associated SOP for Use and Maintenance of Vial Washing Machine and Tunnel Oven were spot checked and found generally satisfactory.

Autoclave validations:
The autoclave Performance Qualification Report of Pulsating Vacuum Sterilizer in Vaccine Section X and Workshop Y was reviewed. This autoclave was used to sterilize filling equipment used in the filling area Y.
The following documents were spot checked:
- Sterilization validation protocol
- Sterilization validation report

Fill line:
The design of the aseptic areas of TIV suite and filling machine had several design and technical limitations that have not been improved in the intervening years. Full consideration has not been given to designing and upgrading the facilities so as to fully permit observation of all critical activities from outside the clean areas.

Filter validations and use of the integrity tester and DI issues:
These issues had been resolved.

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

Laboratory controls (Building X):
The QC laboratory was divided into the general control area, sterile laboratory, microbial limit laboratory, positive control laboratory. The general control areas were mainly used for the chemical or physical tests of raw and subsidiary materials, in-process samples, intermediates, and final products. Among them, sterile laboratory was a Grade A in B area, mainly used for sterility tests; microbial limit laboratory was a Grade C area, mainly used for microbial limit tests; positive control laboratory was Grade C area, equipped with biosafety cabinet, and used for positive bacteria tests in the sterility tests.
The review of the laboratory systems was limited to the review of trend records in the PQRs and discussions regarding the controls and testing of primary packaging materials and the control of printed packaging materials.

5. Materials

Provisions for incoming materials, intermediates and finished products were in place for reception, quarantine and release processes. Appropriate storage conditions were provided. The list of key starting material from animal sources used in the manufacturing processes was reviewed and found acceptable. These were supplied from approved suppliers and subject to internal release.

The spot check review of the material control systems was limited to the review of SUS and filters and discussions regarding the controls and their specification and movements from the storage to the process areas and associated contamination control and sanitization issues.

6. Packaging and labelling system

The packaging lines were well segregated and there was adequate space for the staging of materials.

Part 3	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, **Hualan Biological Bacterin** Co., Ltd. located at **No. 1-1, Hualan Avenue, Xinxiang 453003, Henan People's Republic of China**., was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for pharmaceutical products 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.

DEFINITIONS

Critical deficiency

A *critical* deficiency may be defined as an observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

Major deficiency

A *major* deficiency may be defined as a non-critical observation that:

- has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
- indicates a major deviation from the GMP guide;
- indicates a failure to carry out satisfactory procedures for release of batches;
- indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties;
- consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

Other deficiency

A deficiency may be classified as *other* if it cannot be classified as either critical or major, but indicates a departure from GMP. A deficiency may be o*ther* either because it is judged to be minor or because there is insufficient information to classify it as major or critical.

Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of an *other* deficiency may be categorized as major

Part 4	List of GMP 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.
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. 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.
http://www.who.int/medicines/publications/44threport/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.
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.
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.
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.
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.
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.
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.
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. 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. 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. 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. 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. 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. 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. http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

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