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A WHO guide to good manufacturing practice (GMP) requirements

Part 2: Validation

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GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION
VACCINE SUPPLY AND QUALITY
GLOBAL TRAINING NETWORK

World Health Organization
Geneva
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The Global Training Network is designed for staff of National Control Authorities and selected vaccine manufacturers meeting specific entrance criteria. This document is designed for use by participants in the Global Training Network, specifically for those participating in curricula related to Good Manufacturing Practices.

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Abbreviations

EP:	European Pharmacopoeia
GMP:	Good Manufacturing Practices
MF:	Master Formulae
QA:	Quality Assurance
QC:	Quality Control
QO:	Quality Operations
SOP:	Standard Operating Procedure
TRS:	Technical Report Series (WHO publication)
USP:	United States Pharmacopoeia
WHO:	World Health Organization

1. Introduction and purpose of the guide

This guidance document has been prepared to aid vaccine manufacturers in the preparation and performance of the validation studies required by Good Manufacturing Practices (GMP) of the World Health Organization (WHO). The WHO GMP publications, other GMP Regulations/Guidelines and many publications on the concept and process of validation for pharmaceutical manufacture were consulted during preparation of the Guide. These references are listed in Appendix 3. The emphasis in this guide is on WHO requirements for validation.

The Guide presents a review of the types and extent of validations required by GMP, the preparation of a Master Validation Plan, formats for the equipment and systems qualifications and process and analytical assay validation protocols, and examples of the typical requirements for various validation studies. Validation of computerized systems is not covered in this Validation Guide.

In addition to these examples, the manufacturers who have collaborated on this Guide have contributed a list of titles of their validation documents and one has provided several actual documents as examples. These lists and examples are presented to aid manufacturers in developing the full range of validation documents and information for performance and recording data. These can be used by manufacturers as reference for preparing or revising their own validation protocols. They may also be used to assess IQ and OQ services offerred by suppliers of new equipment..

This guide for Validation is Part 2 of 2: Part 1 is a guide to Standard Operating Procedures and Master Formulae.

2. Good manufacturing practices (GMP)

WHO defines Good Manufacturing Practices (GMP) as "that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization." GMP covers all aspects of the manufacturing process: defined manufacturing process; validated critical manufacturing steps; suitable premises, storage, transport; qualified and trained production and quality control personnel; adequate laboratory facilities; approved written procedures and instructions; records to show all steps of defined procedures have been taken; full traceability of a product through batch records and distribution records; and systems for recall and investigation of complaints.

The guiding principle of GMP is that quality is built in to a product, and not just tested in to a product. Therefore, the assurance is that the product not only meets the final specifications, but that it has been made by the same procedures under the same conditions each and every time it is made. There are many ways this is controlled - validation is that part of GMP that ensures that facility systems, equipment, processes, and tests procedures are in control and therefore consistently produce quality product.

3. Validation

Validation is defined as the establishing of documented evidence which provides a high degree of assurance that a planned process will consistently perform according to the intended specified outcomes. Validation studies are performed for analytical tests, equipment, facility systems such as air, water, steam, and for processes such as the manufacturing processes, cleaning, sterilization, sterile filling, lyophilization, etc. There will be a separate validation for the lyophilizer as an equipment item and for the lyophilization process; for the cleaning of glassware and the cleaning of the facility; and for the sterilization process and for the sterility test. Every step of the process of manufacture of a drug product must be shown to perform as intended. Validation studies verify the system under test under the extremes expected during the process to prove that the system remains in control. Once the system or process has been validated, it is expected that it remains in control, provided no changes are made. In the event that modifications are made, or problems occur, or equipment is replaced or relocated, revalidation is performed. Critical equipment and processes are routinely revalidated at appropriate intervals to demonstrate that the process remains in control.

The validity of systems/equipment/tests/processes can be established by prospective, concurrent or retrospective studies. Prospective validation is data collected based on a pre-planned protocol. This is the most controlled method and is the validation approach presented in this Guide.

4. Protocols

A protocol is a written set of instructions broader in scope than a Standard Operating Procedure (SOP). SOPs are the detailed written instructions for procedures routinely performed in the course of any of the activities associated with pharmaceutical manufacturing. A protocol describes the details of a comprehensive planned study to investigate the consistent operation of new system/equipment, a new procedure, or the acceptability of a new process before it is implemented. Protocols include significant background information, explain the rationale for and the objective of the study, give a full description of the procedures to be followed, set out the parameters to be measured, describe how the results will be analyzed, and provide pre-determined acceptance criteria for making conclusions. Validation studies, stability studies, and clinical studies are examples of written protocols for pharmaceutical manufacturers. Validation protocols are important in ensuring that documented evidence is taken which demonstrates that an equipment item, a system, a process or a method consistently performs at a specified level.

5. Master validation plan

The Master Validation Plan is a document pertaining to the whole facility that describes which equipment, systems, methods and processes will be validated and when they will be validated. The document should provide the format required for each particular validation document (Installation Qualification, Operational Qualification and Performance Qualification for equipment and systems; Process Validation; Analytical Assay Validation), and indicate what information is to be contained within each document. Some equipment requires only installation and operational qualifications, and various analytical tests need to establish only some performance parameters - this must be explained in the master protocol along with some principles of how to determine which of the qualifications are required by each, and who will decide what validations will be performed.

The Master Validation Plan should also indicate why and when revalidations will be performed, either after changes or relocation of equipment or systems; changes to processes or equipment used for processing; or for changes in assay methods or in equipment used in tests.

If a new process or system is implemented, a Design Qualification (DQ) may be necessary. Guidelines for such cases should be included in the Master Validation Plan. A Design Qualification would be necessary when planning and choosing equipment or systems to ensure that components selected will have adequate capacity to function for the intended purpose, and will adequately serve the operations or functions of another piece of equipment or operation. For example: i) a water system must produce sufficient water of specified quality to serve the requirements of the facility including production, testing, and as a source for steam or for a second system producing higher quality water; ii) a steam generator must produce sufficient steam of the correct quality to fulfill all the autoclaving needs and Steam-in-Place (SIP) cleaning procedures of the facility; or iii) the equipment chosen for a particular operation must have sufficient space and access for proper cleaning operations and maintenance.

The order in which each part of the facility is validated must be addressed in the Master Validation Plan. For example the water system should be validated before validating a piece of equipment that uses this water system. The IQ, OQ and PQ must be performed in order: the master validation plan should indicate how to deal with any deviations from these qualifications, and state the time interval permitted between each validation.

6. Change control

A qualification/validation study is designed for defined parameters and measures specified outcomes. Any modifications made to equipment, systems, processes or procedures may change the parameters or affect the expected outcomes. Therefore any change that is made after initial validation is complete must be controlled. "Change control" must be a formal process following a pre-determined procedure set out in a Quality Assurance document (e.g. a QA SOP or in the Master Validation Plan). The change control procedure should include the planning and submission of a proposal for the change with a rationale and anticipated impact on the function, operation or performance. The proposal should be prepared by the department requesting the change and reviewed and approved by QA, management and other appropriate departments (change control team). The effect of the change on the specific system/process under consideration as well as the wider implication for other systems and processes of the facility. Re-validation of the system/process or other systems may be necessary depending on the significance of the change. No changes should be made for any validated, approved equipment/systems/tests/processes without formal review and approval via the change control procedure.

7. Facility systems and equipment

The validation protocols for equipment and systems are normally divided into three segments: Installation Qualification, Operational Qualification and Performance Qualification, abbreviated as IQ, OQ, PQ. For systems and equipment, Performance Qualification is often synonymous with Validation. Depending on the function and operation of some equipment, only IQ/OQ are required. For equipment whose correct operation is a sufficient indicator of its function, and that are monitored and/or calibrated on a regular schedule (e.g. pH meter, incubator, centrifuge, freezer), the installation and operational qualifications are performed. Systems such as air, water, steam, and major equipment which perform critical support processes, such as sterilization (autoclave, oven), depyrogenation (oven or tunnel), or lyophilization, require installation, operational and performance qualifications.

The following table lists the typical categories of systems and equipment which require performance qualification

Systems	Equipment
Air (HVAC)	Autoclave
Compressed air	Depyrogenation oven or tunnel
Pure Steam	Lyophilizer
Raw steam	Continuous flow centrifuge
Purified water	
WFI	
Central vacuum	

Each IQ, OQ, and PQ protocol provides the specific procedure to follow, information to be recorded, a set of acceptance criteria, and a list of materials, equipment and documents needed to perform the validation.

7.1 Installation qualification (IQ)

This document should be written for the critical processing equipment and systems that are used within the facility, e.g. an HVAC system, an autoclave or a pH meter. The IQ should list all the identification information, the location, utility requirements and any safety features of the equipment.

The IQ protocol prepared for each piece of equipment or system lists the name, description, model and identification numbers, the location, utility requirements, connections, and any safety features of the system/equipment which need to be documented. It should verify that the item matches the purchase specifications, and that all drawings, manuals, spare parts list, vendor address and contact number, and other pertinent documentation are available.

7.2 Operational qualification (OQ)

This document outlines the information required to provide evidence that all the components of a system or of a piece of equipment operate as specified. This involves testing of all normal operation controls, all alarm points, all switches and displays, interacting controls, and any other indications of operations and functions. The OQ document should provide a listing of SOPs (or reference to specific manual instructions) for operation, maintenance and calibration; information on the training of operators; and instructions for any static or dynamic tests to show that the equipment operates as expected under normal conditions. Specifications and acceptance criteria must be defined for all the operations. The OQ document should include information on equipment or system calibration, pre-operational activities, routine operations and their acceptance criteria.

7.3 Performance qualification (PQ)

This part of the validation for systems and equipment is performed after both Installation and Operational Qualifications have been completed, reviewed and approved.

The PQ document describes the procedure or procedures for demonstrating that a system or piece of equipment can consistently perform and meet required specifications under routine operation and, where appropriate, under worst case situations. The PQ should include a description of the preliminary procedures required, the detailed performance test(s) to be done, and the acceptance criteria for each test. The PQ also requires that other supporting equipment used during the qualification have been validated (e.g. the steam system must be validated before the autoclave can be validated).

8. Format for an installation qualification protocol

The following format outlines the requirements for an Installation Qualification for equipment and equipment systems. This form provides the information necessary to write an SOP titled "How to Perform an Installation Qualification".

Name of Facility: _____ **page _ of _**

Validation Protocol # _____ Installation Qualification

Title _____

_____

Protocol written by _____

Departmental Approval by _____ Date _____

QA Approval by _____ Date _____

Objective

To ensure that the system/equipment installed conforms to the purchase specifications and the manufacturers literature, and to document the information that the equipment meets specifications.

Scope

To be performed at time of installation, modification, or relocation.

Responsibility

Person overseeing the installation will perform the qualification and record the information.

The responsible engineer will verify the records and write the report.

Quality Assurance will review and approve the IQ Protocol and Report.

Validation Protocol _____ **Installation Qualification** **page** ___ **of** ___
Title _____ **Name of Facility** _____

System/Equipment _____ **Code No.** _____

a Description of the System/Equipment being installed: General description of the function and the main components.

_____

_____

_____

_____

b List of the main components

1 _____ Code # _____

2 _____ Code # _____

3 _____ Code # _____

4 _____ Code # _____

5 _____ Code # _____

6 _____ Code # _____

c Description of any required supporting utilities (piping, connections, water supply).

1 _____ Code # _____

2 _____ Code # _____

3 _____ Code # _____

4 _____ Code # _____

Procedure

Prepare a checklist for all components and parts, including spare parts according to the purchase order and manufacturers specifications.

Record the information for each actual part, component, auxiliary equipment, supporting facilities, and compare to the manufacturers specifications.

Record any deviations to the system/equipment.

Prepare a Deviation Report including the justification of acceptance and impact on the function..

Prepare an Installation Qualification Report: This should include date study initiated; date completed; observations made; problems encountered; completeness of information collected; summary of deviation report; results of any tests; sample data if appropriate; location of original data; other information relevant to the study; and conclusions on the validity of the installation.

Submit the report to QA for review and approval.

Checklist for Component Number _____ Name _____ Code # _____

Component Function: _____

_____

		Required/ Ordered	Actual	Deviations
1	**Model/Serial number**			
2	Specifications			
3	Manual/Booklet			
4	Drawings			
5	Wiring/cabling			
6	Power, fusing			
7	Operation SOPMaintenance SOP Calibration SOP(or from manual)			
8	Input/output controls			
9	Environmental requirements			
10	Test equipment or instruments			
11	Utilities and services			
12	Spare parts list, part numbers and supplier			
13	Other			

(2-01)

Performed by: _____ **Date** _____

Deviations: _____

Verified by: _____ **Date** _____

Validation Protocol _____	Installation Qualification	page ___ of ___
Title _____	Name of Facility _____	

Deviation Report

Deviation(s):

Justification for acceptance:

Impact on operation:

Report Written by: _____ **Date** _____

Installation Qualification Report

Results:

Conclusions

Report Written by: _____ **Date** _____

QA approved by: _____ **Date** _____

9. Format for an operational qualification protocol

The following format outlines the requirements for an Operational Qualification for equipment and equipment systems. This form provides the information necessary to write an SOP titled "How to Perform an Operational Qualification".

Name of Facility:_____ **page _ of _**

Validation Protocol # _____ Operational Qualification

Title _____

_____

Protocol written by _____

Departmental Approval by _____ Date _____

QA Approval by _____ Date _____

Objective

To determine that the system/equipment operates according to specifications, and to record all relevant information and data to demonstrate it functions as expected.

Scope

To be performed after installation, modification or relocation, after the Installation Qualification has been completed.

Responsibility

Person responsible for operating the system/equipment will perform the qualification and record the information.

The supervisor will supervise the study, verify the completion of the records, write the deviation report and the Operational Qualification Report.

Quality Assurance will review and approve the OQ Protocol and Report.

Materials, Equipment, Documents

List of calibration equipment required (Chart 1)

Materials or supplies needed to perform the Operational Qualification

1 _____ Code # _____

2 _____ Code # _____

3 _____ Code # _____

4 _____ Code # _____

5 _____ Code # _____

6 _____ Code # _____

SOPs and datasheets for normal operations of the system under test (Chart 2).

Training records documenting that operators have been trained (Chart 2).

Manuals for equipment (Chart 2).

Procedure

Test and record calibration data for calibrating apparatus and instruments (Chart 1).

Test and record operative condition of control points and alarms (Chart 3).

Test and record outputs (Chart 4)

List of calibration requirements for the system under test and records of the calibration of the system (Chart 5).

Measure and record the results of specific challenge to the system in normal and worst case situation where appropriate (Chart 6).

Record any deviations to the procedures performed.

Prepare a Deviation Report including the justification of acceptance and impact on the operation.

Prepare an Operational Qualification Report: This should include date study initiated; date completed; observations made; problems encountered; completeness of information collected; summary of deviation report; results of control/alarm tests; sample data if appropriate; location of original data; other information relevant to the study; and conclusions on the validity of the equipment/system operations.

Submit to QA for review and approval.

Validation Protocol _____ **Operational Qualification** **page** ___ **of** ___
Title _____ **Name of Facility** _____

Preparation

Chart 1: Calibrating apparatus and instruments.

Apparatus/Instrument	Calibration method	Calibration date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Performed by: _____ **Date** _____

Deviations: _____

_____

_____

Verified by: _____ **Date** _____

Preparation

Chart 2: Document check

SOP Title and number	File Location	QA/QC approval date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Training Records

Course on SOP #	Staff name	Date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Equipment Make and Model	Manual Available
_____	Y [ ] N [ ]
_____	Y [ ] N [ ]
_____	Y [ ] N [ ]

Performed by: _____ **Date** _____

Deviations: _____

_____

_____

Verified by: _____ **Date** _____

Results

Chart 3: Control points and alarms.

Control point/Alarm	Results	Date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Performed by: _____ **Date** _____

Deviations: _____

_____

_____

Verified by: _____ **Date** _____

Results

Chart 4: Outputs

Outputs	Results	Date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Performed by: _____ **Date** _____

Deviations: _____

_____

_____

Verified by: _____ **Date** _____

Chart 5: Calibration of Equipment/System

Calibration SOP (short title and #)	Result	Date

Performed by: _____ **Date** _____

Deviations: _____

_____

_____

Verified by: _____ **Date** _____

Chart 6: Specific challenge of the equipment or system

Test in normal conditions:

Test of worst case situation:
(e.g. start-up after shutdown, temperature recovery time, centrifuge imbalance)

Performed by: _____ **Date** _____

Deviations: _____

_____

_____

Verified by: _____ **Date** _____

Validation Protocol _____	Operational Qualification	page ___ of ___
Title _____	Name of Facility _____	

Deviation Report

Deviation(s):

Justification for acceptance:

Impact on operation:

Written by: _____ **Date** _____

Operational Qualification Report

Results:

Conclusions:

Written by: _____ **Date** _____

QA approved by: _____ **Date** _____

10. Format for a performance qualification protocol

The following format outlines the requirements for a Performance Qualification for equipment and equipment systems. This form provides the information necessary to write an SOP titled "How to Perform a Performance Qualification".

Name of Facility:_____ **page _ of _**

Validation Protocol # _____ Performance Qualification

Title _____

_____

Protocol written by _____

Departmental Approval by _____ Date _____

QA Approval by _____ Date _____

Objective

To determine that the systems/equipment perform as intended by repeatedly running the system on its intended schedules and recording all relevant information and data. Results must demonstrate that performance consistently meets pre-determined specifications under normal conditions, and where appropriate for worst case situations.

Scope

To be performed after the Installation and Operational Qualification have been completed and approved.

To be performed after installation, modification or relocation and for re-validation at appropriate intervals.

Each piece of equipment must be validated before it serves another piece of equipment/system during validation of the latter (e.g. water system before steam generator; steam generator before autoclave).

Responsibility

Person responsible for operating the system or equipment will perform the qualification and record the information.

The supervisor will supervise the study, verify the completion of the records and write the Deviation Report and the Performance Qualification Report.

Quality Assurance will review and approve the Performance Qualification Protocol and Report.

Materials, Equipment, Documents

SOPs for normal operations of the equipment or system under test (including data record forms, charts, diagrams materials and equipment needed). Attach copies.

SOP list:

_____

_____

_____

_____

_____

_____

SOPs specific for performance tests (including data record forms, charts, diagrams, materials and equipment needed, calculations and statistical analyses to be performed, and pre-determined specifications and acceptance criteria). Attach copies.

SOP list:

_____

_____

_____

_____

_____

_____

Procedure

Equipment: Run normal procedure three times for each use (configuration or load) and record all required data and any deviations to the procedure.

Systems: Run for 20 consecutive working days, recording all required data and any deviations to the procedure.

Prepare the Summary Data Record Form (Chart 1)

Evaluation

Attach all completed, signed data record forms.

Complete the Summary Data Record Form (Chart 1)

Perform all required calculations and statistical analyses (Chart 2).

Compare to acceptance criteria (Chart 3).

Prepare Deviation Report including the justification of acceptance and impact on the performance.

Prepare a Performance Qualification Report: This should include: date study initiated; date completed; observations made; problems encountered; completeness of information collected; summary of deviation report; results of any tests; do results meet acceptance criteria; location of original data; other information relevant to the study; and conclusions on the validity of the equipment/system.

Submit Performance Qualification Document to QA for review and approval.

Validation Protocol _____	Performance Qualification	page ___ of ___
Title _____	Name of Facility _____	

Chart 1: Summary Data Record (To be prepared for the specific procedure on test)

Performed by: _____ **Date** _____

Verified by: _____ **Date** _____

Validation Protocol _____ Performance Qualification page ___ of ___ Title _____ Name of Facility _____
Chart 2: Calculations and Statistical Analyses
Performed by: _____ **Date** _____ **Verified by:** _____ **Date** _____

Chart 3: Acceptance Criteria vs. Performance Test Results

Criteria	Results	Pass/Fail

Performed by: _____ **Date** _____

Verified by: _____ **Date** _____

Validation Protocol _____ Performance Qualification page ___ of ___ Title _____ Name of Facility _____
Deviation Report Deviation(s): Justification for acceptance: Impact on operation, function or process:
Written by: _____ **Date** _____ **Verified by:** _____ **Date** _____

Performance Qualification Report

Results:

Conclusions:

Written by: _____ **Date** _____

Verified by: _____ **Date** _____

11. Systems and equipment: examples of IQ, OQ, and PQ protocols

11.1 System: heating, ventilation, air conditioning (HVAC) IQ, OQ, PQ

HVAC IQ

Objective

To demonstrate that the HVAC system installed in building ___, made up of ____ Air Handling Units models # _____ conforms to the purchase specifications and the manufacturers literature, and to document the information that the equipment meets specifications.

Scope

For new installation, modification, replacement, or relocation of any component of the HVAC system.

Responsibility

Facility engineer is responsible for writing the protocol, supervising the performance of the IQ, verifying the data and writing the IQ report.

QA is responsible for approving the protocol and reviewing and approving the data and conclusions.

System/Equipment

Air Handling Units

a) Description:

For each Air Handling Unit (AHU) installed, describe the units and prepare a list of the units, the rooms and quality of air they supply is entered in an HVAC room matrix:

HVAC IQ (continued)

	Room No. 1	Room No. 2	Room No. 3
Room Name			
AHU No.			
Class			
Area (sq. ft.)			
Height			
ST. Pressure (In. WG)			
Temp. (+/- 2 C)			
Humidity RH (%)			
Process Exhaust (cfm)			
Pressure Exhaust (cfm)			
Supply Air Flow (cfm)			
Rm. Ave. Velocity			
Air Changes AC/HR +/- 20%			

b) Typical components for each AHU are:

1) supply fan

2) prefilter

3) reheat coil

4) cooling coil

5) HEPA filters at the diffusers.

c) Describe any required supporting utilities: electrical, water, air inlets, etc.

Procedure

For each AHU, fill in the prepared checklist with the detailed mechanical and electrical specifications, drawings, etc. (as itemized in the IQ format) for each component as listed in the IQ format.

The individual component checklist includes a space to record the information plus any deviations found during the installation check.

Reporting

Responsible person verifies that the information is complete, prepares the deviation report and the Installation Qualification Report and, submits to QA.

HVAC OQ

Objective

To determine that the HVAC model # ____ operates according to specifications, and to record all relevant information and data to demonstrate it functions as expected.

Scope

To be performed after IQ has been completed and approved.

a) For new installation, modification, replacement, or relocation of any component of the HVAC system.

b) Annual re-validation

c) If there is a contamination problem.

Responsibility

Facility engineer is responsible for writing the protocol, supervising the performance of the OQ, verifying the data and writing the OQ report.

QA is responsible for approving the protocol and reviewing and approving the data and conclusions.

Materials, Equipment and Documents

a) Examples of calibration equipment required are: humidity probes, temperature probes, static pressure probes.

b) List any materials needed to perform any of the operation functions

c) Examples of the SOPs that will be needed.
   SOP# ___: Operation and Maintenance of the Air Handling Units
   SOP# ___: Calibration of Temperature Probe
   SOP# ___: Calibration of Humidity Probe
   SOP# ___: Calibration of Static Pressure Probe

d) Training records for personnel operating and maintaining the Air Handling Units

e) Manuals for the components of the systems.

Procedure:

Typical critical instrumentation for calibration: differential static pressure sensors, temperature sensors, humidity sensors, pressure sensors for HEPA filters and prefilters.

Typical control points to be checked are: on/off and modulation, and restarts checked for all supply fans, dampers, airflow switches, electric heaters, emergency power sequence, solenoid valves, temperature control.

Typical alarm points to be checked are: temperature high/low alarm, smoke detector shut-down and alarm, air flow switch control and alarm, and humidity high/low alarm.

HVAC OQ Continued

OQ testing of the full system should test and challenge the operation of the Air Handling Units measuring all the outputs of the integrated system.

If the system is computer controlled, OQ testing must include the computer control and manual override.

All information and data acquired must be recorded in the OQ charts.

Reporting

Responsible person verifies that the information is complete, prepares the deviation report and the Operational Qualification Report and, submits to QA for review and approval.

HVAC PQ

Objective

To determine that the HVAC systems model # _____ perform as intended by running the system as-built, at rest, and operational, for 20 consecutive working days each and monitoring and recording all relevant information and data. Results must demonstrate that performance consistently meets pre-determined specifications under normal conditions, and where appropriate for worst case situations.

Scope

To be performed after the OQ has been completed and approved. Any equipment or system serving this HVAC system must be fully validated before HVAC validation begins.

a) For new installation, modification, replacement, or relocation of any component of the HVAC system.

b) Annual re-validation

c) If there is a contamination problem.

Responsibility

Facility engineer is responsible for writing the protocol, supervising the performance of the PQ, verifying the data and writing the PQ report.

QA is responsible for approving the protocol and reviewing and approving the data and conclusions and for scheduling re-validations

Materials, Equipment and Documents

Materials required are all the items which will be routinely used to test air quality for particulates and microbial counts, the manual operations or computer-programme controlling the facility temperature, humidity, airflow, make-up air, etc.

Documented calibration is required before using the following to measure the facility air:

Micromanometer or Differential Pressure Gauge
Thermal Anemometer
Vane-type Anemometer
Micro-ohmmeter with Airflow Hood
Particle Counter
Microbiological Air Sampler and Media plates

Charts for the time, temperature and pressure recording.

SOPs for each test method, for the operation and calibrations of the equipment used, the data to be recorded, and the criteria for acceptance must be prepared and approved before beginning the performance qualification.

Reference Documents:

IES: Contamination Control Division Recommended Practice 006.2 Testing Cleanrooms.
IES: Contamination Control Division Recommended Practice 023.1 Microorganisms in Cleanrooms.
WHO: Good Manufacturing Practices for Pharmaceutical Products. TRS 823 Annex 1, 1992.

HVAC PQ, continued

Procedure

In this third part of the HVAC validation, tests are performed to show that the air quality meets the specifications for particulates, temperature, humidity, microbial counts, lighting levels, etc. for the specification and classification of each room.

PQ is performed on the facility in three different stages:

"As-built" (no equipment, no personnel)
"At-rest" (equipped but no operations and no personnel)
"Operational" (with personnel, equipment operations)

The following list of tests (except microbial counts) for Air Quality Validation is extracted from the Institute of Environmental Sciences Document: Contamination Control Division Recommended Practice 006.2 Testing Cleanrooms. This document also describes the methods for each test.

Microbial counting methods are described in the Institute of Environmental Sciences Document: Contamination Control Division Recommended Practice 023.1 Microorganisms in Cleanrooms. Microbial counts are performed at the "at-rest" and "operational" stages of performance validation.

The requirements for particulates and microbial counts in air in cleanrooms is extracted from WHO GMP Guidelines TRS 823.

All data is to be recorded on data record forms prepared for the SOPs for each test performed.

A successful performance qualification requires consistent results within specifications for 20 consecutive working days for each of the three stages (as-built, at rest, operational).

Reporting

Responsible person verifies that the information is complete, prepares the deviation report and the Performance Qualification Report and submits to QA for review and approval.

HVAC PQ, continued

Table of air cleanliness classifications from WHO TRS 823. (Ref: 39)

(pasted in, not available in electronic format)

HVAC PQ, continued

Table of Proposed Air classifications and Air and Surface Microbial Limits. PDA Letter (Ref: 23)*

(pasted in, not available in electronic format)

*Source: Regulatory and Industry News, PDA Letter, January 1996.

HVAC PQ, continued

Table of Recommended Tests by Cleanroom Type (IES). (Ref:17)

(pasted in, not available in electronic format)

11.2 Large equipment: Autoclave IQ, OQ, PQ

AUTOCLAVE IQ

Objective

To demonstrate that the Autoclave manufactured by ____, model # _____ and accessories installed in building ____, room ___ conforms to the purchase specifications and the manufacturers literature, and to document the information that the equipment meets specifications.

Scope

For new installation, modification, replacement, or relocation of any critical component of the autoclave.

Responsibility

Supervisor of the Department where the autoclave is located is responsible for writing the protocol, supervising the performance of the IQ, verifying the data and writing the IQ report.

QA is responsible for approving the protocol and reviewing and approving the data and conclusions.

Systems/Equipment

Give a brief description of the autoclave indicating the manufacturer and model name/number, where it is located, what materials it will be sterilizing, any accessories that accompany it (e.g. carts) and provide a short description of how the autoclave functions.

Component List

Typical major components associated with autoclaves are:

> autoclave chamber, baffles, shell insulation, frame, doors, door seals, temperature detectors and probes (RTDs), temperature recording chart, safety valves, vacuum pump, side door motor, sterilization cart, pressure transmitters and gauges, microcomputer control, chamber high water sensor .

Procedure

Fill in the prepared checklists with the detailed mechanical and electrical specifications, drawings, etc. (as itemized in the IQ format) for each component as listed in the IQ format.

The individual component checklist includes a space to record the information plus any deviations found during the installation check.

Reporting

Responsible person verifies that the information is complete, prepares the Deviation Report and the Installation Qualification Report and, submits to QA for review and approval.

AUTOCLAVE OQ

Objective

To determine that the autoclave model # _____ , installed in building ___, room ___ operates according to specifications, to determine the heat /steam distribution in the jacket and empty chamber and to record all relevant information and data to demonstrate it functions as expected.

Scope

a) For new installation, modification, replacement, or relocation of any critical component of the autoclave.

b) If there is a contamination problem.

To be performed after the IQ has been completed and approved.

Responsibility

Supervisor of the Department where the autoclave is located is responsible for writing the protocol, supervising the performance of the OQ, verifying the data and writing the OQ report.

QA is responsible for approving the protocol and reviewing and approving the data and conclusions.

Equipment and Documents

Example of calibration instruments required are:

thermocouples, pressure calibrator, vacuum calibrator, temperature detectors and probes, timers, temperature bath, flow meters. (Certification methods should be referenced)

SOP# ___: Operation, Maintenance, and Calibration of the Autoclave

Training records for personnel operating and maintaining the autoclave.

The calibrating instruments must be certified before being used for calibrating the autoclave.

Procedure:

Typical critical parts of the autoclave to be calibrated are:

temperature sensors, pressure sensors, pressure gauges, pressure switches, pressure transmitters and input/output transmitter.

Typical alarm points to be checked on the autoclave are:

under or over temperature, evacuation too long, sterilization too long, vacuum system failure, door open, failure reading temperature or pressure or both, failure reading load, pressure in chamber with door unsealed, chamber flooded, insufficient vacuum level to perform leak test, low battery,

Proceed with the testing of the functions of the autoclave.

Autoclave OQ continued

Typical OQ tests (specific approved SOPs are required for each test, and specific locations for thermocouples must be pre-determined):

Chamber seal integrity,
vibration of blowers and motors,
door interlock functions,
pressure leak test,
complete residual air removal test (DART),
3 heat distribution studies: (maps the heat distribution in the empty chamber)
3 jacket mapping studies: (demonstrates even heating of the jacket)
determination of the location of any cold spots for the PQ studies.

Reporting

Responsible person verifies that the information is complete, prepares the Deviation Report and the Operational Qualification Report and, submits to QA for review and approval.

AUTOCLAVE PQ

Objective

To determine that the autoclave model # _____ installed in building ___, room ___ performs as intended by repeatedly running the equipment on its intended schedules and recording all relevant information and data for temperature distribution studies and load configurations which will be tested and challenged. Results must demonstrate that performance consistently meets pre-determined specifications under normal conditions, and where appropriate for worst case situations.

Scope

To be performed after the OQ has been performed and approved.

a) For new installation, modification, replacement, or relocation of any critical component of the autoclave.
b) For re-validation.
c) For each additional load configuration.
d) If there is a contamination problem.

Responsibility

Supervisor of the Department where the autoclave is located is responsible for writing the protocol, supervising the performance of the PQ, verifying the data and writing the PQ report.

QA is responsible for approving the protocol, reviewing and approving the data and conclusions and for scheduling re-validations.

Materials, Equipment and Documents

Materials required are all the items which will be routinely sterilized in the autoclave for use in the production process:

glassware, garments, bottles of liquids, tubing, syringes, tubes, filters, wrapping, containers, etc. All items should be wrapped or in the containers that are used to hold these items during the autoclaving process.

Charts for the time, temperature and pressure recording.

Diagrams of the thermocouple locations for each test.

SOPs for each test method, data to be recorded, and the criteria for acceptance must be prepared and approved before beginning the performance validation.

Calibration instruments required are:

thermocouples, pressure calibrator, vacuum calibrator, temperature detectors and probes, timers, temperature bath, flow meters.

Procedure

In this third part of the autoclave validation, tests are performed to show heat/steam penetration into each loads, and the killing of a bacteriological challenge in each load. The measuring instruments must be calibrated before and after each validation study to ensure that they remain within specifications for each run.

Autoclave PQ continued

The tests to be performed would include:

a) loaded chamber heat distribution (demonstrates the steam/heat penetration into each material and load size by thermocouples inserted in each load)

b) biological challenge (shows that the reduction in the biological indicator meets limits - spore strips inserted in the load).

It is important either during validation or during normal operation, to ensure proper steam penetration into dry loads.

For each of the heat distribution, penetration and challenge tests, the SOP should be performed satisfactorily 3 consecutive times to demonstrate that the autoclave consistently meets the acceptance criteria. For the various load configuration and cycles, 3 runs must be done for each using the worst case situation (largest load, or largest mass). For example, the autoclave has 4 different load configurations (A, B, C, D) and uses three different sterilization cycles (#1, 2, 3). If load A uses cycle #1, load B uses cycles #2 and #3, and loads C and D use cycle #3, we have the following requirements for successful validation runs:

3 heat penetration studies for load A at cycle #1
3 heat penetration studies for load B at cycle #2
3 heat penetration studies for load B at cycle #3
3 heat penetration studies for load C at cycle #3
3 heat penetration studies for load D at cycle #3
3 challenge studies for load A at cycle #1
3 challenge studies for load B at cycle #2
3 challenge studies for load B at cycle #3
3 challenge studies for load C at cycle #3
3 challenge studies for load D at cycle #3

This comes to a total of 30 successful runs for the performance validation, with instrument calibrations performed before and after each run.

Reporting

Responsible person verifies that the information is complete, prepares the Deviation Report and the Performance Qualification Report and, submits to QA for review and approval.

11.3 Small equipment: pH meter IQ, OQ

pH METER IQ

Objective

To demonstrate that the pH meter manufactured by _____, model # _____ and accessories installed at _____ conform to the purchase specifications and the manufacturers literature, and to document the information that the equipment meets specifications.

Scope

For new installation, modification, replacement, or relocation of the pH meter.

Responsibility

Indicate the title of the person responsible for writing and performing the IQ

State that QA is responsible for approving the protocol and reviewing and approving the data and conclusions.

Equipment Description:

(The following is a sample description of a pH meter)

The Company X, Model Z pH meter located in the Purification room (Room No. 00), provides fast, accurate pH measurement for preparing buffers and adjusting the pH of in-process samples. It will be used between pH 3.5 and 7 for on-line measurement.

It features a custom liquid crystal display (LCD) which simultaneously displays mode, results and temperature, a sealed keypad with tactile and audible feedback and a port for use with the Company Y, Model P printer or other serial peripheral devices.

The pH meter includes a meter, a Model E electrode with epoxy body, a Model A Automatic Temperature Compensation (ATC) probe and the printer.

Its relative accuracies are +/- 0.005 for the pH; +/- 1.0 C for the temperature and +/- 0.2 mV or +/- 0.05% of reading (whichever is greater) for the millivolts and the relative millivolts.

The pH meter must meet national electrical standards.

List of the Main Components:

1) Company X, Model Z pH meter
2) Company Y, Model P printer
3) Combination electrode, model E
4) Automatic Temperature Compensation (ATC) Probe, Model R

pH Meter IQ continued

Checklist for Each Component:

The checklists depend on the specification of the individual component.

The individual component checklist includes a space to record the information plus any deviations found during the installation check.

Procedure

Fill in the prepared checklist with the detailed mechanical and electrical specifications, drawings, etc. (as itemized in the IQ format) for the pH meter.

The individual component checklist includes a space to record the information plus any deviations found during the installation check.

Reporting

Responsible person verifies that the information is complete, prepares the Deviation Report and the Installation Qualification Report and, submits to QA for review and approval.

pH Meter OQ

Objective

To determine that the pH Meter, model # ___ operates according to specifications, and to record all relevant information and data to demonstrate it functions as expected.

Scope

For new installation, modification, replacement, or relocation of the pH meter.

Responsibility

Indicate the title of the person responsible for writing and performing the IQ

State that QA is responsible for approving the protocol and reviewing and approving the data and conclusions.

Materials, Equipment, Documents:

Standard buffer solutions, pH 4, 7, 10.

Test tubes

SOP# __: Operation, Maintenance, and Calibration of the Model Z pH Meter.

Procedure:

Operation:

Follow the SOP for normal operation (or the manual)

Typical controls to be checked for a pH meter are:

- keypad functions: on/off; mode; calibration; timer; setpoints (date, time).
- print functions: mode; interval.
- setup menu parameters: ready; hold; beep; autoshutoff; slope; resolution; reset.
- printer accuracy
- electrode accuracy

(Note: the actual controls to be tested depend on the specific model of pH meter).

Record the data in the OQ chart.

Calibration:

Following the SOP for calibration (or the manual)

Calibrate the pH electrode
Calibrate the Automatic Temperature Compensation (ATC) Probe

Record the data in the OQ chart.

Responsible person verifies that the information is complete, prepares the Deviation Report and the Operational Qualification Report and, submits to QA for review and approval.

11.4 Typical Content Requirements for Other Equipment/Systems

All equipment will require an Installation Qualification based on its planned use and specifications as defined in the vendor manuals. Recording the information and comparing the actual equipment to the purchase order and to the specifications and design criteria is the basis of the installation qualification for all equipment and systems. The information to be verified is given in the IQ format presented earlier in this guide.

The Operational Qualification will verify the controls and alarms work as specified, again depending on the use and specifications of the equipment. The manuals and SOPs provide the information on how to perform these tests and evaluations. Common to all OQ will be a list of the calibrating instruments that will be used and the methods used to test and/or certify these calibration devices. All calibrating instruments used should be traceable to a national standard, e.g. for USA the NIST (National Institute of Standards and Technology) standards.

The following is an example of the typical requirements for another system.

Water for Injection.

a) IQ for a WFI system:

The typical components to be listed and checked include:

1) holding tank
2) vent filter
3) conductivity meter
4) drains
5) valves (e.g. sample valves)
6) temperature indicating controller
7) heat exchanger
8) pressure gauges
9) pumps
10) evaporator
11) coils (e.g. preheater, condenser, reboiler)

b) OQ for a WFI system:

The typical calibrating instruments would include:

pressure sensors, temperature probes, flow sensors, conductivity meter, microbial sampling apparatus, LAL (Limulus Amoebocyte Lysate) test kit for endotoxin measurement. (Certification methods for these calibrating instruments should be referenced).

The reference documents listed would include:

SOP# ___ Operation and Maintenance of the Water for Injection System

SOPs and acceptance criteria for all analytical tests performed on WFI.

Training records for personnel operating and maintaining the WFI system..

Typical control points to be checked for the integrated system's performance would be:

On/off lamps, modes, cycles, manual override, readouts for all functions, emergency power sequence, temperature control, pressure control, volume control, flow control.

Typical alarm points to be checked are:

Temperature high/low alarm, pressure high/low alarm, volume high/low alarm.

c) PQ for a WFI system:

The PQ would use the same calibrating instruments as listed in the OQ above.

Approved SOPs for each test method, operation and calibration of the test instrumentation, operation of the WFI components being tested, SOPs for analytical tests, and any specific challenge to the system would be required.

In this performance qualification part of the WFI system validation, tests are performed to show that the water quality meets the specifications for WFI quality water for chemical tests, microbial counts, temperature, pressure, flow rate, volume, endotoxin content.

An initial performance qualification release requires consistent results within specifications for 20 consecutive working days. However, the complete performance qualification release requires consistent results within specifications for one year during which all routine maintenance procedures have been successfully performed.

The following are examples of typical parameters to be measured for several types of equipment during the OQ.

Temperature Controlled Equipment.

For example, incubators, fridges, freezers, cold rooms, freezer rooms, incubator rooms, and water baths.

The OQ will establish: temperature uniformity within the chamber, equilibration time after resetting or after a temperature challenge (e.g. leaving freezer door open for a period of time), high/low temperature settings, that all alarms sound at the correct temperature set-points; and that the temperature is monitored for a reasonable period of time and remains within specified limits. If a timer is included in the equipment, it must also be tested to show that it operates and controls the equipment as intended.

Centrifuges

The OQ for all centrifuges must establish the conformance of: actual revolutions per minute (rpm) at several speeds, vs. read-out rpm, imbalance alarms, timers, braking time(s), and temperature control where appropriate.

Blenders, mixers and homogenizers.

OQ must verify the uniformity of the speeds, and timers and temperature controls if present.

Pumps (Air samplers, Peristaltic, Centrifugal, Vacuum pumps, Automatic Diluters)

OQ must verify the flow rates/exhaust rates/delivery rates, valve opening and closures as appropriate, and timers if present.

Backup Power Generator

OQ must test alarms, input and output indicators, connections, recording devices, battery charger, automatic and manual over-ride operation, timers, and testing of response to power failure and resumption.

Controlled Air Equipment

OQ for biological safety cabinets (BSC), laminar flow hoods (LFH), fume hoods, portable clean air stations etc. must be certified at the time of installation. These certification tests are usually contracted out to specialists in the testing of biological safety cabinets. Tests to be performed for this certification typically include: velocity profile, HEPA filter leak scan, alarm points, air flow smoke pattern, UV light intensity, electrical leakage and ground circuit resistance and polarity test, and airborne particle counts. Each hood must also be re-certified on a regular basis (every year, every 6 months etc.) as well as when repaired or relocated. (PQ for biological hoods inside the production area are included in the environmental monitoring of the cleanrooms as a unit).

Measuring Apparatus.

For example, pH meters, conductivity meters, balances, etc.

Switches or keypad functions, display, alarms, battery backup, accuracy, calibration, speed of response, temperature control/timers/printout if present all must be tested during the operational qualification.

Filter (for liquid) Integrity Testing Apparatus.

Pressure gauges used to determine the integrity of filters (e.g. during forward flow or pressure hold tests) after a critical use must be tested against certified pressure measuring apparatus. If bubble point testing apparatus is used, the functions, controls and pressure measurements must be evaluated.

Fermentor

OQ of a fermentor for continuous cell culturing typically includes: sterile envelope hold test, SIP (sterilize in place) heat distribution tests, power shortage tests, data transfer tests, alarm tests environmental condition testing, control system security testing, checking that the following operate correctly: thermostat circulation pump is going in the correct direction, agitation control loop operation (stabilizes to a new set point within a given time), level/foam control loop, pH control loop operation, aeration control loop operation, back-pressure control loop operation, dissolved oxygen control loop operation, feed loop control and temperature control loop operation.

12. Process validation

A process is a series of interrelated functions and activities using a variety of specified actions and equipment which is designed to produce a defined result. To validate the reproducibility and consistency of a process, the full defined process is carried out using validated equipment, under the established procedure usually at least 3 times The process must successfully and consistently meet all acceptance criteria each time to be considered a validated process. In many cases, "worst case" conditions are used for the validation to ensure that the process is acceptable in the extreme case. Sometimes worst case conditions for systems can only really be tested over time and hence must be evaluated using a rigorous long term monitoring programme.

Examples of processes which must be validated in pharmaceutical manufacturing are:

Cleaning
Sanitization
Fumigation
Depyrogenation
Sterilization
Sterile filling
Fermentation
Bulk production
Purification
Filling, capping, sealing
Lyophilization

Each of these categories may apply to several distinct processes in the manufacturing facility. For instance, cleaning process can be the cleaning of glassware, the cleaning of the facility (floors and walls), equipment cleaning such as Clean-in-Place (CIP), or Clean-out-of-Place (COP), cleaning of garments, etc. Sterilization can be the Sterilize-in-Place (SIP) process, glassware sterilization, filter sterilization, steam sterilization, dry heat sterilization, etc.

Each process to be validated must be a specific process clearly described in a Master Formula or in an SOP. All the equipment, the processing parameters, and the specifications at each step must be detailed. Complete descriptions of the identity, code numbers, construction, operating capacity, and actual operating ranges must be defined for the equipment. The processing parameters for all steps must be sufficiently detailed to permit complete reproducibility of the process each time it is performed: time periods, pH, volumes, temperatures, measurements, specifications, acceptable

ranges, etc. The controls and tests and their specifications must be defined. The purity profiles for production processes must be defined for each step. To be considered validated, the process must consistently meet all specifications at all steps throughout the procedure at least three times consecutively.

It is very important that the specifications for a process undergoing validation be pre-determined. It is also important that for all critical processing parameters for which specifications have been set, there must be equipment to measure all of those parameters during the validation study.

Process Validation studies examine a process under normal operating conditions to prove that the process is in control. Once the process has been validated, it is expected that it remains in control, provided no changes are made. In the event that modifications to the process are made, or problems occur, or equipment or systems involved in the process are changed, a re-validation of the process would be required. Very often validation studies require that more measurements are made than are required for the routine process. The validation must prove the consistency of the process and therefore must assess the efficiency and effectiveness of each step to produce its intended outcome.

The following format outlines the requirements for a protocol for Process Validation. (In essence, this form is an SOP titled "How to Write a Process Validation Protocol")

13. Format for a process validation protocol

Name of Facility:_____ **page _ of _**

Validation Protocol # _____ Process Validation

Title _____

_____

Protocol written by _____

Departmental Approval by _____ Date _____

QA Approval by _____ Date _____

Objective:

To determine that process consistently performs as intended by repeatedly running the system on its intended schedules and recording all relevant information and data. Results must demonstrate that the process meets pre-determined specifications under normal conditions, and where appropriate worst case conditions.

Scope

To be performed with validated equipment in the specified location in validated premises. If equipment or systems or the facility are modified or the premises where the process takes place is changed, or the process is relocated, the process must be re-validated after the systems, equipment and facility qualifications, as appropriate, have been performed and approved.

Responsibility

The persons responsible for the process will perform the validation and record the information.

The responsible person will supervise the study, verify the completion of the records and write the report.

Quality Assurance will review and approve the Process Validation Protocol and Report.

Validation Protocol _____	**Process validation**	**page** ___ **of** ___
Title _____ _____	**Name of Facility**	

Materials, Equipment, Documents

Master Formula or SOPs for normal operations of the process under test. (including data record forms, batch record forms, materials and equipment needed).

MF/SOP list:

_____

_____

_____

_____

_____

SOPs for in-process and quality control tests performed during process (validated tests) (including data record forms, materials and equipment needed).

SOP list:

_____

_____

_____

_____

_____

SOPs for test specific to the validation study performed (validated tests) (including data record forms, materials and equipment needed).

SOP list:

_____

_____

_____

_____

_____

Procedure

Performance

Process: Run full process according to SOP three times and record all required data.

Deviations to the procedures must be recorded on the data record forms.

Analytical tests: Perform the routine tests associated with the process according to the SOP. Test results must be approved by QC.

Evaluation

Attach all data record forms and charts.

Perform all necessary calculations and statistical analyses (pre-determined).

Compare to acceptance criteria.

Prepare Deviation Report

(including the justification of acceptance and impact on the process).

Prepare a Process Validation Report

This should include for each validation run: date study initiated; date completed; observations made; problems encountered; completeness of information collected; summary of the deviation report; results of tests and statistical analyses; do results meet acceptance criteria; location of original data; other information relevant to the study.

Conclusions will be made on the validity of the process in individual runs and on the three consecutive validation runs.

Approval

Submit the Document to QA for review and approval.

The Process must meet all specifications for three consecutive runs.

Validation Protocol _____	Process validation	page ___ of ___
Title _____ _____	Name of Facility	

List of attached Data Record Forms

_____

_____

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Verified by: _____ **Date** _____

Validation Protocol _____	Process validation	page ___ of ___
Title _____ _____	Name of Facility	

Calculations and Statistical Analyses

Performed by: _____ **Date** _____

Verified by: _____ **Date** _____

Validation Protocol _____ **Title** _____	**Process validation** **Name of Facility** _____	**page** ___ **of** ___

Acceptance Criteria vs. Test Results

Criteria	Results	Pass/Fail
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
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_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Recorded by: _____ **Date** _____

Verified by: _____ **Date** _____

Validation Protocol _____	Process validation	page ___ of ___
Title _____	Name of Facility _____	

Deviation Report

Deviation(s):

Justification for acceptance:

Impact on process:

Supervisor: _____ **Date** _____

Validation Protocol _____	**Process validation** **page** ___ **of** ___
Title _____	**Name of Facility** _____

Process Validation Report

Results:

Conclusions:

Written by: _____ **Date** _____

QA approved by: _____ **Date** _____

14. Typical content requirements for process validations

It is vital that during all process validation studies, the processes are performed in the "actual" environment under which production is to occur. That is to say all routine peripheral activities associated with this process must be in effect while the validation is being performed. (e.g. number of personnel in facility, exit and entry procedures are in effect, environmental and personnel monitoring is being performed on the prescribed schedule, air system is operating as for regular manufacturing, etc.)

Cleaning, Fumigation, Sanitization Processes

The validation (or re-validation) of these processes includes chemical and microbiological testing of samples taken at pre-determined times and locations within a facility, a system or piece of equipment.

For validation of some cleaning processes, the equipment or surfaces can be exposed to an appropriate contaminant (e.g. protein solution, microbial strain), the process is performed according to defined approved procedures and specifications and then tested to demonstrate efficacy. Validation includes collecting liquid and swab samples for testing of residual product. Typical tests to be performed could include: tests for residual protein, endotoxin tests, microbial tests (bioburden), chemical tests (including chlorine and phosphoric acid), residual levels of cleaning agents, conductivity tests, and pH tests as relevant to the cleaning process under test. All analytical tests must be validated before being used in the validation of the process.

The main considerations in validating a cleaning/sanitization/fumigation process are how much of the previous active product is left, and how much detergent/cleaning agent remains. However there are many tests that should be performed to detect a range of different potential contaminants. These include tests for: microbial presence, excipient presence, endotoxin contamination, particulate contamination, sanitizing agents, lubricants, environmental dust, equipment related contamination and residual rinse water. Worst case scenarios should be taken into consideration. For example if any residual cleaning agent is distributed unevenly across the test surface, then test points must be chosen appropriately.

(The Guide to WHO GMP Requirements, Part 1: Standard Operating Procedures and Master Formulae includes information on the general requirements for the contents of SOPs for cleaning processes).

Sterilization

Sterile filtration of solutions: Validation of this process should include a microbial challenge that will both test the filter and simulate the smallest micro-organism likely to occur in production. Once the filtering process is validated it is important to ensure that all replacement filters will perform at the same level. This can be done by performing both filter integrity tests and performance tests at the same time.

Equipment: Validation for materials sterilized in the autoclave or oven are covered in the Performance Qualification. Sterilize-in-place is covered in the cleaning process description above.

Depyrogenation process

The validation (or re-validation) of a depyrogenation (dry heat, column chromatography, other) process would include the validation of the limits of detection and quantitation of the endotoxin assay, the spiking of samples with endotoxin, running the depyrogenation process according to the approved procedures, and the testing of samples for residual endotoxin. The full process should be tested at least three times to ensure that the process adequately destroys endotoxin and meets the required specifications (commonly an endotoxin content reduction of 3 logs).

Sterile filling

Sterile filling tests the filling process for maintenance of aseptic conditions by performing the filling process with a nutrient media which will easily support bacterial and fungal growth. The filling process is run at full scale according to the Master Formula for at least one fill size (worst case conditions of large volume and number of vials). Facility and system monitoring are performed and recorded during the process. The filled vials are incubated, observed and tested for contamination by the validated sterility test. The process must be sterile for three consecutive runs to be considered validated.

Typically the media filled container is incubated for 14 days or more at a temperature of approximately 25 °C - 35 °C. The media fill is usually performed twice a year for each shift for each filling/closing line, but this will depend on the frequency required by the regulatory authority. The size of the run must be large enough to detect low levels of contamination (e.g. for a contamination rate of 1/1000, 3,000 units are needed to provide 95% confidence). Appendix 5 includes the validation protocol for filling from one of the vaccine manufacturers collaborating on the preparation of this guide.

Mock fermentation

The full scale fermentation of a representative fermentation process is performed to permit the validation of the parts of the process involving connections, sampling, and additions of nutrients etc. The fermentor is prepared and operated in a simulated process with uninoculated nutrient media. This process must follow the Master Formula procedures for the full fermentation process. Three successful consecutive runs at each stage must be obtained for validation approval and will demonstrate that the manipulations made during the actual fermentation process are under control.

Production processes (fermentation, bulk production, purification, filling, lyophilization)

The complete process for each defined batch process must be run according to the approved Master Formula including all the raw material, personnel, equipment and facility preparations, in-process tests, processing, through to the final testing of the batch lot. In addition all facility systems must be monitored (water, steam, autoclave, and environmental monitoring, etc.) on the prescribed schedule. Three consecutive lots must be produced and all facility, equipment, support systems, product specifications, and the process being validated must pass at all steps.

15. Validation of analytical assays

Validation of analytical assays is the process of establishing one or more of: accuracy, precision, linearity, range, limit of detection, limits of quantitation, specificity, and ruggedness as appropriate to the type of assay. For physico-chemical methods there are accepted defined limits for these test parameters (Ref:36). Bioassays are much more variable in outcome and also often use animals and cells in the assay which in themselves are variable, and can have broad acceptance limits. The discussion in this guide is limited to bioassays.

Bioassays

There are three broad categories of bioassays which are commonly used for biological products: binding assays, cell-based assays, and whole animal assays. Some complex assays are in more than one of these categories.

Binding assays are those that involve the binding of two or more molecules. Immunoassays are an example of this type. Binding assays are used for monitoring a molecule during purification steps and for cleaning validations. Binding assays are not generally considered acceptable for potency assays because the presence of a molecule as determined by a binding interaction is not necessarily an indication of the activity of the molecule.

Cell assays are those where the product evokes a measurable response in specific cells: clumping, cell lysis, cell fusion, or generation of a specific detectable chemical. These assays can be more variable than binding assays and must be performed carefully to ensure consistent results. Cell-based assays are often used for potency assays.

Whole animal assays are more difficult and involve the care, maintenance and handling of animals. They are time consuming and highly variable. The biological response of an appropriate species to an active drug is compared to the response to a reference product or to uninoculated controls as a measure of activity. These assays are used for pyrogen assays, general safety assays, and potency assays. Because of their expense, the large number of animals used, the time spent, and their variability, whole animal assays for potency are usually only performed for the final product release.

Binding assays typically have variability (imprecision) in the 5 to 20 % range. Cell and whole animal assays may have variability above 50%.

Depending on the use of the assay, different parameters will have to be measured during the assay validation. WHO and several regulatory bodies and Pharmacopoeia have published information on the validation of analytical procedures (Ref: 4, 7, 18, 33, 34, 36, 38).

Accuracy is the closeness of agreement between the actual value of the drug and the measured value. Spike and recovery studies are performed to measure accuracy: a known sample is added to the excipients and the actual drug value is compared to the value found by the assay. Accuracy is expressed as the bias or the % error between the observed value and the true value (assay value/actual value x 100%). Accuracy is not often possible for biological products because pure standards are not available. For such products, a comparison is usually made to a reference product which is run in parallel in the same assay. Acceptable results are based on specifications for the actual reference value, or specifications for the ratio of the sample value to the reference value.

Precision is the closeness of agreement between the values obtained in an assay. It is expressed as the coefficient of variation (% CV). CV is the standard deviation of the assay values divided by the concentration of the analyte. Several types of precision can be measured: intra-assay precision (repeatability) is the % CV of multiple determinations of a single sample in a single test run; inter-assay precision (also called intermediate precision) measures the % CV for multiple determinations of a single sample, controls and reagents analyzed in several assay runs in the same laboratory; reproducibility is the precision between laboratories usually in collaborative studies and not directly relevant to assay validation in a manufacturing facility.

Robustness is the capacity of an assay to remain unaffected by deliberate changes to various parameters of the method and gives an indication of its reliability during normal assay conditions. The variations could be in room or incubator temperature or humidity, variations in incubation times, minor variations in pH of a reagent, etc. Under each of these conditions, the accuracy and precision or other assay parameter can be measured to see what variations can be tolerated in the assay conditions.

Linearity is the ability of an assay to obtain test results which are directly proportional to the concentration of an analyte in the sample. The determination of this parameter will identify the range of the analytical assay. It can be measured as slope of the regression line and its variance or as the coefficient of determination (R^2) and correlation coefficient (R).

Range is a measure of the highest concentration of an analyte that can be measured with acceptable accuracy and precision. It is the upper limit of the linearity determination. If the relationship between response and concentration is not linear, the range may be estimated by means of a calibration curve.

Selectivity (also termed specificity) is the ability of an analytical assay to measure the analyte in a sample in the presence of the other components expected to be present in the product. This parameter is measured for identity tests, for content or potency tests, and for purity tests to ensure that the assay provides an accurate statement of the identity, potency or purity of a product. Selectivity (specificity), like accuracy, is expressed as the bias or the % error between the measured and known value.

Limits of Detection (LOD) is the lowest amount of the analyte in a sample that can be detected but not necessarily be quantitated as an exact concentration or amount.

Limits of Quantitation (LOQ) is the lowest amount of an analyte that can be measured quantitatively in a sample with acceptable accuracy and precision. The LOQ is a parameter for tests measuring impurities in a drug product.

The following table is based on the WHO document on analytical assay validation (Ref: 38). It indicates what type of parameter must be validated for different types of tests.

Relevant performance parameters for validating different types of analytical procedures					
Parameter	**Identity**	**Impurities**		**Potency**	**Compo-sition**
		Quantit'n	**Limits**		
Accuracy		+		+	+
Precision		+		+	+
Robustness	+	+	+	+	+
Linearity and range		+		+	+
Selectivity (specificity)	+	+	+	+	+
Limit of detection	+		+		
Limit of quantitation		+			

(2-02)

In addition to the above parameters which are common to both physico-chemical tests and bioassays, there have been several suggestions (ref: 16, 21) that additional measurements are important for bioassays partly because of their duration, complexity, and long term storage of biological samples and control and reference material. These include: front-to-back test which determines whether the parameters for early samples on a large test are the same as later samples (because they have been prepared at a different time in comparison to the controls); freeze-thaw stability which uses samples and controls which have been frozen and thawed repeatedly to determine any effects of freezer storage on test results; and lot-to-lot precision which measures the precision of an assay with different lots of cell lines, serum or other highly variable component of the test. The latter is an important test of potency assay precision.

Suggested plans for performing some bioassays are as follows (Ref: 16, 21)

Accuracy

May not be possible for some bioassays because pure samples are not available. May not be required if the method has satisfactory sensitivity and specificity.

Immunoassays only:

Objective: To determine the ability of the assay to measure the expected value.

Procedure:

Use a minimum of 3 spiking concentrations in the excipient solution.

Prepare 2 samples of each concentration

Test the 6 samples in triplicate on one run

Measure expected vs. average measured value

Calculate the % recovery = bias

Precision

a) Intra-assay

Objective: To determine the precision (CV) of a homogenous sample at various points of the curve in a single assay.

Procedure:

Prepare three dilutions of the sample (high/medium/low concentrations in the range).

Test 10 replicates of each dilution of the sample.

Calculate the average and standard deviation for each point on the curve.

Calculate the CV for each point on the curve.

b) Inter-assay

Objective: To determine the precision (CV) of a homogenous sample at various points of the curve between assays.

Procedure:

Prepare three dilutions of the sample (high/medium/low concentrations in the range).

Test triplicates of each dilution of the sample in three different assays.

Do for day-to-day variations

Do for lot-to-lot variations of assay materials

Do for technician-to-technician variation..

Calculate the average and standard deviation for each point on the curve for each individual test.

Calculate the CV for each point on the curve between the assay runs.

Limit of Detection

For a bioassay, the LOD is the minimum concentration of a substance that generates a consistent response greater than the background of the test. Responses of 2 to 3 times the standard deviation of the background are reported as satisfactory limits (Ref: 4, 16, 21)

Example for an immunoassay measuring the OD of samples.

Objective: To determine the value of 3 standard deviations above the background.

Procedure:

Prepare a standard concentration of the product in the appropriate solution.

Prepare a blank solution without any sample (zero concentration).

Perform the immunoassay at least 3 times in duplicate according to the SOP

Measure the OD values for the sample and blank.

Calculate the average OD for the sample and blank.

Calculate and standard deviation of the blank

Calculate the LOD as $\frac{3 \times \text{st dev of the blank}}{\text{OD of sample/concentration of sample}}$

Linearity/Range.

Objective: To measure the closeness of observations to a straight line.

Procedure: Determining the coefficient of correlation R for dilutions of the sample over the range claimed for the assay.

Prepare 6 to 8 sample dilutions across the claimed range

Test each dilution in triplicate for 3 runs

Record expected values, actual values, and % recoveries for each run

Analyze each set of dilutions as a linear curve and calculate R for each assay.

Alternative:

Calculate the accuracy and precision at each dilution.

Range is the highest and lowest concentration with satisfactory accuracy and precision.

If the validation study for an analytical test is well planned it should be possible to design the protocol to consider many of the parameters in a single series of tests, for instance: selectivity (specificity) linearity, range, accuracy and precision for a potency test.

16. Format for an analytical assay validation protocol

Name of Facility:_____ **page _ of _**

Validation Protocol # _____ Analytical Assay Validation

Title _____

_____

Protocol written by _____

Departmental Approval by _____ Date _____

QA Approval by _____ Date _____

Objective

To demonstrate in a laboratory study that the performance characteristics of an assay make it fit for the intended analytical application.

To record the information and data needed to establish the performance specifications for the assay.

Scope

To be performed for new assays, or for current assays when any changes are made to the equipment, procedure, laboratory conditions, technical staff, reagents and starting materials, references/standards/ controls, etc.

All equipment must be validated before being used for the validation of an analytical assay.

Responsibility

Person trained and responsible for performing the analytical test will perform the validation study and record the information.

The supervisor will plan the study, write the protocol, supervise the performance, and verify the completion of the records.

QA will review and approve the protocol before the validation study, and review and approve the data in validation report.

Validation Protocol _____ Assay validation page ___ of ___ Title _____ Name of Facility _____
Materials, Equipment, Documents SOP and Data Record Forms for the assay under test. Materials and equipment as described in the SOP. Reference to documents providing evidence that the equipment to be used is validated and calibrated.
Procedure Performance Specify the conditions for the performance of the test, and the analyses to be made on the data collected, and the acceptance criteria to be met. (Different types of validations studies are needed for different types of analytical tests). Evaluation Attach all data record forms and charts. Perform all the pre-determined calculations and statistical analyses. Compare to acceptance criteria. Prepare the Deviation Report (including the justification and impact on the validity of the assay). Prepare the Analytical Assay Validation Report This should include: date study initiated; date completed; observations made; problems encountered; completeness of information collected; summary of the deviation report; results of tests and statistical analyses; do results of each run of the assay meet acceptance criteria; does the variation between the assay repeats meet the specified criteria; location of original data; and other information relevant to the study. Conclusions will be made on the validity of the assay for individual results and for the replicates. Approval Submit the Analytical Assay Validation document to QA for evaluation and approval.

Validation Protocol _____ Assay validation page ___ of ___ Title _____ Name of Facility _____
Calculations and Statistical Analyses
Performed by: _____ **Date** _____ **Verified by:** _____ **Date** _____

Validation Protocol Title	Assay validation Name of Facility	page ___ of ___

Acceptance Criteria vs. Test Results

Criteria	Results	Pass/Fail

Recorded by: _____ **Date** _____

Verified by: _____ **Date** _____

Validation Protocol _____	Assay validation	page ___ of ___
Title _____	Name of Facility _____	

Deviation Report

Deviation(s):

Justification for acceptance:

Impact on process:

Written by: _____ **Date** _____

Assay Validation Report

Results:

Conclusions:

Written by: _____ **Date** _____

QA approved by: _____ **Date** _____

17. Other types of validation data

17.1 Concurrent

Concurrent validation is based on data collected during actual performance of a process already implemented in a manufacturing facility. In this situation, validation data are collected during several runs of the on-going process and evaluated to determine if the process is valid. A protocol should be written to define the information to be collected and evaluated. This method may suit manufacturers of long standing who have a well-controlled manufacturing process.

17.2 Retrospective

If a product has been in production for a long time, but has not been validated according to a prospective protocol, retrospective validation can, in some cases, be performed if concurrent validation is not a realistic option (e.g. several years worth of bulk vaccine in storage, or facility on a different campaign). An assessment of the product, manufacturing and testing procedures can be examined and analyzed to demonstrate the consistency and completeness of the procedures and processes. This form of validation is not generally accepted for several reasons: the lack of validation protocols usually indicates a lack of documentation, and often data is reported as only pass or fail which does not permit statistical analysis which can only be performed on numeric data. In addition, retrospective analysis can only be made on a system, piece of equipment, or process which has not undergone any revision, repairs or modifications, therefore unless these have been well documented the time periods to be analyzed retrospectively will not be known. This applies also to changes which at the time might have seemed minor, but without a QA assessment and a Master Validation Plan, no specific analysis was made on the possible effects of the change.

For analytical tests, retrospective analysis of reference and control values for many tests can be made if the lot numbers and any changes made to the test parameters, operators, and/or equipment have been well documented. If adequate data are available, a retrospective validation of an analytical assay may be possible.

17.3 Laboratory- and pilot-scale validations

The validation of some production processes cannot always be carried out in the production facility. One example of this is the validation of removal of impurities by individual purification steps in the process. It is not acceptable to bring high levels of unacceptable impurities (endotoxins, DNA, unwanted proteins, contaminating bacteria and viruses) to spike into the process to demonstrate their removal or inac-

tivation by the purification process. Such validation studies are performed in laboratories at a smaller scale designed to approximate the full scale process. Pilot-scale is an intermediate scale which is sometimes used to determine the validity of new or modified processes before full-scale operations are attempted. For both lab-scale and pilot scale validation studies to be acceptable as proof of the validity of the full scale process, it must be demonstrated that the scale-down has been calculated for all critical parameters of the process: times, temperatures, amounts, column sizes, flow rates, pressures, etc.

Appendix 1: Document requirements

Validation protocols

The following is a comprehensive listing of equipment, systems, processes and procedures which should be validated. Not all will be required in all facilities depending on the manufacturing taking place.

A. Waste Systems

1. Domestic sanitary sewer systems
2. Process drain systems
3. Hazardous waste systems
4. Solid waste disposal systems
5. Hazardous emissions systems

B. Air Handling Systems (IQ/OQ/PQ)

1. Heating system
2. Ventilation system
3. Air conditioning system
4. Air filter systems
5. Biological safety cabinets
6. Laminar flow hoods
7. Fume hoods

C. Water System (IQ/OQ/PQ)

1. Purified water
2. Water for injection (WFI)
3. Source potable water

D. Steam Systems (IQ/OQ/PQ)

1. Plant steam (raw steam)
2. Clean steam

E. Cooling Systems (IQ/OQ/PQ)

1. Chillers
2. Cooling towers

F. Gas Systems (IQ/OQ/PQ)

1. Compressed air
    a. Sterile
    b. Non-sterile
    c. Instrument air
    d. Industrial air
    e. Purified air (used for fermentation)
2. Nitrogen systems
    a. Sterile
    b. Non-sterile
3. Other gases
    a. Oxygen
    b. CO2

G. Electrical System (IQ/OQ)

1. Electrical standard
2. Electrical emergency power
3. Electrical back-up power

H. Equipment(IQ/OQ)

1. Production
2. Quality control laboratory

I. Sterilization

1. Steam sterilization (autoclaves)(IQ/OQ/PQ)
    a. Component preparation sterilizer
    b. Terminal sterilizer
    c. Laboratory sterilizer
2. Dry heat sterilization/depyrogenation (IQ/OQ/PQ)
    a. Tunnels
    b. Ovens
3. Terminal filtration process
4. Gas sterilization (IQ/OQ/PQ)
    a. EtO sterilizers
5. Radiation

J. Cleaning Processes

1. CIP (Clean-in-Place) process
    a. Aseptic
    b. Non-aseptic
2. SIP (Sterilize-in-Place) process
3. Facility cleaning processes
    a. Equipment
    b. Clean area
    c. Aseptic area
    d. Sanitization
    e. Garment laundering
    f. General facility cleaning (janitorial)

K. Component Preparation Equipment

1. Container washing equipment (IQ/OQ/PQ)
    a. Manual
    b. Semi-automatic (programmable controllers)
    c. Automatic (computer controlled)
2. Closure washing equipment (IQ/OQ/PQ)
    a. Manual
    b. Semi-automatic (programmable controllers)
    c. Automatic (computer controlled)
3. Washing/depyrogenation/sterilization processes

L Aseptic Solution Preparation

1. Solution manufacture process
2. Solution filtration process

M. Sterile Filling (Aseptic or Terminally Sterilized)

1. Solution filling
    a. Manual
    b. Automatic
2. Lyophilization
3. Container sealing
    a. Manual vial stoppering
    b. Automatic vial stoppering
    c. Ampoule sealing
4. Container capping

N. Finishing

1. Labelling process
    a. Manual
    b. Semi-automatic
    c. Automatic
2. Packaging (boxing) process

O. Manufacturing Processes

1. Fermentation
    a. Seed fermentation
    b. Fermentation
    c. Cell separation
2. Cell growth
    a. Reactor
    b. Roller bottle
3. Buffer preparation
    a. Buffer weigh-up
    b. Buffer preparation
        i. Sterile filtration
        ii. Sterilization
    c. Buffer storage
4. Purification
    a. Purification step 1
    b. Purification step 2, 3, etc.
    c. Purification final step
5. Bulk lyophilization

P. Storage/Warehouse Operations (Storage, Holding, Distribution)

1. Incoming/Receiving
2. Warehousing
3. In process storage
4. Approved finished goods storage
5. Outgoing/distribution/shipping

Q. Analytical Methods

1. Raw materials
2. In-process product
3. Intermediates
4. Final product

R. Other

1. Contractor validation (external manufacture)
2. Vendor validation/supplier audit
3. Animals
    a. Animal care and handling processes
    b. Supplier validation (audit)

Appendix 2: List of validation titles from three vaccine manufacturers

The Validation Protocol titles listed on the following pages have been contributed by the collaborators on this project. These lists have been reproduced as an Appendix to this Guide to Validation to provide examples of the number and diversity of protocols needed for vaccine production and testing. They are listed in the order given by the contributor.

Massachusetts Public Health Biologic Laboratories, Jamaica Plain, Massachusetts

MPHBL Validation and Calibration Documents related to DTP Vaccine

Calibration of Cage Washer Thermocouples
Installation Qualification of Autoclaves
Operation Qualification of Autoclaves
Calibration of Partlow IV One-Pen Recorders
Installation Qualification of Stll Feedwater System
Operation Qualification of Still Feedwater System
Validation of Still Feedwater System
Installation Qualification of Finn-Aqua Still
Operation Qualification of Finn-Aqua Still
Installation Qualification of WFI Distribution System
Operation Qualificationof WFI Distribution System
Validation of Finn-Aqua Still and WFI Distribution System
Validation of Foxboro Distilled Water System: Changeover to Using Water fron the WFI Supply Loop
Start Up Supervision of Chromalox System and Thaw Tank
Operational Qualification of the WFI Loop Extension for the 1995 Vaccine Renovation
Operation and Performance Qualification of Cold WFI System
Installation Qualification, WFI Second Tank Addition
Operational and Performance Qualification, WFI Second Tank Addition
Operational Qualification for the HVAC Systems for the 1995 Vaccine Facility Renovation
Installation Qualification for Classed and UnClassed Cold Rooms
Operational Qualification for All Cold Rooms
Installation Qualification for Incubators
Operational Qualification for Incubators
Installation Qualification for Class 100 Hoods and Fume Hoods
Operational Qualification for Class 100 Hoods and Fume Hoods
Installation Qualification for Refrigerators and Freezers
Operational Qualification for Refrigerators and Freezers
Installation Qualification for the Met-One Environmental Monitoring System
Installation Qualification of the Clean Steam
Operational Qualification of the Clean Steam
Installation Qualification of the Compressed Air

Operational Qualification of the Compressed Air
IQ of the F&D Main Alarm Panel
OQ of the F&D Main Alarm Panel
Validation of Filling Equipment Cleaning
Master Validation Plan for the Vaccine Facility
PQ for Unclassed Cold Rooms Refrigerators, Freezers, and Incubators
PQ for Biological Safety Cabinets and Laminar Flow Hoods
PQ for HVAC
Toxoid Purification Process Validation
Performance Qualification of the Hot WFI Loop for the Vaccine Renovation
Performance Qualification and Process Validation for Sorvall Centrifuge (Toxoid Purification Lab)
Calibration of Hydrometers
Calibration of Sanitary Gagues
Calibration of RCS (Biotest) Viable Air Sampler
Validating & Monitoring of Glassware Prep.
Validation Plan for Computerized Systems at MPHBL
OQ of Calibration Manager
Process Validation Bulk Transfer to Filling
Annual Standardization of Diph Flocculating Antitoxin
Validation Procedure for the Filtration of Diphtheria Cultures
Validation of the Flocculation Test Procedure
Validation of the Ammonium Sulfate Purification Process
NIST Equipment
Validation of Cleaning processes Using Swabs
Quarterly Calibration of Cold Rooms, Incubators, and water Baths
Calibration of Pressure Gauges
Requirements for Validating Assays in QC
QC Testing of Trypicase Soy Broth Medium for Broth Fills Validation
Glassware Cleaning and Validation of Cleaning
Standardization of Thermometers

Biomanguinos/FIOCRUZ, Yellow Fever Vaccine Production Facility, Brazil

Validation protocols related to producing vaccine against yellow fever (in revision stages)

Hot air validation protocol
Hot air sterilization tunnel validation protocol
Laminar flow hood validation protocol
Autoclave validation protocol
pH meter calibration
Balance calibration
Pressure gauge calibration
Thermocouples calibration for validation purposes

Gerencia General De Biologicos Y Reactivos, Mexico City, Mexico

Mexico: DTP Vaccine validation documentation (in progress)

- Validation document guide
- Master plan
- Master plan for each system or process
- CGMP requirements and regulations (rationale for validation)
- Validation procedures
- Acceptance criterion and specifications
- Test procedures
- Calibration and preventative maintenance program
- Protocol
- IQ
- OQ
- PQ

Appendix 3: List of reference articles and publications

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2) Austin P.R., Design and Operation of Pharmaceutical Bio-cleanrooms and Aseptic Areas. Contamination Control Seminars, Michigan, 1994

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8) Commission of the European Communities. Development Pharmaceutics and Process Validation (April 1988). Guidelines on the Quality, Safety and Efficacy of Medicinal Products for Human Use, The Rules Governing Medicinal Products in the European Community, Volume III, 1988

9) Commission of the European Communities. Guide to Good Manufacturing Practice for Medicinal Products. The Rules Governing Medicinal Products in the European Community, Volume IV, Jan 1992

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13) Green C., Cleaning Validation Programs: How to Get Started. Volume 1, Number 1, Journal of Validation Technology, Oct/Nov 1994, pp46-51

14) Guide to Inspections of Validation of Cleaning Processes, Interpharm, July 1993

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22) Naglak T.J., Keith M.G., Omstead D.R., Validation of Fermentation Processes. BioPharm, July-August 1994, pp28-36

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Sources for obtaining copies of the some of the references:

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BioPharm: Advanstar Communications, Marketing Services, 7500 Old Oak Blvd, Cleveland, OH, 44130, USA

Canada: Publishing Division of Canada Communications Group,Ottawa, Canada, K1A 0S9

Commission of the European Communities: Office of Publications of the European Communities, 2 rue Mercier, L-2985, Luxembourg.

Institute for Applied Pharmaceutical Sciences: 144 Tices Lane, East Brunswick New Jersey, 08816, USA

Institute of Environmental Sciences: 940 East Northway Highway, Mount Prospect, Illinois, 60056, USA

International Standards Organization: Geneva, Switzerland

Interpharm Group of Companies: 1358 Busch Parkway, Buffalo Grove,Illinois, 60089, USA

Parenteral Drug Association (PDA) 7500 Old Georgetoen Road, Suite 620Bethesda Maryland, 20814, USA

Parenteral Society, The: 6 Frankton Gardens, Stratton St Margaret,Swindon, Wiltshire

U.S. Code of Federal Regulations (CFR): Superintendant of Documents,US Government Printing Office, Washington DC 20402, USA

United States Pharmacopoeia (USP): US Pharmacopeial Conventions Inc., Order Processing Dept, PO Box 2248, Rockville, Maryland, 20852, USA

U.S. Food and Drug Administration: Office of Regulatory Affairs, 5600 Fishers Lane, Rockville Maryland, 20857, USA

World Health Organization: Office of Publications, WHO, Geneva, Switzerland

Appendix 4: Glossary

(Numbers in parentheses are the Reference numbers in Appendix 3. WHO definitions have been used where available.)

acceptance criteria: Specific criteria for results of either process monitoring or a test. Criteria are defined in a validation or qualification protocol and must be met in order for the process to be considered validated or the equipment to be qualified. (19)

accuracy: The accuracy expresses the closeness of agreement between the value which is accepted either as a conventional true value (in house standard) or an accepted reference value (international standard e.g. Pharmacopoeial standard) and the value found (mean value) obtained by applying the test procedure a number of times. Accuracy provides an indication of systematic errors. (7)

analytical procedure: The analytical procedure refers to the way of performing the analysis. it should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: The sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc. (33)

bias: The error between the observed mean of the analytical method and the true value (nominal value). Bias may be positive (yielding high results) or negative (yielding low results). There may also be no difference, in which case bias is zero. (4)

calibration: The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling- or the values epresented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established. (39)

change control: A formal process in which changes to equipment, systems, procedures, or processes are proposed by individuals or units planning to implement them. the changes are reviewed by qualified representatives of Quality Assurance and other appropriate disciplines to determine whether they will effect the status of the validation or qualification. The reviewers shall determine whether it is required to validate the system or take other action necessary to maintain the validated state of the system. (19)

coefficient of determination (R^2): The ratio of the variation explained by a fitted model to the total variation. The larger the coefficient, the better the fit. If

the fitted model is linear, the coefficient is the square of the correlation coefficient. (4)

coefficient of variation (CV): The percentage variation in a set of numbers relative to their mean. CV is often referred to as the Relative Standard Deviation (RSD). (4)

control: Controls resemble the unknown in composition and are assayed at the same time under the same test conditions by the same method. The results of these tests are used in calculating the mean and standard deviation of the test. Controls are used to measure accuracy. (4)

correlation coefficient (r): The square root of the Coefficient of Determination. A measure of the closeness of observations to a straight line. The closer the coefficient is to ±1, the stronger the linear relationship. (4)

critical areas: Areas where sterilized products or container/closures are exposed to the environment. (32)

critical parameter: An operating variable that identifies the conditions under which a product is manufactured and must be controlled in order to obtain desired or specified product attributes. (19)

critical process: A process that may cause variation in the quality of the pharmaceutical product. (39)

critical surfaces: Surfaces which come into contact with sterilized product or containers/closures. (32)

D value: The time (in minutes) at a given temperature needed to reduce the number of microorganisms by 90%. (32)

freeze/thaw stability: A validation of a given drug sample's ability to undergo multiple freezing and thawing steps. A single drug sample is frozen and thawed multiple times. After each freeze/thaw cycle, an aliquot is removed. this is repeated until samples that have been frozen 0-5 times are obtained. All aliquots are assayed in triplicate and values are compared to determine stability of the drug compound. (21)

front-to-back: Aliquots of a single sample are assayed at different physical positions in the assay; that is, they are handled near to or far from (in time) control samples. Values are compared to determine if different intra-assay handling affects the observed concentration. (21)

installation qualification (IQ): Documented verification that, at the time of installation, equipment and equipment-related systems (i.e., support systems or utilities) comply with the recommendations of the manufacturer, as well as with design specifications, system specifications, and appropriate codes. (19)

intermediate precision: Intermediate precision expresses within laboratories' variations. Different days, different analysts, different equipment, etc. (33)

intra-assay precision: Repeatability is also termed intra-assay precision. (33)

limit of detection (LOD): The lowest amount of analyte in a sample which can be detected but not quantitated as an exact value. The LOD is mostly a parameter of limit tests. (7)

limit of quantitation (LOQ): The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products. (33)

linearity: The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample. (7) (33)

lot-to-lot precision: The precision of multiple determinations of a single sample analyzed in various runs using different lots of material such as assay components, test animals, and wash buffers. (21)

operating range: A range for an operating variable, defined by an upper and lower limit, which is permitted in the validated process. (19)

operational qualification (OQ): Documented verification that equipment or equipment systems perform in accordance with manufacturers specifications and process requirements and that the appropriate GMP systems (e.g., training, calibration, and maintenance, etc.) are in place. (19)

overkill sterilization process: A process which is sufficient to provide at least a 12 log reduction of microorganisms having a minimum D value of 1 minute. (32)

performance qualification (PQ): Documented evidence that a process step, total integrated process system, or analytical method performs as intended and that it produces an in-process material, product, or test result that consistently meets appropriate specifications and the requirements defined in the protocol. It is important that clear and specific acceptance criteria be established for each critical parameter. (19)

precision: The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: Repeatability, intermediate precision and reproducibility (q.v.). Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution. The precision of an analytical procedure is usually expressed as the variance, standard deviation, or coefficient of variation of a series of measurements (33). Precision provides an indication of random errors. (7)

process system: The combination of process equipment, procedures, and support systems (e.g. HVAC, air, environmental control, etc.) that has been assembled to effect a specific process. Procedures include GMP support procedures (e.g. training, calibration, and maintenance) that must be in place and practiced in order to remain in compliance with regulations. (19)

prospective validation: The execution and documentation of pre-approved test protocol, which is designed to prove that a process performs as intended, prior to the release of a manufactured product for distribution. A minimum of three batches of product is required. If reduced batch sizes are manufactured, each must be at least one-tenth the production batch size or 100,000 units, whichever is larger.(19)

protocol: A documented plan, which is reviewed and approved prior to execution, for the test of a process, system, or piece of equipment. Upon completion, the protocol and results serve as the basis for the documentation that the process performs as intended. (19)

proven acceptable range (PAR): A range for an operating variable throughout which it has been demonstrated and documented that a process consistently yields acceptable product. The PAR must include the defined operating range and may extend beyond that range. It should be determined during the process development phase and demonstrated during validation. The PAR may be expanded through the product life cycle with appropriate validation protocol, supporting data, and documentation. (19)

qualification: A documented procedure which demonstrates that a piece of equipment or process is designed, installed, and operated properly. (19) (Generally equipment is validated by installation qualification, operational qualification, systems by installation, operational and performance qualification. Process validation and Performance Qualification are often synonomously used).

range: The range of the test procedure is the interval between the upper and lower levels of analyte (including these levels) for which the procedure has been demonstrated as suitable with precision, accuracy and linearity using the method as written. (7)

reference standard:..Any material of known identity and purity or potency. An official reference standard is one obtained from an official source such as BP, or USP, or WHO. A house reference standard may be obtained by thorough characterization for identity and purity or potency relative to an official reference standard, or by determination of absolute purity by other techniques. Depending on the intended use (qualitative or quantitative) and the nature of the assay, a greater of lesser degree of purity is acceptable. (4)

repeatability: Repeatability expresses the precision under same conditions: same analyst, same apparatus, short interval of time, identical reagents. (7)

reproducibility: The reproducibility expresses the precision under different conditions for instance: laboratories, reagents from different sources, analysts, days, apparatus from different manufacturers, etc. (7) Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology). (33)

revalidation: The verification of the performance of the method following a change in the material analyzed for the methodology used. These changes should not adversely affect the results obtained relative to the original method. (4)

robustness: See ruggedness.

ruggedness: The degree of reproducibility of test results obtained by the analysis of the same samples under a variety of minor modifications to the standard test conditions, such as different assay temperatures, mobile phase compositions, flow rates, or injection volumes. Ruggedness is test results of operational and environmental variables of the method, Ruggedness also includes broader concepts checked through a collaborative study: the lack of sensitivity of results to changes in equipment, laboratory, and analyst. Also called robustness. (4)

selectivity: See specificity.

sensitivity: For physicochemical assays, the ability to detect small differences in concentration (the ratio of the change in response of the method to the change in concentration of the analyte, or the slope of the analytical calibration curve).

For non-physicochemical assays (e.g. biological assays), the incidence of true positive results obtained when a test is used for animals known to have the disease or condition. (4)

$$\text{Sensitivity} = \frac{\text{True Positive}}{\text{True Positive + False Positive}} \times 100$$

specificity:

1) Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degredants, matrix, etc. This definition has the following implications:

Identity test: To ensure the identity of an analyte.

Purity tests: To ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e., related substances test, heavy metals, residual solvents content, etc.

Assay (measurement of content or potency): To provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample. (33)

2) The specificity of a method is its ability to measure accurately and specifically the analyte in the presence of components that may be expected to be present in the sample matrix. A method may be "specific" for one or more components of a mixture, but "non-specific" for others. Specificity may often be expressed as the degree of bias of text results obtained by analysis of samples containing added impurities, degradation products, related chemical compounds, or placebo ingredients, when compared to test results from samples without added substances. The bias may be expressed as the difference in assay results between the two groups of samples. Specificity is a measure of the degree of interference (or absence thereof) in the analysis of complex sample mixtures. (4)

standard deviation (SD): The square root of the variance. (4)

sterilization filter (for liquid): A filter which, when challenged with the microorganism. Pseudomonas diminuta, at a minimum concentration of 10/7 organisms per cm^2 of filter surface, will produce a sterile effluent. (32)

test procedure: The test procedure is the total operation necessary to perform the analysis of an analyte: preparation of the sample, of the reference substances or preparations, of the reagents, use of the apparatus, calibration curve, formulae for the calculation, number of replicates and operating procedure for the replicates etc. (7)

trueness: Accuracy is sometimes termed trueness. (18, 33)

validation plan: A documented plan (Validation Master Plan) that describes the policy, philosophy, strategy, and methodology for validating a site, process, or product. The plan can be used as an executive summary within a company or to introduce regulatory personnel to a validation project. The plan should identify responsibilities, as well as equipment and processes requiring qualification or validation. It also may include schedules for an overall process. (19)

validation program: An organized effort designed to provide assurance that all equipment is qualified and processes are validated and that these qualifications and validations are maintained according to current industry practice and regulatory requirements. (19)

validation: The documented act of proving that any procedure, process, equipment, material activity, or system actually leads to the expected results. (39)

variance (Var): A measure of the dispersion of the points about their mean. The standard deviation, that is, the square root of the variance, is also used as a measure of dispersion. (4)

worst case: A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure. (32)

Appendix 5: Validation protocols contributed by a vaccine manufacturer

Massachusetts Public Health Biologic Laboratories

(the examples comprising this Annex were pasted in from original hard copies, and are not available in electronic format)