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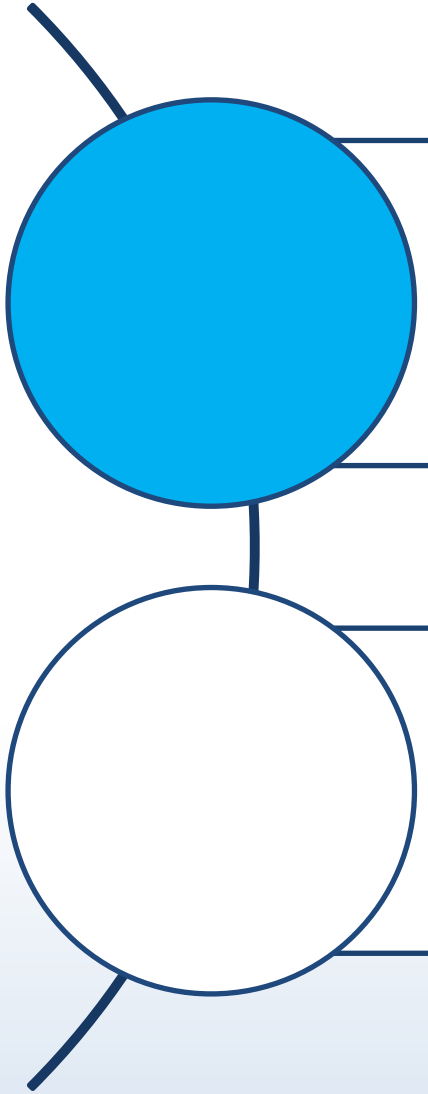
Lecture 5: Planning, Organisation, and Documentation

Topics



Prerequisites and Planning

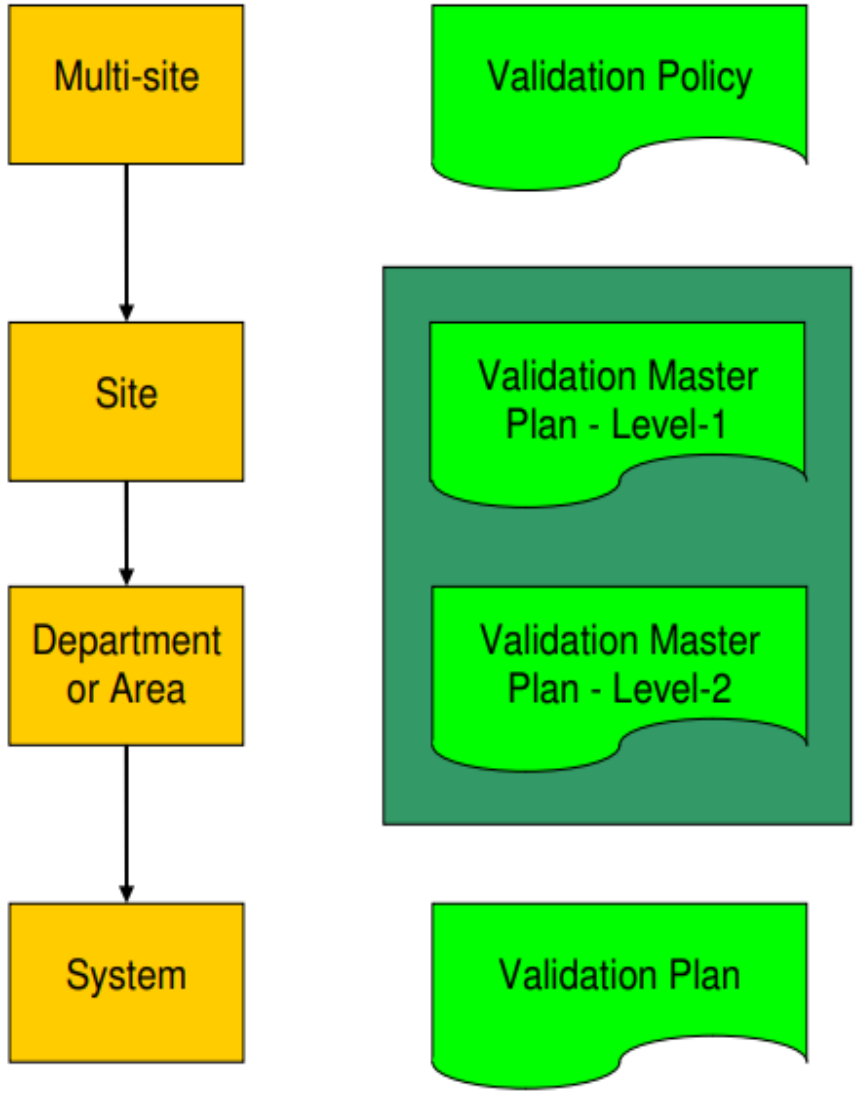
Organisation and Documentation

Validation Prerequisites

Process validation requires that the following are already established:

- Validated analytical assays.
- Calibrated instruments.
- Qualified production support systems.
- The process fully developed, characterized, and documented
- Ranges for operating parameters should be established and justified from development studies.
- Any scaled-down model used in process characterization or validation should be justified as being representative of the full-scale unit operation.
- A multi-function process validation team should be assembled.

Validation Planning Hierarchy



- **Validation Policy:** a company's general, over-arching approach to process validation. Important/useful for companies with multiple sites i.e. consistency.
- **VMP (Level 1):** Describes the validation requirements for the facility and provides a plan for meeting those requirements.
- **VMP (Level 2):** Describes the validation requirements of a specific process/area within the facility e.g. Cleaning/Sterilisation, Manufacturing Process, Analytical Methods, etc.
- **Validation Plan/Protocol:** Describes the process/system to be validated, and how validation will be conducted e.g. bioreactor. Includes: sampling, tests, acceptance criteria…

Planning

- A multi-function process validation team should be assembled.
- The team's first assignment is to design and assemble the Validation Master Plan (VMP).
- The VMP should present an overview of the entire validation operation, its organisational structure, its content, and planning. VMP is a document that summarises the firm's overall philosophy, intentions, and approach to be used for establishing performance adequacy.
- Process validation protocols should then be written describing in detail the procedures to be followed to produce documented evidence that the process has been validated.

Validation Master Plan (VMP)

- Regulators expect that a Validation Master Plan (VMP) will be used – although not mandatory!
- For large projects (e.g. new facility), separate VMPs may enhance clarity (e.g. process VMP, cleaning VMP, etc.)

VMP	
	1. Validation Policy
	2. The organisational structure including roles, responsibilities, and schedules for CQV activities
	3. Summary of the facilities, equipment, systems, and processes within the scope of the VMP, and the qualification and validation status/requirements of each
	4. Change control and deviation management
	5. Analytical methods and testing strategies, including guidance on developing acceptance criteria
	6. References to existing documents
	7. The qualification and validation strategy, including requalification, where applicable

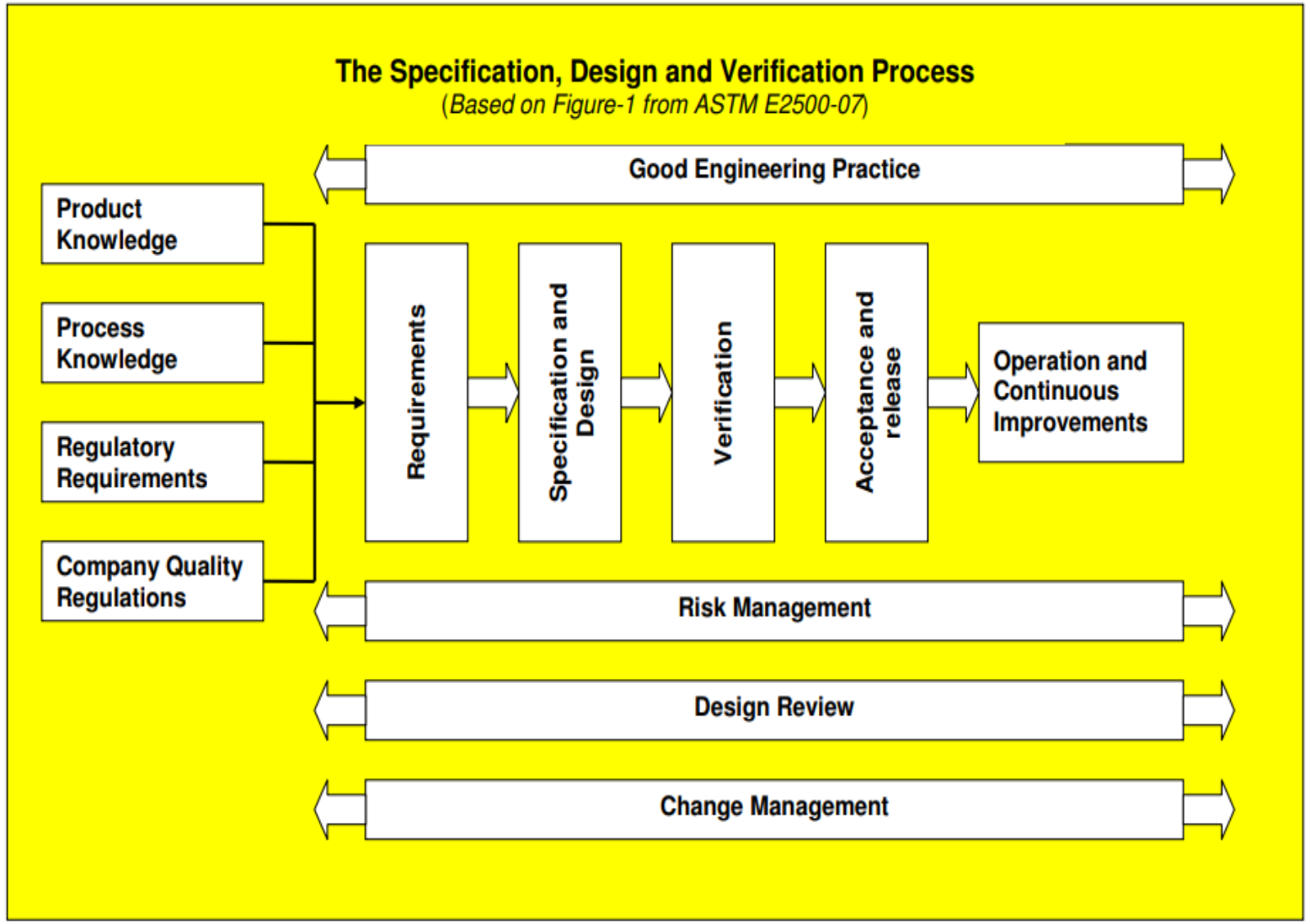
Validation Protocols/Plans (VP)

- Each individual equipment/system will have its own **Validation Protocol/Plan (VP)** (e.g. bioreactor, CIP skid), depending on its complexity**.**

- An example of the information that a VP may include:

URS/FDS	Design Qualification (DQ)	Risk Assessments
Commissioning	Installation Qualification (IQ)	Operation Qualification (OQ)
Performance Qualification (PQ)	Test Acceptance Criteria	Safety and Training Criteria

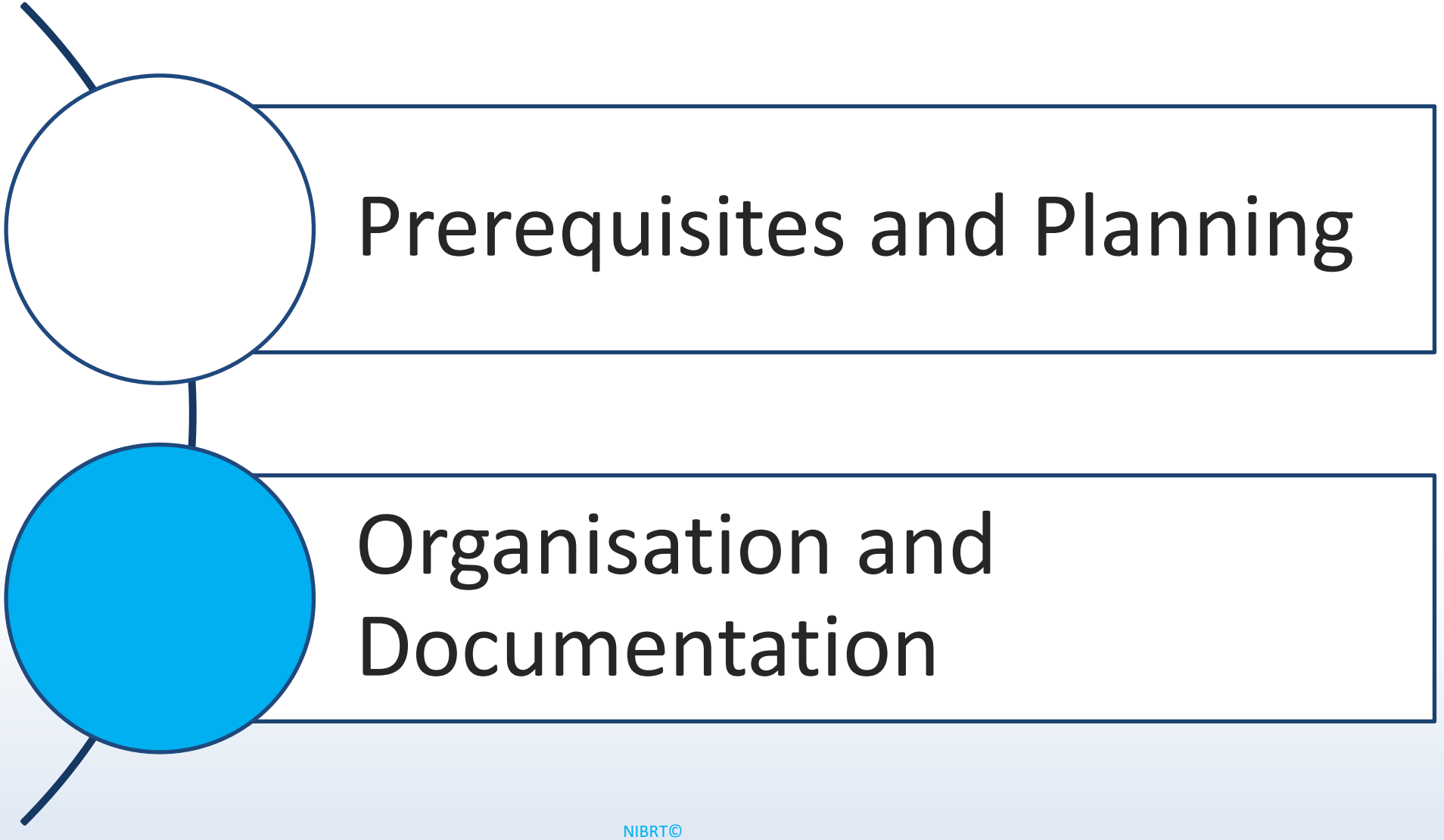
Specification, Design, and Verification Process



In addition to planning, the following are considered critical to modern validation from the outset:

- Product and Process Understanding
- Specification and Design
- Risk Assessment
- Quality Risk Management
- Good Engineering Practice
- Continuous Verification
- Continuous Improvement

Topics


Prerequisites and Planning
Organisation and Documentation

Documentation

- Documentation at each stage of the process validation lifecycle is essential for effective communication in complex, lengthy, and multidisciplinary projects. Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each stage of the lifecycle.

- The degree and type of documentation required is greatest during Stage 2: Process Qualification, and Stage 3: Continued Process Verification.

- Studies during these stages must conform to cGMPs and must be approved by the quality unit in accordance with the regulations.

- Good Documentation Practices (GDPs) are *"those measures that collectively and individually ensure documentation, whether paper or electronic, is secure, attributable, legible, traceable, permanent, contemporaneously recorded, original, and accurate" (WHO).*

GDP Examples

Some general examples of GDP best practices when filling in documentation include:

- All handwritten entries should only be made in Blue ink using a ballpoint pen.
- All entries should be clear and legible.
- The use of whitener or correction fluid is not permitted.
- The preferred date format is DD MMM YYYY e.g., 25 JAN 2022.
- All comments should be initialed and dated by the person entering the comment.
- If any errors are made by individuals while making handwritten entries, the person making the entry shall neatly strike out the incorrect letters/numbers with a single line, correct the entry, and initial and date.
- All blank spaces are to be completed or N/A'd, initialed and dated with a reason if not obvious.

User Requirements Specification (URS)

- Information that serves as the basis for further specification, design, and verification of a manufacturing system (i.e., what does the end-user want?).

- C&Q activities should be structured such that at the end of the C&Q process there is documented evidence that demonstrates that the user requirements have been met.

- ISPE separates user requirements into two categories:
  - Process User Requirements (PURs) are related to product quality and/or GMP regulatory compliance. These requirements must be qualified, or verified as present and operating per design, and documented/approved by Quality Unit.
  - General User Requirements (GURS) are not related to product quality or GMP. These requirements may be critical to personnel safety and/or non-GMP regulatory compliance and should be verified during commissioning activities.

PURS Example – Manufacturing Vessel

Requirement Category	URS Reference	Requirement
General	TK-001-GMP-001	The vessel shall be suitable for the preparation of buffer solutions made of various excipients and water.
Environmental	TK-001-GMP-002	Vessel shall be suitable for operation in an EU Grade C cleanroom environment
Utility	TK-001-GMP-003	The Vessel shall be designed to operate with the following utilities - WFI - 8 barg (max operating), >80degC - PUW - 8 barg (max operating), 20+/-5degC - Clean steam - 3 barg, 143degC - Process Air - 7 barg (max operating), ambient (0.22 micron filtered) - Nitrogen - 7 barg (max operating), ambient (0.22 micron filtered) - Instrument air - 7 barg (max operating), ambient - Chilled Water & Glycol mix - 2 to 30degC (jacket service) - Electrical power to mixer 400V, 3 Phase, 50Hz
Equipment	TK-001-GMP-004	All process connections to the vessel shall be sanitary tri-clamp design.
Equipment	TK-001-GMP-005	The service connections to the vessel jacket shall be non-drip
Equipment	TK-001-GMP-006	The Vendor shall provide a free draining sampling point at the lowest possible position on the vessel for the connection of a NovAseptic sampling device.
Equipment	TK-001-GMP-007	The location of the sample point shall facilitate sampling at the vessel min fill volume of 30 litres. .
Equipment	TK-001-GMP-008	The Vendor shall provide the vessel with a magnetic drive mixer for the purpose of dissolving buffer excipients in WFI and mixing liquids during pH adjustment.
Equipment	TK-001-GMP-009	The vessel shall be capable of achieving mixing speeds of between 120 to 240 RPM.
Process	TK-001-GMP-010	The vessel shall be capable of having a representative sample taken at the minimum stirred volume.

GURS Example – Manufacturing Vessel

Requirement Category	URS Reference	Requirement
Equipment	TK-001-GEP -002	All process piping shall be welded using automatic machine butt welded and Tri clamp type joints
Equipment	TK-001-GEP -003	The Vessel shall be jacketed to allow cooling of the vessel contents.
Equipment	TK-001-GEP -004	The mixer shall be fitted at the bottom of the vessel and have an angled shaft.
Equipment	TK-001-GEP -005	The mixer shall be capable of operating over a vessel fill volume range of ≤60 to 300 litres.
Process	TK-001-GEP -010	The process steps shall be controlled by a PLC using process recipes
Process	TK-001-GEP -011	The vessel shall have an operating volume of ≤30 to 300 litres
Process	TK-001-GEP -012	The vessel shall have a jacket for the supply of chilled glycol for process temperature control. (2 to 45 degC)
Process	TK-001-GEP -013	The vessel jacket shall have a design pressure range of Full Vacuum to 5 barg
Process	TK-001-GEP -014	The vessel shall be capable of being moved between locations with the jacket full.
Process	TK-001-GEP -015	The vessel package shall include an over-pressure relief valve on the jacket service supply complete with a vent pipe terminating 150mm above the floor.

Design & Construction

- A Functional Design Specification (FDS) is a more detailed document which is generated by the vendor and is based off the URS document. It describes how the design of the newly developed machine is going to fulfill the requirements of the end-user.

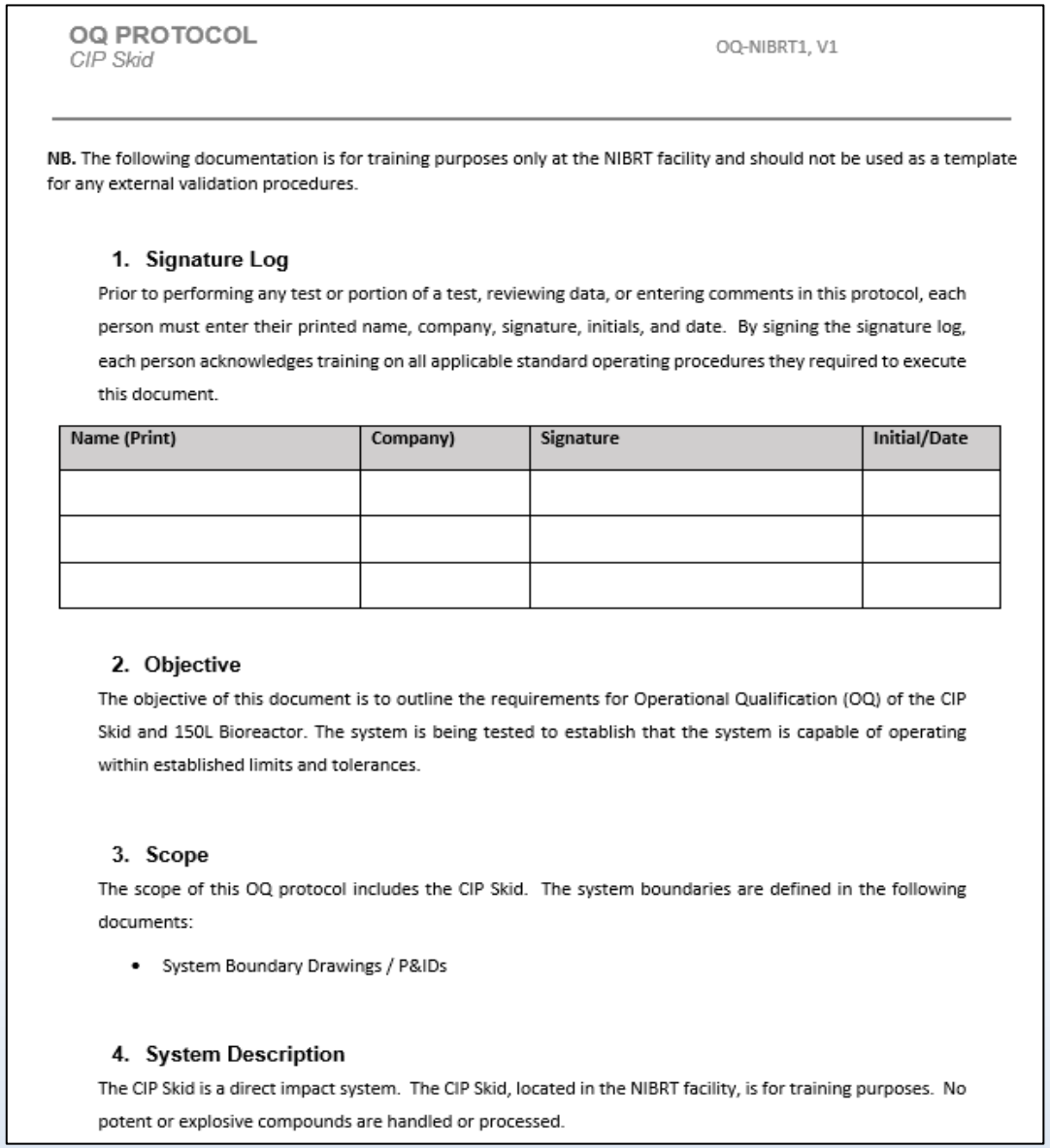
- General arrangement drawings (GAs) present the overall composition of an object and indicate the locations of main piping and system components.

- P&IDs are detailed GMP drawings that are used for design and construction. They are the drawings that provide functional descriptions of systems and their components.

- Following Design Qualification (DQ) based on the above, C&Q tests are completed on the constructed equipment to verify that it has been constructed as per design, is safe to use, and carries out the functions it is required to.

Validation Protocols

- If the equipment is complex, the VP may be broken up into separate Protocols (e.g. IQ protocol, OQ protocol).
- Protocols should outline the purpose, scope, objectives, responsibilities, tests, and acceptance criteria for CQV activities.
- A validation report should be prepared, summarising results, commenting on deviations, and drawing appropriate conclusions, including recommendations to correct deficiencies (PIC/S II Guide).



OQ PROTOCOL
CIP Skid

OQ-NIBRT1, V1

NB. The following documentation is for training purposes only at the NIBRT facility and should not be used as a template for any external validation procedures.

1. Signature Log

Prior to performing any test or portion of a test, reviewing data, or entering comments in this protocol, each person must enter their printed name, company, signature, initials, and date. By signing the signature log, each person acknowledges training on all applicable standard operating procedures they required to execute this document.

Name (Print)	Company)	Signature	Initial/Date

2. Objective

The objective of this document is to outline the requirements for Operational Qualification (OQ) of the CIP Skid and 150L Bioreactor. The system is being tested to establish that the system is capable of operating within established limits and tolerances.

3. Scope

The scope of this OQ protocol includes the CIP Skid. The system boundaries are defined in the following documents:

- System Boundary Drawings / P&IDs

4. System Description

The CIP Skid is a direct impact system. The CIP Skid, located in the NIBRT facility, is for training purposes. No potent or explosive compounds are handled or processed.

Identification of Personnel or Signature Log

- All testing protocols/documents should have a Signature Log for identifying all individuals involved in carrying out or “executing” testing activities, or reviewing the execution of testing activities

Signature Log

Designated personnel, assigned the responsibility for executing or reviewing execution of this document (not the approvers), will sign, initial ar date the corresponding sections listed below:

Name	Signature	Initials	Company	Date

Test Instrument Calibration Verification

- Before commencing testing activities, it should be verified that all instrumentation is calibrated and within calibration expiry dates

TEST INSTRUMENT CALIBRATION VERIFICATION

Verify that all Test Instruments used within this commissioning protocol have current calibration certification, valid during the execution of this test. Attach a copy of the calibration certificates to this protocol.

MANUFACTURER	MODEL	SERIAL NO. / ASSET NO.	CALIBRATION DATE	CALIBRATION DUE DATE	CALIBRATION CERTIFICATE REFERENCE	INITIALS	DATE

Pre-Startup Safety Review

- Pre-Startup Safety Review (PSSR) inspections are performed prior to start-up to ensure that all hazards have been identified and resolved, and that the system can be safely started.
- These are executed and documented by the Project Team which includes EHS, CQV, and Systems.
- A completed PSSR form should be attached to the Commissioning Protocol.

Job Hazard Analysis Worksheet

- Job Hazard Analysis is the process of taking a close, critical look at each step of a process or operation to identify and mitigate hazards or potential accidents in each step.
- Perform a JHA for each type of work. List the job, location, and scope. Include experts from different departments
- Additionally, the Job Hazard Analysis serves as the primary assessment tool for PPE selection

Location: List the site and the location on the site (if applicable) in which the job is to be completed.		Prepared By: Date:
Job: List the Job.	Scheduled Start Date: Enter the estimated start date.	Reviewed By: Date:
Briefly Describe the Job: Give a brief description of job.		
Required PPE: List the required and any supplemental PPE. Add PPE to this section as it is identified during the Analysis. Supplemental PPE:		
Required Permits: List any required permits to be obtained prior to the commencement of this job.		
General Comments: Add any additional comments.		

Task	Potential Accidents or Hazards	Methods to Minimize Hazards

Control of Hazardous Energy: Lockout/Tagout

- Lockout/Tagout (LOTO) involves the practices and procedures used to prevent the release of potentially hazardous energy while performing activities such as maintenance, testing, or inspections.

Attachment 1: Hazardous Energy Control/Isolation Form

Part A: Must be completed by the Authorized Employee

Date: _____ Equipment Name/Description: _____

Purpose for Energy Isolation: _____

Affected Departments: _____

Part B: Identify the energy sources and method of isolation.

Energy Source	Energy Isolating Device (ID)	As Found State	Isolated (Yes / No)	Energy released within work boundaries (Yes / No)	Initial / Date	Lock Removed & Device Returned to As Found State (Yes / No)	Initial / Date
			Yes / No	Yes / No		Yes / No	
			Yes / No	Yes / No		Yes / No	
			Yes / No	Yes / No		Yes / No	
			Yes / No	Yes / No		Yes / No	

Part C: Authorization to proceed with work, servicing, etc. – verification that all hazards have been identified and isolated, and any stored energy within the work boundary has been relieved.

Authorized Employee: _____ Date: _____

Lock Out/Tagout Checked By: _____ Date: _____

Part D: Authorization to return equipment/utility to service -- verification that all locks have been removed, devices positioned as needed to restore the system to the desired state.

Authorized Employee: _____ Date: _____

Test Scripts

- Within each Validation Protocol, the specific testing to be carried out should be documented in individual Test Scripts.
- Upon completion of each test step, the result will be assessed against the acceptance criteria, and assigned either a ‘pass’ or ‘fail’.
- Where a test step fails, a Deviation Report will be generated.
- Each completed test script will also be designated as either ‘pass’ or ‘fail’.
- A second person should verify the executed test and supporting documentation.

9. Testing

9.1 Test Case 1 – Functional Test

Acceptance Criteria:	CIP Skid operates as expected
Test Details:	Execute steps as documented
Tools/Materials Required:	None

Test Step	Description	Expected Result	Actual Result	Pass/Fail	Executed by: Initial/Date
1.	Select cycle 59	“Cycle 59” is displayed.	“Cycle 59” is _____.		
2.	Start cycle from SCADA	Cycle remains idle.	Cycle _____.		
3.	Review OAR and confirm	“OAR” is displayed on SCADA Screen	“Confirm OAR ” is _____.		
4.	Cycle 59 Starts	Cycle starts.	Cycle _____.		
		System running light turns on.	System running light _____.		

Punch List

- Punch lists are often used to document missing or incorrectly tagged items, incorrect structural components, high-level overview of certain issues, etc.

- Action items are typically put into clear categories which indicate the criticality of the deficiency/issue. For example:

Issue Date : 01 JAN 2022

Punchlist Categories/Definitions:
Cat 1 = Safety/Operationally Critical; **Cat 2** = Necessary; **Cat 3** = Design extras; **Cat 4** = Client Extras

Punch No.	System No.	Location	Phase	Contractor	Works Description	Comment	Status (Open/ Close)	Punch Category	Contractor Sign-off	NIBRT Sign-off
1	BR-003	UPS-002	IQ	Vendor01	Gas inlet filter housing FIL-801	Tag missing from gas inlet filter housing FIL-801	Open	3		

Deficiency Form/Punch List

Action items are typically put into clear categories which indicate the criticality of the deficiency/issue. For example:

1. Category 1 (Critical): typically, must be resolved prior to the completion of the current phase testing. In the event of a Critical action item, the testing will either be put on hold, or the specific test will be skipped until the issue is resolved. All critical action items must be resolved and signed off by the client and retesting will be at the discretion of the client.

2. Category 2 (Major): must be resolved prior to current phase testing completion or progression to further testing stages. Major items do not require retesting by client; however, documented evidence is required that the repairs were performed successfully, or the issue was resolved.

3. Category 3 (Minor): must be resolved no later than equipment startup with every effort made to resolve the action items prior to equipment delivery.

4. Category 4 (Extras): are not necessary for equipment functionality but were requested by the client as a system extra/preference. Do not necessarily have a definitive resolution date but should be resolved prior to full startup to satisfy client requests/URS specifications.

Deviation Forms

Deviation Form					
This form is to be used to document any exception noted during execution of this protocol. An individual form is to be used to address each exception. Copies may be made, and pages attached with additional details as required.					
Deviation #:		**Test Case #:**		**Test Step #:**	
Expected Results/Protocol Requirements					
Deviation/Protocol Exception Description					
Initiated by: (Initial/Date)					
Investigation Results					
Response/Corrective Action Plan					
Re-Test Required:	Yes / No	**Why:**			
Prepared by: (Initial/Date)					
CQV Review by: (Initial/Date)					
QA Review by: (Initial/Date)					

- Deviations from the approved validation protocol, test acceptance criteria, or specifications must be documented, investigated, and addressed.
- A Deviation Form is used for this.
- When tests could not be carried out as planned:
  - Describe the issue.
  - Outline how it has been done instead, or an intended resolution/investigation process.
  - Justify any decisions
- An overview of all deviations that occurred during validation should be included in the final Validation Report.

Change Control

- Any changes to equipment or procedures are subject to a Change Control process.
- Change control ensures that proposed changes are justified so that the process is not altered without a thorough review and proper documentation.

"A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state." (EU GMP Annex 15).

	Changes Requiring Control		**Changes Not Requiring Control**
	Major Change	**Minor Change**	**No Relevance to GMP**
Significance of Change	Influences product quality or process reliability	Influences a unit operation requiring control	No relevance to GMP or authorization
Example	Change to the process parameters	Replacement of apparatus part of the same design	Change to working times

Periodic Re-Validation & Validation Report

- Direct Impact equipment should be re-validated on a regular, defined basis (e.g., yearly) to confirm validation status.

- Following validation/yearly revalidation, a Validation Report will be generated summarizing all validation/revalidation activities and the validated state of critical equipment.

- The Annual Validation Summary Report covers:
  - all revalidation and new equipment qualifications performed
  - all Change Control Requests (CCRs) performed
  - a full list of all deviations identified during revalidation
  - calibration and preventive maintenance planned, and maintenance protocols added.

Fast-Tracking: Leveraging

- Some tests may be required across multiple stages of CQV. Is it always necessary to repeat these tests?
- Leveraging of previously completed test results can improve the project's overall efficiency and timelines by reducing duplication of testing (where applicable).
- Leveraging of tests must be predefined in the VMP/VP.
- If testing is being leveraged from previous documents (e.g. FAT, SAT, etc.), a copy of the leveraged data must be attached to the current protocol.

Leveraging

Leveraging of test results is only acceptable when:

- The testing was performed under controlled circumstances and Good Documentation Practices (GDP).
- The test results are checked by a qualified individual.
- No modifications have been made to the equipment or specifications after approval of the previously completed test.
- The reasoning behind leveraging of the test results is scientifically justified and outlined in a pre-approved protocol.

- **The Traceability Matrix** is used to determine when testing is required, and which tests may be leveraged during CQV. The current version of the Traceability Matrix should be used at all times.

Traceability Matrix

- A Traceability Matrix is a way to track testing and leveraging opportunities across different stages of the CQV lifecycle.
- It is also used to confirm when testing was completed, or when certain testing was leveraged, at each stage.
- The Traceability Matrix helps to keep track of CQV testing activities, and provides a succinct visual description of past, present, and future validation testing requirements.
- The Traceability Matrix should be updated regularly, included in the testing protocol documentation for each stage of CQV activities, and signed-off after completion of each CQV stage for a given process/equipment piece.
- It is a key document for streamlining/fast-tracking the overall validation effort.

Traceability Matrix e.g., OQ Tests

URS #	Brief description	FAT	SAT	Com	IQ	OQ	PQ	Remarks
	Operational and Functional Requirements PW Storage & Distribution							
OR-18	The PW Storage and Distribution System shall consist of the following stages. - Storage tank - Distribution Loop with Heat exchangers for Cooling and Heating - Ozone generation - UV Unit for Ozone Destruction	FAT-03 **Passed**	SAT-03 **Leveraged FAT**	IC-03 **Leveraged FAT**	IQ-03 **Passed**	OQ-03 **Leverage IQ**		**Leverage IQ P&ID walkdown.**
OR-23	Operational Parameters to be measured & alarmed for Storage/Distribution System: a. Conductivity (uncompensated for temp.) and TOC. b. Temperature. c. Pressure at the POU to be above pressure of user. d. Flow in the distribution loop to be turbulent at all times. e. Sanitization:	n/a	n/a	OC-08 **Passed**	n/a	OQ-08 **Leverage OC**		**Test Passed in OC. Acceptance Criteria met. Test is Leveraged.**
ER-9	The internal surface of Storage tank must at all times be wetted during operation.	n//a	n/a	IC-07 **Passed**	n/a	OQ-07 **Test to be carried out**		**Re-test during OQ. IC testing not sufficient for OQ.**
OR-19	It must be possible to take a sample: - Downstream the Storage tank - Post UV lamp - At each POU - In return loop (close to storage tank)	n/a	n/a	IC-23 **Passed**	IQ-23 **Leveraged IC**	OQ-23 **Leverage IC**		**Leverage IC testing**
PR-2	Produced water to meet minimum requirements for PW quality [13]: - Bioburden $\leq$ 1000 CFU/ml - Absence of coliforms and P. Aeruginosa and B. cepacia - Endotoxin $\leq$ 0.5 EU/ml - Conductivity $\leq$ 1.3 µS/cm @ 20°C - TOC $\leq$ 500 ppb (0.5 mg/l) - Nitrates $\leq$ 0.2 mg/l (0.2 ppm) - Heavy metals $\leq$ 0.1 ppm	n/a	n/a	n//a	n//a	OQ-26 **Test to be carried out**		**3 Day testing required for OQ**

Fast-Tracking: Other Methods

Bracketing: only batches on the extremes of certain predetermined specifications(e.g., strength, batch size) are tested during process validation. It is assumed that validation of any intermediate levels is represented by validation of the extremes.

Family (Grouping) Approach: similar equipment are grouped together and treated as a “family”. The family of equipment can undergo reduced validation exercises:

e.g. 3 identical bioreactors –

- Bioreactor #1 = 3 x PPQ runs
- Bioreactor #2 = 1 x PPQ run
- Bioreactor #3 = 1 x PPQ run

Thank You

Resources

- ASTM E2500-07 " Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Systems and Equipment" (2007)
- ISPE Good Practice Guide – Good Engineering Practice (2008)
- ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems and Equipment (ISPE FSE Guide) (2011)
- ISPE Good Practice Guide: Applied Risk Management in Commissioning and Qualification (2011)
- ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification (2001)
- ISPE Baseline® Guide: Volume 5 2nd Edition – Commissioning and Qualification (2019)
- EudraLex Volume 4 - EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use
- European Good Manufacturing Practice (EU GMP) Part I - Basic Requirements for Medicinal Products
- EU GMP Annex 1 – Manufacture of Sterile Medicinal Products
- EU GMP Annex 15 – Qualification and Validation
- EU GMP Annex 20 – Quality Risk Management
- FDA 21 CFR Part 210 – Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs; general.
- FDA 21 CFR Part 211 – Current good manufacturing practice for finished pharmaceuticals.
- ICH Q9 – Quality Risk Management
- ICH Q10 – Pharmaceutical Quality System
- PIC-006 Validation Master Plan Installation and Operational Qualification Non-Sterile Validation Cleaning Validation
- PIC-008 Explanatory Notes for Pharmaceutical Manufactures on the preparation of a Site Master File.
- www.ivtnetwork.com