Controlled Environment Commissioning and Qualification
“Using a Phased Approach to meet schedule demands”

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Effectively Integrating C&Q with Construction & Startup Activities

• Setting the Stage:
  • There’s a firm construction schedule
  • There’s a firm manufacturing startup schedule

• Question – Guess what’s in the middle ??

• Answer - The Quality Systems

• C & Q is usually the “odd-man-out” in this scenario
Effectively Integrating C&Q with Construction & Startup Activities

• WHY ?? …(the usual suspects)
  - Construction delays; delivery issues; punchlists not completed
  - Manufacturing startup dates get pulled in due to operations or product related issues, validation runs etc.

• Results…
  - Commissioning and Qualification timelines usually get compressed (aka “SQUEEZED”)
  - This program outlines a phased approach to Cleanroom and Utilities Qualification while maintaining Quality and Regulatory requirements plus meet the plant’s business requirements

Applicable Documents

• 21 CFR 820 – QSR (Quality System Regulations)
• 21 CFR 210 & 211 – cGMP’s for Combination Prod.
• ISO-13485 Medical Device – Quality Management
• ICH Q7A - FDA cGMP’s for API’s
• ICH Q9 – FDA Quality Risk Management
• ASTM Standard (E2500-07)- Commissioning
• USP <1116> Microbiological Evaluation of CE
• USP <645> Purified Water Conductivity Testing
• ISO-14644 (Parts 1-4) Cleanrooms & Associated CE’s
• ISO- 8573-1(Part 1) Compressed Air Purity
• IES – Illumination Society
Phased Approach to Qualification Execution

• Intent is to develop a Controlled Environment and critical utility Qualification Strategy that allows manufacturing lines to be installed, validated, and begin Human-Use product builds

• Using this strategy we can document and execute a logical and defendable Qualification Plan to commission, certify, & qualify CE’s and systems as construction and startup is completed

• Ultimate goal of this phased approach is to accommodate an expected “staggered” manufacturing

• Develop a “Phased” Quality Plan approach if necessary
  • Allow the Qualifications to be split up into phases for each of the areas being constructed
  • Main sections of the plan should include:
    ➢ Commissioning and Pre-Funct / Functional testing
    ➢ Qualification (MVP’s; IQ, OQ & PQ testing)
    ➢ System Acceptance

• Generate, execute, and approve each document set as the sections of the project is turned over
Phased Approach to Qualification Execution

• For Commissioning:
  • Complete and approve a “Design Intent Document” (DID)
  • Develop commissioning plans that will incorporate a segregated approach
    ➢ HVAC systems
    ➢ BAS / Central Monitoring system
    ➢ CDA
    ➢ High Purity water
  • Integrate commissioning early in the construction schedule
  • Have document formats agreed to up front

Phased Approach to Qualification Execution

• For Qualification:
  • Develop an “all encompassing” Quality Plan that documents clearly this approach
  • Develop multiple Master Validation Plans
  • Focused based IQ; OQ; & PQ’s; as the system’s get turned over based on Commissioning completion
  • Integrate commissioning test results in Qualification & Validation documents
Phased Approach to Qualification Execution

• Expect manufacturing to push the envelope

• Not all equipment will be installed at the same time

• Ultimate goal of this phased approach is to accommodate an expected “staggered” manufacturing process validations

Initial Steps

• Create Project Quality Org Chart
• Define Roles and Responsibilities
  • System Owner’s / SME’s
  • 3rd Party Commissioning Team
• Develop Project Quality Scope
  • Use MS Project to define task list
  • Assign durations
  • Assign Responsible owners (key !! for resources)
• Develop multiple Master Validation Plans (MVP) that documents in detail the scope of each Qualification with Acceptance Criteria
Some Base Assumptions to a Phased Qualification Approach

- Document requirements increase threefold
- Infrastructure should be commissioned and approved “prior” to starting Qualification
- Controlled Environments must pass “as built” certifications on schedule
- Preliminary Certification report submitted to Quality Team for Review
Constraints to this Approach…

• Executing Qualification tests while construction to other areas still –on going
• Working under “Clean” Conditions
• Critical Utilities commissioned and passed
• Systems and controls that “overlap” infrastructure that’s completed and not-completed (how to test ? )

Constraints (continued)

• Any deviations and corrective actions remediated and re-tested

• Final approvals on all Qualification Reports need to occur before manufacturing is released
Qualification Requirements - Master Validation / Qualification Plans –(MVP’s / MQP’s)

• Heart of this Qualification approach
• Usually first document read by auditor
• Describes in detail what your going to do and why *(that’s the rationale)*
• Specifics on systems being Qualified and level of Qualification (risk-based)
• Describes when manufacturing can start *(at which point in Qualifications)*

Qualification Requirements (IQ’s; OQ’s & PQ’s)

• IQ – (as built conditions) for CE
  • As – Built Certification completed (verify only)
    • 72 hour Temperature / Humidity / DP trends accepted
    • RCP drawings approved and verified
    • Non-Viable Particulate Counts Pass (verify only)
    • Light levels certified (verify only)

• IQ – (as built) for HP H₂O & CDA
  • Commissioning Report Verifications
  • CDA Certification Reports Verifications; Approved
  • CDA System Component verifications (piping; tags)
  • HP H₂O ( tags; certs; instruments calibrated; SOP’s drafted)
  • As-built drawings completed or red-lined
  • All material certifications reviewed and approved
Qualification Requirements (cont.)

- OQ testing – CE (at-rest / in-operation)
  - SOP’s approved (Cleaning; PM; EM)
  - Microbial Sampling Plan (Airborne, Surface & Water)
  - Process equipment moved in and connected
  - OQ duration - 24 hour / 5 Day operational (functional) tests
    - Temperature trends -(can use chart recorders for data)
    - Humidity trends- (chart recorders for data)
    - DP trends - (manual documentation during test period)
    - CMS action limit alarm tests (if applicable)
  - Deviations remediated
  - OQ summary report approved

  CE & systems released for Process Validation runs
  (NOTE: product is NOT for human use applications at this stage)

Qualification Requirements (cont.)

- OQ testing for Critical Utilities – (in-operation)
  - Operational tests at spec (per Design Intent) conditions
    - Pressure
    - Flows
    - Control Logic
  - Worst Case challenge (if applicable)
    - “Worst case identification needs to be defendable”
  - Alarms (alert/action levels)
  - Sampling Plans (H₂O / CDA)
  - SOP’s are completed and approved
  - Deviations remediated
  - OQ summary report approved
Qualification Requirements (cont.)

- PQ testing – CE (in-operation - routine)
  - PQ duration (to prove repeatability) min 2-3 manufacturing weeks
  - SOP’s approved (Cleaning; PM; EM)
  - Microbial Sampling Plan (Under Routine Monitoring)
  - Manufacturing Line running in-human use product
  - Subsequent Equipment Move in and connections
  - PQ summary report approved

- Cleanroom and systems released for in-human use manufacturing

Qualification Requirements (cont.)

- Master Validation Reports
  - Summarize Qualification results
  - Identify Discrepancies Root Causes and Resolutions
  - System Acceptance documented
  - Approve MVR’s
Qualification Requirements - Additional Manufacturing Equipment Moves

- Manufacturing line 2,(N) install in CE –
  - Create Change Control documents
    - Amend Sampling Plan drawing
    - Cleaning SOP’s
    - Amend Layout drawing
  - Generate new PQ protocol for CE testing
    - Additional EM monitoring to new line (plus existing)
    - Temperature / Humidity Data (during install and start-up of new line)
    - DP Data (during install and startup)
    - Existing product builds are “at-risk” and go on hold
    - Generate and Approve new line PQ summary report

Qualification Requirements - Additional Manufacturing Equipment Moves

- PQ Report Approval signifies…
  - Release of new equipment for process validation runs
  - Existing lines’ production (at-risk) comes off product hold and can be shipped
  - CE ready for next line move in.
Thank you
Questions / Comments

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