ENGINEERING PHARMACEUTICAL INNOVATION

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

Phased Approach to Qualification Execution

- 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

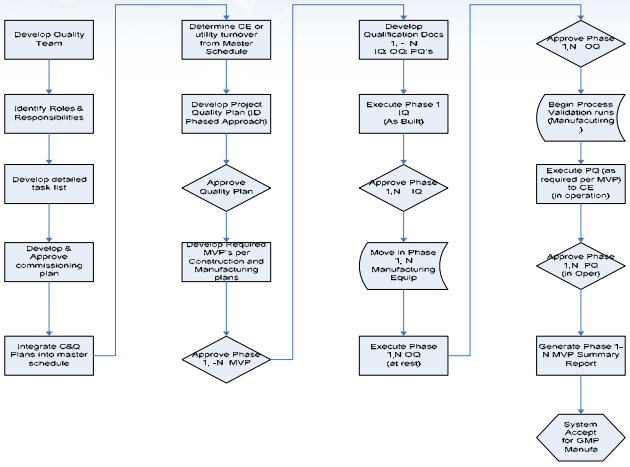
Phased Approach to Qualification Execution

- 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

Overview Flowchart



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 H_2O & CDA**
    - Commissioning Report Verifications
    - CDA Certification Reports Verifications; Approved
    - CDA System Component verifications (piping; tags)
    - HP H_2O (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 (H_2O / 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.

Q&A

Thank you

Questions / Comments

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