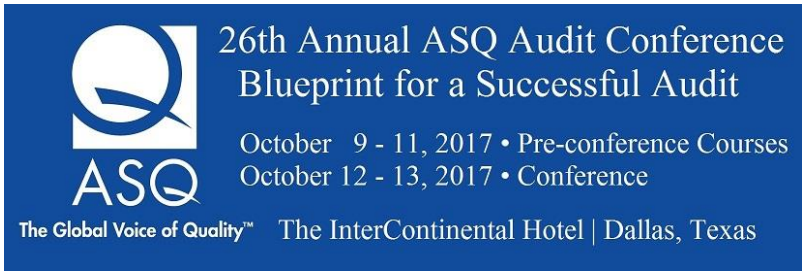

ASQ Audit Division
The Global Voice of Quality™

Audit Validation Programs Like a Champ (When your time is limited!!)

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FDA 483 Observations

CFR Reference	483 Frequency	Short Description	Long Description	Program Related Item
21 CFR 820.70(g)	3	Equipment design and installation	Equipment used in the manufacturing process has not been appropriately [designed] [constructed] [placed] [installed] to facilitate maintenance, adjustment, cleaning, and use. Specifically, ***	C&Q, URS
21 CFR 820.70(a)	2	Process control procedures	Process control procedures that describe any process controls necessary to ensure conformance to specifications were not [established] [defined] [documented] [implemented]. Specifically, ***	PV (PPQ), CPV
21 CFR 820.30(g)	2	Design validation - simulated testing	The design was not validated under actual or simulated use conditions. Specifically	Process Design, PV (PPQ)
21 CFR 211.110(a)	65	Control procedures to monitor and validate performance	Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically, ***	PV (PPQ), CPV
21 CFR 820.70(a)	54	Process control procedures, Lack of or inadequate procedures	Process control procedures that describe any process controls necessary to ensure conformance to specifications have not been [adequately] established. Specifically, ***	PV (PPQ), CPV
21 CFR 820.70(a)	30	Production processes	Production processes were not [developed] [conducted] [controlled] [monitored] to ensure that a device conforms to its specifications. Specifically, ***	PV (PPQ), CPV
21 CFR 820.75(b)	15	Lack/Inad procedure-Monitoring/Control of Validated Proces	Procedures for monitoring and control of process parameters for a validated process have not been [adequately] established. Specifically, ***	PV (PPQ), CPV
21 CFR 820.75(b)(2)	11	Documentation of validated process performance	There is [no] [inadequate] documentation of [monitoring and control methods and data] [the date performed] [the individual performing the process] [the major equipment used] for a validated process. Specifically, ***	PV (PPQ), CPV
21 CFR 820.70(g)	10	Equipment Installation, Placement, Specified Requirements	The [appropriate design, construction, placement, and installation of manufacturing equipment have not been ensured] [equipment used in the manufacturing process does not meet specified requirements]. Specifically, ***	C&Q, URS
21 CFR 820.70(g)(2)	4	Periodic equipment inspections	Periodic inspections of equipment [were not] conducted to ensure adherence to applicable maintenance schedules [were not documented]. Specifically, ***	Periodic Review

*Reference: http://www.fda.gov/ICECI/Inspections/ucm381526.htm#devices

FDA 483 Observations

CFR Reference	Frequency	Short Description	Long Description	Program Related Item
21 CFR 211.160(b)	133	Scientifically sound laboratory controls	Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity. Specifically, ***	CV, PPQ, TMV
21 CFR 211.113(b)	70	Procedures for sterile drug products	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed]. Specifically, ***	PPQ
21 CFR 211.67(a)	65	Cleaning / Sanitizing / Maintenance	Equipment and utensils are not [cleaned] [maintained] [sanitized] at appropriate intervals to prevent [malfunctions] [contamination] that would alter the safety, identity, strength, quality or purity of the drug product. Specifically, ***	CV
21 CFR 211.42(c)(10)(v)	57	Cleaning System	Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the [room] [equipment] to produce aseptic conditions. Specifically, ***	CV
21 CFR 211.68(b)	55	Computer control of master formula records	Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Specifically, ***	CSV, C&Q
21 CFR 211.110(a)	52	Control procedures to monitor and validate performance	Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically, ***	CPV
21 CFR 211.63	48	Equipment Design, Size and Location	Equipment used in the manufacture, processing, packing or holding of drug products is not [of appropriate design] [of adequate size] [suitably located] to facilitate operations for its [intended use] [cleaning and maintenance]. Specifically, ***	C&Q, URS

FDA 483 Observations

CFR Reference	Frequency	Short Description	Long Description	Program Related Item
21 CFR 211.113(b)	48	Validation lacking for sterile drug products	Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include [adequate] validation of the sterilization process. Specifically, ***	C&Q, PPQ
21 CFR 211.165(e)	47	Test methods	The [accuracy] [sensitivity] [specificity] [reproducibility] of test methods have not been [established] [documented]. Specifically, ***	CV, PPQ, TMV
21 CFR 211.58	29	Buildings not maintained in good state of repair	Buildings used in the [manufacturing] [processing] [packing] [holding] of a drug product are not maintained in a good state of repair. Specifically, ***	Periodic Review
21 CFR 211.42(a)	17	Buildings of Suitable Size, Construction, Location	Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable [size] [construction] [location] to facilitate cleaning, maintenance, and proper operations. Specifically, ***	C&Q, URS
21 CFR 211.42(c)	11	Defined areas of adequate size for operations	The [separate or defined areas] [control systems] necessary to prevent contamination or mix-ups are deficient. Specifically, ***	C&Q, URS
21 CFR 211.67(b)(3)	8	Cleaning SOPs/instructions	Procedures for the cleaning and maintenance of equipment are deficient regarding sufficient detail of the methods, equipment, and materials used in the cleaning and maintenance operation, and the methods of disassembly and reassembling equipment as necessary to assure proper cleaning and maintenance. Specifically, ***	CV
21 CFR 211.67(b)(5)	8	Cleaning SOPs/equipment protection	Procedures for the cleaning and maintenance of equipment are deficient regarding the protection of clean equipment from contamination prior to use. Specifically, ***	CV, CHT
21 CFR 211.68(b)	8	Backup file not maintained	Failure to maintain a backup file of data entered into the computer or related system. Specifically, ***	CSV, C&Q
21 CFR 211.68(b)	7	input/output verification	Input to and output from [the computer] [related systems of formulas] [records or data] are not checked for accuracy. Specifically, ***	CSV, C&Q

Auditing Validation

- How to cover Validation adequately when time is limited?
  - Focusing on key issues in various disciplines
  - Focus on an equipment train for product or products of interest
    - Will cover other Quality Systems such as
      - Calibration
      - Preventive Maintenance
      - Unplanned Maintenance
      - Operational Procedures
      - Cleaning Procedures

Auditing Validation

- Initial Questions are:
  - Is there a Site Validation Master plan
    - Does it cover all of the disciplines for Validation:
      - CSV
      - CV
      - C&Q for EFU
      - PV or PPQ
  - Ask for inventory list of all validations conducted at the site
    - Should be part of the Site Validation Master plan
    - Ask for the Periodic Review Schedule (CPV, Cleaning, and Equipment, Facility, Utility)

Auditing Validation

- Are there Program Policies for each of these disciplines?
- Does each Masterplan or policy outline the lifecycle of that discipline:
  - Does the document or documents cover Stage 1, Stage 2 (A&B), Stage 3
    - Conception to development/characterization to confirmation to monitoring to retirement/deactivation/decommissioning

- Once there is an understanding of the product/process and Equipment Train
  - Focus document requests around this process (equipment train)

Auditing Validation

- Pull all related documents for this product
  - Equipment Train
    - IOQ and PQs
  - Process Validation (PPQ)
  - Cleaning Validation
    - Clean Hold Times
    - Dirty Hold Times
    - Campaign Studies
  - Test Method Validation
    - Analytical
      - Assay
      - Content Uniformity/Dissolution
      - Active and Cleaning Agent
    - Microbial

Process Validation

- Understand what type of validation they perform at the facility (this should be in the Masterplan or Policy)
- **Prospective Validation**: is conducted before a new product is released for distribution or, where the revisions may affect the product's characteristics, before a product made under a revised manufacturing process is released for distribution.
- **Concurrent Validation**: is the concurrent release of batches prior to completion of the PPQ study. "Concurrent validation is appropriate for processes used infrequently for various reasons such as to manufacture drugs for which there is a limited demand (e.g., orphan drugs, minor use and minor species veterinary drugs) or which have short half-lives (e.g., radiopharmaceuticals, including positron emission tomography drugs). Concurrent release is also appropriate for drugs that are medically necessary and are being manufactured in coordination with the Agency to alleviate a short supply."
- **Retrospective Validation**: No longer allowed by the Agency

Process Validation

- There are three stages of Process Validation.
  - Stage 1 – Process Design – The process used for the manufacturing of commercial product is defined during this stage based on knowledge gained through process development and OQ activities.
  - Stage 2 – Process Performance Qualification (PPQ) – During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
  - Stage 3 – Continued Process Verification – Ongoing assurance is gained during routine production that the process remains in a state of control.

Process Validation

- Stage 1—Process Design (Process Design/Technology Transfer)
  - The Product Development Report and/or Technology Transfer Summary Report must be completed and approved prior to the initiation of the PPQ study.
    - Any additional studies or assessments to understand process variability must be conducted under an approved protocol or Technical document.
    - Data must be generated to support the Critical Process Parameters and Key Process Parameters operational ranges (establishment of upper and lower limits) for the specific manufacturing process that will undergo the PPQ study.
- Technology Transfer Report or Development Report (review to look at CPP ranges and data to support PPQ)

Process Validation

- PPQ Study Design
  - The PPQ batches must use the same manufacturing process that is intended for commercialization.
  - All raw materials and components used in the PPQ study shall have successfully completed applicable incoming inspection requirements.
  - Test methods required for the PPQ study must be qualified or validated prior to the execution of the study.
  - To address potential variability, the design of the study must include evaluation of 2 different lots of active RM
    - If not fully assessed in Stage 1
- Focus Audit efforts on the Sampling Strategy and study design

Process Validation

- PPQ Sampling Strategy
  - Heightened sampling is required in PPQ
    - Blend Uniformity
    - Dosage Uniformity
    - Physical Attributes (e.g. tightened AQL approach)
  - Significant Process Events
    - Determine what events occur in the process to identify sampling locations for validation exercise
  - Stratified Sampling
    - Inter and Intra Batch consistency must be included to assess robustness of the process
      - Intra – Demonstration that batch consistency is from first piece to last piece inspection
      - Inter – Demonstration that batch is consistent from batch to batch on same equipment train/process

Process Validation

- The CPPs must be run at established nominal/midpoint values of the operating range.
- Specifications and/or pre-determined acceptance criteria cannot be changed during the PPQ study due to excursions or failures.

- Final Report
  - Focus on Deviations in the PV Report
    - Root Cause
    - Corrective Action
    - NO Replacement Batches
  - Summary of Results against Acceptance Criteria

Process Validation/Continued Process Verification

- Stage 3
  - If full confidence was not gained in the PPQ study, continued heightened sampling would be conducted under a CPV program/protocol
  - Heightened validation sampling may be required to be continued after the study to gain confidence of inter and intra-batch consistency, if the sample population was not of significance during the PPQ study.
  - The heightened sampling and testing must be summarized and an input to the CPV plan.

Process Validation/Continued Process Verification

- Stage 3 – Heightened Sampling
  - If full confidence was not gained in the PPQ study, continued heightened sampling would be conducted under a CPV program/protocol
  - Heightened validation sampling may be required to be continued after the study to gain confidence of inter and intra-batch consistency, if the sample population was not of significance during the PPQ study.
  - The heightened sampling and testing must be summarized and an input to the CPV plan.

Continued Process Verification (CPV)

- Stage 3 – CPV Program
- Post PPQ when no Heightened Sampling Required
- The data must be trended and reviewed, per the CPV protocol or plan, by personnel with adequate training in statistical process control techniques.
- Data Review and Reporting Frequency –
  - Establish how frequently the data will be analyzed and reported, following the principles below.
    - Frequency of evaluating/reporting to be performed in the CPV Plan must be determined based on factors such as process capability identified from the initial CPV assessment data,
    - the PPQ and other aspects of the process understanding including process complexity, production volume, and experience with similar products and processes.

Continued Process Verification (CPV)

- Process variability must be periodically assessed; sampling and/or monitoring adjusted accordingly.
- To assess CPV and detect process drift, the following items (at a minimum) must be considered:
  - Trending and tracking deviations, investigations, and quality events
  - Complaints
  - Out-of-specification and out-of-trend findings
  - Process Yields
  - Process data, including CPPs, KPPs, and CQAs
  - Records for incoming components and raw materials

Process Validation CFR References

- Lack of Appropriate Development (Stage 1)
  - CFR 820.75(b)
- Lack of Appropriate Process Control Strategy (Stage 1)
  - CFR 211.186(a)
  - CFR 211.110(c)
- Lack of appropriate Process Validation (PPQ Studies) (Stage 2B)
  - CFR 211.100(a)
  - CFR 211.110(a)
  - CFR 820.30(g)
- Lack of Continued Process Validation Program
  - CFR 211.180(e)
  - CFR 820.70(a)

Cleaning Validation

- Stage 1
  - Has the Right Cleaning Agent been chosen?
  - Development of an appropriate Cleaning Process and demonstration of the following:
    - Choosing the Right Cleaning Agent
    - Try different manufacturers of cleaning agents
    - Be aware of safety issues for operators in the manufacturing area
    - Be aware of long term damage to equipment parts (e.g. soft metals, plastics, rubber, etc.). Cleaning Agent compatibility
    - Application Use: CIP, want non-foaming/sudsing

Cleaning Validation

- Stage 1 – Acceptance Criteria (Pre-determined)
- NOEL, Therapeutic Dose or 10 ppm
  - All are part of MACO (Maximum Allowable Carryover) calculations
  - Typically, a company with use NOEL or Therapeutic and 10 ppm and chose the tightest criteria for each worst case active
  - If criteria is greater than what can be visibly seen by the naked eye, is the acceptance criteria providing the confidence that you need to state the cleaning process is effective?

Cleaning Validation

- Laboratory (methods to be validated)
- ICHQ2(R1) Requirements have been met
- Coupon Recovery
  - MOCs that will be swabbed
  - Rinse
  - Swab
- Specificity Testing (Swab interference, etc.)
- LOD/LOQ
- Solvent/Swab Stability
- LOD verified on coupon studies

Cleaning Validation

- Matrix Rationales
- Ensure that all excipients are covered and included in rationale
- Ensure that toxicity levels are determined for each component
  - Ensure that toxicity is considered when determining worst case marker
  - Toxicity can be represented in the acceptance criteria
  - Ensure pharmacological potency is considered when determining worst case marker

Cleaning Validation

➢ Stage 2

- All studies should include the following:
  - Visual inspection
  - Microbial testing (especially if manual process and if using any potable water in the process even if the final rinse is USP or IPA)
  - Active testing
  - Cleaning Agent testing
- All microbial and analytical methods must be validated with recovery studies on all Materials of Construction.
- All Materials of Construction and Surface Area Calculations must be defined in the protocol
- Adequate number of swabs should be per equipment based on hard to clean/product or water hold up locations
- Swab Diagrams/Pictures

Cleaning Validation

- Training
  - All individuals performing swabbing including microbial and analyte must be qualified
    - Demonstration of recovery must be performed for all chemical analysis
    - Aseptic Technique must be demonstrated for all microbial sampling
  - Visual Inspection
    - Operators, Quality and Validation personnel must be qualified through coupon or other means on visual inspection to an acceptable level. Level is defined and determined through testing

Cleaning Validation

- Campaign Studies (based on number of lots or days)
  - Major Cleaning after the number of lots of days
- Clean Equipment Hold Studies
  - Evaluates Storage
    - Microbial concerns
- Dirty Equipment Hold Studies
  - Can be incorporated in the original CV design

Cleaning Validation

- Stage 3
- Cleaning Monitoring Program/Surveillance Program
- Periodic Swabbing
  - Manual cleaning processes – more frequent swabbing (1x CV run)
  - CIP systems require less swabbing results (1x CV Run)
- Automated Processes
  - Review of:
    - investigations,
    - change controls,
    - addenda validation/qualification,
    - unplanned maintenance work orders
    - Planned maintenance
    - Calibration (specifically out of tolerance)

Cleaning Validation CFR References

- Lack of Cleaning Validation and appropriate Cleaning Validation (Stage 1 through 3)
  - CFR 211.67(a)
  - CFR 211.67(b)
  - CFR 211.42(c)(10)(v)
- Lack of appropriate Clean Equipment Hold Time Studies
  - CFR 211.67(b)(5)

Equipment Qualification

- User Requirement Specifications (URS) are required for each asset and/or system.
  - The URS is based on knowledge of a specific manufacturing process.
  - The URS is derived from critical aspects, including CQAs, CPPs and KPPs (including control limits and accuracies), process capabilities, process capacity, operability, asset availability, environmental considerations, safety and other attributes that have influence on product quality.

Equipment Qualification

- URS
  - Design requirements for equipment/systems controlling both CPPs and KPPs will be specified in the URS.
  - Resources used to support development of these requirements will include, but are not limited to:
    - Quality Standards for HVAC, compressed gases, process and Computer Systems Validation.
    - Vendor Specifications
    - Engineering Specifications (e.g. piping, instruments, etc.)
  - The URS is revised to incorporate additional CPPs that may be identified through the design phase, development studies or OQ studies.

Equipment Qualification

- Installation Qualification
  - IQ contains test cases to document confirmation of proper installation of the equipment/system according to design specifications.
  - This involves confirmation of the installed components of a piece of equipment, including supporting infrastructure.
  - IQ also involves confirmation of the existence of maintenance and calibration controls, such as draft work instructions.
  - IQ documents the proper installation and other static features of the equipment according to the user requirements.

Equipment Qualification

- What to expect to see in an IQ (not all inclusive):
  - Lubricant list Verification
  - System Walk down Verification
  - Major Components Verification
  - Utilities Verification
  - Instrumentation Calibration Verification
  - Input/output Loop Verification
  - Installed Application Software Verification
  - Control System Access Security Verification
  - Safety Assessment Verification
  - Hardware Installation Verification
  - P&ID or Drawing Verification

Equipment Qualification

- Operational Qualification
  - IQ testing must be completed prior to commencement of OQ testing.
  - This involves confirmation of the functional requirements and operational specifications. On more complex systems, an integrated performance run should be conducted at the end of the OQ to confirm the system functions as intended.
  - The OQ protocol documents the proper operation of the equipment according to user requirements and design specifications.
  - Simulated product may be used to conduct the OQ for manufacturing equipment for functionality testing only.
  - The operational ranges of testing will include a set of conditions encompassing the full range of design and intended use range, including target set points.

Equipment Qualification

- What to expect in an Operational Qualification Testing, as applicable to system:
  - Safety Interlock & E-stop Test
  - System Alarm & Interlock Test
  - Power Failure & Recovery Test
  - Operator Interface / Functionality Test
  - Controls Function Test
  - Sequence of Operations
  - Operational Range Verification
  - Maximum Capacity / Peak Demand Testing
  - Environmental Conditions Testing (Room Temperature/ Relative Humidity Mapping, Differential Pressure Verification, etc.)
  - Testing and Balancing
  - HEPA Filter Integrity Testing
  - Procedures/Work Instructions Verification
  - PM/Calibration Verification
  - Static or Empty load testing

Equipment Qualification PM & Calibration

- Pull Maintenance Records
  - Look at annual
  - Bi-annual
  - Monthly
  - Weekly, etc.
- Are the records complete?
  - Do the tasks and frequencies match what was in the Qualification Documentation?

Equipment Qualification

- Performance Qualification

- Performance Qualification (PQ) testing will take place after a successful OQ.
- This is equipment, utility, facility PQ.
- PQ is documented verification that all aspects of a system, that could affect product quality, perform as intended and consistently meet pre-determined acceptance criteria under typical manufacturing conditions for an extended testing duration.
  - The PQ testing will challenge the operation and performance of the installed system under maximum load condition, worst case load configurations, or worst case manufacturing conditions.
    - Provide rationale for specified worst case conditions where applicable.

Equipment Qualification

- What to expect to see in a PQ:
  - Dynamic Testing (Room in operation for 24 to 72 hours)
  - Fully loaded testing (chambers, autoclaves, etc.)
  - Seasonal effects on a system like a warehouse (winter, summer mapping)

Equipment Qualification

- Periodic Review (Stage 3)

- Demonstration that the equipment is maintained in a qualified state
- Review of:
  - investigations,
  - change controls,
  - addenda validation/qualification,
  - unplanned maintenance work orders
  - Planned maintenance
  - Calibration (specifically out of tolerance)
- Evaluate holistically if equipment is in a state of control

Equipment Qualification

- Periodic Review (Stage 3)

- Pull the Periodic Review packages for the same Equipment that you pulled for Equipment Qualification
- Determine if all documents were assessed
  - Specifically:
    - unplanned maintenance work orders
    - Planned maintenance (any investigations if not completed within time frame of procedure)
    - Number of CAPAs associated with the equipment
- If equipment is breaking down excessively, then most likely the equipment is not in a state of control; therefore, not in a qualified state

Equipment Qualifications CFR References

- Unqualified Equipment (lacking test cases, missing qualification documentation, etc.
  - CFR 211.68(a)
- Lack of Project Qualification Plans
  - CFR 211.22
- Lack of appropriate automation or PLC qualification in the Equipment Qualification including lack of Back up Test Cases
  - CFR 211.68(b)

How to Audit Validation

Questions?