

Process Validation from a Contract Manufacturer's Point of View

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Overview

- Types of Process Validation
- CMO/Customer Relationships
 - What customers should expect
 - Case study: CMO developed process
 - Case study: customer developed process
 - Case study: approved product
- Precursors to Successful Process Validation

Types of Process Validation

- Process Validation can be broken down into two types:
 - Technical studies
 - ◆ Lab scale studies
 - ◆ Scaled down equipment
 - ◆ Samples from manufacturing scale
 - ◆ Define acceptable operating ranges/limits
 - Consistency study
 - ◆ GMP batches produced at scale
 - ◆ Increased monitoring, sampling, analysis
 - ◆ Commonly used for Phase III clinical supply
 - ◆ Demonstration of process control and reproducibility.

CMO/Customer Relationships

- What customers should expect from their CMO:
A unified process transfer effort
- Integrated approach to process development, scale up, and validation
 - Cross functional process team
 - ◆ Development
 - ◆ Manufacturing
 - ◆ QA & QC
 - ◆ Engineering & Facility Validation
 - ◆ Supply Chain
 - ◆ Regulatory

CMO/Customer Relationships

- What you should expect from a CMO:
 - A process validation master plan
 - Project timelines
 - ◆ Protocol drafting, review, & approval
 - ◆ Study execution & raw data auditing
 - ◆ Report drafting, review, & approval
 - ◆ Results implementation
 - ◆ Incorporation into BLA submission
 - ◆ Responsible parties for each section
 - Studies co-designed by customer and CMO
 - Person on plant involved in technical details

CMO/Customer Relationships

- What you should expect from a CMO:
A plan tailored to your needs
 - All studies may not be completed prior to PAI
 - ◆ Risk versus resource decision
 - ◆ Follow-up studies may be requested by regulatory agencies
 - Plan for follow-up work post approval
 - ◆ Generic or minimal studies may need expanding after product approval
 - ◆ Process changes will be forced upon you by facility and raw material changes over time

CMO/Customer Relationships

- Case Study #1: CMO developed process
 - CMO is the logical best candidate for executing process validation studies
 - Customer benefits from existing infrastructure of CMO
 - ◆ The process fits the plant
 - ◆ Study logistics are minimized
 - ◆ Development personnel feel ownership of process
 - ◆ Based on CMO's generic process and experiences

CMO/Customer Relationships

- Case study #2: customer developed process
 - “Drop-in” the process into CMO’s facility
 - ◆ Process may not properly fit the plant
 - ◆ Customer may not be cognizant of scale up challenges
 - ◆ Run the process prior to finalizing studies
 - Process likely to change during transfer
 - ◆ Technical studies may not mimic manufacturing conditions & practices
 - ◆ Joint study design is an effective means to harmonize
 - Customer needs to recognize that CMO will be asked to defend process validation during audits

CMO/Customer Relationships

- Case study #3: approved product
 - Customer looking to free up internal capacity or to 2nd source to meet increased market needs
 - Customer developed the process and has a proven manufacturing history
 - Process fit may require significant facility changes
 - ◆ Heavy draw on engineering & validation resource
 - Customer is the best candidate for process validation study design
 - ◆ CMO will need to perform some work
 - ◆ Focus is on consistency study
 - ◆ Technical studies are required

Precursors to Successful Process Validation

- Reliable GMP batch production
 - Experience is critical
 - ◆ Pilot batches mitigate transfer & scale up risks
 - ◆ Don't assume you have a robust process until you run it
 - The process must fit the facility
 - ◆ Ideally, the facility should be taken into consideration during process design
 - ◆ Facility constraints may clash with process constraints
 - Requires reliable business systems
 - ◆ QA, QC, facilities, engineering, supply chain

Precursors to Successful Process Validation

- Defined study requirements
 - Sampling requirements must be clearly defined
 - ◆ Sample points & volumes specified
 - ◆ Sample logistics (storage, handling, shipping)
 - ◆ Assay preparation & execution dependent upon sampling plan
 - ◆ Sampling is indicative of clarity of study design
 - Responsibilities must be clearly defined
 - ◆ Timelines are critical to identifying critical path constraints
 - Ideally, study should be managed by someone not engaged in experimental work

Precursors to Successful Process Validation

- Open channels of communication between customer and CMO
 - Person on plant involved in technical details of study
 - Unified process team must be visible to customer
 - Frequent communication is critical for sustained efficiency
 - ◆ Weekly meetings leading up to batches
 - ◆ Daily conversations when in production
 - ◆ Real time updates to study schedule
 - ◆ Continuous updates keep participants focused

Conclusions

- Process Validation builds on process development and scale-up
- Process Validation requires effective project management
 - Experience is key to proper planning and execution
 - Availability of resource is key to execution
- CMO and customer must work as a team
 - Clear goals and timelines
 - Defined risks and responsibilities