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THE ROLE OF SAMPLING IN PROCESS VALIDATION AND COMPREHENSIVE PROCESS VERIFICATION OF BIOPHARMACEUTICALS

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Disclosure

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Agenda

Process Validation Lifecycle

Product Attributes

Defect Rating Criteria

Process Sampling

Summary

Process Validation Lifecycle: Stages

FDA's 2011 Process Validation (PV) Guidance states:

"Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes process validation activities in three stages:

- *Stage 1 – Process Design: the commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities;*
- *Stage 2 – Process Qualification: during this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.*
- *Stage 3 – Continued Process Verification (CPV): on-going assurance is gained during routine production that the process remains in a state of control. "*

Process Validation Lifecycle: Sampling Flow

Process Development (1):

Development & pilot lots

Estimate non-conformance rates for Critical Quality Attributes (CQA) (Lagging Indicators)

Identify technical linkages of Critical Process Parameters (CPP) & Critical Material Attributes (CMA) to CQAs (Leading Indicators)

Product Performance Qualification (2):

Discrete number of lots

Heightened Sampling: explore CQAs conformance to specifications…

Heightened Monitoring: verify CPPs & CMAs in state of control…

Continued Process Verification (3A):

Discrete number of lots

Heightened Sampling: assure CQAs conformance to specifications, explore sampling reductions if justified…

Heightened Monitoring: confirm CPPs & CMAs remain in state of control…

Continued Process Verification (3B):

Continuing Series of Lots

Reduced sampling (now justified): assure process quality consistent, control state is maintained…

Heightened sampling resumed if acceptance criteria not met or product quality has declined to unacceptable level

Process Validation Lifecycle: Stages 3a & 3b

Stage	Activity
3a - Initial CPV activities are engaged	Parameter and attribute selection, based on previous assessments of criticality, available data, and identification of optimal parameters and attributes for process success.
	Determination of CPV trend limits, based on developing a reference data set, identifying a suitable total of batches to set limits, charting batch data and applying trend rules, and confirming an effective system design.
	Developing and documenting appropriate responses to statistical signals and recalculating CPV limits as required.
3b - Routine monitoring activities are engaged based on the CPV plan	Evaluation of statistical signals and consequent evaluation criteria are developed and documented;
	Real time data reporting practices are initiated and established;
	Summary reports are generated for review on a periodic schedule
	The CPV plan is reviewed relative to desired objectives and revised if necessary
	Expansion of information from new process inputs may be considered and included in the CPV plan;
	Communication with regulatory agencies regarding CPV assessments will be initiated

Product Attributes

Examination of product attributes (e.g., CQAs) is required to determine impact of not meeting acceptance criteria.

New product attributes might be unique to the proposed product or modeled on similar attributes assessed for a comparable product.

Likewise, they may be identified and confirmed during the Process Validation Lifecycle activities required to document development, verification, validation and future manufacture of the product.

Attribute performance is based on evaluating the impact of the defect reflective of the attribute upon product functionality or clinical effect to a user.

Risk-based evaluation is also used to identify the impact of a product defect.

Defect Rating Criteria

These criteria can be based on:

- Common defects experienced with a similar product
- Historically observed defects for the product's dose modality (e.g., oral solution, injected solution, tablets, capsules)
- Risk-based assessment of hazardous situations/failure modes experienced with the product
- Evaluation of product performance relative to current test methods or other necessary standards

Assessment of these criteria is completed by:

- Laboratory testing of product vs. required quality attributes
- Functional testing of product to meet operational requirements
- Visual examination for any historic or newly identified cosmetic defects

Defect Rating Criteria

Product sampling based on defect rating criteria was initially used in the Aerospace industry in the 1950's and 1960's.

This approach was adopted within the pharmaceutical industry in the 1970s and 1980s.

There is no industry-wide consensus on specific percent defective levels used to characterize product defects.

Defect Rating Criteria

Dr. Wayne Taylor, a leading expert on acceptance sampling in the pharmaceutical, medical device and diagnostics industries, cited the following percent defective levels were commonly used to assess medical devices for product defects:

Defect Type	Nonconformity Impact	% Defective
Critical	Health and Safety: presents a health hazard	0.065%, 0.1%, 0.25%
Major	Functional: degrades product function or fitness for use, causes a user inconvenience, and potentially generates a complaint	0.25%, 0.4%, 0.65%, 1.0%
Cosmetic	Visual: affects product appearance or high quality image; does not impact usability/ functionality	2.5%, 4.0%

Process Sampling: Biopharmaceuticals

Product sampling can be completed at beginning, middle and end portions of the batch.

Sample size calculations are completed to assure sufficient data are available to achieve desired power for statistical estimates.

This is done to assure homogeneity exists within the batch for critical quality attributes associated with product strength and performance.

For product visual inspection, a suitable sample collected using a documented sampling plan approach (e.g., AQL or 100% inspection) is assessed for visible characteristics such as discolored solution, debris or particulate in the solution or defects such as glass, rubber or steel/iron particles.

Process Sampling: Analytical Testing

Biopharmaceutical products are assessed using analytical test methods for the following reasons:

- Appropriate analytical methods are necessary to effectively compare products for similarities and differences
- Gains in process knowledge are evident as improvements to method detectability and sensitivity are implemented
- Detailed characterization of Biopharmaceuticals is possible through Mass Spectrometry, HP-SEC, SDS-PAGE and other test method types
- Accurate and precise analytical methods provide improved definition and control of product attributes
- Analysis of product attributes such as purity & stability, molecule sequencing, glycosylation properties, molecule size heterogeneity and higher order structures is completed with analytical test methods.

Process Sampling: Biopharmaceuticals

Sampling for quality attributes is necessary during each stage of the PV Lifecycle. Attributes to be examined may consist of the following product characteristics:

- Liquid-filled syringes must be free of metal, glass, fibers, particles or other foreign materials, contain the correct product, and not be discolored, contain precipitate or be underfilled/empty.
- Syringes must not have broken/incomplete seals debris, contain the correct product, or are free of scratches, cracks or fractures.
- Drug solutions must display appropriate potency or purity results, as well as satisfactory results.
- Additionally, quality attributes may also be tested to support homogeneity and/or equivalence inferences for multiple batches.

Summary

Product sampling is completed in all stages of the Process Validation Lifecycle.

Lots are sampled to assess quality attributes related to product performance and appearance; defects are examined relative to product functionality and/or patient impact.

Heightened sampling is used during Product Performance Qualification (stage 2) and Continued Process Verification (stage 3A) to explore, then assure CQAs' conformance to specifications.

Lot sampling and evaluation is extended to Continued Process Verification (3B) stages to monitor process performance based on lagging indicators. Sampling level is typically reduced, yet can be heightened if process nonconformances or poor performance are observed.

Thank You!