EMA Expert Workshop on Validation of Manufacturing for Biological Medicinal Products

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Process Validation-Enhanced Approach

Continuous Process Verification

Brendan Hughes

EGA
Making Medicines Affordable

EuropaBio™
The European Association for Bioindustries

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Agenda

- Definition and purpose of validation
- The process knowledge lifecycle
- Process knowledge during PD
- Sources of process knowledge
- Use of small scale models
- Evolution of a control strategy
- Confirmation at scale
- Continued process verification
- Lifecycle management using Continued process verification

Process validation

- *…establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications*
- *Evolving landscape with greater focus on a Lifecycle Approach*
- *PV approach likely to be a continuum from 'traditional' to 'enhanced'*
  - *'Enhanced' PD do not always provide for 'Enhanced' PV and 'Enhanced' PV incorporating Continuous process verification can be conducted with varying amounts of process understanding; a control strategy is the enabler*

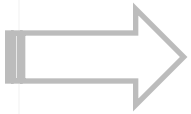
Pre-requisites for Process Validation

Product knowledge

- Criticality assessment
- Structure function studies
- Prior knowledge

Process knowledge

- Univariate and multivariate analyses
- Prior knowledge (platform)
- Scale down and model studies



Control Strategy

- Parametric and attribute control
- On-line/at-line/off-line
- Settings to detect in-control/out-of control and trending
- Actively managed as part of production , batch disposition and continuous improvement

Development of product and process knowledge

CQA

Lab-based examination (bioassay, binding)
Pre-clinical studies
Clinical studies and outcomes

Lab-based process development

CPP

Pilot scale batches for tox supply
Clinical manufacture
Scale-up batches

Role of scaled-down models

Cost: lower fixed assets needed for experimentation

Time: Faster turnaround between runs. More data.

Data density: Higher ‘n’ of runs using multiple identical equipment sets

Flexibility: Easy to improvise and experiment

- Complex interaction studies
- Replication for statistical validity
- Data rich-process knowledge

Challenge: Extrapolation of rich database of knowledge to full-scale (see presentation Frank Zettl)

Development of a control strategy

- Fundamentally exists to describe and manage the influence of CPP on CQA
- Comprehensive with quantitative criteria
  - Raw material controls
  - Control of intermediates
  - Process parameter control
  - Multi-step, multi factor CPP for single and multiple attributes
  - Yields attribute control within acceptable ranges for manufacturing

Control Strategy-across a biotech process

Biosynthesis	Purification	Degradation
Make right product	Select and protect	Preserve
Raw materials Process controls in Bioreactor to manage cell growth and product quality In process measurements	Raw materials Chromatography and filtration control Microbiological control	Parametric control Formulation Storage

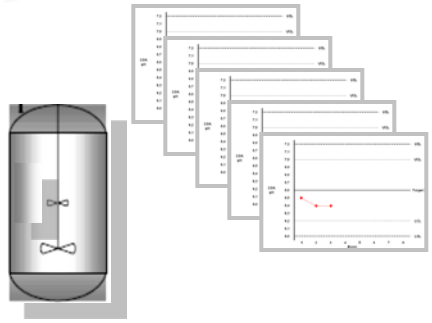
Control strategy examples

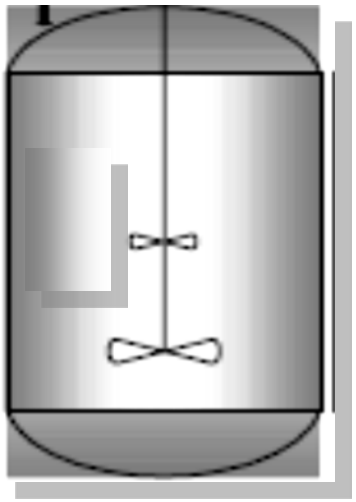
	BIOREACTOR	DOWNSTREAM	Formulation and Fill
			
HCP	• Culture duration • Culture conditions • (VCD as output)	• Column operating parameters • Column lifetime • (IPC for HCP as output)	
Glycan	• Culture conditions • Raw material	• Chromatography selectivity • Bioburden control • (Control Temp/Conductivity)	
HMW	• Culture conditions	• Chromatography selectivity • Control of generation • In process testing	• Formulation process • Filling process • Storage • Final product testing

Confirmation at scale

- Multiple runs
- Information density
- Interaction data

- Limited number runs
- At-scale data for all Unit Ops
- Key stage in confirmation of PV





- Extensive evidence of process performance
- Examination of performance at multiple parameter set points

Forms the basis for Continuous Process Verification

- Limited number of runs at full-scale
- Focus on confirmation of control strategy at scale
- Limited ranges explored
- Selection of set-points and testing to maximise value of at-scale-data
- Cannot directly test edges of Design Space at scale

Continuous and Continued Process Verification

Continuous

- Continuous Process Verification: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.
- Demonstration that the process is validated (under specified control)
- Based on control strategy and process knowledge
- Applied at various scales and stages
- Composite of data from lab and various scale manufacturing
- Can include multiple data sources (IPC, batch, in-line at line off-line)

Continued

- Demonstrating the maintenance of the validated state
- Part of ongoing manufacturing and lifecycle management
- Can include some or all of the data sources used to demonstrate Continuous Process Verification

Continued (ous) process verification

Integrated	• Design based on process knowledge • Testing and monitoring designed to assess control and maintenance of validated state
Measurement	• In-line/At-line/Off-line • Attribute and Parameter • Established control, alert, reject limits
Analysis	• Statistical analysis • Link to plant and lab automation systems
Actively managed	• Continuous monitoring and review • Continuous improvement

Continued (ous) process verification: what to measure?

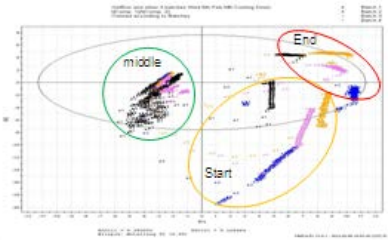
- Critical Parameters and Critical Attributes
  - Based on Process and Product Development
- What role for measurement of attributes shown to be non-critical for efficacy?
  - Markers of process consistency
  - Only if non-redundant or indicator status
  - Knowledge develops over time and batch manufacture experience
- Material and intermediate attributes linked to CQA outcomes
- Indirect or indicator parameter or attributes demonstrating drift or loss of control
  - Multi-signal/multi-parameter probes
  - Shear forces, gas exchange rates, column-ligand density, non-critical attribute abundance or quality

Continued (ous) process verification: data treatment

- Univariate and importantly multivariate analysis to evaluate interactions
- Trending and analysis
  - Setting of limits
  - In-specification
  - In-trend
- Alert and action limits
  - Maintenance of product quality
- Continuous improvement
  - Moving process performance to optimal
- Process change and improvement
  - Using Continuous process verification to demonstrate maintenance of control following process change

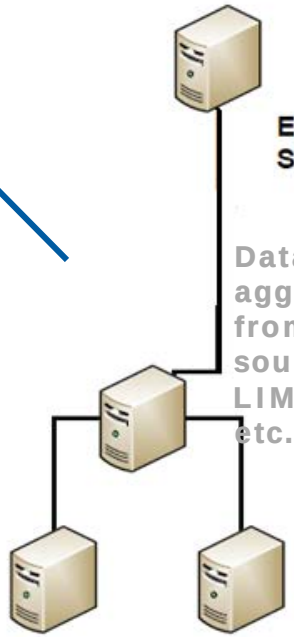
Example: Infrastructure for effective process monitoring/ Continued and Continuous Process Verification

SIMCA 13 – Off-line



- Multivariate analysis. Describe the 'golden batch' with process data.
- Watch and be alerted for batches deviating from 'golden batch'.
- React.

Data analysis and processing

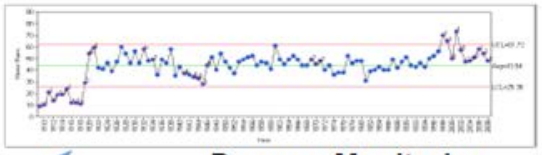


Enterprise Server

Data aggregation from various sources e.g., LIMS, MES etc.

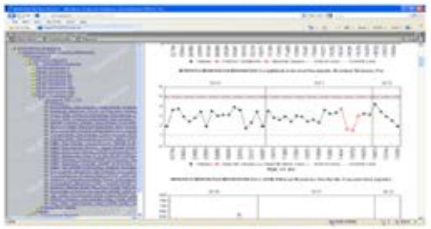
Web Clients
- PCs
- Process Monitoring
- email alert
- Automated reports

- Charting data using SPC tools.
- Apply analytical rules e.g., Western Electric rules to interpret charts.
- Use totality of process knowledge to 'correct' process if alerted



Process Monitoring
- shift in key parameter. WHY?

Process Dashboards
- email alerts on excursions



On-demand reports

Lifecycle management: Role of process verification

- Process Maintenance and Improvement
  - Response to drift or variability
- Demonstration of control after process change
  - Equipment
  - Scale
  - Raw material
- Based on well-designed Continued Process Verification program
  - Confidence of control by analysis of key indicators of process control and validation

Filing requirements

- Continuous Process Verification: data supporting this will be in the filing
- Continued Process Verification is a prospective proposal
- The design basis for the Continued Process Verification program may be described in the filing but the data are in the GMP system
- Location of these descriptions in the filings?
- Important linkage between review and inspectorate

- THANK YOU