EMA Expert Workshop on Validation of Manufacturing for Biological Medicinal Products

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Traditional Validation - Upstream

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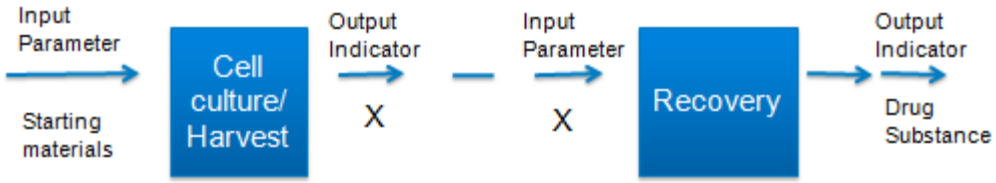
Process Parameters and Performance Indicators

- Process Parameters: Defines the **input** variable that can be directly controlled in the process
- Performance indicators: Defines calculated or measured process **output.**
  - A process indicator from one step might be the parameter for the next step in the process. E.g. protein content from the harvest becomes the process parameter for the recovery step.



- Using prior knowledge, development information and risk assessments, parameters are classified into:
  - Critical with impact on product quality,
  - Non-critical with no impact to product quality

Examples of Process Parameters and Indicators

- Inputs
  - Process Parameters
    - Temperature, Starting Cell Density, etc
    - Raw material attributes
- Outputs
  - Critical Quality Attributes
    - Glycosylation, C-terminal processing, etc
  - Performance Indicators
    - Seed train parameters – final cell density, etc
    - Cell concentration and/or Viable cell count at harvest, integral of viable concentration, bioburden, mycoplasma etc. from the production culture
    - Product concentration/ titer at harvest
    - performance indicator from the harvest but process parameter in the load for the recovery step
  - Consistency Indicators - Output
    - pH profile - a consistency indicator, but is not a process performance indicator

Parameters, Control Strategy and Validation

- The definition of the Parameters is confirmed during process characterization and a control strategy is developed based on understanding of risks to product quality
- Control strategy is confirmed under manufacturing conditions during Process Performance Qualification or Process Validation
- A Process Verification plan is developed using the control strategy

Parameter Classification for Process Validation and Life-cycle Management

- Classification of parameters beyond critical and non-critical helps in:
  - Controlling process consistency in addition to product quality
  - Prioritizing the variables for study and monitoring
  - Re-categorization of parameters based on evolving process understanding (Continuum of Criticality), in defining of the Life-cycle management program
  - The extent of effort required to justify parameters. It should be commensurate with their risk to process consistency and product quality

Process Validation is evidence that the process operates within established parameters, performs effectively and **reproducibly** to produce product that meets **specifications** and **quality attributes**

Different Stages of Process Life-cycle Management

Stage	Activity	Rationale	Information in the file
Process & Product Design	Definition of Quality Target Product Profile (QTPP)	Understanding of safety, efficacy and purity	Definition to justify process validation and control strategy approach
Process Development & Characterization	Identification of: 1- Critical Process Parameters 2- Process Indicators	Assessment of parameters and indicators from each step that might impact the product quality	Information should be included to justify process validation approach
Design of Control Strategy	Defining controls. Determining routine testing, IPC, Specifications, Stability monitoring	Controlling the process for the production of product that meets the quality requirements defined in QTPP	Information from process validation should be included in support of the control strategy Process Description and Manufacturing Controls section
Process Evaluation and Verification (Process Validation)	Define acceptance criteria, limits & ranges Verify performance	Verify performance of Control Strategy and that the process consistently produces product that meets quality	Data to support ranges should be included Validation results
Life Cycle Management through Continued Process Verification	-Assessment of control strategy based on monitoring and analysis -Assessment of process changes	Ensure that the Control Strategy is valid and process performs consistently	IPCs

Parameter information for Filing

- If the intent of life-cycle management is continuous learning and improvement of the process, then:
  - Filing should contain information related to critical parameters as part of the control strategy
  - Filing of limits for non-critical parameters should not be required since the limits are likely to change with continuous learning and improved process understanding.

Validation of continuous processes and perfusion processes (1)

- A “Batch” is defined based on the purification, as the load for the down stream
- Strategies for defining batches:
  - **Option 1:** Sub-batches/ harvests from diverse times are not combined for a down stream load
  - **Option 2:** Sub-batches/ harvests from diverse times or from one or several “starts” are combined for a down stream load
- Pooling and sampling strategies should consider understanding of process and product quality variability and the controls in place. Selected strategies should be verified during Process Validation.

Validation of continuous processes and perfusion processes (2)

- Demonstrating that product of the required quality is consistently generated throughout the production period, including under conditions of maximum preculture length combined with maximum production period.
- Characterization or retrovirus expression, including under conditions of maximum preculture length combined with maximum production period.
- A downstream batch can be performed during PPQ that represents worst-case (“early” and “late”) material from the production period.
- Similarly, consistency of impurity removal of the capture step may be demonstrated with material from the worst-case of the production period

Variability of biological raw materials

- Extent of understanding:
  - Complex and undefined raw materials, such as biological raw materials, often require small scale model testing, based on impact to product quality
    - Prior experience from other processes and scale down data should serve as the foundation of understanding.
  - There should be an effort to characterize the extent of variability due to the raw material
    - Different lots to ensure adequate process robustness, by monitoring at large scale using as many lots as possible during development and clinical production.

Raw materials information for Filing

- Data for filing
  - Data on impact of variability based on multi-lots, small scale model testing. If variability is known to be high then risks have to be mitigated via the control strategy
  - Second source suppliers:

    Risk mitigation could include qualification of a second source of supplier. Use of small scale model data or pilot scale studies coupled with data from Continued Process Verification of legacy processes could provide the assurance.
  - It is not feasible to use all potential suppliers during process validation, (e.g. soy hydrolysate). This may not be viewed as a requirement.

Single Use Equipment and Facilities

Single use equipment would be considered in one of two ways

- For product contact single use material (e.g. Cell bags) – the treatment is similar to critical raw materials.
- Risk assessments should capture risks from leachables and extractables, primary and secondary sources of manufacturers of product contact materials, etc.
- Detectability of problems is higher in upstream processes than in downstream. Example – abnormal cell growth in bags that have quality issues.

- Equipment and facilities process validation considerations should be similar to process validation in traditional equipment
- The difference from multi use material is that single use material do not need cleaning validation and SIP, however, suitability for use must be demonstrated

Genetic Characterisation of Cells & Limit of *In Vitro* Cell Age (LIVCA)

- Expression Construct Analysis
  - The Purpose is to confirm the correct coding sequence is incorporated into the cell
  - The Aim is to detect gross mutations in product sequence
  - Transcript analysis is relevant for multi-copy integrants
- "The limit of cells is determined from production cells expanded from **pilot plant** or **full production scale** to the proposed cell age or beyond" (ICH Q5 A&B)."
- Performed during development and scale-up. Not necessarily part of process validation.
- LIVCA is performed at a representative scale. Additional passages of cells may be performed such that the EOP cell age exceeds what will be routinely encountered during commercial scale production

End of Production Cells

- End of Production (EOP) cells from expansion of WCB to **pilot and full scale**
- Integrity of expression construct in EOP's determined once for each MCB at full scale
- Where direct comparison with MCB not possible can use surrogate markers (e.g. nutrient consumption rates).