PRACTICAL IMPLEMENTATION OF THE LIFECYCLE APPROACH TO PROCESS VALIDATION

Webinar

Speakers: Bruce Davis & Line Lundsberg-Nielsen
23 April 2020
Bruce S. Davis
Principal
BD Global Consulting

Bruce is a professional engineer with many years experience in the pharmaceutical industry. He runs his own consultancy and training company on science and risk-based solutions including process validation, technology transfer and other related subjects.

He has carried out a wide range of work internationally across the industry including small and large companies, development to manufacturing, from generic medicine suppliers to ATMPs.

He is an experienced trainer for ISPE and prior to this was Chairman of the ISPE Board in 2007/8. He co-lead the development of several guidance documents including ISPE’s technology transfer guide.

Before starting his business, he worked for AstraZeneca, where he had responsibility for putting in place international facilities.

He likes to bring clarity to the complex world of developing and manufacturing medicines.
Speaker

Line Lundsberg-Nielsen, PhD
Director
Lundsberg Consulting Ltd

Line is a physicist and holds a Ph.D. in Process Analytical Technology. Her background is pharmaceutical manufacturing and development.

She runs her own pharma and biopharma consultancy business providing services based on science & risk principles in the areas of QbD, PAT, Control Strategy, Process Validation, Qualification and Tech Transfer as well as serves as a Managing Consultant at NNE.

Line has been a member of ISPE for +15 years and has served many roles. She is currently the chair of the global PAT & LCS CoP, active in the Pharma 4.0 SiG, co-author of the Process Validation Good Practice Guide and one of the ISPE Process Validation training instructors.
Agenda

1. International regulatory guidances & terminology
2. PV lifecycle – the 3 PV stages
   1. Process Design - Stage 1
   2. Process Qualification - Stages 2.1 and 2.2
   3. Continued Process Verification - Stage 3
3. Summary & next steps
4. Q&A
Scope of webinar

We WILL cover:
- International aspects including FDA & EU
- Validation lifecycle
- The 3 Process Validation stages

We will NOT cover:
- Equipment & facility qualification
- Analytical Method validation
- Cleaning validation
- Computer Systems Validation
- Transportation validation
Terminology – trying to avoid confusion
We will use the following terms

‘Validation’
▪ Treated as a general umbrella term

Qualification
▪ ‘Is the equipment/utility designed to work as intended and confirmed to function within the ranges intended?’

Process Validation (PV)
▪ ‘Does the process deliver the intended product to the patient – also in the future? i.e. an agreed Control Strategy is established for the product lifecycle’
Regulatory Guidance that impact PV

US
- FDA PV Guideline 2011

EU
- Drug Product (includes submission) 2016
- Biotechnology (includes submission) 2016
- Annex 15 - GMP - Qualification & PV 2015
- ATMP – GMP - Qualification & PV 2018

PIC/S
- Similar to EU

ICH – is important
- eg ICH Q9 – Quality Risk Management – built into many GMPs
Important that companies are clear regarding terms to use internationally

<table>
<thead>
<tr>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>The whole process is called <strong>Process Validation (PV)</strong></td>
<td><em>(Pharmaceutical Development or Process Design)</em></td>
</tr>
<tr>
<td><strong>Stage 1</strong></td>
<td><strong>Stage 1</strong></td>
</tr>
<tr>
<td>Process Design</td>
<td><em>(Qualification)</em></td>
</tr>
<tr>
<td><strong>Stage 2</strong></td>
<td><strong>Stage 2</strong></td>
</tr>
<tr>
<td>Process Qualification (PQ)</td>
<td>User Requirements Specification (URS)</td>
</tr>
<tr>
<td><strong>Stage 2.1</strong></td>
<td>Design Qualification (DQ)</td>
</tr>
<tr>
<td>Qualification of equipment &amp; utilities</td>
<td>Factory Acceptance Test (FAT)</td>
</tr>
<tr>
<td></td>
<td>Site Acceptance Test (SAT)</td>
</tr>
<tr>
<td></td>
<td>Installation Qualification (IQ)</td>
</tr>
<tr>
<td></td>
<td>Operational Qualification (OQ)</td>
</tr>
<tr>
<td></td>
<td>Performance Qualification (PQ)</td>
</tr>
<tr>
<td><strong>Stage 2.2</strong></td>
<td><strong>Stage 2.2</strong></td>
</tr>
<tr>
<td>Process Performance Qualification (PPQ)</td>
<td><strong>Process Validation (PV)</strong></td>
</tr>
<tr>
<td><strong>Stage 3</strong></td>
<td><strong>Stage 3</strong></td>
</tr>
<tr>
<td>Continued Process Verification (CPV)</td>
<td>Ongoing Process Verification (OPV)</td>
</tr>
</tbody>
</table>
Definitions of Process Validation

FDA (lifecycle definition)
“The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.”

EMA (activity definition)
“The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medical product meeting its predetermined specifications and quality attributes.”
FDA PV Guidance

GMP focus

Principles

• Design quality, safety, & efficacy into the product
• Quality cannot be assured merely by inspection & testing
• Control each step of a manufacturing process to assure the finished product meets all quality attributes
• 3 Stage approach
• Understanding variability and impact on product quality
EU Guidance – Drug Product

Submission focus

Lifecycle approach: link development, validation & process

‘State of control’ for routine commercial manufacture

PV to confirm Control Strategy adequate to process design & product quality

Validate manufacturing process before product is marketed

- Validation of manufacturing process = second stage in product lifecycle
- First stage (process design) covered in ICH Q8
- Third stage (OPV) covered under Annex 15
EU Guidance – Biologics – Drug Substance
Submission focus

- **Process Evaluation**
  - provide evidence the manufacturing process is appropriately designed & controlled

- **Process Validation**
  - (as earlier)

- **Process Verification**: Studies to confirm manufacturing process can:
  - perform effectively; meet predetermined acceptance criteria, on X number of batches

- **Note API also covered by:**
  - ICH Q7 (GMP) & Q11 (Development & manufacturing of drug substance, small & large molecule)
EU Guidance – Annex 15: GMP focus

- Lifecycle - ICH Q8, 9, 10 & 11,
- Qualification - URS, DQ, FAT, SAT, IQ, OQ, PQ
- PV should ensure process consistently produces product quality, ref quality attributes & process parameters

EU Guidance – ATMPs

- Fragility of the product
- Product lifetime
## Process Validation Purpose

- Demonstrate homogeneity within a batch and consistency between batches
- Process Understanding
- Understanding sources of variation
- Understanding the impact of process and material variability on the product quality
- Established Control Strategy to control variation in a manner commensurate with the risk it represents to the process and product
Validation in product lifecycle – diagrammatic (EU & US)

Process Design (FDA)
Pharmaceutical Development (EU)

Develop Control Strategy based on Product Quality Attributes

Process Qualification (FDA)
Process Validation (EU)

Demonstrate effectiveness of Control Strategy in commercial manufacture

Continued (FDA)
Ongoing (EU)

Process Verification

<table>
<thead>
<tr>
<th>3a</th>
<th>3b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heightened</td>
<td>Routine</td>
</tr>
<tr>
<td>sampling &amp; testing until variability is understood</td>
<td>monitoring program</td>
</tr>
</tbody>
</table>

Monitor process performance & variability during product life-cycle

Legacy products typically enter lifecycle in Stage 3
PV lifecycle – level of testing & monitoring

1. Process Design
2.2 PPQ (PV)
3. Commercial Manufacturing

- Control Strategy is dynamic over the lifecycle
- Level of Testing
- Variability
- Estimate
- Established
- Change introduced/CAPA
- PAT Implemented
- Monitoring
- QC Testing
- Time/Process Knowledge

Could vary based on approach

©2020 ISPE – ALL RIGHTS RESERVED
PV STAGE 1 – PROCESS DESIGN
# Process Design Goal and Principles

## Process Design Goal

- To design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes
- Establish a Control Strategy ensuring the product will meet the CQA requirements

## Process Design Principles

- Patient focused
- Science & Risk based approach (QbD)
- Knowledge Management
- Cross-functional
- Understanding impact on variability on product quality
QbD principles for Process Design

Starts with the patient in mind
Iterative and happens in parallel
As a minimum ranges for CPPs must be established and interactions understood

QTPP → CQAs → Product & Process Development → CPPs & CMAs → Ranges, Design Space → Control Strategy → Continual Improvement

The CQAs (Critical Quality Attributes) are used as “measures” of the QTPP (Quality Target Product Profile)
Identification of CPPs (Critical Process Parameters) and CMA (Critical Material Attributes of starting an in-process material)
Controls of CQAs and how they are “manufactured”, CPPs and CMAs

©2020 ISPE – ALL RIGHTS RESERVED
Process Design Deliverables

**CQA:** A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (Q8)

**CPP:** A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (Q8)

**CMA:** A material attribute of either a raw/starting material or intermediate that has an impact to a critical quality attribute and therefore should be monitored or controlled to ensure the process products the desired quality

**Control Strategy:** A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (Q10)
### Examples of Typical CQAs

<table>
<thead>
<tr>
<th>Drug Substance</th>
<th>Bios DS</th>
<th>Solid Oral</th>
<th>Parenteral</th>
<th>Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impurities</td>
<td>Protein Content</td>
<td>Bulk Density</td>
<td>Appearance</td>
<td>Potency</td>
</tr>
<tr>
<td>Residual solvent</td>
<td>Aggregates</td>
<td>Flowability</td>
<td>Identity</td>
<td>Homogeneity</td>
</tr>
<tr>
<td>Assay</td>
<td>Host Cell Protein</td>
<td>Foreign Matter</td>
<td>Assay</td>
<td>Flow Properties</td>
</tr>
<tr>
<td>LOD</td>
<td>Biopotency</td>
<td>Blend Uniformity</td>
<td>Impurity</td>
<td>Sieve Particle Size</td>
</tr>
<tr>
<td>Color</td>
<td>Endotoxins</td>
<td>Blend Potency</td>
<td>Sterility</td>
<td>Bulk/Tap Density</td>
</tr>
<tr>
<td>Particle Size</td>
<td>Sterility</td>
<td>Final Potency</td>
<td>Endotoxins</td>
<td>Appearance</td>
</tr>
<tr>
<td>Solution Clarity</td>
<td>Peptide Map</td>
<td>Particle Size</td>
<td>pH</td>
<td>Aerosolizability</td>
</tr>
<tr>
<td>Particle Morphology</td>
<td>Residual DNA</td>
<td>Content Uniformity</td>
<td>Particulate Matter</td>
<td>Actuation Force</td>
</tr>
<tr>
<td>Bulk Density</td>
<td>Acidic Species</td>
<td>Dissolution</td>
<td>Volume</td>
<td>Pouch Seal Integrity</td>
</tr>
<tr>
<td></td>
<td>Disintegration</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## CPPs

<table>
<thead>
<tr>
<th>Examples of Typical CPPs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Solid</strong></td>
<td><strong>Parenteral</strong></td>
</tr>
<tr>
<td>Impeller Speed</td>
<td>Stopper material</td>
</tr>
<tr>
<td>Sieve Size</td>
<td>Order of Addition</td>
</tr>
<tr>
<td>Lubricant - Specific Surface Area</td>
<td>Sterilization Temperature/cycle</td>
</tr>
<tr>
<td>Blend Uniformity</td>
<td>Shelf Temperature</td>
</tr>
<tr>
<td>Ribbon Uniformity</td>
<td>Drying Time</td>
</tr>
<tr>
<td>Air Flow</td>
<td>Air Flow</td>
</tr>
<tr>
<td>Particle Size Distribution</td>
<td>N₂ Flow Rate</td>
</tr>
<tr>
<td>Mill Speed</td>
<td>Holding Time</td>
</tr>
<tr>
<td>Holding Time</td>
<td>Humidity</td>
</tr>
<tr>
<td>Ejection Force</td>
<td>Mixing Speed</td>
</tr>
</tbody>
</table>
Process Design tools

- **CQA**
  - **Dissolution**
    - High shear wet milling
      - Drug Substance - Particle Size Distribution
      - How to control: FBRM (focused beam reflectance measurement + PAT technique) value used directly in Dissolution algorithm
      - Acceptance Criteria: 5 μm < D90 < 30 μm
    - Dispensing - drug product process
      - Magnesium Stearate - Specific Surface Area
      - Value determined on receipt
      - Acceptance Criteria: 3000-12000 cm²/g
    - Lubrication
      - Lubrication time, LubT
      - Time
      - Acceptance Criteria: 1 to 8 minutes
    - Compression
      - Tablet hardness
      - Crushing force determined at-line
      - Crushing force 60 to 110N, target 85N
QRM based Process Design completion

Risk Assessment before process development

<table>
<thead>
<tr>
<th>Unit Ops/ CQAs (Severity)</th>
<th>Formulation Composition</th>
<th>Blending</th>
<th>Lubrication</th>
<th>Compression</th>
<th>Coating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance (3)</td>
<td>H</td>
<td>L</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Identity (4)</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Assay (4)</td>
<td>M</td>
<td>M</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>UDU (4)</td>
<td>H</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>L</td>
</tr>
<tr>
<td>Dissolution (4)</td>
<td>H</td>
<td>L</td>
<td>H</td>
<td>M</td>
<td>L</td>
</tr>
<tr>
<td>Impurities (4)</td>
<td>H</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Microbiology (3)</td>
<td>M</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Water Content (4)</td>
<td>M</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
</tbody>
</table>

After process development & Control Strategy implementation

<table>
<thead>
<tr>
<th>Unit Ops/ CQA (Severity)</th>
<th>Formulation Composition</th>
<th>Blending</th>
<th>Lubrication</th>
<th>Compression</th>
<th>Coating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UDU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impurities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water Content</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

© ISPE QbD GPG, Part 2, Illustrative Example 2011
POLL #1

What are the PV Stage 1 deliverables? (Select all that apply)

- CQAs, CPPs, Material attributes
- Process flow diagram
- Ranges/design space for the CPPs and material attributes
- Scale implications
- Control Strategy
STAGE 2 – PROCESS QUALIFICATION

2.1 – QUALIFICATION OF EQUIPMENT, FACILITIES, UTILITIES & SYSTEMS

2.2 – PROCESS PERFORMANCE QUALIFICATION
“During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. “
PV STAGE 2.1 – QUALIFICATION
Stage 2.1 - Qualification

• Qualification must be done
• Covers equipment, utilities, systems
• Note computer validation, analytical methods, other supply chain validations eg transportation, are separate, but must be done prior to stage 2.2
• Important a science & risk based approach used during Stage 1, to understand ranges over which equipment etc must be qualified
• Qualification steps – ref Annex 15
• Good Engineering Practice for ‘non product quality’ aspects
• ASTM E2500 may be applied (optional)
PV STAGE 2.2 – PROCESS PERFORMANCE QUALIFICATION (PROCESS VALIDATION IN EU)
Objectives of PPQ (Process Validation)

**PPQ Objectives**

- Demonstrate the process will produce quality product i.e. verification of the Control Strategy
- Understand variability
- Use statistics as appropriate
- Recognise uncertainty (risk) in the decision process
- Justify the outcome i.e. number of commercial scale PPQ/PV batches
ISPE PV discussion paper (2016) on determining the number of batches for PPQ suggests understanding Residual Risk from:

- Product knowledge
- Process understanding
- Control Strategy

It also suggests other statistical- and experience-based approaches.
Readiness for PPQ (PV)

Key point is to have enough information to be confident that the PPQ will pass (failure is potentially business damaging & could impact patients)

Consider the following drivers:

• Commercial drivers
• Quality drivers
• Motivational differences between Development & Manufacturing

Many other prior aspects need to be in place eg:

• Equipment qualification
• Analytical methods
• Operator training
• SOPs, batch records procedures & documentation

Assess confidence of successful batches beyond PPQ using appropriate statistics
# PPQ considerations and activities

## PPQ considerations

- Main intent is to verify the Control Strategy
- What will actually be done at PPQ?
- Who will take charge?
- What support is needed e.g. for operators or equipment?
- Write and approve PPQ protocol
- Put in place extensive testing programme during PPQ to maximise learning
- What statistics, tools for data collection, analysis & presentation?

## PPQ activities

- Execute PPQ runs
- Analyse & present data
- Resolve & close any non-conformities
- Write PPQ report
- Propose a CPV (Stage 3) programme
- Sign off PPQ before moving to Stage 3
PaQLInol: 5 PPQ batches were manufactured. Content uniformity were analysed. Based on the data presented here, can PaQLInol be launched?

- Yes
- No
- Yes, but heightened monitoring must continue till variability of content uniformity is understood
PV STAGE 3 – CPV/OPV
Continued (Ongoing) Process Verification
Goal and Principles

**CPV/OPV Goal**
- Ongoing assurance is gained during routine production that the process remains in a state of control
- Understand impact of variability & demonstrate Control Strategy is robust beyond the variability
- Stage 3a: Heightened sampling and testing until variability understood
- Stage 3b: Routine monitoring programme

**CPV/OPV Principles**
- Science & Risk based
- Programme established from outcome of PPQ/PV
  - Founded on data
- Use of Statistical metrics & Knowledge Management
- Monitoring CQAs, CPPs & CMAs regularly
- Verifying the Control Strategy delivers products meeting the CQA requirements
- Continual improvement initiatives
Process Validation Lifecycle
Control, Capability & Performance

**PPQ-Stage 2**

Is process capable of reproducible commercial manufacture?
- Establish State of Control
- Product Acceptability

**CPV-Stage 3a**

Does process remain in a state of control (the validated state) during commercial manufacture?
- Process Stability
- Process Capability
- Process Performance

**CPV-Stage 3b**

Continued assessment of Stage 3a metrics, plus:
Does evaluation of routine product and process data provide detection of undesired process variability?
- Process Drift Identification
- Product Quality Drift Detection

Connecting Pharmaceutical Knowledge

©2020 ISPE – ALL RIGHTS RESERVED
Use of statistics in PV

- **Control Charts** – to show if the process is in control, stable, capable
  - Control limits reflect normal variability in the process
  - If a point plots outside the control limits, the process is out of control
  - If all points are in control, the process is stable
  - If all points are within specifications, the process is capable
  - Useful to identify special cause variability (drift, error, breakdown) from common variability

- **Robust Process**
  - Acceptable quality and performance while tolerating input variability
Use of statistics in PV

Process capability
- Measurement of how capable a process is
- Process Capability (Cp, Cpk): How the process could perform in the absence of special cause
- Process Performance (Pp, Ppk): How the process has performed. Does not require statistical control
- Always look at all data supporting the calculations
Design of a CPV/OPV programme

WHAT
Attributes and Parameters

WHEN
How Often

WHO
Statistician? Process SME?

HOW
Charts State of Control
Poll #3

CPV/OPV is required for:
(Select all that apply)

- Newly launched products
- Small volume products
- Over the counter products
- ATMP or biotech products
- Drug substance
Summary

- FDA, EU & PIC/s requirements are similar & based on ICH Guidances
- ‘State of control’ over whole lifecycle (from development to end of life)
- 3 Stage approach gives clarity
  - Stage 1 – understand design & develop Control Strategy
  - Stage 2 – qualify manufacturing equipment & demonstrate commercial scale manufacture
  - Stage 3 – maintain control of quality for ever
- Use science and risk-based approach (CQAs + Control Strategy)
- Use statistics as appropriate (includes control charts etc) to build confidence re quality of next product or batch
- Legacy products - must have a Control Strategy & demonstrate robustness through a CPV/OPV programme
Additional Learning Opportunities

**ISPE Support**
Click on each item below to learn more

- Good Practice Guides
- Training programmes
- PV papers
- International or local PV conferences
Q&A

Contact Information

Line Lundsberg-Nielsen, PhD
Director, Lundsberg Consulting Ltd
line@lundsbergconsulting.com

Bruce Davis
Principal, BD Global Consulting
bruce@brucedavis1.com

Upcoming Webinars

• 6 May - Defining and Achieving Operational Readiness
• 21 May – Selection of Single Use Components

Topic Ideas or Feedback?
Send to ispeak@ispe.org