The New Process Validation Paradigm

Overview & ISPE Resources

Connecting a World of Pharmaceutical Knowledge

ISPE

ISPE Boston Chapter Meeting
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Presenter:
Peter Levy
Principal
PL Consulting, LLC
peter@plevyconsulting.com

With Thanks to Joanne Barrick (Eli Lilly)

Connecting a World of Pharmaceutical Knowledge

Presentation Outline

- FDA Process Validation Guidance (2011)
- Specific ISPE Initiatives
  - ISPE Discussion Paper Efforts on PV
    - Papers posted on ISPE Web-Site
    - Papers in progress
- Other Available Resources
  - A-Mab Case Study
  - PDA Technical Reports

Guidance for Industry Process Validation: General Principles and Practices

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

What is Process Validation? Shift in Emphasis

- … “process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.”*
- Objective – understand and control input variability & its impact to the process to assure consistent product quality and reliable supply

* Reference: FDA Guidance for Industry, Process Validation: General Principles and Practices, January, 2011

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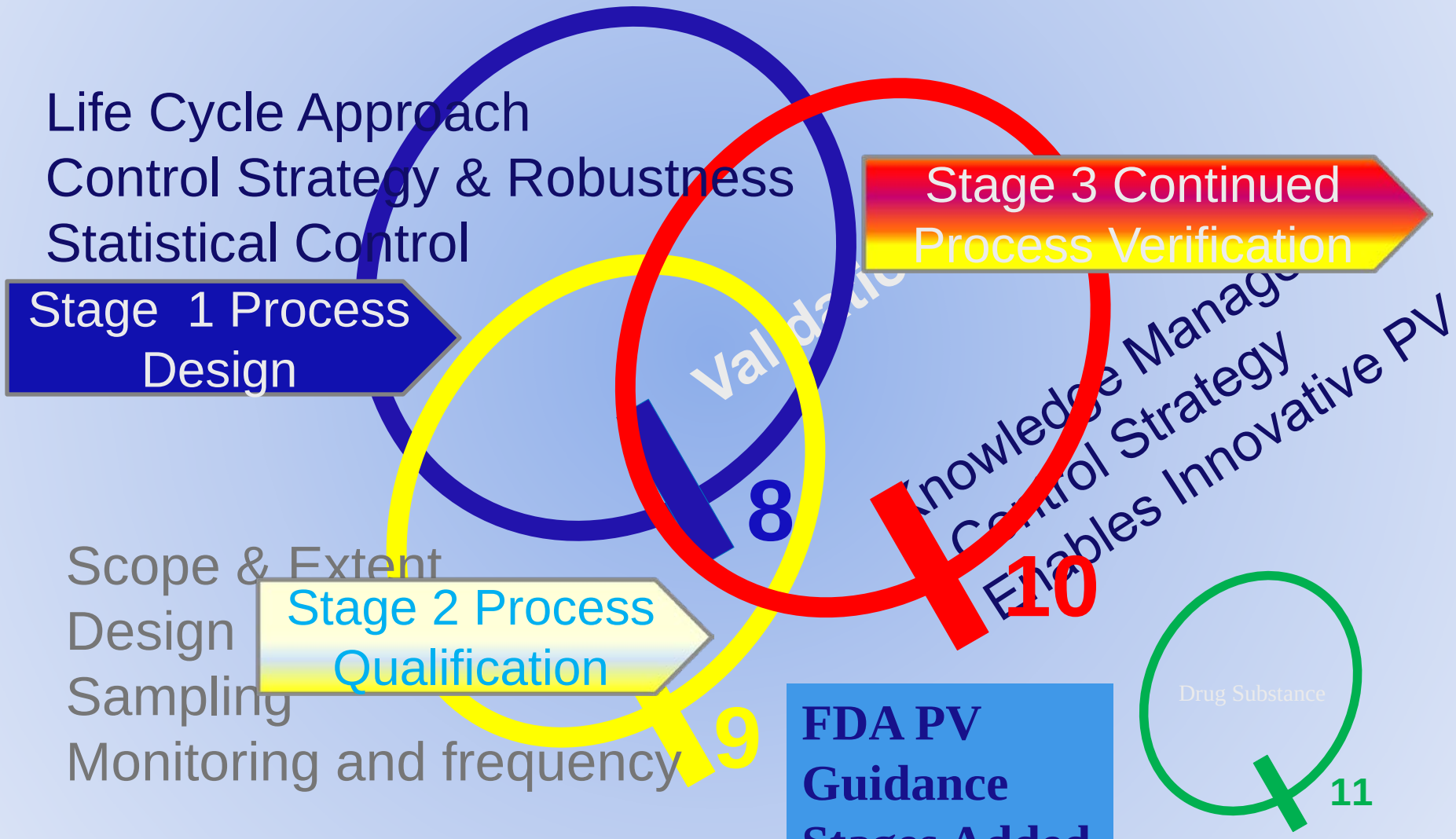
How does Lifecycle Approach to Validation Integrate with ICH ?



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FDA Guidance
Process Validation - Three Stages

FDA Product Life Cycle - Process Validation

Stage 1 – Process Design

- Defines the commercial process

Stage 2 – Process Performance Qualification

- Confirms the process design capable, in commercial production. Control strategy adequacy

Stage 3 – Continued Process Verification

Commercial Mfg	
3a	3b
Heightened Sampling & Testing until variability understood	Routine Monitoring Program

- Ongoing assurance process remains in a state of control

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What is “New” - Challenges?

- Science and Risk based PV/PPQ - product and process understanding, good science, statistical confidence
  - Statistically based sampling plans and acceptance criteria
    - PPQ/PV and routine release
  - Justification of the number of PPQ/PV batches
- Acceptance criteria across batches (Process Capability / Consistency)
- Enhanced sampling and testing beyond PPQ exercise
- Application beyond DS & DP process?
  - Cleaning
  - Shipping

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ISPE INITIATIVES RELATED TO PROCESS VALIDATION

ISPE PV Initiative Strategy and Deliverables

- Increase understanding of new paradigm for process validation by leveraging previously completed ISPE PQLI work products as a foundation
- Assist industry in practical implementation of lifecycle approach to PV
  - Focus on unmet needs
    - Minimize redundancy and collaborate with PDA
- Deliverables
  - Conferences/training/workshops, examples, validation related decision making tools/processes
  - “Short”, focused documents

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ISPE PV Discussion Papers on Significant Implementation Challenges

- Topic 1 – **Determining and Justifying the Number of PPQ Batches**
- Topic 2 – **Applying Continued Process Verification Expectations to New and Legacy Products**
- 460 comments received from limited distribution to ISPE Communities of Practice
  - Topic 1
    - 37 respondents (10+ companies)
  - Topic 2
    - 30 respondents (10+ companies)
- Posted on ISPE website August 2012

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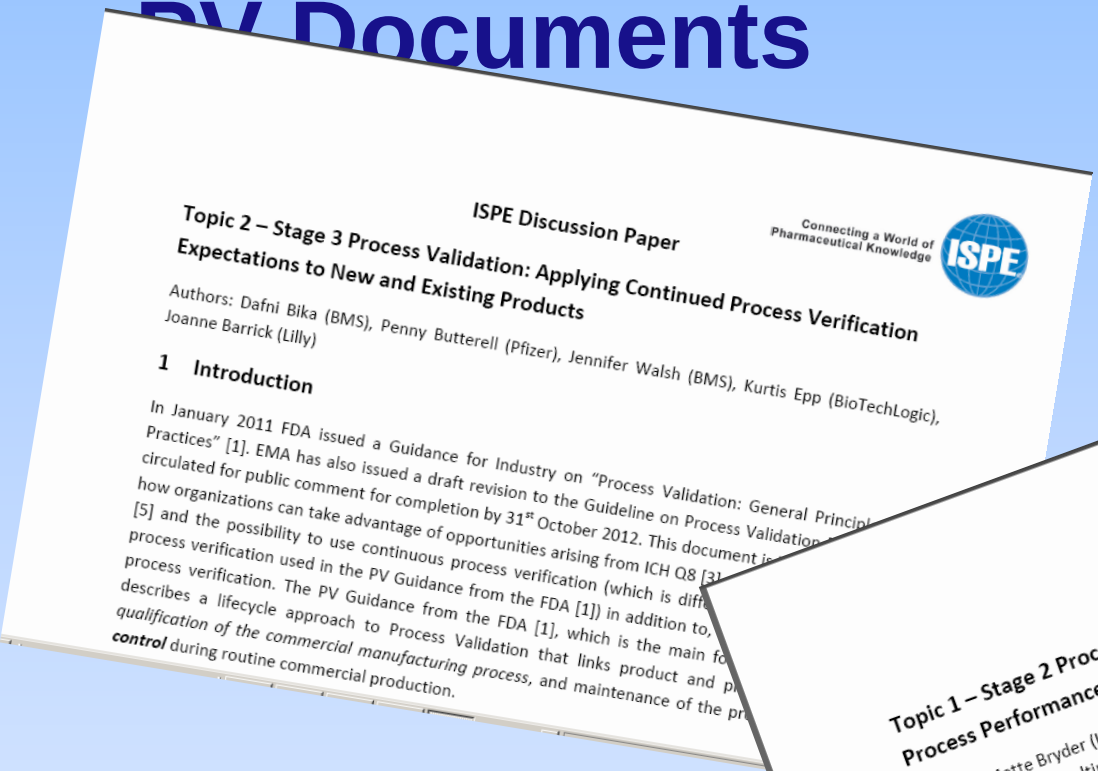
PV Documents



ISPE Discussion Paper

Connecting a World of Pharmaceutical Knowledge

Topic 2 – Stage 3 Process Validation: Applying Continued Process Verification Expectations to New and Existing Products

Authors: Dafni Bika (BMS), Penny Butterell (Pfizer), Jennifer Walsh (BMS), Kurtis Epp (BioTechLogic), Joanne Barrick (Lilly)

1 Introduction

In January 2011 FDA issued a Guidance for Industry on "Process Validation: General Princip
Practices" [1]. EMA has also issued a draft revision to the Guideline on Process Validation
circulated for public comment for completion by 31st October 2012. This document is
how organizations can take advantage of opportunities arising from ICH Q8 [3]
[5] and the possibility to use continuous process verification (which is diff
process verification used in the PV Guidance from the FDA [1]) in addition to,
process verification. The PV Guidance from the FDA [1], which is the main fo
describes a lifecycle approach to Process Validation that links product and p
qualification of the commercial manufacturing process, and maintenance of the pr
control during routine commercial production.

ISPE Discussion Paper

Connecting a World of Pharmaceutical Knowledge

Topic 1 – Stage 2 Process Validation: Determining and Justifying the Number of Process Performance Qualification Batches

Authors: Mette Bryder (Lundbeck), Harold Etling (Eli Lilly), Jeff Fleming (Pfizer), Yanhui Hu (Abbott), Peter Levy (PL Consulting)

1 Introduction

Since the adoption of the ICH Q9, Quality Risk Management (QRM) [1], by the Pharmaceutical industry, the importance of the QRM approach and its benefits has become evident. This trend invites re-examination of established practices. One such example is the widely adopted concept that validation is a one-time activity and that three consecutive successful validation batches is sufficient to demonstrate process reproducibility. It is recognized that successful manufacture of three consecutive batches may not necessarily provide assurance of process reproducibility, as routinely relying on three sequential batches alone does not always provide strong confidence that the process will continue to deliver product that consistently meets quality acceptance criteria.

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Access & Availability

- Papers are available on ISPE website (http://ispe.org/)
- Access – Free access to all (members and non-members)
  - Publications
    - Discussion documents

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ISPE Discussion Papers in Progress

- Acceptance Criteria and Sampling During PPQ
- Case Study: Applying Different Statistical Techniques to the Same Data Set – Impact on Results/Conclusions
- Impact of Lifecycle Approach to PV for Biotech Processes
- Working with Contract Manufacturers (for PV Studies)

Upcoming ISPE Conferences with PV Sessions

- cGMP Conference: June 11-13, Baltimore, MD
- 2013 Biotechnology Conference: Looking Ahead to the 4th Decade, August 27-28, Durham, NC
- Proactive Compliance Conference, October 7-8, New Brunswick, NJ
- 2013 Annual Meeting: Quality Throughout the Product Lifecycle, November 3-6, Washington, DC

OTHER RESOURCES

Biotech Process Validation Documents of Interest

- A-MAB Case Study
  - Biotech process/product development
  - Stage 1 in current PV Paradigm
  - In the public domain
- PDA TR-42
  - Process Validation of Protein Manufacturing
  - Published in 2005

Biotech Process Validation Documents of Interest

- PDA TR-60
  - Process Validation – A Lifecycle Approach
  - Published in 2013
- PDA TR-14
  - Validation of Chromatography Processes
  - Initially published in 1992, updated in 2009
- PDA TR-15
  - Validation of TFF Processes
  - Initially published in 1992, updated in 2009

QUESTIONS ???

Stage 3 – Post PPQ Monitoring

Kurtis Epp
BioTechLogic, Inc.
Lessons from 483s
Process Validation Track
February 27-28, 2012

PQLI Product Quality Lifecycle Implementation

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Sub-Team & White Paper Authors

- Dafni Bika – BMS (Sub-Team Leader)
- Penny Butterell – Pfizer
- Kurtis Epp – BioTechLogic
- Joane Barrick – Eli Lilly
- Jennifer Walsh – BMS
- Gert Molgaard – NNE Pharmaplan

Charter & Scope of ISPE Sub-Team Document

- **Charter:** Write a relatively short (< 20 pages), example-driven document, to help expound on methodology for selecting PV Stage 3 parameters and attributes for monitoring/trending.
- **Scope:** Small & large molecules, sterile & non-sterile products, drug substance & drug product, combination products, new & legacy products

The Essence of Stage 3 Validation

- Goal: Assurance that the process **remains in a state of control**
- Activity: **Ongoing** analysis of product and process data to identify and assess sources of process variability and impact to product quality

Major Challenges for CPV Implementation

1. How to select the appropriate parameters and attributes for CPV assessment.

2. How to analyze CPV data, once collected.

3. How to respond to process variability.

CPV Parameter & Attribute Selection

FDA Guidance on Process Validation (2011):

"We recommend continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until sufficient data are available to generate significant variability estimates."

"Variation can also be detected by timely assessment of defect complaints, out-of-specification findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports. Production line operators and quality unit staff should be encouraged to provide feedback on process performance."

CPV Starting Point

Start with the qualified control strategy, then…

- Determine whether risk assessment needs to be performed (legacy product) or updated following PPQ (new product) to document understanding of correlation between process parameters and CQAs (assumes inclusion of CQA severity ranking).
- Assess current process capability.
- Assess potential impact of raw material variability.
- Assess knowledge of operational risks.
- Assess robustness of predictive models.

Triggers for Ramping Up CPV Testing

- Legacy products not validated according to QbD may have information “gaps” that need to be filled with enhanced CPV testing
- Raw material, component, or operational variability assessed as “high risk” for potential impact to product attributes
- PPQ data showed that predictive models were not as robust as initially thought, so process characterization conclusions not as certain
- Others?

Triggers for Ramping Down CPV Testing

- Process variability targets (e.g., Cpk) successfully achieved during PPQ
- Critical parameter or attribute not subject to statistical assessment, so either more subjective trending (data tables) or existing quality systems are sufficient for ensuring the validated state
- Others?

Data Analysis

- Statistical control limits – using calculated upper and lower control limits as well as SPC rules to trend data
- Capability analysis – measuring how well the process satisfies/meets CQAs and customer requirements using Cp/Cpk (short-term) and Pp/Ppk (long-term)
- Certain parameters (e.g., bioburden & endotoxin) may not be subject to statistical analysis, but could be “trended” by a more subjective data assessment (rather than waiting for a failure before taking action)

Data Analysis

- **Statistical control limits**
  - Strength: ease of interpretation
  - Strength: well defined rules for assessing various OOT results
  - Weakness: cannot formally apply rules (e.g., Western Electric) until a statistically appropriate number of data points (e.g., n ≥ 25)
- **Process Capability**
  - Strength: applicable with fewer data points, depending on assigned CQA risk level and desired confidence level (e.g., n ≥ 7)
  - Strength: defines “control” against established acceptance criteria
  - Weakness: not as easy to observe slight trend shifts

Process Impact

- Statistical limits should not be confused with routine acceptance criteria. An “out-of-control” or “out-of-trend” result should trigger an investigation to understand source of variability, but does not necessarily constitute batch failure or loss of the validated state
- CPV Plan should prescribe what actions are taken to correct/control variability identified via CPV assessment

Real Biologics Example - Challenges

1. Limited amount of data at the commercial scale prior to PPQ (e.g., two representative engineering batches for the current large molecule example)
2. Intra-batch sampling is not typically relevant to biologics unit operations, outside of bulk drug substance and drug product filling due to one large pool being progressed downstream.
3. There are typically a considerable number of parameters assessed during the PPQ exercise that are not subject to variability estimates (e.g., data are below a method's LOQ/LOD, data are not subject to normal distribution, Pass/Fail results).
4. High cost associated with many enhanced testing procedures (e.g., residuals testing)

Real Biologics Example - Assumptions

- Stage 1 Process Design according to QbD principles was performed
- Quality risk assessment was performed and all high risk “non-parameter” variables (e.g., raw materials, components, equipment, facility, operations) were appropriately risk-mitigated
- One unit operation is discussed, though same principles could be applied to an entire manufacturing process

Real Biologics Example – Parameter & Attribute Selection

Critical Operating Parameter	Normal Operating Range
None	
In-Process Control	**Limit(s)**
Packed Bed Height	32.0 ± 2.0 cm
Number of cycles since last passing HETP test	< 5
Total Number of Previous Uses on Resin	< 32
Column Backpressure during Equilibration, Load, Wash, and Elution	≤ 25 psig
Outlet pH (offline) at End of Equilibration	5.0 ± 0.2
Protein Load per Volume of Resin	≤ 20 g/L

Real Biologics Example – Parameter & Attribute Selection

Critical Operating Parameter	Normal Operating Range	Include in CPV	Action/Rationale
None			
In-Process Control	**Limit(s)**	**Include in CPV**	**Action/Rationale**
Packed Bed Height	32.0 ± 2.0 cm	No	Not subject to normal distribution; failure cannot be predicted by data; failures addressed under existing quality system (i.e., deviation investigation)
Number of cycles since last passing HETP test	< 5	No	
Total Number of Previous Uses on Resin	< 32	No	
Column Backpressure during Equilibration, Load, Wash, and Elution	≤ 25 psig	No	
Outlet pH (offline) at End of Equilibration	5.0 ± 0.2	No	
Protein Load per Volume of Resin	≤ 20 g/L	No	

Real Biologics Example – Parameter & Attribute Selection

In-Process Acceptance Criteria	Acceptance Criteria
Eluate Endotoxin	Alert Limit: ≥ 5 EU/mL Action Limit: ≥ 10 EU/mL
Eluate Bioburden	Alert Limit: ≥ 10 CFU/10 mL Action Limit: ≥ 50 CFU/10 mL
Step Yield (A_{280})	≥ 75%
Eluate Purity (RP-HPLC)	≥ 85%
Additional Sampling	**Acceptance Criteria**
Eluate Host Cell Protein Content	< 500 ng/mL
Eluate DNA Content	< LOQ

Real Biologics Example – Parameter & Attribute Selection

In-Process Acceptance Criteria	Acceptance Criteria	Include in CPV	Rationale
Eluate Endotoxin	Alert Limit: ≥ 5 EU/mL Action Limit: ≥ 10 EU/mL	Yes	Compare to historical commercial data for assurance of consistency of environmental, water, and equipment microbial control
Eluate Bioburden	Alert Limit: ≥ 10 CFU/10 mL Action Limit: ≥ 50 CFU/10 mL	Yes	Compare to historical commercial data for assurance of consistency of environmental, water, and equipment microbial control
Step Yield (A_{280})*	≥ 75%	Yes	Control chart to continuously verify that desired unit operation output is consistently met.
Eluate Purity (RP-HPLC)	≥ 85%	Yes	Control chart to continuously verify that desired unit operation output is consistently met since PV batches had downward trend.
Additional Sampling	**Acceptance Criteria**	**Include in CPV**	**Rationale**
Eluate Host Cell Protein Content	< 500 ng/mL	No	Adequately demonstrated removal during PV batches; consecutive PPQ batches were all > 10x lower than the acceptance criterion
Eluate DNA Content	< LOQ	No	Adequately demonstrated removal during PV batches; consecutive PPQ batches were all < LOQ

Real Biologics Example – Parameter & Attribute Selection

- Four parameters identified for inclusion in the formal CPV exercise were eluate endotoxin, eluate bioburden, step yield, and eluate purity by RP-HPLC.
- Compile and trend data from twenty-five commercial scale batches (including two representative pre-PPQ engineering batch as well as the three PPQ batches) and assess on an ongoing basis.
- CPV strategy to be re-assessed after twenty-five batches.

Real Biologics Example – Data Analysis

AEX Eluate Endotoxin Data

Lot Number	Result (EU/mL)	Lot Number	Result (EU/mL)
Engineering #1	< 0.5	004	2
Engineering #2	1	005	< 0.5
001 (PPQ #1)	2	006	1
002 (PPQ #2)	< 0.5	007	1
003 (PPQ #3)	< 0.5	008	< 0.5

AEX Eluate Bioburden Data

Lot Number	Result (CFU/10mL)	Lot Number	Result (CFU/10mL)
Engineering #1	4	004	0
Engineering #2	0	005	1
001 (PPQ #1)	1	006	2
002 (PPQ #2)	0	007	1
003 (PPQ #3)	0	008	0

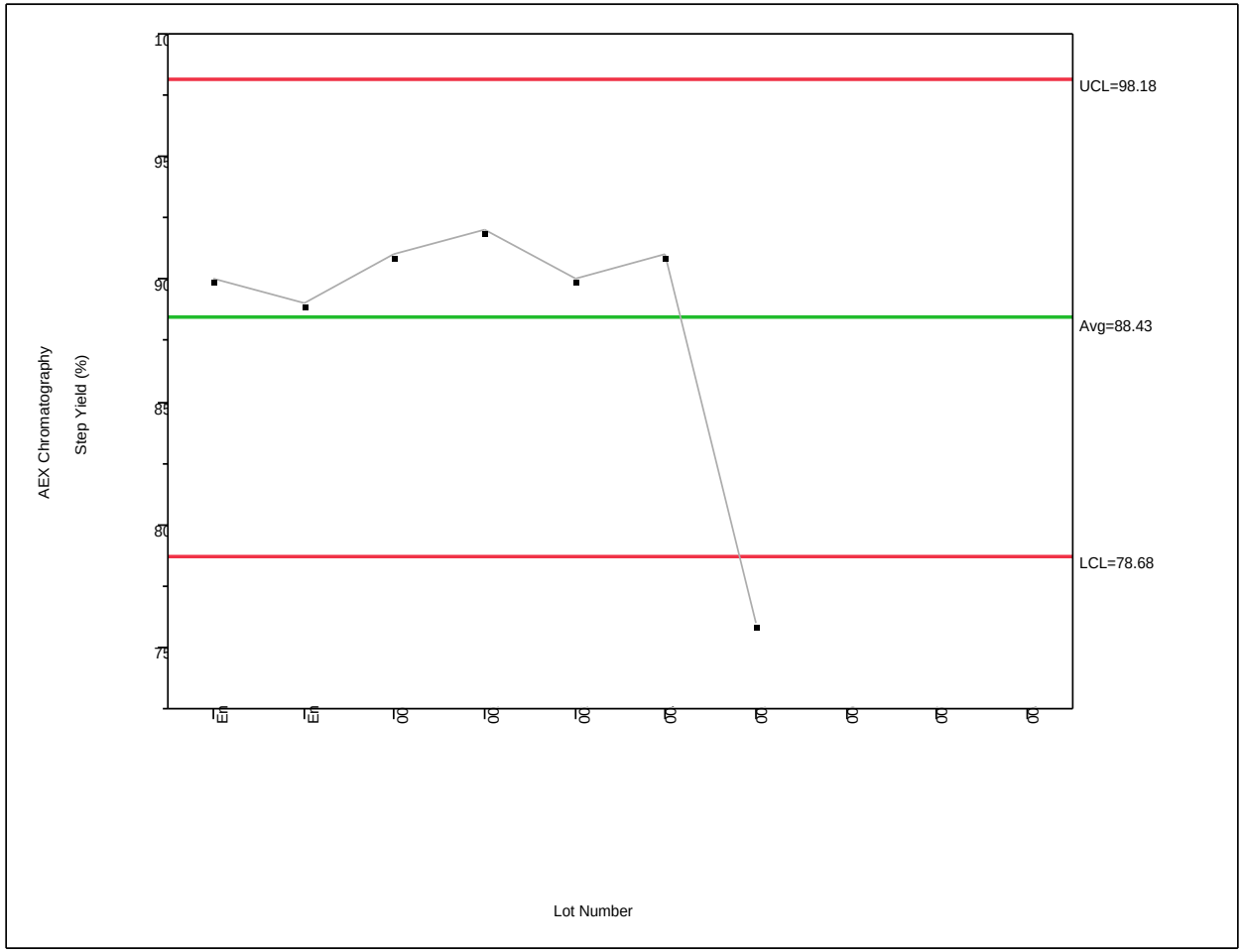
Real Biologics Example – Data Analysis

- Neither eluate endotoxin or bioburden are subject to normal distribution since results are frequently at or near the Limit of Detection for the respective analytical methods.
- Data cannot be control-charted or subjected to Cpk, but they can be tabulated and subjectively assessed for observable trends.

Real Biologics Example – Data Analysis

- While step yield does not impact the defined Critical Quality Attributes for this process, it is considered a performance indicator and important for maintenance of the validated state.
- As CPV data were collected and control-charted, a value was obtained for lot 005 that prompted an investigation. The control chart showed a clear out-of-control result, although the defined in-process acceptance criterion was met. This result was investigated to ensure that it wasn't caused by an unknown source of process variability.

Real Biologics Example – Data Analysis



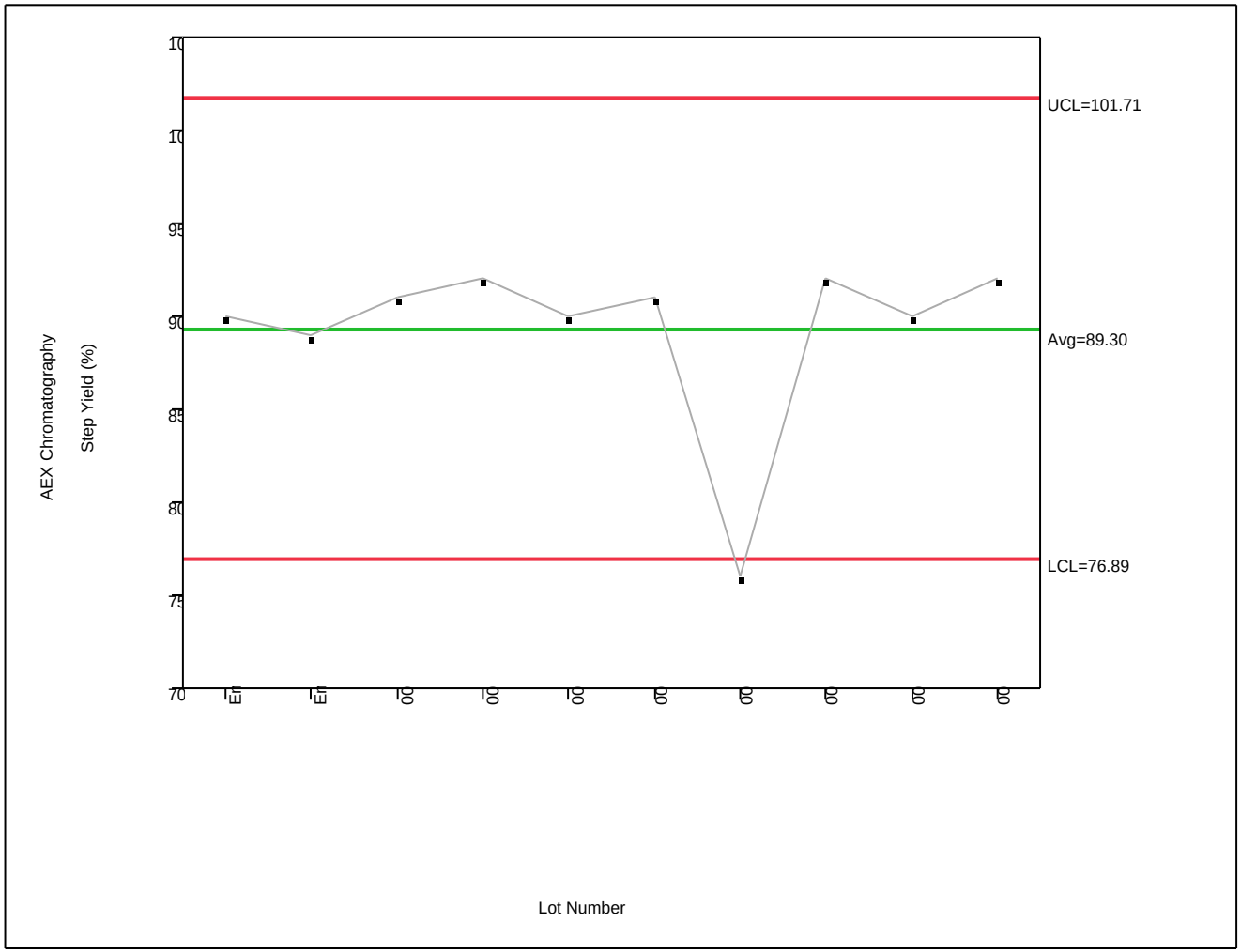
IPAC: ≥ 75%

Lot 005: 76%

Real Biologics Example – OOT Investigation

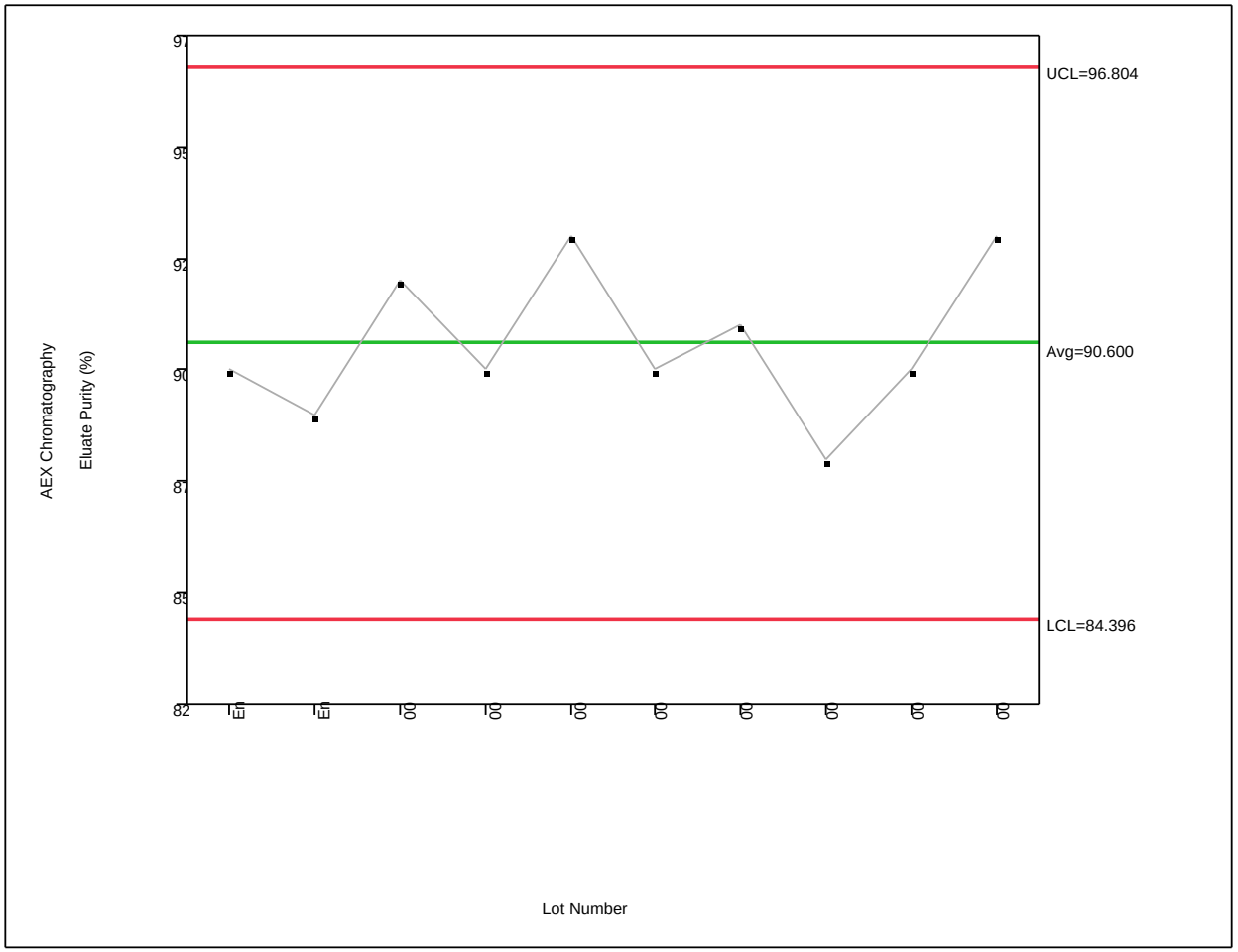
- Lot 005 was investigated immediately to assess the out-of-control limit result. While the step yield met the pre-defined in-process acceptance criterion of ≥ 75%, the result of 76% was below the calculated lower control limit.
- Upon investigation, it was determined that an operator had switched over to the waste fraction prematurely on the back side of the main peak collection (Target: 0.2 AU; Actual: 0.5 AU).
- Out-of-control value explained by operator error, resulting step yield value met the defined in-process acceptance criterion, and out-of-control result is not attributable to inherent process variability, so no impact to the validated state.
- **Possible outcome (risk mitigation): implement automation to reduce likelihood of this failure mode**

Real Biologics Example – Data Analysis



IPAC: ≥ 75%

Real Biologics Example – Data Analysis



IPAC: ≥ 85%

Summary - Realized Benefits of CPV

1. Batch-by-batch data analysis (i.e., control charts updated after every batch) enables real-time confidence in the validated state.

2. Trending (OOT result) triggered an investigation that may not otherwise have been performed, leading to a potential control strategy improvement.

3. CPV data package will become the basis for the Annual Product Review.