ISPE PQLI PV TEAM – OVERVIEW OF DISCUSSION PAPERS

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IABS Statistical & Data Management Approaches to Biotechnology Drug Development
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Slides on the ISPE PV team background and activities were provided by Joanne Barrick (Lilly) and Jenn Walsh (BMS), the PV team co-chairs.

Objective of PQLI®

ISPE's initiative, Product Quality Lifecycle Implementation, PQLI®, is focused on providing guidance on practical implementation of concepts described in ICH guidelines Q8, Q9, Q10 and Q11

Utilizing science to enhance process understanding and improve quality and supply reliability

Objective - Practical technical guidance to improve quality & supply reliability

Good Practice Guides on criticality determination, design space identification, control strategy development and a comprehensive Illustrative Example published - Nov 2011

Change Management in May of 2012

Process Performance & Product Quality Monitoring – June 2013

Current focus areas include Lifecycle Approach to PV, Quality Metrics, Breakthrough Therapies, Knowledge Management and Continuous Manufacturing

PQLI Guides

PQLI Overview Good Practice Guide

Product Quality Lifecycle Implementation (PQLI) from Concept to Continual Improvement:

Part 1: Product Realization using QbD, Concepts and Principles

Part 2: Product Realization using QbD, Illustrative Example

Part 3: Change Management System as a Key Element of a Pharmaceutical Quality System

Part 4: Process Performance and Product Quality Monitoring System (PP&PQMS)

ISPE PQLI *PV* Initiative Strategy and Deliverables

Assist industry in practical implementation of lifecycle approach to Process Validation

Focus on **unmet needs**

Increase understanding of new paradigm for process validation by leveraging previously completed ISPE PQLI work as a foundation

Deliverables

Conferences, workshops, forums, examples, validation related decision making tools/processes, training

Discussion papers - short and focused

ISPE PQLI Process Validation Team 2017

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Erica Stolz, Independent

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Tulio Teixeira, BMS

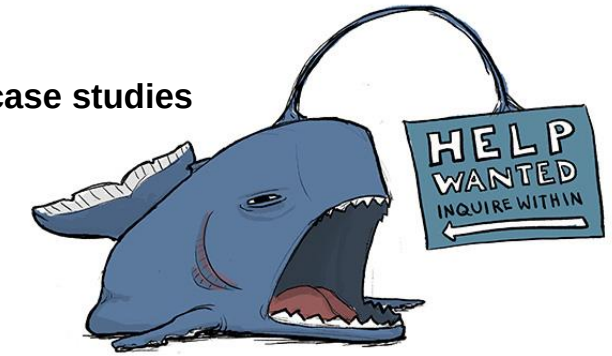
Cheng Tong, Hisun-Pfizer

John Wade, Eli Lilly

PQLI Process Validation Team Update

Discussion Papers and Good Practice Guide

- **Discussion papers issued in 2016/early 2017**
  - Determining and Justifying Number of Batches for PV – Supplement
  - PV for Legacy Products
  - Packaging Validation
- **Papers nearing finalization**
  - Process Validation of Continuous Manufacturing
  - Acceptance Criteria for PV Stage 2
  - Detailed Packaging Validation
- **Papers on the horizon**
  - Breakthrough therapy PV
- **Good Practice Guide – Lifecycle Approach to PV**
  - Completion expected by December 2017
  - Cross Functional SME team developed content including case studies



Typical Annual Conferences

- ISPE Annual Meeting PV session
- ISPE Lifecycle Approach to PV
- ISPE Statistics in Support of Lifecycle Approach to PV

PV Training - 2017

- Remaining: September & December 2017 (details follow)

ISPE PV Discussion Papers

Stage 2 PV: Determining & Justifying the Number of PPQ Batches
Lifecycle Approach to Biotech Process Validation
Stage 3 PV: Applying CPV Expectations to New & Existing Products
Evaluation of Impact of Statistical Tools on PPQ Outcomes
Application of PV Lifecycle Approach to Legacy Products
Application of Lifecycle Approach to PV at Contract Manufacturers
Selecting and Justifying Number of Batches for PV - Supplement

Overview of Packaging Validation for Drug Products
Process Validation in the Context of Continuous Manufacturing
Acceptance Criteria for Stage 2 PPQ
PV for Packaging for Oral Solid Dosage

Discussion Papers w Statistical Content

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Process Validation in the Context of Continuous Manufacturing
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Selecting and Justifying Number of Batches - Supplement

- 4 approaches
- Tolerance interval – ensure that it is within specification
- Bayesian – using the probability of a batch to meet specifications
- ANOVA – using stage 1 within- and between- batches variation to ensure that batches will be within a certain range
- Variability from similar process used as acceptance criterion

Acceptance Criteria for Stage 2 PPQ

- Sampling concepts
- Sampling criteria during the validation lifecycle
  - high level of sampling in Stage 1 and 2, reduced for stage 3
- Enhanced control strategy
  - Applying process control to leading indicators, e.g., CPPs, CMAs
- Sampling plans, OC curves, AQL vs RQL

PV for Packaging for OSD

- Why PV for packaging?
  - Gap identified – help in implementation
  - Offer initial thoughts, promote further discussion
- Paper 1 – High Level Overview
- Paper 2 - OSD Focus

Key Elements for PV for Packaging for OSD

- Risk Assessment
- Number of Batches
- Within-Batch Sampling & Acceptance Criteria
- Choosing AQL/RQL
- Statistical Analysis for PPQ
- CPV

Where and what statistical methods are proposed?

- Within-batch sampling and acceptance criteria
- Choosing AQL vs RQL
- Statistical analysis of PV and CPV data

Note: Number of batches largely based on risk assessment and practical considerations

Within-Batch Sampling & Acceptance Criteria

- Tied together
  - Acceptance criterion chosen to ensure, with pre-specified confidence that process will consistently meet specification
  - Number of samples chosen to ensure acceptance criteria are met if process is performing as expected
- Acceptance criteria based on statistical intervals
  - Parametric (Normal) Tolerance Intervals for continuous data
  - Confidence Intervals (Binomial) for proportion non-conforming (attribute data)
  - Bayesian Intervals (continuous or attribute data)

Within-Batch Sampling & Acceptance Criteria

- **Examples**
  - **The 2-sided 95%/99% tolerance interval for closure torque in each batch will be within specifications**
  - **The 1-sided 95% confidence interval (upper bound) on the proportion non-conforming in each PPQ batch is less than 1%**
  - **There will be 95% probability that 92% of CU results within a batch will meet specification**

AQL vs RQL – for attribute data

- Emphasis on RQL as an acceptance criterion for PV
  - High defect rate associated with low acceptance (usually 10%), reduction in RQL is a better driver for aiming for higher quality
- Choosing RQL
  - Often selected in conjunction with AQLs chosen for Stage 3 monitoring, based on RQL of the resulting sampling plan
    - Set RQL equal to AQL – very conservative
    - Set RQL equal to some fraction of the Stage 3 RQL
    - Set RQL equal to AQL but with higher acceptance probability

A few examples

AQL	Sampling Plan for Release	RQL for Release	RQL for Validation	Probability of Acceptance at RQL	Number of Samples within Batch	Acceptance Criterion for Validation
0.065%	200, 0/1	1.15%	0.065%	0.1	3550	0/1
0.065%	200, 0/1	1.15%	0.570%	0.1	400	0/1
0.065%	200, 0/1	1.15%	0.065%	0.2	2475	0/1

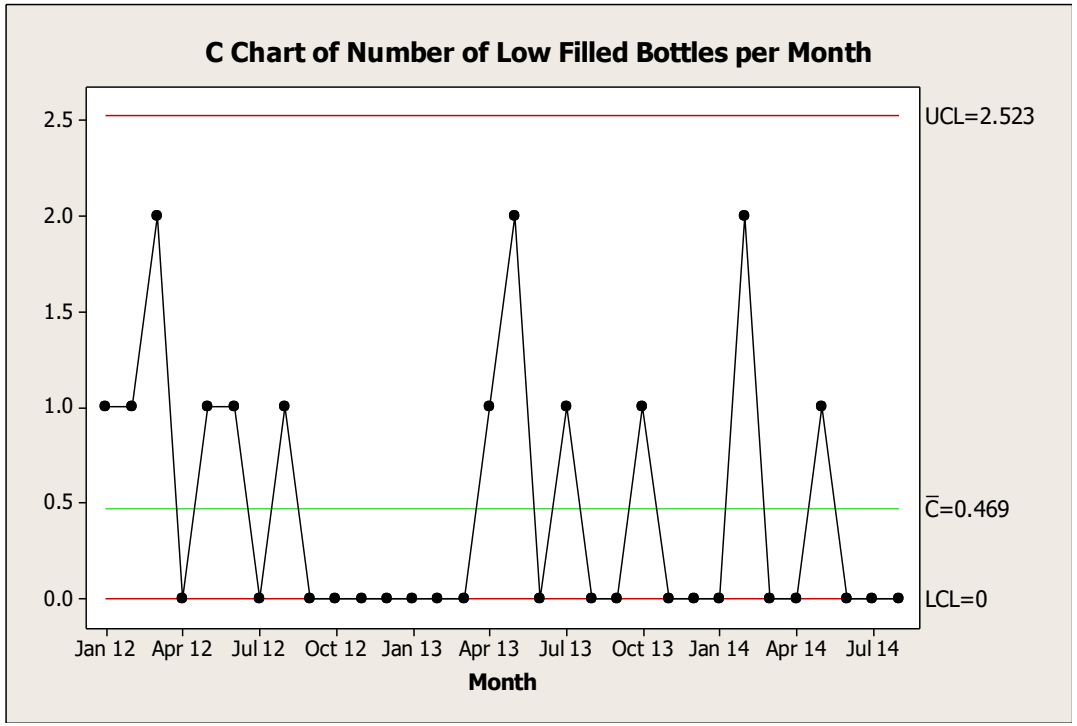
Statistical Analysis - PPQ

- Within-batch analyses
  - According to within-batch acceptance criteria
- Between-batch analyses
  - Limited in scope due to small number of batches
  - Compare within-batch results across batches
  - May be visual, risk based
  - Assess what analyses needed for CPV – heightened sampling

Statistical Analysis - CPV

- Focus on between-batch
- Control charts
  - Mostly discrete data – number of defects
  - P, C, U charts
- Process capability
  - Evaluate number of defects across multiple consecutive batches
  - Estimate an upper bound for the true “process” defect rate

Control chart



Process capability – one criterion

Defect Rate	Capability
Observed defect rate > AQL	Not capable
Observed defect rate < AQL, 75% upper bound > AQL	Marginally capable
75% upper bound < AQL	Capable
95% upper bound < AQL	Highly capable

For zero (0) observed defects and an AQL of 0.065%

Number of Batches	Number of Samples Inspected per Batch	Total Number of Samples	95% Upper Bound on Observed %Defectives	75% Upper Bound on Observed %Defectives	Capability Assessment*
30	200	6000	0.050	-	Highly capable
30	100	3000	0.100	0.046	Capable
30	60	1800	0.166	0.077	Marginally Capable
50	60	3000	0.100	0.046	Capable
100	60	6000	0.050	-	Highly capable

***not necessarily the "true" state, only what we are able to claim with confidence**

Summary

- ISPE PQLI team has been active for a number of years
- Progress in the implementation of PV guidance
- Many guidelines, discussion papers – useful resource, for small AND large molecules
- Join the team