The Israel Chapter of PDA

העמותה לקידום המדע והטכנולוגיה הפרמצבטית בישראל

Live Online Webinar

Continued Process Validation:

Monitoring Intra-batch and Inter-batch Variation

by

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15:30 – 18:00h

BR Consulting

❑ Continued Process Verification

CPV is the term used by the FDA.

A system or systems for detecting unplanned departures from the process as designed to identify problems and determine whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control.

Source: FDA PV Guide Glossary – 2011

❑ Ongoing Process Verification

OPV is the term used by EMA

Process Verification

From → To

2 Process Qualification → 3 Contn'd Process Verification

FDA WARNING LETTER

Torrent Pharmaceuticals Ltd — MARCS-CMS 585255 October 08, 2019

"Process validation evaluates the soundness of design and state of control of a process throughout its lifecycle. Each significant stage of a manufacturing process must be designed appropriately and assure the quality of raw material inputs, in-process materials, and finished drugs.

- *Process qualification studies determine whether has been an initial state of control established.*
- *Successful process qualification studies are necessary before commercial distribution of drugs.*
- *Thereafter, ongoing vigilant oversight of process performance and product quality is necessary to ensure you maintain a stable manufacturing operation throughout the product lifecycle."*

EU GMP Annex 15: Ongoing Process Verification

"Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated"

"The extent and frequency of ongoing process verification should be reviewed periodically. At any point throughout the product lifecycle, it may be appropriate to modify the requirements taking into account the current level of process understanding and process performance. "

Analysis of time-ordered data

When do you perform the analysis?

On-line or frequently

To take immediate action

Retrospectively

Product Review/ Quality Review

Frequent CPV/OPV Reports

On going process verification should be used to support the validated status of the product in the Product Quality Review, *Annex 15*

Annual APR/PQR Report

Intra-batch and inter-batch Variation

Regulatory Requirement:

Monitoring intra-batch and inter-batch variation!

During PPQ (Stage 2) and after PPQ (Stage 3)

Verde Cosmetic Labs
United States

FDA WARNING LETTER LLCMARCS-CMS 622534
MARCH 30, 2022

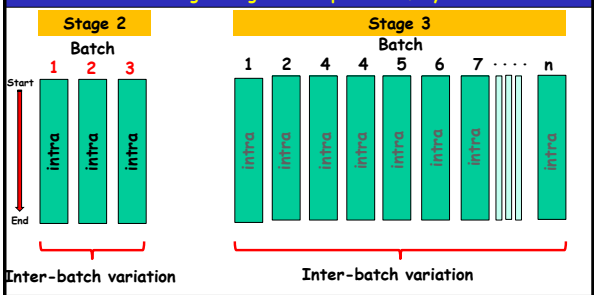
*"You also have not described how you will ensure that you **maintain a consistent state of control** thereafter for each of your drug products.*

*.... Describe your program for **process performance qualification**, and **ongoing monitoring** of*

both intra-batch and inter-batch variation

*to ensure a **continuing state of control.**"*

Monitoring throughout the product lifecycle!



PPQ is just an Initial State of Control

STAGE 2

A few process validation runs!

"Process qualification studies determine whether an initial state of control has been established."
FDA

Enhanced Sampling → Enhanced Testing

Knowledge emerges best from Control Charts!

Routine sources of variability?

- Multiple batches of API
- Multiple batches of excipients
- Different operators
- Equipment changes
- Changing versions of analytical methods
- Alternative analytical
- different sources of analytical reference standards
- Etc…

More sources of variation are captured!

Statistical Measures for Variation

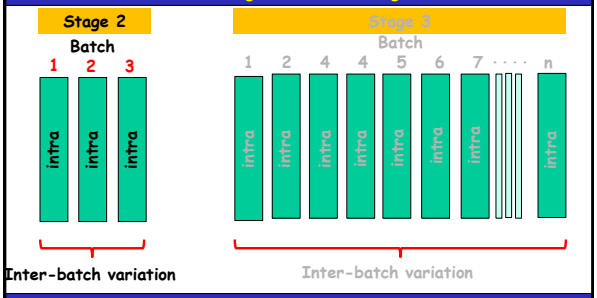
- Standard Deviation (SD) — absolute spread of data $s = \sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{n-1}}$
  - %RSD (Relative Standard Deviation) $\mathrm{RSD} = \frac{s}{\bar{x}} \times 100\%$
  - Variance $Var = s^2$
- Range (Max-Min)
  detects short-term variation

Comparison of variances | Comparison of batches means | Comparison against specifications (Process Capability) | Graphical evaluation

Monitoring Variation at Stage 2

Intra-batch Variation in Stage 2

Monitoring Variation at Stage 2



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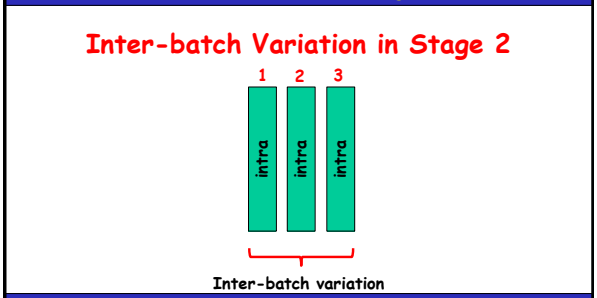
Inter-batch Variation in Stage 2



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Process data in the real-life world

- Process data are rarely random
- Many process data are not normal
  - * microbial counts cannot be negative!
  - * Impurity levels cannot be negative
- Process data are rarely independent
- Process data are often autocorrelated
  - high values follow high values
  - Low values follow low values
- Process data are often generated during campaigns of batches

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Practical Statistical Methods

Classical Statistical Methods

The classical textbook methods (ANOVA, Bartlett, F-tests) simply may not work well on pharmaceutical data sets because they assume normality and equal variances.

Although classical hypothesis tests detect statistically significant differences between lots, these differences are not practically meaningful

Practical Statistical Methods

- Does not require data normality or assuming an approximate normality
- Works with unequal sample sizes
- Avoids misleading p-values
- Focuses on practical equivalence, not theoretical equality
- Aligns with ICH Q8/Q9/Q10, FDA PV guidance, and SPC practice
- Matches how real manufacturing behaves

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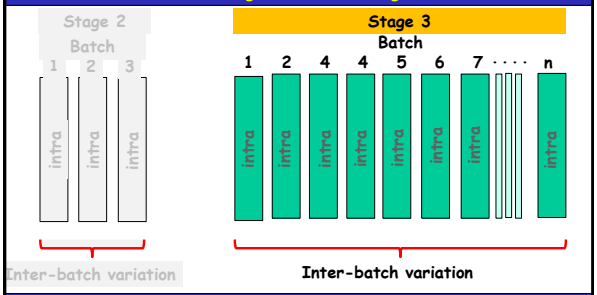
Monitoring Variation at Stage 3



Monitoring Variation at Stage 3

Intra-batch Variation in Stage 3

Intra-batch Variation in Stage 3

Depth of intra-batch and frequency of monitoring must be risk-based, data-driven, and proportionate to process understanding.

Examples of Risk factors

Criticality of the Parameter (CPP/CQA Importance)	
Process Capability (Cp, Cpk, Ppk)	Low? High?
Historical Intra-Batch Variability	
Process Maturity	New? Stable? after changes?
Severity of Potential Failure Modes	
Raw Material Variability	Supplier changes?

Solid Dosage forms

Examples of CPP / CQA
❑ Blend Uniformity (CQA)
❑ Content Uniformity (CQA)
❑ Granule Particle Size (CQA)
❑ Lubrication Time (CPP)
❑ Tablet Weight (CQA)
❑ Tablet Hardness (CQA)
❑ Tablet Thickness (CQA)
❑ Compression Force (CPP)
❑ Granulation Moisture (CPP)
❑ Coating Weight Gain (CPP/CQA)

Intra-batch Variation in Stage 3

Example of relaxed sampling and testing in DU Homogeneity!

In Stage 3

Dosage Units (Samples)
During filling or compression, take at least 1 dosage unit from at least 30 locations spread approximately equally across the batch including at the beginning and end of run

30 dosage units are samples!

In Stage 2

Dosage Units (Samples): During filling or compression, take at least 3 samples from at least 40 locations across the batch

120 dosage units are samples!

Source: ISPE BUCU doc.

Monitoring Variation at Stage 3

Inter-batch Variation in Stage 3

The purposes of CPV/OPV

1. To detect unusual variation
2. Ensure product quality
3. Enable process improvement

→ To maintain a state of control

State of control. A condition in which the set of controls consistently provides assurance of acceptable process performance and product quality.
EU GMP Annex 15, 2015

Observational Data

Process data | **Performance Indicators** of Analytical Procedures | **EM data** | **Stability results**

IPC | Finished product

- Chemical attributes
- Biological attributes
- Physical attributes
- Bioburden

To be trended!

How would you evaluate inter-batch variation?

FDA WARNING LETTER

EyePoint Pharmaceuticals, Inc. – 679747
USA

c. Your Manufacturing Operations and Engineering organizations **did not generate statistical process control charts to monitor manufacturing process performance (and control)** as required by procedure.

You generated various statistical process control charts during our inspection of your facility and **identified four previously unrecognized adverse trends** including those associated with damage to cores and poor polyvinyl alcohol capping that required investigation per your procedure..

Strategy of Control Charting

Stage 3a

1. to understand the sources of variation in the process
2. to re-confirm the QbD design space or PAR
3. to establish that the process is in control
4. to estimate the in-control parameters of the process.

Heightened sampling and testing may be required until sources of variability are understood

Stage 3b

1. on-line monitoring of future observations by using the control limits
2. to determine if the process continues to be in control

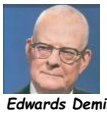
PAR: Proven Acceptable Range

Out of Control

(Unpredictable State)

"...State of statistical control is not a natural state for a manufacturing process.

It is instead an achievement, arrived at by elimination, one by one, by determined effort, of special causes of excess variation."



W. Edwards Deming
1900 -1993

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Practical SPC rules are also required to evaluate Control charts for the purpose of determining is a state of control prevails

Practical SPC Rules for CPV/OPV

R. Bar, Pharmaceutical Technology 45(11), pp.46-53, 2021

Also referenced in the Revised TR 60, 2026

Trending Process Data for OPV/CPV

Speaker

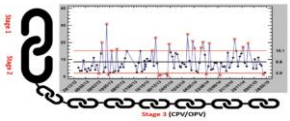
Dr Raphael Bar
BR Consulting

GMP Certification Programme
Certified Validation Manager

Trending of Process Data for OPV/CPV

Advanced Level Live Online Training on 15-17 October 2025

Next course: October 14-16, 2026



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