Implementation of a CPV program

and how challenges are addressed

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IFPAC 2015, Arlington, 28 January 2015
It is all about understanding variation

*FDA Guidance for Industry on Process Validation (2011)*

...A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control that is appropriate for the manufacturing process. Manufacturers should:

1. **detect the presence and degree of variation**

2. **understand the sources of variation**

3. **understand the impact of variation** on the process and ultimately on product attributes

4. **control the variation** in a manner commensurate with the risk it represents to the process and product
Stakeholders: their concerns and expectations

How can I get all of this accomplished?

One quality system needed for a heterogeneous set of manufacturing sites

I don’t have enough resources to run such a comprehensive program

IT systems are built on a 5-year timescale

When to start a root cause investigation?

How can I explain these customer complaints?

How can I get all of this accomplished?

What causes instability in my process?

Another GxP system

I don’t have enough resources to run such a comprehensive program

3-stage approach to validation

Understand factors, interactions

Too many manufacturing deviations

Remain in the validated state

Ready for inspections

Highlight unexpected data

Early warning for upcoming problems

Another GxP system

Stakeholders: their concerns and expectations

I don’t have enough resources to run such a comprehensive program

How can I get all of this accomplished?

One quality system needed for a heterogeneous set of manufacturing sites

IT systems are built on a 5-year timescale

When to start a root cause investigation?

How can I explain these customer complaints?

What causes instability in my process?
The following decisions must be made in development of the CPV program:

1. **What** data to trend and **how** and **when** to trend the data,

2. **When** and **how** to **analyze** the data and where in the organization this should occur,

3. **When** to **take action** based on the data analysis, and

4. **How** to **implement** such a program across an organization.
Existing building blocks

- QC Release
- Analytics
- APQR
- Quality
- Manual
- IT system: transactions
- QTPP → CQA
- RCI methodology
- OOS investigation procedure

IFPAC 2015 | A. Zilian | 28 Jan 2015 | Continued Process Verification program © 2015 Novartis Pharma AG | Public

2. APQR: IT support for data compilation and analysis

3. Define CPV long term goal, update quality system and define implementation plan

4. Build experience with CPV for CQA

5. CPV for CQA: IT support for data compilation, analysis and reporting

6. Pilot CPV based on all relevant variables

7. IT support to compile all variables and perform their analysis
Poor process performance
[1] example from an Annual Product Quality Review
Acceptable process performance

[1] example from an Annual Product Quality Review
Good process performance

[1] example from an Annual Product Quality Review

Project: Uniformity of Dosage.MPJ; Worksheet: UNIFORMITY OF DOSAGE.MTW; 10.01.2015
Product portfolio: in control & capable

[1] Example

- Products are characterized by volume, deviations, Ppk
- Prioritize products with high risk of failure, many process deviations
IT system for APQR

[2] IT support for data compilation and analysis

- analyze, report
- select, drill down
- record

- statistics
- graphical

- Insight

- Time Series
- Relational
- Unstructured

- Process
- Batch transactions (LIMS)
- Text reports (quality events, reports)
CPV implementation for legacy products

[3] scope for monitoring

Existing global IT systems

IT Systems to be built

- low volume
- numerous manuf. deviations
- numerous complaints
- life-saving high volume

CQA QA

IPC CPP MA

products
variables
The data trended includes

- process output variables, ‘CPV phase 1’
  (product quality attributes which reflect the overall process performance)

- process input variables, ‘CPV phase 2’
  (contributing factors including process parameters, raw material quality attributes, packaging parameters, environmental parameters, IPCs) which have an impact on the final product quality.
Roadmap for Continued Process Verification

[3]

- **CPV PROTOCOL**
  - CQA Yield
  - MA
  - CPP
  - IPC
  - Quantitative Variables
  - Events
  - Changes
  - Deviations
  - Complaints

- **Phase 1**
  - Batch
    - capture data
    - respond to excursions
    - correlate events vs. CQAs and facilitate PQR/APR
  - Periodic
    - maintain control charts
    - respond to trends, shifts
    - respond to performance
  - Annual
    - quantify variability
  - CPV REPORT

- **Phase 2**
  - reassess variables and update control limits
Implementation strategy

[3]

- The strategy for implementation of CPV is to encourage implementation of process monitoring as soon as possible in a “ramp up” process: activities are phased in, step by step.

- This way manufacturing sites can get used to using the tools and techniques and get people trained in a step-wise fashion, and begin to reap benefits of CPV, even on a limited scale, as soon as possible.

- Update the quality system
  - Quality Manual, applicable to all divisions of the company
  - Global SOP, applicable to all manufacturing sites
Statistical signals: when to take action

- Outside specifications
  → reject the batch

- Inside specifications
  → potential problem
    - Failure against limit: outlier, OOE
    - Failure against other run rules (trends shifts, oscillations)

→ False alarm?
→ identify root cause
Analyzing and Evaluating Data: example

[4] when to take action?

- OOE data is out-of-expectation; what is the assignable cause?
What is the appropriate level of investigation?

[4] -- what is the risk to product quality?

- Level of investigation and CAPA to be commensurate with the risk to product quality

- How large is the excursion?
- Is it a recurring event?
  - Even a perfect process has an expected number of outliers of 1 in 300
  - With 4 Nelson rules active, the false alarm rate is about 1 in 100
Critical Process Parameter trending

[6] Example: Dissolution and total air volume

- CQA and CPP is shown for all batches

In this example,
- CPP is well within proven acceptable range
- Instability of CPP has no effect on CQA
- CQA data is not yet completed
- CPP is well within normal operating range
- Criticality?
- Response?
- Statistical signals from many parameters!
IT system for CPV

Detect exceptions

- analyze, report
- select, drill down
- record

- statistics
- graphical

- Insight

- Time Series
- Relational
- Unstructured

- Process (Historian)

- Batch transactions (LIMS, MES)

- Text reports (quality events, reports)
IT system for CPV

After exception is detected

- analyze, report
- select, drill down
- record

Investigate root cause

- statistics
- graphical

Time Series
- Process (Historian)

Relational
- Batch transactions (LIMS, MES)

Unstructured
- Text reports (quality events, reports)
Conclusion: CPV program decisions

1. What data to trend and how and when to trend the data,

2. When and how to analyze the data and where in the organization this should occur,

3. When to take action based on the data analysis, and

4. How to implement such a program across an organization.

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