



Continuous Quality Verification

An Approach to Process Validation

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Agenda

- Abstract
- Background to case study
- Topics Discussed
- Common Positions
- Areas for Further Work

CQV Abstract

- Traditionally, process validation has demonstrated the reproducibility of a process, based primarily on repeatability and testing of the end product. Using Continuous Quality Verification (CQV), processes are continuously verified as being capable of providing the desired product quality as an alternative to reliance on data generated from a few production lots.
- Implementation of CQV involves the continuous monitoring, evaluation and adjustment, as necessary, of the process. CQV moves away from validation as a discrete exercise and is consistent with a lifecycle approach to process validation. This presentation will provide an overview of CQV as an approach to process validation and the circumstances under which CQV may be used. It will show the primary elements of this approach as applied to the implementation of continuous processing for an existing product. How CQV links to real-time release and the expected impact of CQV on regulatory filing content will also be discussed.

Terminology

Continuous Process Verification: *An alternative approach to process validation in which manufacturing process performance is **continuously monitored and evaluated**.* (ICH Q8)³

Continued Process Verification - *a stage (Stage 3) of the Process Lifecycle, after Performance Qualification (Draft FDA Guide)*¹

Continuous Quality Verification (CQV) *is described as an approach to process validation where manufacturing process (or supporting utility system) performance is **continuously monitored, evaluated and adjusted as necessary**.* (ASTM)²

References: 1) FDA Draft Guide on Process Validation (2008) and 2) ASTM E2537-08: Standard Guide for the Application of Continuous Quality Verification to Pharmaceutical and Biopharmaceutical Manufacturing; 3) ICH Q8- Pharmaceutical Development.

Elements of Continuous Quality Verification



Background to Case Study

- Established Product (traditional filing):
 - Oral solid dosage form, 2 strengths (common blend)
- Process change:
 - Implementation of continuous manufacturing process
 - Implementation of real-time release testing
 - Implementation of CQV as an alternative to conventional process validation
- Regulatory Timelines:
 - Expected to be filed as a Type II Variation via the EMEA pilot for Worksharing in the first half of 2010

Status of Project

- Development work ongoing (DoE and process modelling) to establish enhanced process understanding and identify any CPPs specific to continuous process
- Control strategy proposed based on current understanding of continuous process
 - to be finalised once development is complete
- Continuous processing line under construction
 - System verification target completion date Q2 2010
- CQV plan drafted – One-time studies to compare CQAs for batch vs CP process; initial process performance evaluation

Control Strategy

<u>CQA</u>	<u>Batch Process</u>	<u>Cont Process</u> (RTR Testing)
Blend Uniformity		On-line NIR
Tablet Content Uniformity	HPLC	On-line blend NIR + tablet weight
Tablet Assay	HPLC	On-line blend NIR + tablet weight
Dissolution	Dissolution	At-line disintegration



Topics Discussed

- Traditional validation versus continuous verification approaches
- Applicability of CQV to different scenarios e.g. small and large molecules
- Indirect monitoring of CQAs
- Relationship between RTR testing and CQV
- Use and verification of models
- Data included in the dossier for review vs inspection
- Number of initial evaluation production batches prior to commercialisation
- Definition of a batch for a continuous process



Common Positions

Continuous vs Conventional Process Validation

- The objectives of both CQV and a conventional x-lot validation approach are the same
 - to support commercialisation of a product; and
 - to ensure that the process consistently meets its pre-determined quality attributes
- Both process validation approaches continue to be acceptable alternatives.

Applicability of CQV

Q Can CQV be applied to large molecules considering the complexity of the process and do we have an examples?

A CQV can be applicable to small and large molecules, new and existing products.

- We are evaluating how CQV could be implemented for bios. Our approach to gaining process knowledge (and thus understanding of the relationships between CQAs and potential CPPs) is applied to small and large molecules.
- CQAs (and associated methods) for biotherapeutics can be quite different from small molecules and some quality attributes will be harder to monitor real-time than others.

Indirect monitoring of a CQA

- The relationship between a CPP and a CQA is well understood and an appropriate model has been developed
- In this case, it is acceptable to monitor the CPP as an alternative to the CQA
- Ref: ICH Q&A 2.3 Control Strategy Question 10

Relationship between CQV and RTR

- CQV and RTR testing can be applied independently
- However, there are synergies between the two when they are applied together
 - e.g. the ability to respond more quickly to data generated and monitored in real time (as opposed to waiting for traditional QC testing)
 - Tools such as PAT allow more frequent sampling vs traditional testing leading to improved process understanding.
 - Batch release of product still is performed by a QP. It can be done immediately after the batch is made because all of the RTR testing data is available.



Areas Requiring Further Work

Use and verification of models

- Regulators are concerned about how models are managed and how outliers are handled

Q When using models, how will we ascertain that the model is appropriate?

A This will be determined case by case, using iterative risk assessment and development studies and/or prior experience

Q How will we periodically re-verify the model?

A We will do this as part of the initial one-time evaluation, but our control strategy includes continuous monitoring and evaluation which can be fed back into the model e.g. a periodic correlation of NIR vs HPLC

Review of data vs inspection

Q What will we include in our submission?

A The validation section will include a process validation scheme for critical process parameters and critical steps describing our approach to CQV

- A scientific justification (for our CQV approach) will be included in section P2. based on our risk assessment, design of experiments and modelling
- CQV plan, data and reports will be available for inspection

Number of CQV evaluation batches?

- One full scale commercial batch may be sufficient for commercialisation (i.e. for a process change or new process), provided that, for example:
- A process is well-characterized and understood, and is known and documented to have no scale dependencies
 - through e.g., prior knowledge, experimentation, and/or risk assessment
- There are significant development data at lab and/or pilot scale
- There are no critical equipment dependencies
- Continuous monitoring as required for CQV is in place

How do we define a batch for a Continuous Process?

- The batch will be defined by a period of time, yet to be determined for our case study.
- The batch size needs to be defined for business reasons (e.g. batch release) and lot traceability