Continuous & Continued Process Verification

Presented by Eoin Hanley
4 July, 2016
This session will cover

- Quick recap on PV Lifecycle stages & Annex 15
- Continued (Onoing) Process Verification
- Continuous Process Verification (PAT)
- Continuous Manufacturing: benefits, challenges & examples
US FDA “Process Validation”

1. Process Design

2. Process Qualification

3. Continued Process Verification

Process Improvement & Innovation
Basic principle is that a drug should be produced that is **fit for its intended use**.

This is achieved by:

- Ensuring that quality, safety and efficacy are **designed/built** into the product
- Quality **cannot be adequately assured** merely by I-P and FP inspection/testing
- Each step of a manufacturing process is controlled to assure that the FP meets **all quality attributes** including specifications
What does a successful PV program look like?

- **To establish control:**
  - Understand the **sources** of variation
  - Detect the **presence** and **degree** of variation
  - Understand the **impact** of variation on process/product
  - **Control** the variation in a manner commensurate with the risk to process/product
  - Throughout the lifecycle—**including changes**
  - Evaluation of the **state of control**
Annex 15: Process Validation

Process Development
- Design Space
- Concurrent Validation
- Process Development/Design Space

Process Validation Approaches
- Continuous Process Verification
- "Hybrid Approach"
- "Ongoing Process Verification"
- Traditional Approach
- Retrospective Validation

Ongoing Process Verification during Lifecycle
Annex 15: Process Validation

- Process Design
- Continuous Improvement
- Process Validation
- Continuous Process Verification
- Ongoing Process Verification
Continued Process Verification

“Continued or Ongoing Process Verification”

Continual assurance - system for detecting unplanned departures/undesired process variability

Change in the validated state of the process could impact product. Detected by:

- Change Control
- Periodic Monitoring
- Data Trending Review
- Calibration and PM
- Knowledge of operational parameters (Control Strategy) and Design Space
Continued Process Verification

US FDA: “Continued monitoring & 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”

Basis for routing sampling and monitoring:

- Level of sampling
- Frequency of sampling
- Can be adjusted to a statistically appropriate and representative level
- Periodically assessed
Continued monitoring

Process Design  |  PV (PPQ)  |  Commercial Manufacturing

Level of QC Lab Testing

- Could vary based on approach
- Variability estimate established
- Post-periodic review signal
- Change/improvement introduced
- PAT implemented

Monitoring

Time / Process Knowledge
CPP’s and process alarms

- Control range of Critical Parameters
- Control Strategy around Critical Process Parameters
- Within the Design Space
- Easy to implement and control
- Demonstrates proper performance of the process
Change Control

- Maintain validated state via review and approval of changes made
- Further understanding of the process & variations
- Changes of materials, FSE, personnel and procedures
- Review by cross-functional SME’s
- Pre-approval by Quality
- All changes tracked & trended
- Planned & unplanned
Periodic monitoring

- Demonstrates consistency of initial results
- Ongoing feedback programs to collect and analyse data
- Part of an approved protocol (Annex 15)
- Evaluate the state of control of the process
  - Statistical process control
  - Data from automation
- Risk-based Routine Monitoring Program
- May identify process/product problems
- May indicate areas for process improvements
  - Back to Stage 1 and Stage 2
Data trending & review

- Even well-designed processes must include in-process control procedures
  - Verify the **quality attributes** are appropriately controlled
  - Action & alert levels for process parameters
  - Analytical data from routine monitoring
  - Samples must **represent** the batch under analysis
- **Sampling Plan** must result in **statistical confidence**
  - Intra- and inter-batch variation
Batch must meet predetermined specification
  - Trending helps identify potential issues
  - May feed into a CAPA system
  - Specifications must be correctly derived

It is all about evaluating process stability and process capability

Should guard against overreaction to individual events as well as failure to detect unintended process variability

Must be reviewed by the Quality Unit
Statistical tools & techniques

Detect variation

Characterise it

Determine the root cause
Maintenance

- Ensures process remains **in control**
- Maintain the qualification status of facility, utilities, systems and equipment
  - Monitoring & scheduling
  - Maintenance (planned & unplanned)
  - Calibration
- Assess the data **periodically**
  - **Re-qualification required? How much?**
Training

- Training on revised procedures & forms
- Specific training - statisticians or trained personnel
- New personnel
- Re-training of operators based on operator errors
- Periodic training - personnel may have an impact on variation?
- Re-training for certain processes i.e. process simulation/media fills, gowning practices etc

Training is always important
Annual Product Review/Product Quality Review

- **Overall** periodic review of the validated state
- Also product quality complaints, adverse events etc
- Frequency of the review may be based on a risk assessment (also refer to new US FDA Guidance for Industry Request for Quality Metrics, July 2015)
- Review of regulations/CGMP
- Documented with conclusions
- Recommend planned improvements
Continuous Process Verification

“An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated” (ICH Q8)

An alternative to traditional PV

Can be part of a hybrid approach

Processes must be shown to be robust and ensure consistent product quality before any product is released to the market
Continuous Process Verification

- **High degree of assurance** in the science-based control strategy
- Quality by Design approach
- Undergo regular evaluation
  - PAT/SPC may be used as tools
- Need to determine the **number of batches** to demonstrate process capability
Process Analytical Technology

• Intended to support innovation, efficiency and risk-based decisions
• **Industry is slow** to adopt innovative systems
• Timely analysis of critical quality attributes
• Control loops to adjust processing conditions-output remains constant
• Can provide a **higher degree** of process control
• Will have different Design & Process Qualification stages
• US FDA Framework and ASTM guides

“Quality cannot be tested into products; it should be built-in or should be by design”
Process Analytical Technology

Looking for gains in quality, safety and/or efficiency:

- Reducing cycle times
- On/in/at-line measurement/control
- Prevent rejects/re-processing
- Real-time release
- Increasing automation to reduce human errors
- Improving energy/material use
- Increasing capacity
- Facilitating continuous processing to improve efficiency & manage variability
Continuous Manufacturing processes

“Batch” vs “Continuous”

Definition of “batch” and “lot” in CFR’s are applicable to continuous processes.

Innovative to pharma industry, but not to petrochemical, food, automotive, etc

Continuous flow reactors (US FDA and University of Washington) using Raman data

© PharmOut 2015
Continuous Manufacturing processes

**Considerations:**

- Residence Time Distribution (RTD)
- Sampling
- Process control & monitoring
  - Real Time Release Testing
- Collection of product
Residence Time Distribution (RTD)

- Continuous material flow into the system
- RTD describes the non-ideality of flow
- Can be evaluated by tracer studies
Sampling

Sample frequency should be suitable for the system dynamics

- Capable of seeing potential disturbances

Probe/sample location(s) representative of entire vessel

Sample interface

- Remains constant over the process (no fouling)
Sampling considerations

Sample acquisition time
- Compare to unit dose (volume/mass)
- Consider flow past the probe

Is the measurement representative of the whole?
Process control

Long periods of operation in CM

High degree of automation

- E.g. Product diversion to waste if out of specification

Ensure process is operating as intended

- Control start-up, shutdown
- Control of critical parameters
- Detect process upsets
- Correct process drifts
Process monitoring

- It would be **challenging** to assure quality in many continuous manufacturing systems without **appropriate** on-line monitoring and/or multivariate tracking and trending.

- **Adequate monitoring** allows rejection of **non-conforming material** made during process upsets, while keeping the ‘**good**’ material.
Real Time Release Testing

“The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls” - ICH Q8(R2)

Continuous manufacturing naturally lends itself to RTRT approaches
Material traceability

- **Multiple lots** of raw material and API may be used in a single run
- Should have the ability to **trace** raw material and API lots to finished products. (Importance of RTD)

**Traceability of disturbances through the system**

- Diversion of material made during disturbances
- Clear definition of criteria for determining “good” product
Collection of product considerations

When is product deemed acceptable to collect?

- During process start-up and shut-down periods?
- After a disturbance (spike in feed rate)?
- Have all components reached desired state?

Example: For concentration or material property?
  - Are measurements other than concentration of active component(s) needed?
Considerations for Batch/Lot

How to define a batch/lot at the product collection step?

- Production time period?
- Amount of material processed?
- Production variation (e.g., different lots of feedstock)?
- Other definition?
Example: CM of tablets

- **Traditional oral solid dosage process:**
  - High inventory
  - Long lead times (i.e. actual time is 2 days but total time is 30-60 days)
  - Long changeovers
  - Off-line analysis etc
Example: CM of tablets

GEA ConsiGma™

• Powder supply
• High shear mixing & granulation
• Segmented fluid bed dryer
• Granule conditioning unit
• Rotary tablet press

• Continuous coater

Example: CM of tablets

- Easier to move 1 kg than 1 tonne
- Minimum amount of product in the process
- No scale-up. Same size equipment from pilot to CM.
- Time saved from lack of scale-up
- Removes “inertia” from the manufacturing system
Section recap?

- Continued Process Verification
- Continuous/Ongoing Verification
- PAT & Continuous Manufacturing
Thank you for your time.
Questions?

Eoin Hanley
Technical Manager

eoin.hanley@pharmout.net
www.pharmout.net