The Role of Criticality Analysis in Controlling Pharmaceutical Processes

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Criticality Analysis

• What do we mean by “Criticality Analysis?”
  – Criticality = the state, or degree of being of the highest importance
  – Criticality Analysis = establishing that which is most important, and how important it is

• How do we use it?

• During Development we carry out “Criticality Analysis” which is the assessment of…
  – Attribute Criticality
  – Process Criticality
    • Input materials
    • Process parameters
Use of Criticality in a Process Flow

**Stage 1**
Identify Performance Requirements

**Stage 2**
Identify possible Critical Quality Attributes

**Stage 3**
Perform Initial Cause and Effect Matrix

**Stage 4**
Perform Criticality Assessment

**Stage 5**
Formal Risk Assessment on Critical and Key Aspects of the Process

**Stage 6**
Conduct Process Validation

**Stage 7**
Continuous Process Improvement

- Tablet QAs
- DPI QAs
- DS QAs

Triggered by predefined criteria
Typical example – drug product intermediate

• Three step process
  – Dissolution (Process A)
  – Spray Dry (Process B)
  – Secondary Drying (Process C)
• Drug product intermediate then goes to formulation
• Drug product process is adjusted based on bulk density and Dv50 of the intermediate
• Need to determine and control Dv50 and bulk density of the drug product intermediate coming out of Process C
  – But they are actually ‘generated’ in Process B
Impact of changing input parameters on compression
Consider the particle size application (PPS)

• Why?
  – Particle size is a CQA!

• What?
  – Prediction model correlating to off-line data
  – ‘Instantaneous’ data for in-process control (IPC)
  – ‘Cumulative’ data for real-time release

• Where?
  – Within the process

• When?
  – During production to allow parameters which impact particle size to be adjusted, if necessary

• How?
  – Optimized commercial on-line measurement
PPS – actually two applications

• Generate an ‘instantaneous’ IPC value to allow feedback control
  – Requirements
    • Representative of powder being generated at that time – criticality describes how fast/how frequent
    • Process model built on off-line data so has to correlate to those values – describes acceptable method bias
    • Precision determined by criticality – how much measurement variability can be tolerated does the measurement?
    • Range and linearity – from criticality
    • Robustness has to be ensured

• Generate an RTR Dv50 value representative of the whole batch, which will also enable feed-forward control
  – Requirements
    • Has to predict what the Dv50 would be after secondary drying
    • Has to be truly representative of the whole batch
    • Precision determined by criticality – how much measurement variability can be tolerated does the measurement?
    • Range and linearity – from criticality
    • Robustness has to be ensured
How do we ensure the measurement is representative?

- Appropriate selection of sampling location
  - Powder flow is linear (post vortex breaker)
  - However it’s in the ‘shadow’ of the vortex breaker
- Tried commercially sampling systems
  - Poor correlation with off-line data
- Current sampling arrangement is the result of empirical testing of various restrictions and funnel configurations
  - Has been proven to generate the best equivalency to off-line data
  - Covers 25% of the cross sectional area, i.e. 1/4 of production runs through the analyzer!
With this ‘sampling’, it must to easy to get the data we need…?

• No!
• Criticality determines the precision we require
• Let’s look at the instantaneous data
• Precision is not good enough
• The powder flow in the process equipment is maintained by the use of pneumatic hammers
So we just average it, don’t we?

• Yes and no
• An 8-min moving block is used because it lets us remove the influence of the operation of the hammers without losing information on process trends
• And we know from the criticality analysis
  – How fast the process is likely to change (and need adjusting)
  – But also the amount of change we can tolerate before having to make corrective action
How do we know this works?

- We have a degree of process understanding (in the process model) that allows us to ‘drive’ the process to make any particle size we want
- So we can verify the performance of the measurement system by making a small change in the process and watching how it responds
- Make a change expected to move the Dv50 by 3 µm
  - Dv50 responds immediately and stabilizes in ~8 minutes (one block of data)
Correlation between on-line and off-line: linearity

Measured Values

\[ R^2 = 0.99 \]

on-line Dv(50)

off-line Dv(50)
What about the robustness of data?

- The expected obscuration value is known (for this sample density) and is used as a system suitability criteria
  - Check if there is powder of the expected density in the analyzer
- Plus we know the what the raw scatter signal pattern looks like and check the intensity of the detector ring associated with the peak of the PSD
  - We make sure that the scatter pattern is due to our product and not simple window obscuration!

- Only data which pass both for the entire 8-min average are displayed
- Atypical changes in the process cause changes in transmission and signal intensity, seen in the very next data point
  - So the 8-min average is used for IPC
  - But a process failure is seen after 5 s by the system suitability criteria
What about the RTR application?

• What if we average the IPC values & apply a prediction model?
  – That would give an average Dv50 for the data we have
  – But it would NOT ensure the data is fully representative of the batch

• Need to add ‘selection criteria’ to ensure the data is equally weighted and no gaps occur
  – % batch coverage
  – Only data from expected process events (sampling, start-up, etc.)
  – However, we don’t really want an average of the averages

• So instead, we create a cumulative PSD
  – Made up of every ‘good’ 5 s data point
  – At the end of the batch simply read off the cumulative Dv50
  – Apply prediction model to convert to expected Dv50 after secondary drying
  – Use that value to release the batch and feed that value forward for compression step
Does it work?

Dry PS

- ▲ Dry ps (measured directly off-line)
- • Dry ps (predicted from on-line data)

Batch number

1 2 3 4 5 6
Doing the criticality analysis establishes….

• All the important attributes

• The acceptable operating range of those attributes
  – Combined together, these describe a Process Map

• All the important parameters and how they impact those attributes

• Also the relative importance of those parameters in bringing about a change
  – Combined together, these describe a Control Model
  – Process + Control Model = Process Understanding

• The Control System is configured to act on fixed parameters (the recipe)
  but is ‘driven’ by variable parameters for the Control Model
What does this all look like together?

All raw data archived allowing the recreation of PSD and all attribute values.

System suitability applied 8 min moving block average applied to all valid data to give un-bias corrected wet dv(50) for control. In addition a cumulative un-bias corrected dv(50) from all.

Batch recipe control via DeltaV software. Bias correction applied to wet dv(50) to give Wet ps. 8min average Wet ps value used in Process Model and displayed on DeltaV control screen. Archived along with other process data. Cumulative Wet ps taken and used to predict Dry ps. Dry ps entered on COA.
On going method verification – “3 leg stool”

- Primary mechanism is via comparison of:
  - Dry Dv50 (predicted from on-line) to dry Dv50 (expected from our Process Model)
  - If difference is less than 4 µm then performance is verified
  - If not, then an off-line Dv50 is measured (post secondary drying) to test if the deviation comes from the on-line measurement or Process Model

- Also critical to conduct model maintenance over the lifetime of production!
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