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ENGINEERING PHARMACEUTICAL INNOVATION

Validation – Leveraging for Compliance

Maurice Parlane
Principal / Director
New Wayz Consulting Ltd

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Presentation Outline

- Current validation practice
- Enhanced qualification management
  - Discussion and examples
- Knowledge from PQ
- Enhanced process monitoring
- Summary

Current Validation Practice

- Current philosophy
  - Process validation is a regulatory activity
  - Qualify facility and equipment
  - Make 3 representative validation batches
  - Document results with little or no analysis of the robustness of the process

Qualification – Current State

- Qualification is typically to deliver compliance at the time its executed only.
- Measures to manage dynamic information are not integrated with qualification
- Contractors are used to manage resource – qualification is a “practice” – Not necessarily a system integrated with GxP controls at an organisation

Key Qualification Information

- System is dynamic - Systems “fall” out of qualification in time if not managed
- Dynamic or “Live” system features may
  - be required to change through life of process
  - be difficult to maintain in static protocols
  - often be managed in other GxP systems.

Qualification – Leveraged State

- Key qualification information is dynamic or live.
- Qualification documentation requires minimal maintenance and is linked into GxP systems
- Qualified state is evident
- Planned change impact is straight-forward to assess and manage

Managing dynamic information

- Key to management of dynamic information
  - Qualification SOP
  - Protocol rationale defines a “snapshot in time”
  - Information linking strategy
  - Appropriate change control over GxP systems
- Qualification of Live information
  - Link qualification to a managed system as well as demonstrate current compliance .

System Qualification Information

- Examples of dynamic system information
  - Documents
    - Functional Specifications
    - Technical data for critical devices
    - Design Reviews / Criticality Assessments
    - Operational SOPs
    - Schematic / Overview Drawings (e.g. P&IDs)
  - Managed and updated through planned change
  - GMP critical data should be evident
  - Avoid duplication and/or highlight controlled data.

Example of Functional Specification based on qualification “as a practice”

UR No	FR No	Clause	Specification	Requirement
U17	F17	5.9.1	IPC Report	IPC report generated at the conclusion of group weighing sequence.
U18	F18	5.9.2	Aborted IPC Report	IPC report is automatically generated when an IPC is aborted.
U19	F19	5.11.1	Balance check	Balance performance checks can be performed on demand or at specified time intervals.
U20	F20	5.13	Automation software	Automation software settings available for editing by user depending on user access.
U21	F21	5.16.1	Program Access	Access to the program will be by a valid combination of ID code and password.
U22	F22	5.16.2	Keyboard time-out	Show ability to lock the keyboard in the event of no activity in the specified time period
U23	F23	5.16.3	Edit batch no and product code	Able to call up specific product/batch specifications only as allowed by limits set by user of appropriately high level access rights
U24	F24	5.16.4	Power loss	In the event of power loss data collected up to time of power loss can be reported.

Example of Functional Specification for management of dynamic system

3.4.3 Log-in to PC and Application

The PC has a generic log-in which enables the different users to log in using the same PC log-in and password. The system supports up to 100 users.

Once logged into the PC users need to log in to the application module. They are required to enter log-in details to confirm information, actions and changes in the system. The User names are recorded in the transaction log and included in various reports.

A single ID profile provides access to all three modules within the application.

There are four levels of access which are described below. Functionality available at successively higher levels of access will include all of the access functionality of the preceding access levels.

Operator : access for data collection, performance of calibration tests and comments on the transaction log. Able to edit product details and/or exclude results from batch details if authorised by the administrator.
Reporter : access as per operator plus access to reporting functions.
Administrator : access as per operator and reporter plus access for editing (but not authorising) of product specifications, system details and password files to administrator level if authorised by authoriser.
Authoriser : access as per operator, reporter and administrator plus authorisation of product specifications, editing of passwords at authoriser level and editing/viewing of system security configuration.

Example of SOP where GMP critical information is highlighted

Return the LWF Empty out weight to its normal value, which must be above the LWF "Re-fill Weight" (usually around 38-40kg) after the final IBC of Milling is finished.

Remove full IBC when the "Full IBC" alarm pauses the system or the system has shut down automatically on completion of the Milling process (as per Docking/Undocking at Filling Station SOP-IPM 5.16)

Record the required details in the BM1.

2. CONTROLLING MILLING PARTICLE SIZE DISTRIBUTION

2.1 Sampling

Milling samples are taken from the sample point below the rotary valve (RVO930U1).
Sample after the second pulse (after 10 sec pause).

The first sample is taken between 10 and 15 minutes after product has begun being milled then take another 2 samples within the remaining hour, at least 15 minutes apart. Continue to sample three times every hour, with each sample at least 15 minutes apart.

For each new IBC ensure that a sample is taken between 10 and 15 minutes after product has begun being milled from that IBC, and then take another 2 samples within the remaining hour, at least 15 minutes apart.

Continue to sample three times every hour, with each sample at least 15 minutes apart until completion of the IBC.
If the process is paused for more than 1 hour ensure that a sample is taken between 10 and 15 minutes after product has commenced milling.

System Qualification Information

- Examples of Dynamic IQ Information
  - Equipment Components
    - Make, Model Number, Tag Number
    - Key specifications, e.g. calibration limits
    - Evidence of suitability for use (calibration / functional tests)
  - Links to Maintenance management / ERP system
  - Typically documented in device register
  - Identify managed records of this data

Example of Device Register where GMP critical information is managed

SAP ID	Description	Make & Model	Crit	Rationale	Calibration	Maintenance
451345	Automatic In-Line Checkweigher	Garvens VS2	1	Equipment item performs critical function	Challenge [O] at batch start, hourly and end SOP 12-211	52 wk [E] safety inspection 26 wk [M] drive mechanisms
451345-01	Load Cell	Weightec 19825-1A	1	Weighs of filled cartons	13 wk [C] Calibration Range: 0 – 150g AF = +/- 0.2g AL = +/- 0.1g SOP 18-404	13 wk [C] Check mounting and connections
451345-02	PLC / HMI	Siemens S7 313C	1	Calculates weight limits and generates eject logic	Not required	Operator verifies settings at start-up SOP 12-211 52 wk [E] verify program version
451345-03	Air jet reject station	Festo 516	4	Rejects under or overweight carton – confirmation sensor fitted	Not required	26 wk [M] check and clean air jet and fittings
451345-04	Photocell sensor	Sick 456-252/86	1	Confirmation of ejection of under or overweight carton from conveyor	Challenge [O] at batch start-up SOP 12-211	26 wk [E] check sensitivity

Critical device information is highlighted

System Qualification Information

- Examples of Dynamic IQ Information
  - Product Contact Materials
    - Pipework, pumps, filters valves, fittings and elastomers
    - Hoppers, chutes, tooling
    - Lubricants
  - Recorded in GMP documents (drawing or schedule)
  - Identify SOPs for controlling use/replacement
  - Identify records location (e.g. MMS or register)

System Qualification Information

- Examples of other Dynamic Information
  - Process Control & Monitoring settings and access
    - Refer directly to relevant SOPs and records
- Evidence of qualified state
  - Critical device functional challenges
  - In-Process test results
  - Cleaning records
    - Identify monitoring SOPs and ensure data is captured
    - link to data and location

Key Qualification Information

- Qualification Matrix
  - Identify systems, not documents where applicable
  - Management document, not a qualification deliverable
  - Enables rapid establishment of qualification status
  - Record key links for planned change

Example Qualification Matrix

Section 1: System Documents

Document Name	Document No	Ver	Location	Planned Change
System Description	26001-SD-001.1.pdf	01	X:\Validation\GxPdocs\FLS\SD	2005/019
Device Register	26001-DR-001.2.pdf	02	X:\Validation\GxPdocs\FLS\DR	2005/019
FLS Fill and Pack - Layout	14329-01.pdf	B	X:\Drawings\GxPdwgs\FLS	2005/019
FLS Filler P&ID	14329-02.pdf	D	X:\Drawings\GxPdwgs\FLS	2005/019
FLS Filler – Pipework ISO #1	14329-03.pdf	B	X:\Drawings\GxPdwgs\FLS	2005/019
FLS Filler – Pipework ISO #2	14329-04.pdf	B	X:\Drawings\GxPdwgs\FLS	2005/019
FLS Filling – Critical Device datasheets	FLS-OM-Vol 1 Section 9	02	Validation Compactus\A4	2005/019
FLS Packing Critical Device datasheets	FLS-OM-Vol 4 Section 9	01	Validation Compactus\A4	2005/019
FLS HVAC Critical Device datasheets	FLS-OM-Vol 6 Section 9	01	Validation Compactus\B1	2005/019

Section 2: SOPs

Operation of FLS Fill and Pack	SOP-FLS 007.123	04	X:\SOP\Issueddocs\FLS	2005/019
FLS Environmental Monitoring	SOP-FLS 007.001	01	X:\SOP\Issueddocs\FLS	2005/019
Compressed Air Monitoring	SOP-FLS 000.019	03	X:\SOP\Issueddocs\Serv	2005/019
FLS Dept CS Access Register	SOP-FLS 007.700	03	X:\IT\SysSecurity\FLS	2005/019

Example Qualification Matrix

Section 3: Control System

Document Name	Document No	Ver	Location	Planned Change
Specification	FLS_Acme 2006-01.ilf	02	X:\ENG\GxPprograms\FLS	2005/019
Configuration : FLS Fill & Pack Set-up	SOP-FLS 007.123 Att 1	03	X:\SOP\Issueddocs\FLS	2007/101
FLS Process View – Back-up and recovery plan	SOP-FLS 007.701	01	X:\IT\SysSecurity\FLS	2005/019

Section 4: Qualification Evidence (Legacy Docs)

FLS Filling – Installation Qualification	26001-IQ-001.1.pdf	01	Validation Archive \2005\19	2005/019
FLS Blister Pack – Installation Qualification	26001-IQ-002.1.pdf	01	Validation Archive \2005\19	2005/019
FLS Carton – Installation Qualification	26001-IQ-003.1.pdf	01	Validation Archive \2005\19	2005/019
FLS Secondary Pack – Installation Qualification	26001-IQ-004.1.pdf	01	Validation Archive \2005\19	2005/019
FLS Filling – Operational Qualification	26001-OQ-001.1.pdf	01	Validation Archive \2005\20	2005/019
FLS Packing – Operational Qualification	26001-OQ-002.1.pdf	01	Validation Archive \2005\20	2005/019
FLS Process View – Software Review	26001-SR-002.1.pdf	01	Validation Archive \2005\21	2005/019
FLS Process View – Hardware IOQ	26001-IOQ-001.1.pdf	01	Validation Archive \2005\21	2005/019
FLS Process View – Application IOQ	26001-IOQ-002.1.pdf	01	Validation Archive \2005\21	2005/019

Example Qualification Matrix

Section 5: Qualification Evidence - Current

Document Name	Document No	Ver	Location	Planned Change
Fill Weight	SOP-FLS 007.123	04	X:\SOP\Issueddocs\FLS	2005/019
Blister Integrity Test	SOP-FLS 007.123	04	X:\SOP\Issueddocs\FLS	2007/019
Air Quality Testing - Particulate	SOP-FLS 007.001	01	W:\GMPdata\Air Quality\ FLS.xls	2005/019
Air Quality Testing	SOP-FLS 007.001	01	W:\GMPdata\Enviro\ FLSMicro.xls	2005/019
Water Quality Testing	SOP-FLS 000.005		W:\GMPdata\Water\ FLS_PW.xls	2005/019
Compressed Air Monitoring	SOP-FLS 000.019	03	W:\GMPdata\CompAir\ FLS_CA.xls	2005/019

Section 6: Planned Change

Planned Change	Description
2005/019	Introduce FLS filling and Packing
2007/101	FLS Fill and Pack Control – Change Fill weight limits

Performance Qualification

- Performance Qualification - possible scenarios
  - New product onto existing or partially existing equipment and facility
  - New product onto new equipment and facility
- Typically
  - Some OQ or optimisation work has been done
  - Sometimes a “trial” batch is scheduled
  - Select three prospective PQ batches

PQ - Current state

- Scenario one - Existing Process
  - Typically conducted in-house
  - Process behavior is often understood
  - Knowledge of process is often anecdotal
    - Ongoing monitoring on trends rather than predictive (some exceptions)
    - Often includes manageable sources of variation / error

PQ – Current state

- Scenario Two – New Project
  - Often involves contractors or vendors for qualification
  - Focus is generally on equipment and facility
  - Optimisation (process understanding studies) tend to be short cycle activities if performed
  - Typically process understanding is limited
    - Influences on process specs is understood, but difficult to test
  - Understanding tends to be focused on equipment or operator influences

PQ - Current state

- Impediments to process understanding
  - APIs and excipients to challenge the process are not available for PQ work or logistics prevent use
  - Changes to process attributes may be masked by time trends or other variation
  - True nature of variability in critical specifications of API or excipients is not well understood
  - PQ product is not fully equivalent to live product
  - Time pressure to realise the value of investment.
  - PQ is completed to demonstrate compliance vs specification over typically 3 batches

PQ – Leveraged state

- Validation and applied production technology
  - Process Validation
    - Regulatory compliance program
    - Requires documented program of pre-requisite qualification in a structured program
    - Demonstrates that facilities, production equipment and supporting systems are fit for purpose
  - Applied production technology
    - The science of understanding a process, its natural variability and responses to influences and managing these to bring about a controlled predictable process.

PQ – Leveraged state

- PQ studies baseline a minimum compliance position after validation batches are complete
- Applied production technology is used to build the compliance position boundaries
- PQ is a dynamic state within qualified bounds
  - Effect of critical inputs is quantified
  - Effect of operational procedures is quantified
  - True performance vs specification becomes evident

Regulatory Environment

- Recent industry interest
  - Process Analytical Technology
    - Measurement to better understand the “voice” of a process
    - Linked to process understanding to control or monitor performance with a high degree of confidence
  - Quality by Design (ICH Q8)
    - The “Design Space”. Where processes are understood to a point where variation to inputs or process conditions is understood in terms of final product specifications.
- The time seems right to look beyond PQ

Reality check

- PAT, QBD – Great in theory, but……
  - Many products pre-date this type of paradigm
  - Development rigor is still lacking from many products
  - Input materials are often not well characterised
  - Not uncommon to find products with poor specifications vs process performance
  - Fortunately, the incidence of such products is diminishing
  - Knowledge of what or how to measure for PAT is lacking or technology is limited

PQ – Leveraging

- Applied production technology
  - Can be applied post PQ to new or existing processes
  - Take process understanding from validation and develop this to enhance process knowledge
  - Improve compliance position – Dynamic PQ
- Leverage the current state of the process
  - Investigate the PQ results to understand capability
  - Continuously improve process understanding

PQ – Leveraging

- Other good reasons to leverage
  - Avoid waste or off-spec product
  - Supports Product Quality Review (PR)
  - Provide solid foundation for deviation investigations
  - Opportunity for PAT
  - Opportunity for enhanced OE

Implementation of Dynamic PQ

- Capture material, IPC and finished product data
  - Conduct review to identify known process drivers
    - Operator adjustments (typically not trended vs effect)
    - Intermediate process (e.g. blend) variations
  - Pareto studies to identify possible oversights
    - Effect of shift changes
  - Consider ALL raw material specs
    - Often a sub-set are tested, may need to review CoA
- Set up a trending database
  - Typically a spreadsheet
  - Consider GMP controls if data is to be implicated

Implementation of Dynamic PQ

- Routine production trending
  - Monitor known process drivers
    - Environmental factors in process and storage
    - Physical properties
    - Process variations - setpoints / operating settings
    - Raw material variations
  - Identify impact of process drivers on validated specifications
  - Build data around target performance (10-30 batches)

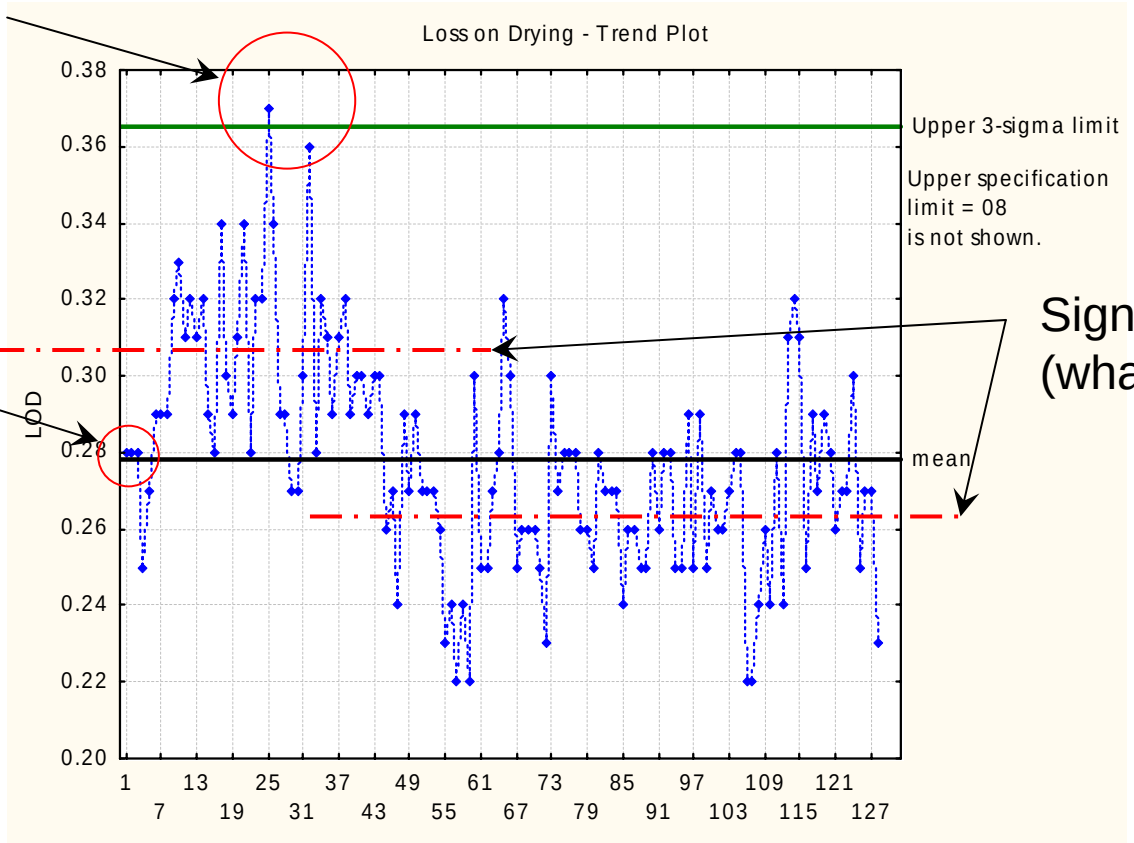
Implementation of Dynamic PQ

- Develop understanding of “normal” variation
- Observe significant effects
  - Analyse PQ and historical data
  - Beware of perceived effects;
    - Unable to discern the effect from normal variation
    - Effect not significant in light of variation
- Quantify effects in terms of impact on key process specifications

Significant effects

Significant event? (complies)

PQ batches



Significant effect (what changed?)

Masking of Effects

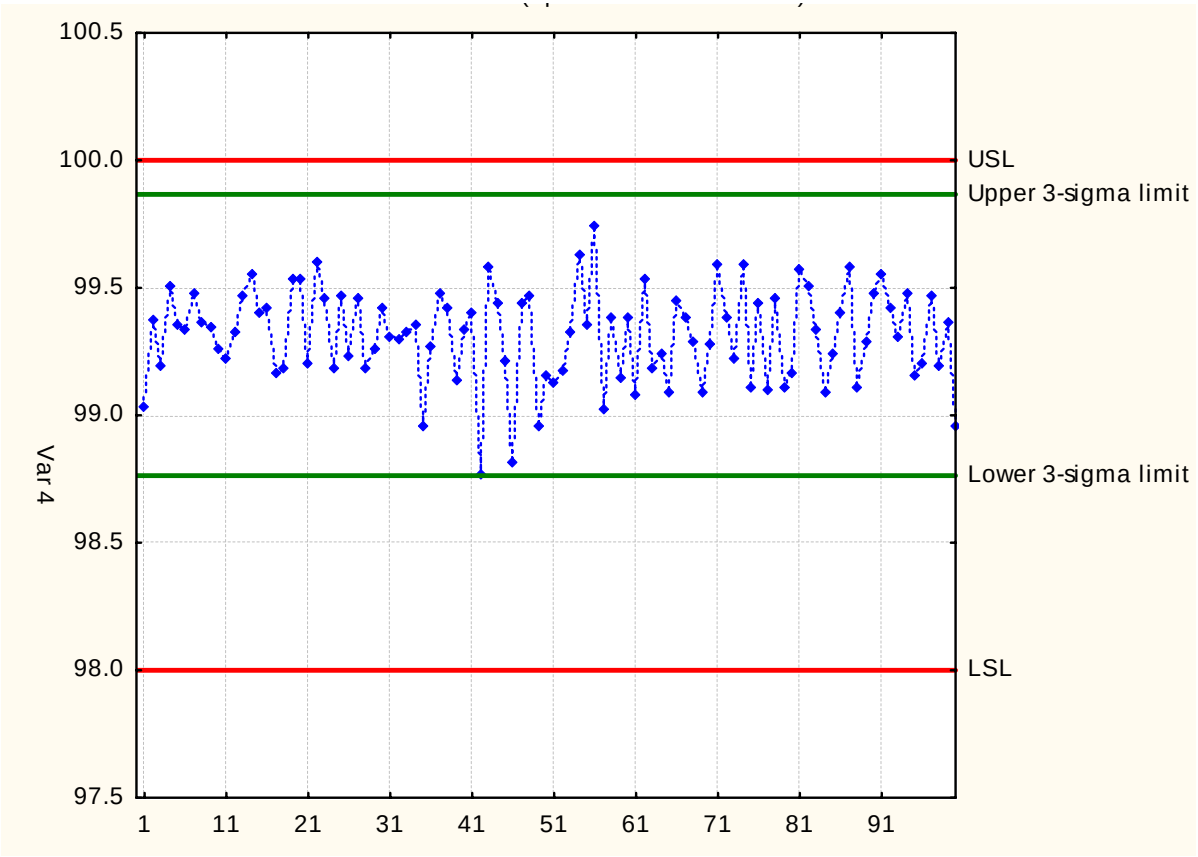
- Special Cause Variation
  - Variation which is not part of the real process
    - Deliberate variations in process parameters
    - Variations in process inputs
    - Staffing changes
  - Consider methods to eliminate or quantify special cause variation from review

Normal process variation

Well controlled process

- Targeted high
- In specification

Could investigate correction to targeting, depending on priority



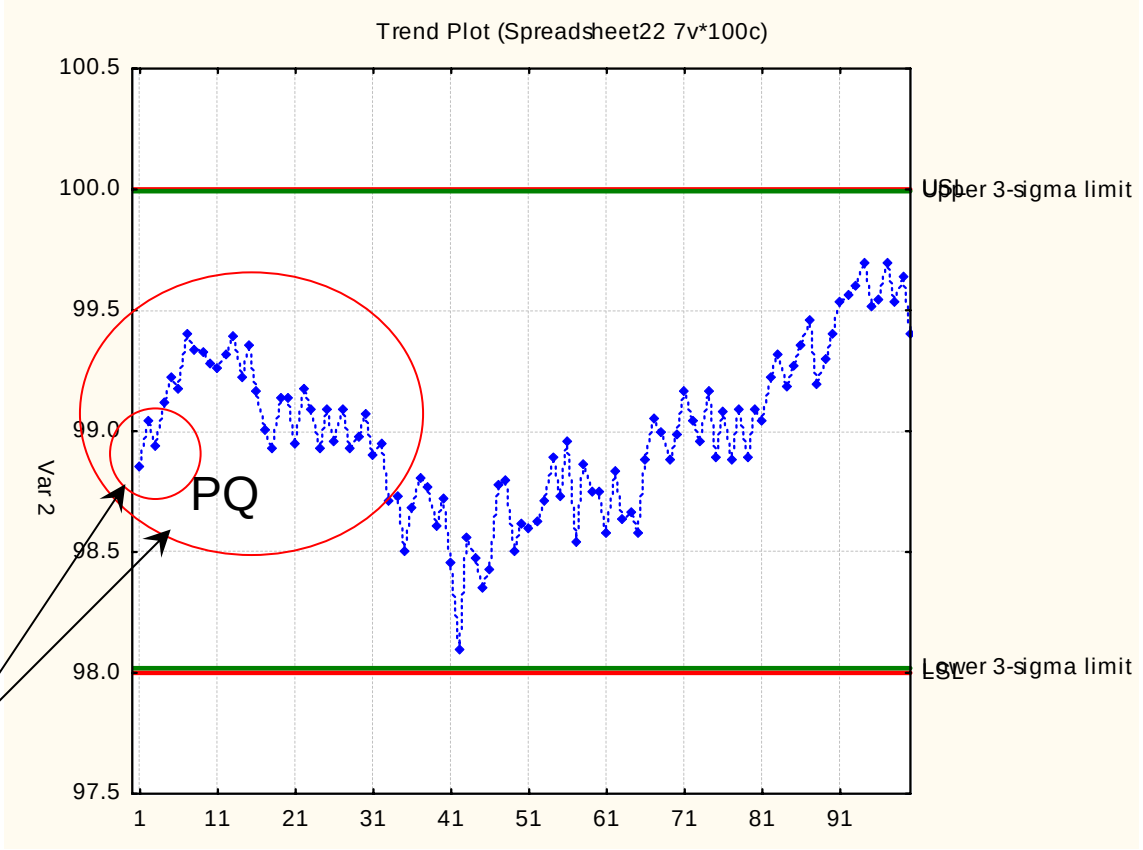
Special cause variation

Apparently well controlled process

- Variability acceptable
- Standard deviation may be misleading
- May fail specification

Investigate correction to special cause variation

Well controlled?



Additional methods

- Consider “indirect impact” analysis
  - Characterise the process with deterministic tests
    - CARR and Hausner ratios for flowability
    - NIR for blend characteristics / moisture
  - Introduce to monitor effect of multiple inputs
  - If a significant effect is found, consider introduction of this testing under change control.

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Outcomes

- Understand process impact of inputs
  - Range of allowable input material specifications
  - Impact of operator adjustments
  - Range of allowable process parameters
  - Range of allowable environmental conditions
- Understand the magnitude of these wrt normal variation in the process
- Consider PAT opportunities

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Dynamic PQ reports

- Investigative work is conducted outside of validation as no GMP impact
- No significant findings?
  - Process is robust and no harm done
  - Retain data for Product Quality Review
- Significant finding(s)?
  - Opportunity to improve
  - Prepare addendum to PQ via planned change
- Cite review of process data and conclusions

Summary

- Enhance qualification to manage dynamic information
- Link qualification to GxP systems
- Track in qualification matrix
- Use applied production technology to characterise process performance after PQ
- Develop understanding of key inputs
- Enhanced process knowledge provides opportunities to utilise PAT to monitor and control a process
- Revisit PQ reports at appropriate times with new data and conclusions
- Continue monitoring for Product Quality Review

Thank You…

- Questions?

- Contact Details

Maurice Parlane

☎ +64 9 419 8029

✉ maurice.p@newwayz.co.nz