Implementation of QbD for Existing Products An Example from GSK Australia

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B.Sc (Hons) from Monash University in 1990

Started at Glaxo (as it was called then) in 1991 as a Development Chemist in Pharmaceutical Development

- Worked on the development of Blow-Fill-Seal (BFS) products for nebulisation and Dry Powder Inhalation (DPI) products

Moved into Manufacturing/Quality Assurance for GSK in 2001

- Led the QC Technical and Laboratory Operations and Steriles and Inhaled Product Groups

Moved to Technical as a Technical Project Leader in 2009

- Work on the interface with R&D and GMS called NPI – New Product Introduction
- Sterile and Inhaled New Products for Current and Emerging Markets
- Collaboration with Monash University Institute of Pharmaceutical Science (MIPS)
- Manage the implementation of Product Lifecycle Management (PLM) (or QbD) at site – “Product Owner” for all DPI products

GlaxoSmithKline

MONASH University
Pharmacy and Pharmaceutical Sciences

OVERVIEW OF TODAY

- QbD = Key Quality requirements for the development, manufacture and control of drug products
  - Drug Product Pharmaceutical Development
  - Quality by Design (QbD) Approaches
  - Product Control Strategy
  - Product Lifecycle Management (PLM) Approach to ensure ongoing Product Robustness
- How these feed into the final registered details
  - Drug Product Pharmaceutical Development
  - Control of Critical Steps (In Process Controls – IPC)
  - Drug Product Specifications
- Example of Ventolin Nebules
  - Virtual product tour where we will follow the product through the manufacturing and how the Product Control Strategy supports the Quality and Robustness of the Product Manufacture process

Drug Product Pharmaceutical Development

- The aim of **Pharmaceutical Development** is to design a quality
  - Product
  - Manufacturing Process
- to ***consistently*** deliver the intended performance of the product
- Provides scientific understanding to support the establishment of
  - **Design Space**
  - **Specifications**
  - **Manufacturing Controls**

Design Space:
The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of final drug product quality

"Quality **cannot be tested into products;** Quality should be built in by design"

Working within the design space is NOT considered a change
Movement outside the design space is considered to be a change
(Likely to initiate a regulatory post approval change process)

Minimal Approaches

"Oliver" Top Gear Africa Challenge
Gets the job done but the journey can be rough, interrupted, require frequent changes and always the potential for catastrophic failure

- **Components of the Drug Product**
  - Drug Substance/s
  - Excipient/s
- **Drug Product**
  - Formulation Development
  - Overages
  - Physicochemical and Biological Properties
- **Manufacturing Process Development**
- **Container Closure System**
- **Microbiological Attributes**

All aspects that are ***Critical to Product Quality*** should be determined and control strategies justified

Critical formulation attributes and process parameters are generally identified through an assessment of the ***extent*** to which their ***variation*** can have ***impact on the quality of the drug product***

Left to Right Thinking

Enhanced Quality by Design (QbD) Approaches

Toyota Hilux (Top Gear North Pole Special)
More ROBUST Approach to the Challenge

- Choose to conduct Pharmaceutical Development studies that can lead to an **enhanced** knowledge of product performance over a **wider range** of material attributes, processing options and process parameters.
- Demonstrate a higher degree of understanding
- Facilitates an expanded design space
- Opportunity to develop flexible regulatory approaches:
  - risk-based regulatory decisions (reviews and inspections)
  - manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review
  - reduction of post-approval submissions
  - real-time quality control, leading to a reduction of end-product release testing

Right to Left Thinking

Enhanced, Quality by Design Approaches (Combination of ICH Q8, Q9 and Q10)

- Defining the **Quality Target Product Profile**
- Identifying potential **Critical Quality Attributes**
  - Drug Substance
  - Excipients
  - Drug Product
- Conduct a **Risk Assessment** (ICH Q9) to link Material Attributes and Process Parameters to Drug Product CQA and build a **Design Space**
- Use the enhanced product and process understanding in combination with quality risk management to establish an appropriate **Control Strategy**
- **Implement Product Lifecycle Management by continuous** evaluation of innovative approaches to improve product quality (ICH Q10)

Quality Target Product Profile (QTPP):
A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy
of the drug product.

Critical Quality Attribute (CQA):
A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

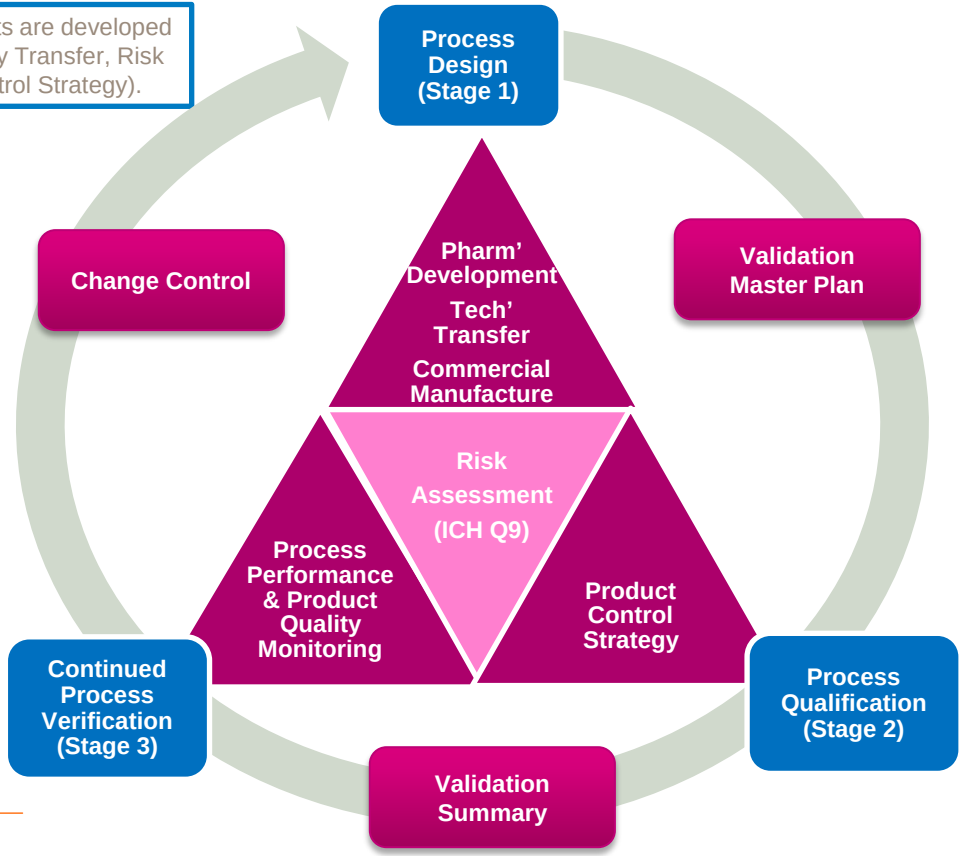
Critical Process Parameter (CPP):
A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

GSK has implemented a phased introduction to enable a clear end-to-end understanding of our products and processes which ensures:

Process robustness
Batch uniformity (within/between)
Ongoing improvements to current performance
Regulatory Compliance with emerging expectations

Validation Lifecycle Approaches (ICH Q10)

Stage 1 Process Design documents are developed (Development History, Technology Transfer, Risk Assessment, Draft Product Control Strategy).



For Existing Products - Pragmatic Start with Stage 3 (Data Trending)

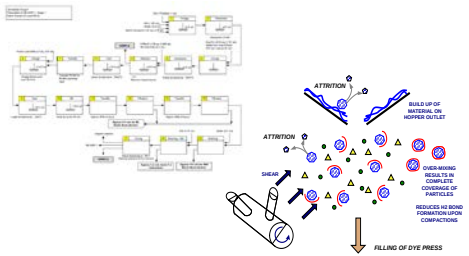
Stage 3 is used to capture changes, trend and demonstrate that the process is still operating in a state of control.

Stage 2 the Product Control Strategy is demonstrated to be fit for purpose.

Risk Assessment

- **Product & Process Risk Management**

- Risks are associated with the quality, safety and efficacy of the product itself
  - How the product behaves during processing
  - How it interacts with equipment, devices, packaging and its environment.
- Single team, structured approach focussed on product and process understanding
- Supports development of good control strategies and standard work
- The RA is maintained through the product lifecycle, regularly reviewed and updated in response to change
- Key Tools
  - Process Definition Diagrams
  - Mechanism Maps
  - Failure Mode and Effects Analysis (FMEA).



AIM: To predict risks based on knowledge and process understanding and implement mitigation plans to prevent issues from occurring

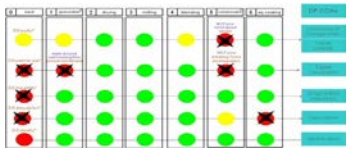
RA's if correctly executed (leading to an effective control strategy) will reduce the likelihood of problems occurring.

Product Control Strategy

- **A control strategy is designed to ensure that a product of required quality will be produced *consistently*.**
  - Derived from the Risk Assessment (plus any pharmaceutical development studies which have identified sources of *variability* that can impact *product quality* and should be controlled)

- A control strategy can include the following:
  - Control of input material attributes based on an understanding of their impact on manufacture process or product quality
  - Product specifications
  - Controls for unit operations that have an impact on downstream processing or product quality
  - In-process or real-time release testing in lieu of end-product testing
  - A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

- A control strategy can include different elements. For example, one element of the control strategy could rely on end-product testing, whereas another could depend on in process testing.
- Used to define the batch manufacturing record, testing regime, validation approach and registered product specification



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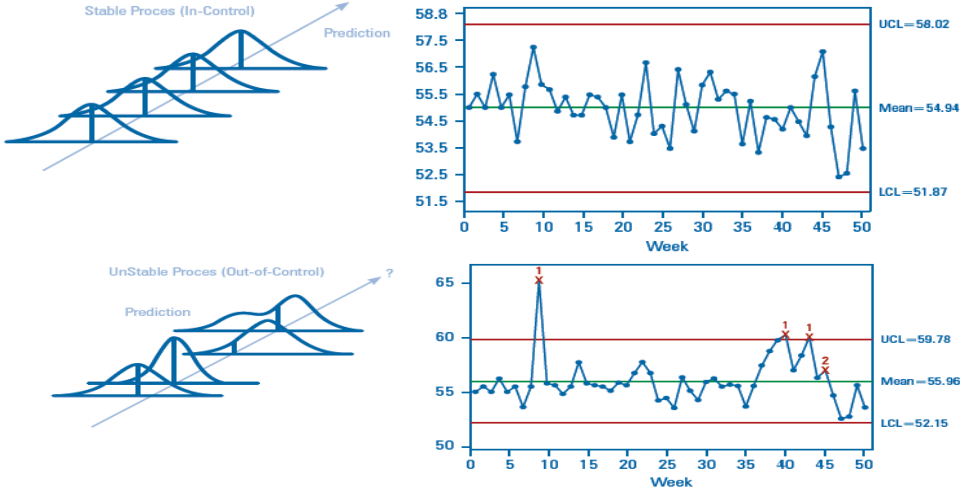
Process Performance and Product Quality Monitoring

- Data trending provides us feedback on what the process is doing
  - Verification of a statistically stable process
- A Regulatory expectation of ‘Continued Process Verification’
  - Expected to be **predictive** and **anticipatory** of failure
  - Batch by batch, week by week, or similar



Regulators expect that we can do this for all our products

CHANGE CONTROL – BECAUSE NOTHING STAYS THE SAME!

- Innovation
- Continual Improvement
- Output of process performance and product quality monitoring
- CAPA (Corrective and Preventative Action)

DRIVE PRODUCT CHANGE

- All changes MUST be evaluated properly using an effective change management system that
  - Is Timely and Effective
  - Provides a high degree of assurance there are no unintended consequences of the change.
  - Utilises quality risk management to evaluate ALL proposed changes against
    - The Marketing Authorisation
    - Design Space (where established)
    - Current Product and Process Understanding.
  - Involved expert teams contributing the appropriate expertise and knowledge from relevant areas (e.g., Technical, Manufacturing, Quality, Regulatory Affairs and Medical), to ensure the change is technically justified
  - Monitors the effectiveness of the change after implementation
- The cumulative effect of change should also be undertaken at regular intervals (usually through Process Performance and Product Quality Monitoring) to confirm product quality

VENTOLIN NEBULES (VNS)

- *SALBUTAMOL is a selective β2 adrenoceptor agonist.*
  - *At therapeutic doses it acts on the β2* adrenoceptors of bronchial muscle, with little or no action on the heart. With its fast onset of action, it is particularly suitable for the management and prevention of asthma attack
  - Available in many respiratory dose formats (DPI, MDI, Oral Syrups, Respirator Solutions)
- VENTOLIN NEBULES (VNS)
  - *Solution Dose form administered to the lungs with the use of a portable nebuliser system*
  - *Available as both 2.5mg/2.5mL and 5mg/2.5mL strengths*
  - Marketed in Australia and many markets across Europe, Middle East, Asia, Africa, North and South America.

Table 1. Composition of Ventolin Nebules, 2.5 mg/2.5 mL

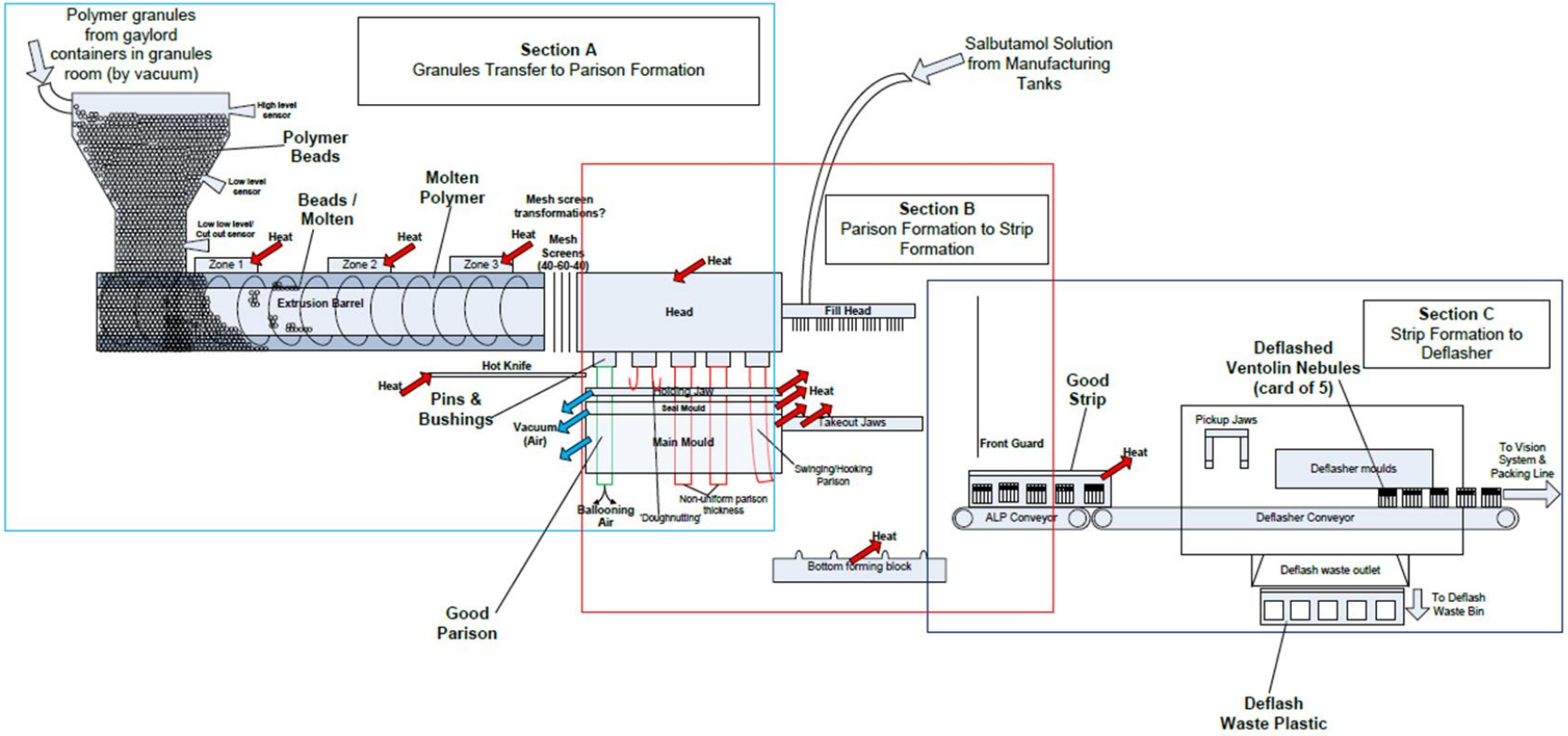
Ingredients	Quantity mg per Nebule	Quantity mg per mL	Function	Reference to Standards
Active Ingredient				
Salbutamol Sulphate	3.0	1.2	Active	PhEur
Other Ingredients				
Sodium Chloride	22.5	9.0	Osmotic agent	PhEur
Dilute Sulphuric Acid	qs	qs	pH adjustment	BP
Purified Water	to 2.5 mL	to 1 mL	Solvent	PhEur

VNS DRUG PRODUCT CQA's

Drug Product Specification Test	Pressurised Metered Dose Inhalers	Dry Powder Inhalers		Products for Nebulisation		Non-Pressurised Metered Dose Inhalers
		Device-Metered	Pre-Metered	Single Dose	Multi-Dose	
(a) Description	Yes	Yes	Yes	Yes	Yes	Yes
(b) Assay	Yes	Yes	Yes	Yes	Yes	Yes
(c) Moisture content	Yes	Yes	Yes	No	No	No
(d) Mean delivered dose	Yes	Yes	Yes	No	No	Yes
(e) Delivered dose uniformity	Yes	Yes	Yes	No	No	Yes
(f) Content uniformity / Uniformity of dosage units	No	No	No	Yes	No	No
(g) Fine particle mass	Yes	Yes	Yes	Yes*	Yes*	Yes
(h) Leak rate	Yes	No	No	No	No	No
(i) Microbial / microbiologicallimits	Yes	Yes	Yes	Yes***	Yes	Yes
(j) Sterility	No	No	No	Yes**	No	No
(k) Leachables	Yes	No	No	Yes	Yes	Yes
(l) Preservative content	No	No	No	Yes***	Yes***	Yes***
(m) Number of actuations per container	Yes	Yes	No	No	No	Yes

* For suspensions.
** If the product is sterile.
*** If a preservative is present.

- **Derived from**
  - **Regulatory Guidance on Inhalation Products (EMEA/CHMP/QWP/49313/2005)**
    - Based on Dose Form/Intended use of the product
    - Ventolin Nebules is Single Dose Nebulised Product
  - **Standard aqueous drug product specification tests. Refer to ICH Q3B (Impurities) and ICH Q6A (Specifications)**
    - e.g. ID, degradation products, pH, isotonicity
- Specification values based on
  - Observed range of variation in batches evaluated *in-vivo* studies
  - Process Capability data
  - Stability data
  - Note different tests and limits may apply at release versus shelf life . Shelf life acceptance criteria should be derived from stability data and the changes observed on storage


Polymer granules from gaylord containers in granules room (by vacuum)
Section A
Granules Transfer to Parison Formation
High level sensor
Polymer Beads
Low level sensor
Low low level/ Cut out sensor
Beads / Molten
Molten Polymer
Mesh screen transformations?
Heat
Zone 1
Zone 2
Zone 3
Mesh Screens (40-60-40)
Extrusion Barrel
Head
Fill Head
Salbutamol Solution from Manufacturing Tanks
Section B
Parison Formation to Strip Formation
Hot Knife
Pins & Bushings
Holding Jaw
Seal Mould
Main Mould
Takeout Jaws
Vacuum (Air)
Swinging/Hooking Parison
Ballooning Air
'Doughnutting'
Non-uniform parison thickness
Good Parison
Bottom forming block
Section C
Strip Formation to Deflasher
Good Strip
Front Guard
Deflashed Ventolin Nebules (card of 5)
Pickup Jaws
Deflasher moulds
To Vision System & Packing Line
ALP Conveyor
Deflasher Conveyor
Deflash waste outlet
To Deflash Waste Bin
Deflash Waste Plastic

VNS CONTROL STRATEGY
IMPLEMENTING THE PRODUCT CONTROL STRATEGY

- CQAs / CPPs (and their defined ranges) define the Design Space

Compliance with Control Strategy = **Assurance of Final Product Quality**

- What's needed is to **translate** this Control Strategy **effectively** into STANDARD WORK across all product and process operations
- Consider 4 Areas:

Capability

- The capability of the people maintaining, setting-up, running and managing the process (**Understanding**)

Engineering

- The processes for maintaining the validated state of the equipment over the long term (**Reliability**)

Setup

- The way the equipment is setup to ensure the CPPs / CQAs are under control at the start of the batch **(Batch Document / SOP)**

Ongoing operation

- What is measured / trended and what actions are taken to ensure the CQAs / CPPs remain under control (**IPC Checks / Product Quality Monitoring)**

Compliance with Control Strategy

Ideas for how to Integrate Product Control Strategy into Production

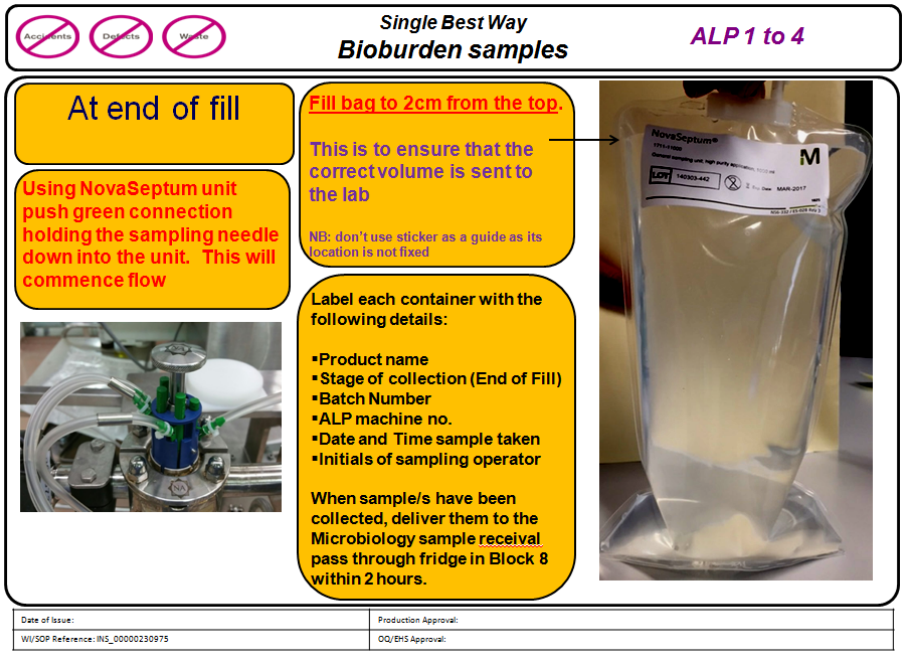
Product Robustness Boards and Single Best Ways

Product Robustness Boards are being developed

- Situated in Production
- Reviewed regularly by Production/Technical/Quality/Validation
- Contain
  - Summary PCS information
  - Ongoing Process Performance Information as it related to Product Quality/Robustness
  - GEMBA sheets to enable PCS understanding across the value stream to be assessed

- Intended to enable a focus on the Product and share and improve people capability and understanding

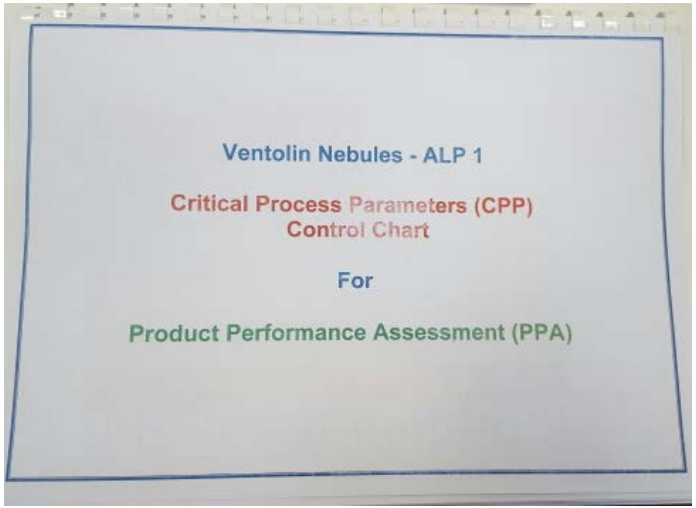
Single Best Ways (SBW's) in place for steps that are critical to the process/considered higher risk of going wrong

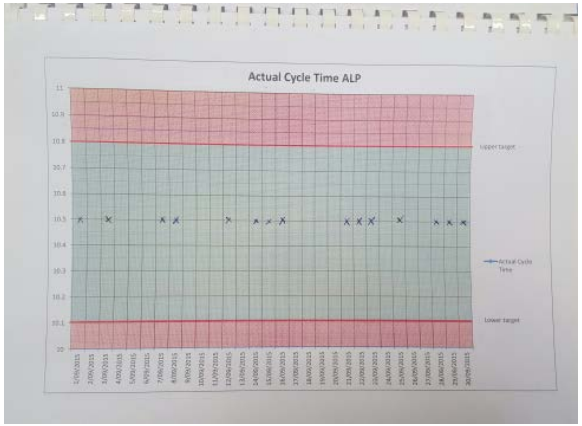


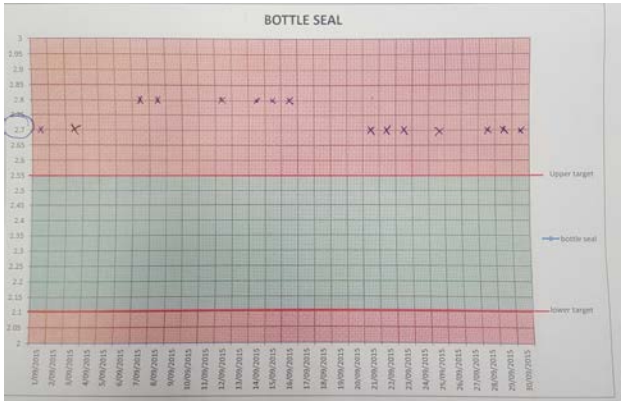
Ideas for how to Integrate Product Control Strategy into Production

Critical Process Parameters (CPP) Control Chart

As part of the PPA process the CPP's (as identified in the Control Strategy) are also trended at the point of use by operators.







Process Performance and Product Quality Monitoring
(Product Performance Assessment - PPA)

Formal Review by Wider PPA Team

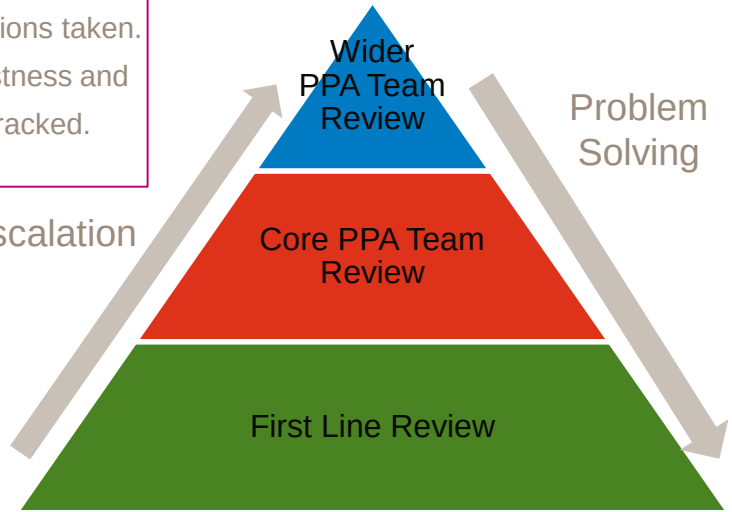
Review each Product Dashboard and escalation items. Review and approve all decisions taken. Ensure appropriate actions are in place to mitigate all risks and confirm product robustness and capability. Issue Product Dashboard and PPA Log with all actions and decisions tracked. Escalate serious risks to SQC.

Routine Review by Core PPA Team

Detailed statistical review of each product. Major rule breakages identified and escalated to Wider Team. Initiate PSG's. Implement JDI's. Prepare Product Dashboard and PPA Log for Wider PPA Team Review.

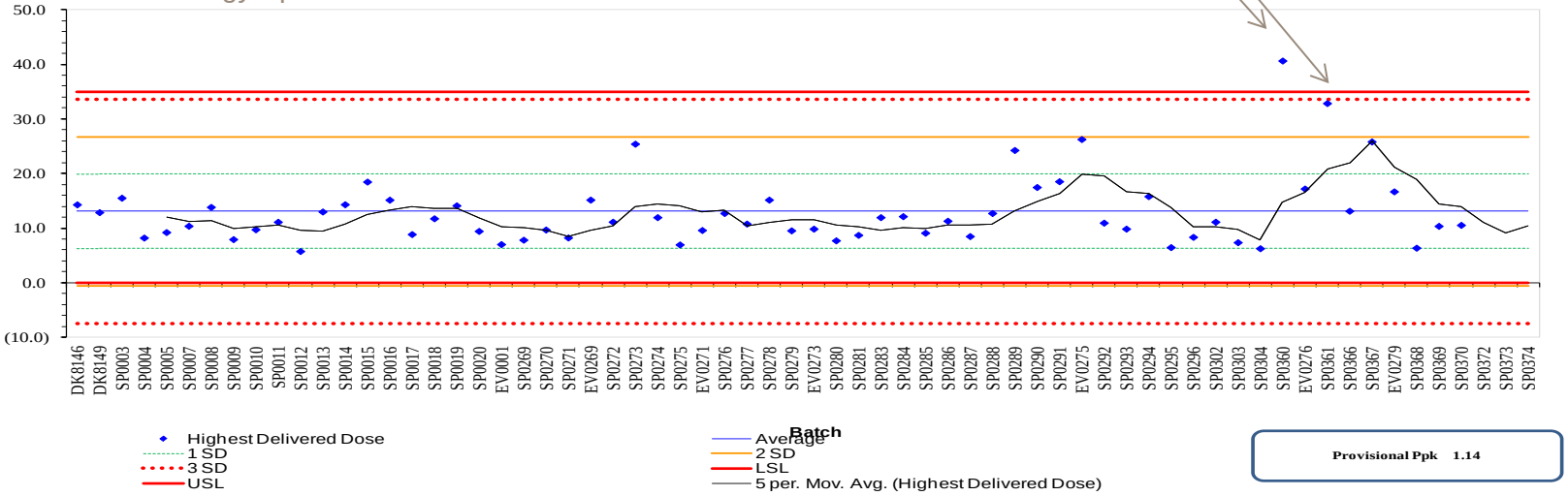
Data Entry and Review by Data Owners

Known changes are recorded in data entry sheet. Issues identified to escalate to Core Team.



Signal to Stop – An Example of the Value of Real Time Product Quality Monitoring and knowing your Product and when something “feels wrong”

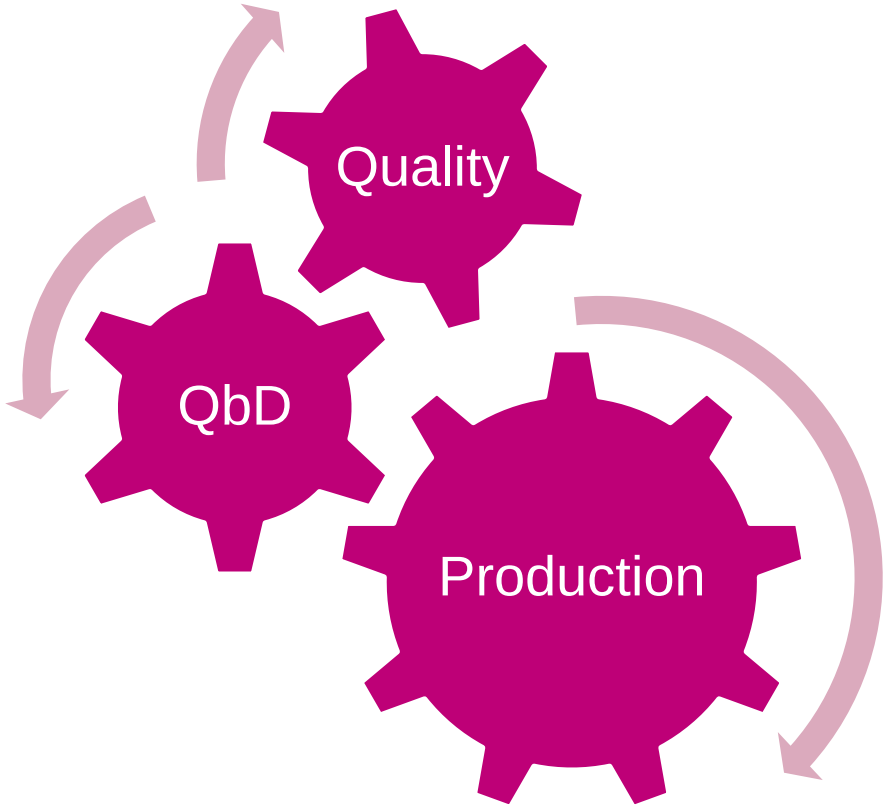
- Dry Powder Inhaler Product – Uniformity of Delivered Dose (Highest Individual Dose) Trend
- Trend shows typical variation given the nature of the test (sample prep, individual dose test)
- Sudden change with high (OOS) result
- Campaign had already made further batches – another high result (Atypical) noted
- Considered sufficiently unusual to trigger a “**signal to stop**”
- RCA determined to be due to inappropriate storage of the current lot of API
- Manufacture commenced with new lot of API – trend returned to normal.
- Control Strategy Updated



Benefits of QbD to Existing Products

- Benefit to *PRODUCT QUALITY*
  - Captures the key Quality requirements for a drug product
- Benefit to *MANUFACTURING PROCESS PERFORMANCE*
  - Improves Operational Efficiency
  - Less Down time
  - Better Yields
- More Robust Manufacturing Processes

  = a More Robust Product
- Benefit to the Patient at the end of the Supply Chain



QUESTIONS ?


There is a person at the end of our supply chains
Everything we do is to ensure they can do more, feel better, live longer

BACKUP SLIDES

Control Chart Rules

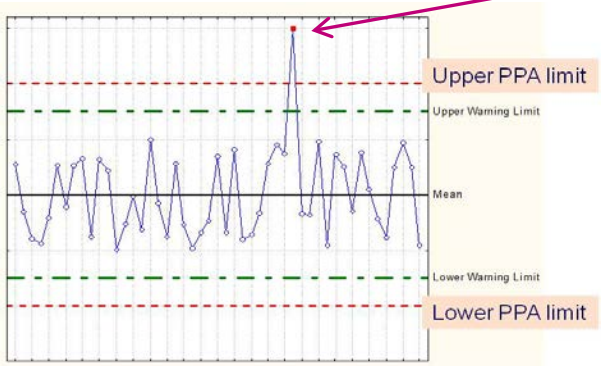
- Documented Data Trending Plan states what parameters are trended for each product
  - Typically trend all drug product and input material CQA's (Critical Quality Attributes) and Critical Process Parameters (CPP's) as determined in the RA
  - Trend against historical data (typically a minimum of 30 batches)
  - Look for PPA Rule Breakages using three Control Chart Rules

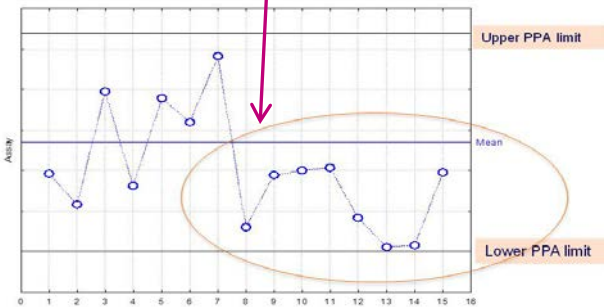
Control Chart Rules

Run Rule 1: Single point outside 3 std deviations

Run Rule 2: 8 consecutive points on one side of center line

Run Rule 3: 7 consecutive points increasing or decreasing





Capability (Ppk) Interpretation

P_{pk}	OOS Risk (PPM*)	Process Status
$P_{pk} > 2$	<0.002	Highly capable
$2 > P_{pk} > 1.33$	0.002 -63	Capable
$1.33 > P_{pk} > 1$	63 - 2700	Marginally capable (Risk of OOS)
$P_{pk} < 1$	>2700	Incapable (Significant risk of OOS)

*PPM=Parts Per Million

Low Ppk

- Process Off Target and Low Variability (Ppk<Pp)
- Process On Target and High Variability (Ppk≈Pp)

Note

- Ppk interpretation in PPM is based on the assumption of data distribution is Normal
- Non-normal data distribution needs different approach of capability assessment