



Process Controls Understanding and Controlling Component Manufacturing Processes

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Overview

- Understanding the Product
 - Critical performance and quality attributes
- Understanding the Manufacturing Process
 - Critical process variables and parameters
- Defining the required Controls & Limits
 - Which and why?
- Implementing
- Cost vs. Value

Introduction

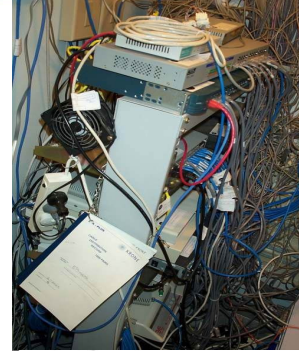
- Understanding and controlling...why is it particularly important for OINDP components?
- IPAC-RS GMP Guideline : « *OINDP components...critical to the use and performance of the product* »
- They are used in complex pharmaceutical products, generally comprising:
 - API
 - Propellant and/or excipients
 - Container closure system
 - often multiple-components and multiple-materials which may also....
 - Perform a critical metering/delivery function
- All of which are individually complicated....
- And combined are very complicated, together with potential for interactions

- The Guideline defines examples of OINDP device components, sub-components, and materials

Device Type	Primary Packaging component (n-1)	Sub-Component or material (n-2)	Sub-Component or material (n-3)
Metered Dose Inhaler (pMDI)	Can Valve Actuator Dose Counter Breath Triggered Device	Aluminium for can Polymer coating for can Ferrule Spring Gaskets Polymers for moulded components	Ferrule – grade of aluminium Ferrule – stamping (tooling, lubricants, process) Ferrule - anodising (process, surface residues) Spring wire (lubricants, processing aids)
Dry Powder Inhaler (DPI)	Assembled device Blister strip Dessicant	Polymers Spring Foil laminate Polymer blister Silica gel	Gasket input materials (base polymer & fillers etc, sources of extractables, process) Polymer input materials (antioxidants, process)
Nasal Spray	Bottle Tube Pump Actuator Nozzle	Glass Aluminium Ferrule Spring Gaskets Polymers	
Solution Inhaler or Nebuliser	Drug container (blister pack, reservoir, ampoule) Device and mouthpiece Atomiser / nozzle	Polymers Foil laminate Glass	

The Route to Process Control

- IPAC-RS GMP Guideline ref.4.1:
 - « *Acquiring and using process data and information* »
 - « *Monitor, measure and analyse* »
- But where to begin?
- Modern technology, with the inherent capability to control many variables and capture data, makes it seem « simple »
- Regardless of manual or high-tech methods, there are two draw-backs:
 - Expense to do it (resource, hardware and software costs, equipment complexity)
 - Expense to analyse it (resource)
- Process control & data is only adding value if it is being effectively used to make decisions
 - process under control?
 - product quality achieved?
- Otherwise, it is simply adding cost



- We need a structured approach and plan to achieve Process Control
- To ensure that we identify the right attributes and variables to work on
- And that route starts with....
The end Product!
- Guideline: « ...consider...the types of product characteristics, which then determine the types of measurement... » ref 8.2.3
- Therefore effective (and cost effective!) process control is:
 - Identification of the essential product characteristics – the Critical Attributes of the product
 - Identification of, and control of, the key process variables to assure those attributes are achieved

Considering the Product Attributes

- An OINDP product or sub-component may have 1000's of attributes
 - Mechanical: component dimensions, actuator stem block flow rate, spring force
 - Functional: assembled dimensions, filling/emptying rate, force/distance to actuate an assembled pump or valve, Peak Inspiratory Flow Rate of DPI
 - Aesthetic: pantone colour range, colour consistency, entrained particles
- But only a few are truly « *critical to the use and performance of the product* »
- So there is a need to identify and rank attributes by criticality:
 - The Critical Quality Attributes (CQA)
- The Quality by Design (QbD) ICH Q8 guide defines a CQA as :
 - « 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 »
- So the first step on the route process control is to identify the CQA's

CARE ! :

- CQA's may be impacted by other variables beyond the scope of individual supplier activity
- QbD advocates the « holistic » approach – consideration of all sub-component and material processes with regard to the final pharmaceutical product CQA's
- But this may be restricted due to confidentiality between suppliers or customer-supplier
- If components and processes are being designed and controlled in isolation, then there is a risk that: The controls are not appropriate to assure final product function, compatibility
- I.e. we may find unwanted interactions, or incompatibilities
- Controls should always be considered with regard to: Final Pharmaceutical Product (where possible)

The Critical Quality Attributes

- Not all attributes are equally critical to the customer or end-user
- Some attributes may be « nice-to-have », but actually have no impact on the finished product performance
- Some may be obligatory, e.g. defined in Regulatory guidelines
- And a few will be truly critical to product performance
- Use appropriate tools to identify and rank the attributes
- Many different tools and techniques, e.g Quality Function Deployment
- Example Tool: FMEA.....

FMEA

- *Failure Mode*: The manner by which a failure is observed
- *Failure Effect*: The consequences a failure has on the operation, function or functionality
- *Failure Cause*: Defects in design, process, quality ref: Wikipedia
- FMEA may seem an odd tool to use for identifying and ranking attributes
- However, it actually does far more:
- FMEA stimulates the step-wise process of:
 1. Identifying potential quality defects in the product (Consider them as « anti-CQA's »)
 2. Identifying potential root causes
 3. Identifying process controls to prevent or detect
- Bonuses:
 - Numerically and process-driven tool
 - Inherent ranking of CQA's (identify the critical few)
- Consider the following example from a project to development process controls for MDI manufacture

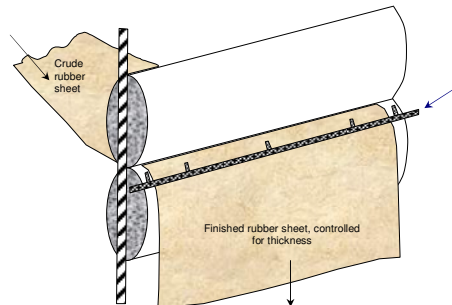
- Project involved n + n-1 working together to re-define appropriate process controls
- Therefore Severity is based upon impact to patient
 - ✓ holistic: – component process, through pharmaceutical product, to end-patient

Severity	Effect	Rank	Mode	Effect	Causes	Root Causes	Process Controls
May result in death or serious injury	Critical	10	→ No emitted spray →	→ Patient cannot achieve relief →	→ Leakage (reduced doses) →	→ 1, Gasket thickness incorrect 2, Fibres 3, Inclusion in surface →	→ 1, Thickness Control 2 & 3, Vision Systems →
May result in serious injury	Very High	8			→ Stem does not return →	→ Gasket inner diameter too small →	→ Vision System →
Non-critical functional impact	Low	5			→ Blocked stem →	→ 1, Mould tool pin broken 2, Pin actuating mechanism defective →	→ Flow testing →

- Resulted in the development of the following Process Control:

Issue: Gasket thickness critical to MDI function

- Current method: sampling, manual measurement
- New method: sensor array across width of rubber sheet



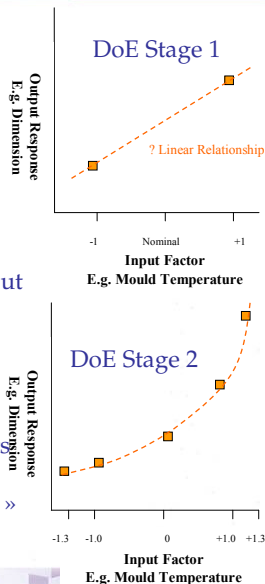
- Sensor Array
- Calibrated against surface of roller
 - Continuous monitoring of sheet thickness across entire width
 - Higher degree of measurement accuracy

- Assurance of thickness control, across entire length and width of sheet
- Potential for « real time product release » (PAT)

The Critical Process Variables

- Once the CQA's are known, the Critical (few!) Process Variables (CPV's) must be identified
- Tools include:
- Process mapping
 - Identify all process variables which may impact the CQA
 - Operating equipment cycle time, speed, temperature, pressure, humidity
 - Other equipment parameters, dimensions
 - Consider the holistic process:
 - Waiting/storage time and conditions
 - Possibly maximum limits for time and/or temperature
 - Possibly a minimum limit – e.g. time required for Formaldehyde to leach from POM acetal post-moulding
 - Work across all levels of the supply chain where possible!!
- Brainstorm and use of « prior knowledge », + other classic Risk Analysis tools (ICH Q9)

- Multivariate Analysis
 - Particularly useful for investigating interactions between variables
 - Requires existing data set
- Design of Experiments
 - Stage 1: Screening for the critical few
 - Use for establishing which variables have an effect
 - Limited information on relative degree of effect and interactions
 - Requires some information to define low & high input settings (-1 & +1)
 - But a great tool for first-pass identification of the Critical Few
 - Stage 2: Modelling of the critical few
 - Use for fully understanding the Critical Few
 - Allows to work outside the classic -1 & +1 DoE limits
 - Verify linearity
 - Identifying the « Design Space » & « Edge of Failure »

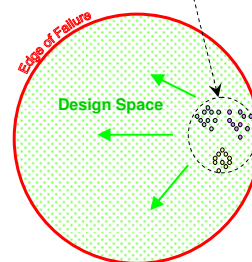


Establishing Control Limits

- One option is simply to define nominal limits
- Possibly based on experience or existing current/similar processes (« It works! »)
- However this is not recommended
 - May actually be working close to the Edge of Failure
 - May not be working in the optimum range (↑operating costs)
- Current thinking proposes the exploration of the operating limits
- Sometimes referred to as Design Space:
 - limit or range of a parameter or variable which are demonstrated to assure the required product quality (CQA!)
- ...i.e. CPV can move within the Design Space without effect on a CQA
- With requirement to fully explore up to the Edge of Failure
 - and assure that control limits are strictly controlled within

- Process Control Variables may be set randomly
- Assumption is made (based on subsequent approval of the manufactured batches) that we have assured robustness within the limits. However....
 - No confidence to step outside those limits if change is required later
 - Don't know if the Edge of Failure lies just outside those limits
- Establishment of Design Space gives many benefits:
 - Edge of Failure is absolutely identified
 - Enables process limits to be set on understanding
 - and not where you happen to have nominally set it!
- Possibility to open up the process limits, whilst staying within the Design Space
 - Greatest assurance of process capability
 - Reduced wastage, risk of failure/rejects etc
- Able to demonstrate Process Mastery (not Mystery)
- Confidence to change « Working within the Design Space is not considered as a change» ref: ICH Q8

Control limits may be set randomly, or on a few early batches ($\pm 3\sigma$)



However the Process is poorly centred within the true robust Design Space, and close to Edge of Failure

- Quick Recap:
 - Define Product CQA's – the critical few
 - Define CPV's – the critical few
 - Define the CPV limits – the Design Space

- Benefit of only controlling the few CPV's is....
- Only controlling what is necessary to assure CQA's
 - Only monitoring essential data
 - Not based upon technical capability to do so
 - Gathering data at random does not bring understanding or decision
- Opportunity for lower equipment costs (go lo-tech!)
- Processes centred within Design Space & Edge of Failure
- Not rejecting on non-critical attributes

Only adding VALUE
Reduction in costs
Reduced Cost of Poor Quality

Implementing Controls & Monitoring

- Guideline proposes use of Process Analytical Technology (PAT)
 - *« OINDP Suppliers are encouraged but not required to become familiar with the principles of PAT and to implement it where appropriate and possible into their manufacturing processes » 7.3.1.3*
- PAT guide issued by the FDA in September 2004:
 - **Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance**
- In fact is one of the four key guides that form the « framework » of Quality by Design



* Also Revision 1

- The goal of PAT is to understand and control the manufacturing process:
 - « The Agency considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing)... »
 - « The foundation of PAT is a firm understanding of the manufacturing process...entails understanding the critical parameters of a product and their relationship to the critical control points in the manufacturing process »
- PAT is not simply monitoring as many process parameters as possible – just because you can!
- PAT is **design** and **control** of manufacturing processes
 - PAT begins at the stage of concept of the product, and therefore the design of equipment and to assure process control
- Only required for Critical Process Variables
- Gives real-time assurance that CQA's will be achieved
- Permits real-time product release
- Eliminates requirement to manufacture, sample, test and wait
- Eliminates potential to miss defects (sampling!)

Other Process Controls

- Typically process controls are only considered for standard mechanical-physical attributes (dimensions, strength, hardness, force)
- However some other attributes may impacted by the process
- Extractables:
 - Often assumed to originate from raw material sources deep within the supply chain (n-2, -3 or -4!),
 - E.g. Fatty acids from tallow/stearates
 - Some do derive from the n-1 or n-2 process
 - Antioxidants
 - Rubber mixing process may have CPV's (temperature etc)
 - Also storage ex-mixing/vulcanising (conditions or delays)

- Processing aids
 - Moulding lubricants
 - Detergents used to wash components
 - Attention: classification and control of residues of processing aids is becoming a standard demand from FDA!
 - Therefore capability of processes to remove/control/limit such aids is important
- Colorants
 - Effect of moulding CPV's on consistency of dispersion of colorants
 - Moulding parameters (and colorant dispersion) can influence the final electro-static properties of components
 - Which in turn affect the behaviour of drug suspension/powder particles

Summary

- *The critical performance requirements of the product define the appropriate process controls*
- *Define process controls and the limits through careful evaluation of process variables*
- *Time spent exploring the Design Space will permit wider process control limits*
- *The route to process control:*

Product CQA ⇒ CPV (for CQA) ⇒ Design Space ⇒ Process Controls

- *PAT is a powerful idea:*
 - *Design of equipment, process and controls specifically to assure CQA's*
 - *Continuous monitoring of critical process controls*
 - *Reduced QA costs and waste*

delivering solutions

shaping the future

Valois 
Pharmaceutical Division

Thank you for your attention

Questions?