2nd EMEA Workshop for SMEs: ***"Focus on Quality"***

"Quality by Design". Process Analytical Technology and Risk-based CMC development

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Overview

- Current and desired state in Pharmaceutical Manufacturing
- How to deliver the desired state (QbD)?
- Relevant regulatory guidelines
- What is Process Analytical Technologies (PAT)?
- What is Design Space?
- Design Space and lifecycle management
- Quality by Design in NCE submissions
- Quality by Design /PAT and Veterinary medicinal products
- EMEA PAT team

Current state

Pharmaceutical Products are of good quality

– Quality itself is not the issue

We need to get it **'Right First Time'** and then to **continue to improve**

But pharmaceutical development and manufacturing **could be improved**

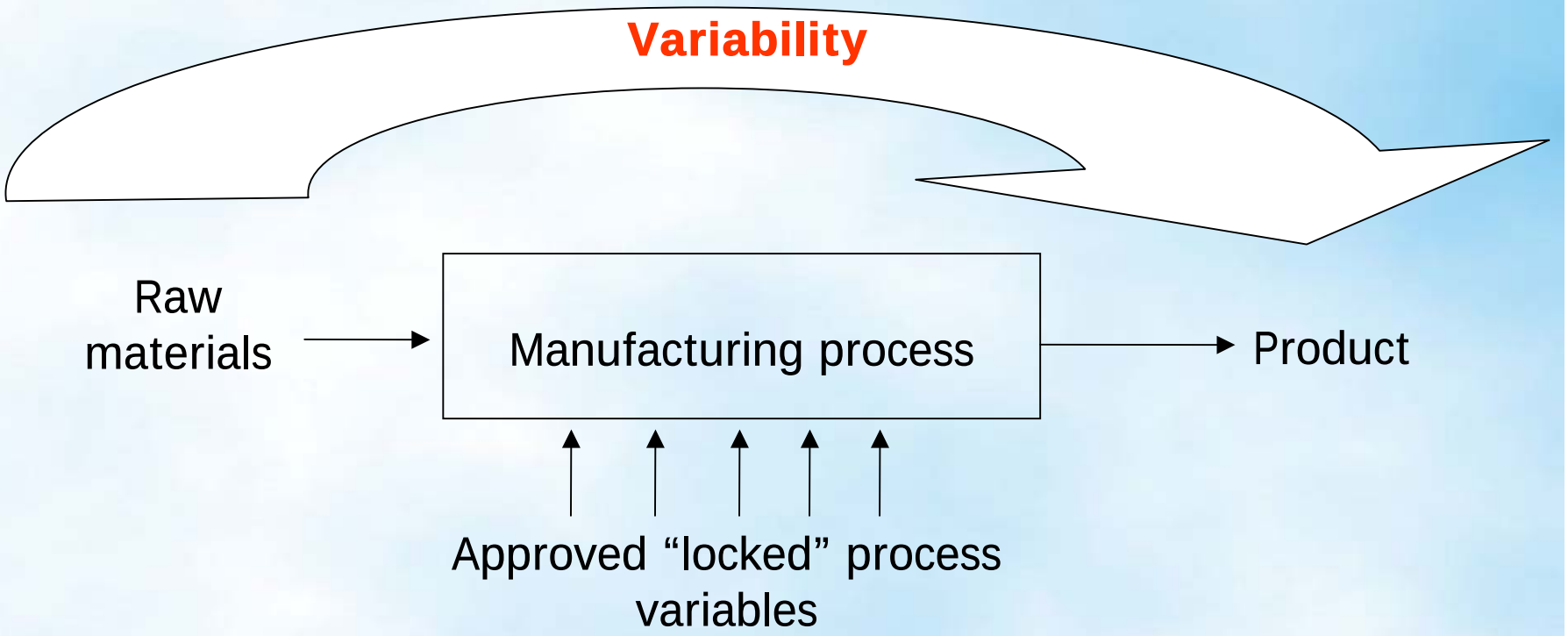
	Sigma	ppm Defects	Yield	Cost of Quality
Pharma	2σ	308,537	69.2%	25-35%
	3σ	66,807	93.3%	20-25%
	4σ	6,210	99.4%	12-18%
Semicon	5σ	233	99.98%	4-8%
	6σ	3.4	99.99966%	1-3%

Table from: PriceWaterHouseCoopers, 2001,Productivity and the Economics of Regulatory Compliance in Pharmaceutical Production

Current state: The "problem" is variability

(W. Edwards Deming)

Uncontrolled variability in e.g. properties of the starting materials or the manufacturing process affects the quality of the medicinal product.



How can variability be reduced?

By obtaining ***increased process and product understanding*** in order to ***identify*** and appropriately ***manage*** critical sources of variability and hence achieve ***"right first time"*** performance.

Need for a shift in paradigm:

From compliance

To enhanced product and process understanding

Desired state

- Product quality and performance achieved and assured by **design of effective and efficient manufacturing processes**
- Product specifications based on **mechanistic understanding** of how formulation and process factors impact product performance
- Continuous **"real time" quality assurance**

How to deliver the desired state?

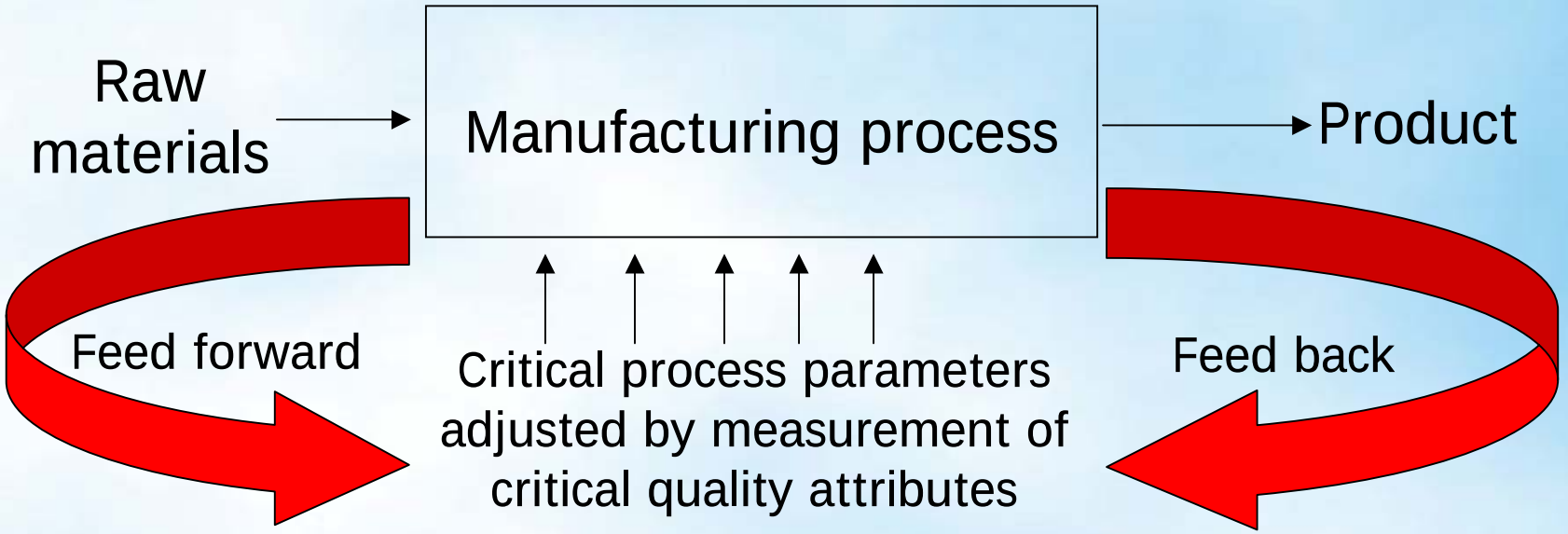
! **Invest in Pharmaceutical Development**

- Identify critical material and process parameters affecting product quality (using prior knowledge, risk management tools, DOE, MVA)
- Understand and if possible express mathematically their relationship with the critical quality attributes
- Design a process measurement system to allow on-line or at-line monitoring of critical quality attributes
- Design a control system that will allow adjustment of critical quality attributes

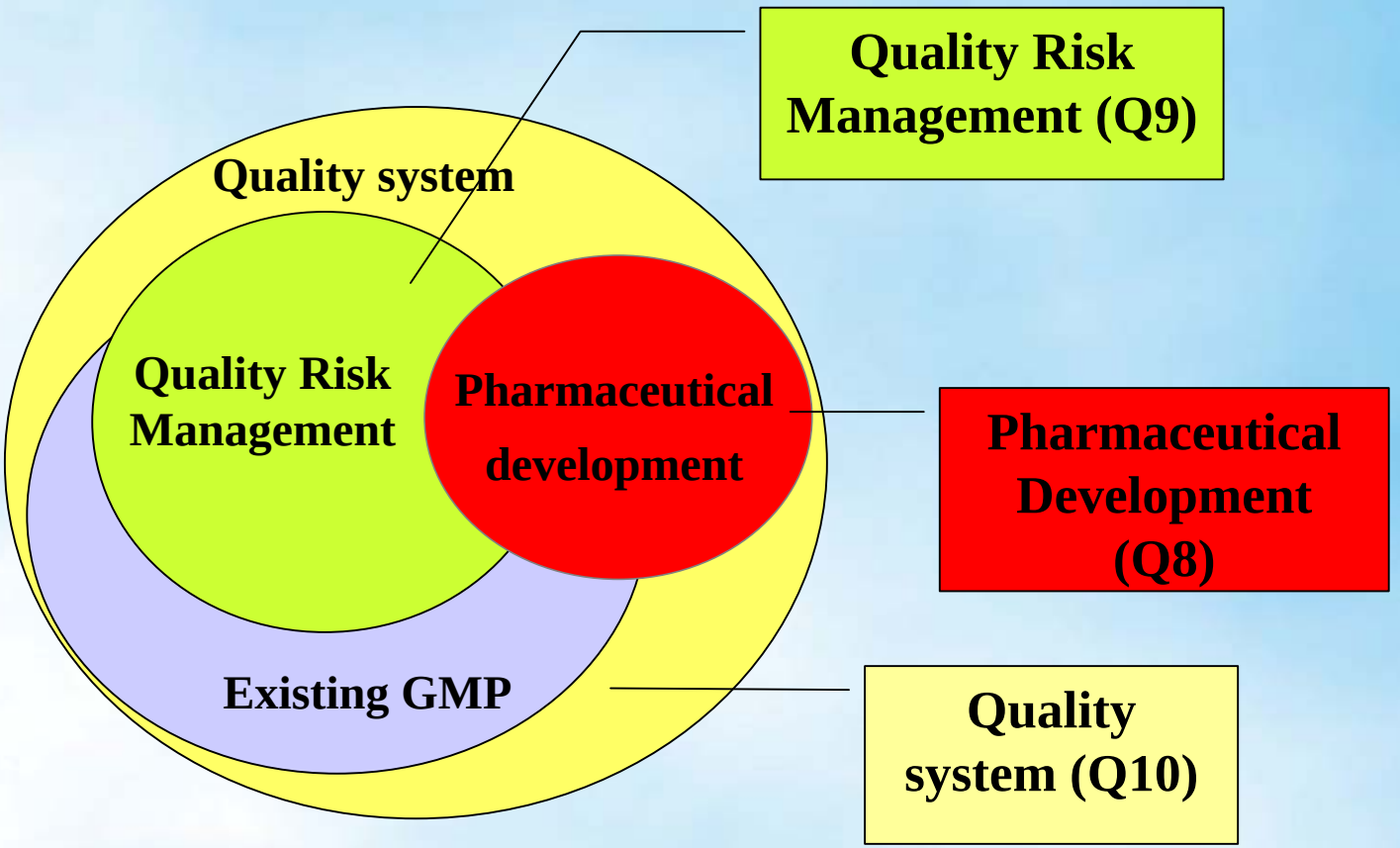
! Implement a **quality system that allows continuous improvement**

! The focus is on Process / Product Understanding

not on advanced online monitoring of the process



Regulatory toolkit to support the Desired state



ICH consensus vision on Quality: “Develop a harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to risk management and science”

ICH Q8
Pharmaceutical Development

- **“Quality cannot be tested into products; quality should be built in by design”**
- Introduces a new (optional) development paradigm

ICH Q8

Traditional

- Empirical development
- Data Driven
- Retrospective
- “Test to document quality”
- Acceptance criteria based on batch data
- Variability not understood and avoided /Focus on reproducibility

Q8

QbD

- Systematic development
- Knowledge driven
- Prospective
- Science and Risk based assurance of Quality
- Acceptance criteria based on patient needs
- Variability explored and understood (**Design Space, PAT**)

From: John Berridge: An Update on ICH Q8 (5.10.06)

What is Process Analytical Technologies (PAT)?

- A system for designing, analysing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality

- **PAT is a useful tool to achieve the desired state.**

PAT tools

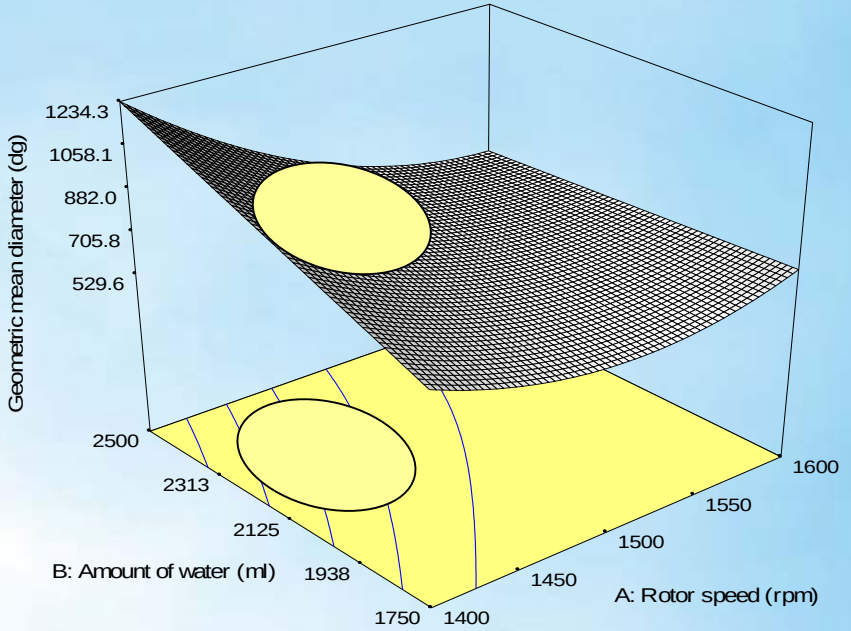
- Multivariate tools for design, data acquisition and analysis
- Process analyzers
- Process control tools
- Continuous improvement and knowledge management tools

What is Design Space?

ICH Q8 definition:

“The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality” (ICH Q8)

Example of a Design Space



Traditional method

Carry out the granulation in a rotor granulator using the following approved ranges

-Rotor speed: 1000-1100 rpm

-Amount of water: 1750 ml ±5%

-Spray pressure: 2.5-3 bar

Design Space

Carry out the granulation in a rotor granulator to create particles at size <criterion> varying the rotor speed, amount of water and spray pressure according to the relationship:

Size = f(rotor speed) + f(amount of water) + f(spray pressure)

Implications of Design space

- Increased flexibility
  - Working within the design space is not considered as a change
- Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process

Design Space and Lifecycle management

- The Design Space applies throughout the product life-cycle

- Continual improvement facilitated
- The review of variations regulation will take into account QbD submissions to enable easier updates of the dossier

QbD in NCE submissions

QbD applicable both to APIs and Finished Products

- **Pharmaceutical Development**
  - Systematic, establishment of design space
- **Manufacturing process**
  - Not set, but adjustable within design space
  - Lifecycle approach to validation → continuous process verification, alternative strategies to the conventional 3 batches approach are acceptable
- **Process controls**
  - PAT tools utilised with feed forward and feedback controls
- **Product specifications**
  - Based on desired product performance with relevant supportive data
- **Control strategy**
  - Quality controls shifted upstream. Possibility of real-time release or reduced end-product testing

QbD/PAT and Veterinary medicinal products

- No VICH guidance under development equivalent to ICH Q8, Q9 and Q10
- However, the use of the ICH guidelines is possible
- VICH have acknowledged that similar guidance to ICH Q8, Q9 and Q10 could be developed for Veterinary medicinal products in the future (when further experience has been gained in the ICH forum)

EMEA PAT team

www. emea.europa.eu/Inspections/PAT

General objective:

- Prepare a harmonised approach within EU on assessment of applications and performing GMP inspections of systems/facilities for Process Analytical Technology, including quality by design principles and manufacturing science in the context of PAT for Human and Veterinary products.

Composition:

- Assessors and GMP inspectors and BWP members
- EDQM-observer
- Support from EMEA secretariat

EMEA PAT team Objectives

- Forum for dialogue with applicants on QbD/PAT aspects
- Review “mock” submissions of PAT related applications
- When requested, to provide specialist input into dossier assessment and scientific advice
- Communicate the outcomes to the relevant WPs
- Identify training needs of assessors and inspectors and organise training

Experience so far :

- Approx. 10 QbD and /or PAT MAAs approved or under evaluation
- Several at pre-submission stage
- Q&A document published on the EMEA website

Thank you for your attention!