

“New quality paradigm: Quality by Design” ICH Q8-9-10

QWP: Quality Assessors Training, 26-27.10.09

**Evdokia Korakianiti, PhD
Quality Sector, EMEA**

Overview

- Current and desired state in Pharmaceutical Manufacturing
- How to deliver the desired state (QbD)?
- Example
- Relevant regulatory guidelines
- What is Design Space?
- What is Process Analytical Technologies (PAT)?
- Assessing QbD – PAT dossiers
- Useful Guidance
- EMEA PAT team

Current state

Pharmaceutical Products are of good quality

» End-product quality is not the issue

But pharmaceutical development and manufacturing could be improved

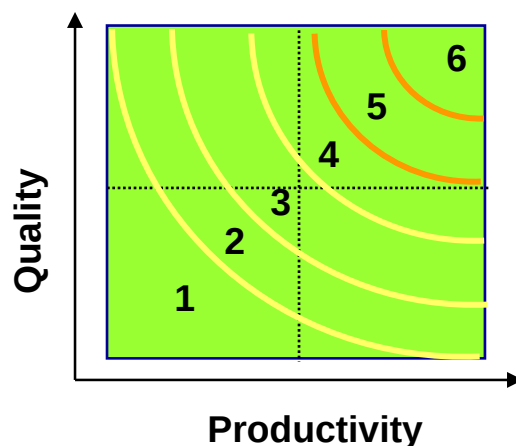
- Batch failures and reworks

5-10% of the pharm. batches have to be discarded or reworked

- Long cycles times
- Manufacturing processes often “frozen” following regulatory approval
- Opportunities for improvement offered by new technologies are often missed

Current state

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



- 6 σ - World class
- 5 σ - Superior
- 4 σ - Healthy
- 3 σ - Average
- 2 σ - Not capable
- 1 σ - Not competitive

Is this clinical relevant?

- In some cases poor performance will only affect the ability to manufacture (e.g. yield)
- However in some others, it might affect clinical performance

Examples:

- Recently recalled (Viracept, Neurpo) or withdrawn products (lonsys) that demonstrated poor product and process understanding that led to product failures and regulatory action
- Appearance of a new polymorphic form on a marketed product; influence on in vitro dissolution rate: influence on bioavailability?
- 3 variants of a medicinal product were not bioequivalent (combination of pilot scale and commercial scale batches (drug substance/drug product)).

Current State

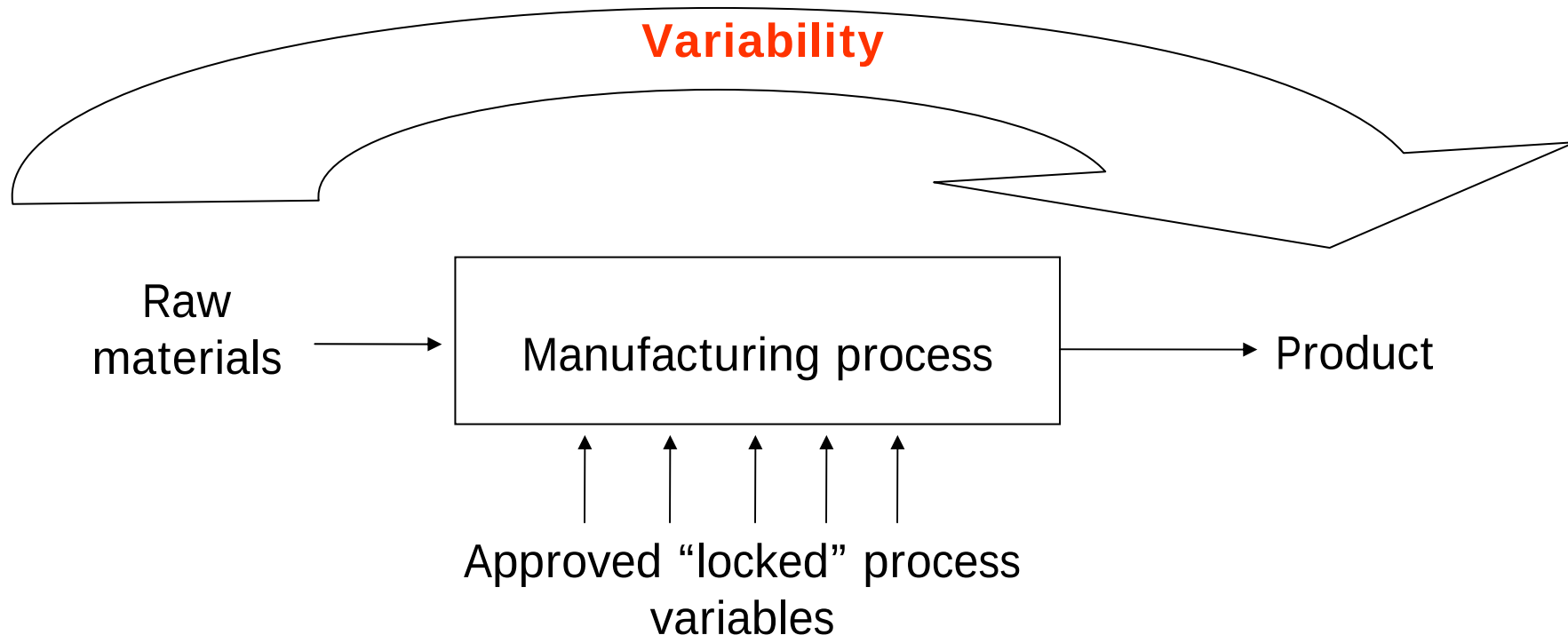
We need to get it **'Right First Time'**
and then to **continue to improve**



Current state:

The “problem” is variability (*W. Ed. Deming*)

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

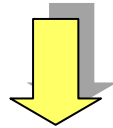


How can variability be reduced?

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:

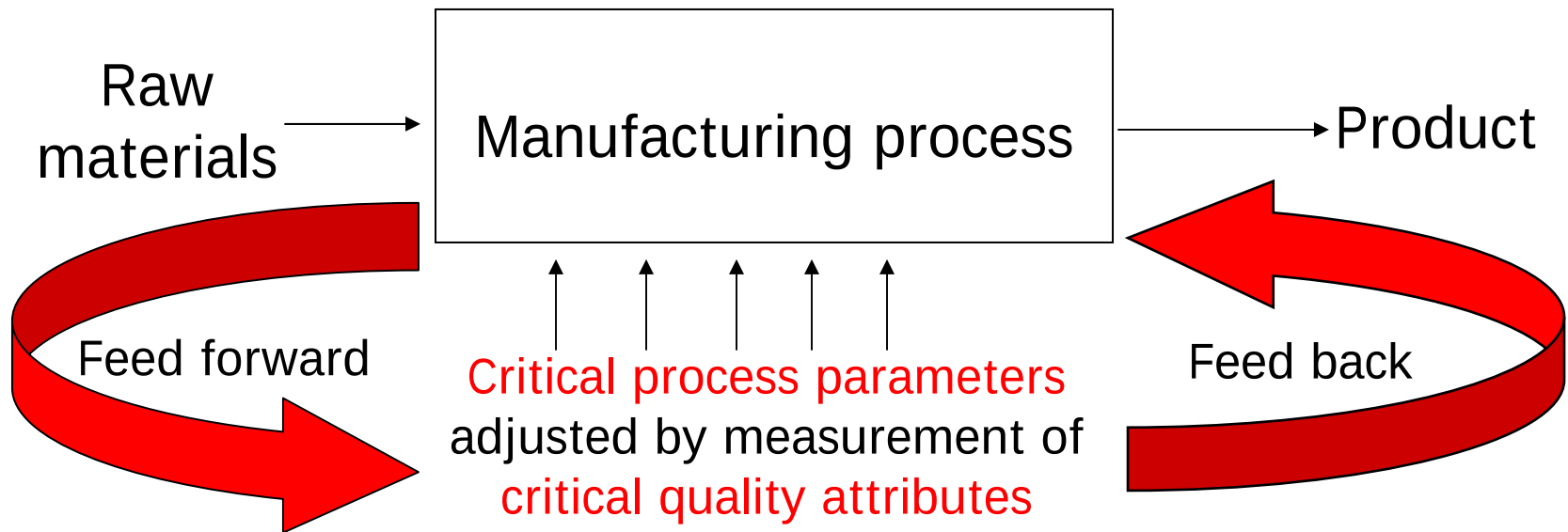
From compliance



To enhanced product and process understanding

that will allow design of effective and efficient manufacturing processes and "real time" quality assurance

! The focus is on Process/ Product Understanding
not on advanced online monitoring of the process



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**

Example

- **Examp~~l~~ain** is a very **simple** product manufactured with a simple process – 'real life cases' will add more complexity
- Main purpose is to **exemplify** fundamental principles and key concepts and to show how
 - » prior knowledge,
 - » risk management tools,
 - » Design of Experiments (DoE)
 - » Mutivariate Data Analysis (MVDA)can be used to reach in depth process understanding

Examp~~l~~ain Mock P2 EFPIA submssion more details

<http://www.efpia.eu/Content/Default.asp?PageID=559&DocID=2933>



Exemplin – Brief Description

- **Immediate release solid dosage form**
 - » Tablet of 200 mg containing 20 mg drug substance
 - » Biopharmaceutical Class 2 (low solubility, highly permeable)
 - » Conventional, wet granulated tablet formulation
 - » Some potential for degradation
- **API Properties**
 - » High bulk density, crystalline, single stable polymorph
 - » Primary amine salt

1st step: Identify Target Product Profile

Description	Round normal convex uncoated tablet
Identification	Positive
Assay	20 mg $\pm$ 5% active at time of manufacture
Degradation products	Qualified meeting ICH Q3B and Q6A criteria
Dissolution	Immediate release
Uniformity of dosage units	Meets pharmacopoeial acceptance criteria
Microbiological limits	Meets pharmacopoeial acceptance criteria

3rd step: Knowledge baseline

- **Gather existing knowledge**
 - » Include all sources of knowledge (internal reports, historical production trends, scientific publications for similar processes/products)
- **Identify product and process parameters that might affect product quality (Fish-bone diagram)**
- **The goals of this step are to:**
 - » Identify the Risk associated with the existing process
 - » Identify the knowledge gaps

4th step: Identify CPPs : Initial Risk-Based Classification

Impact of Unit Operations on Quality

Unit operations Quality attributes	Raw Material	Granulation	Drying	Magnesium Stearate Blending	Compression
Dissolution	high	high	low	high	high
Disintegration	high	high	low	high	high
Hardness	low	low	low	high	high
Assay	low	low	low	low	low
Content uniformity	low	high	low	high	high
Degradation	low	low	high	low	low
Stability	low	low	high	low	low
Appearance	low	low	high	low	high
Identification	low	low	low	low	low
Water	low	low	high	low	low
Microbiology	high	low	low	low	low

Influence:

high

low

4th step: Identify CPPs FMEA

- Based on the fishbone diagram, each variable can be assessed in detail by an FMEA procedure
- A Risk Priority Number (RPN) number. (RPN= impact (I) x probability (P) x detectability (D)) is assigned to each variable

FMEA example for granulation

Parameter	Event	Effect	Severity (S)	Probability (P)	Detectability (D)	Risk Priority No (RPN=SxPx D)
Amount of granulation liquid	Higher amount	Larger granules → dissolution profile affected	3	2	1	6

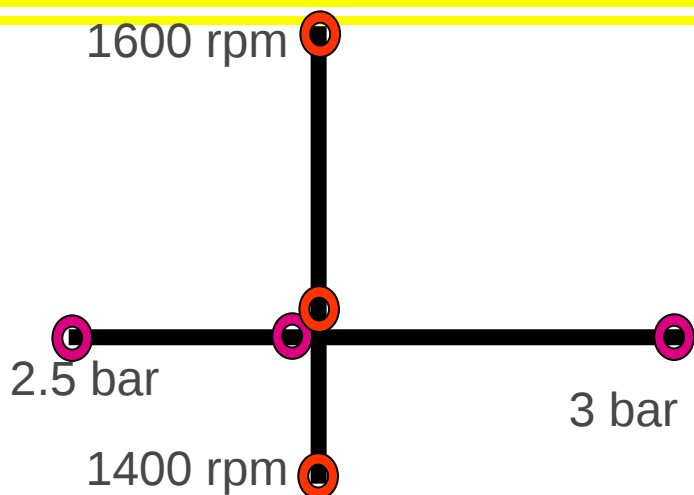
Severity	Score
Minor	1
Major	2
Critical	3
Catastrophic	4

Probability	Score
Very unlikely	1
Remote	2
Occasional	3
Probable	4
Frequent	5

5th step: Develop process understanding - Experiments (DOE)

- Experimental strategy, where **the parameters** (factors) under study are **varied together in a structured way** instead of one at a time
- The experimental data are used to create **models that link the factors with the responses**
- Most commonly fitted models: linear or quadratic
- Compared to one factor at a time:
 - » Less number of experiments
 - » Identification of interactions between variables
 - » Less confounding (if the effects of variables are mixed up, cannot correlate product changes with product characteristics)
 - » Identification of relative significance of variables

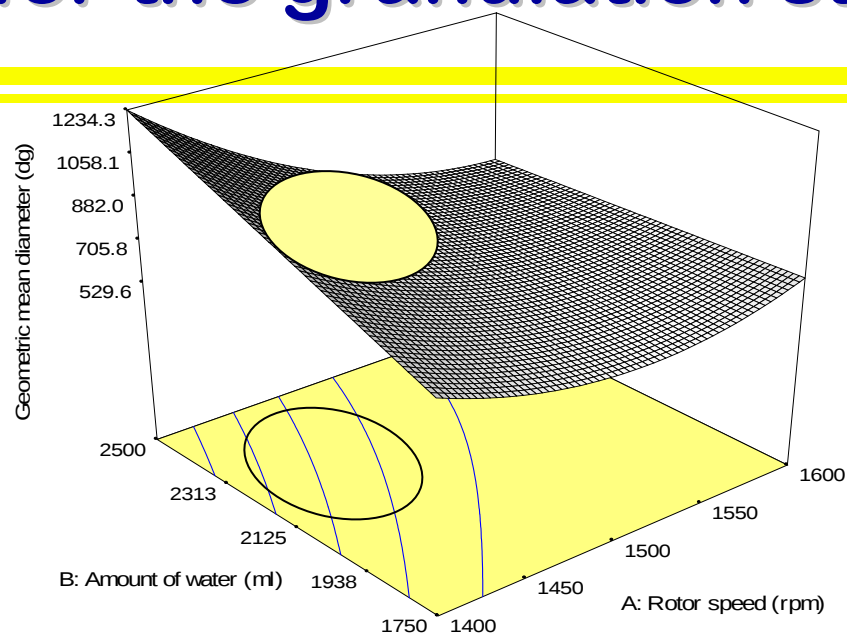
Example of DOE for the granulation step



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 $\pm 5\%$
- Spray pressure: 2.5-3 bar



DOE

Carry out the granulation to create granules at size <criteria> varying the amount of water, mixer speed and mixing time according to the relationship:

$$\text{Size} = f(\text{mixer speed}) + f(\text{amount of water}) + f(\text{mixing time})$$

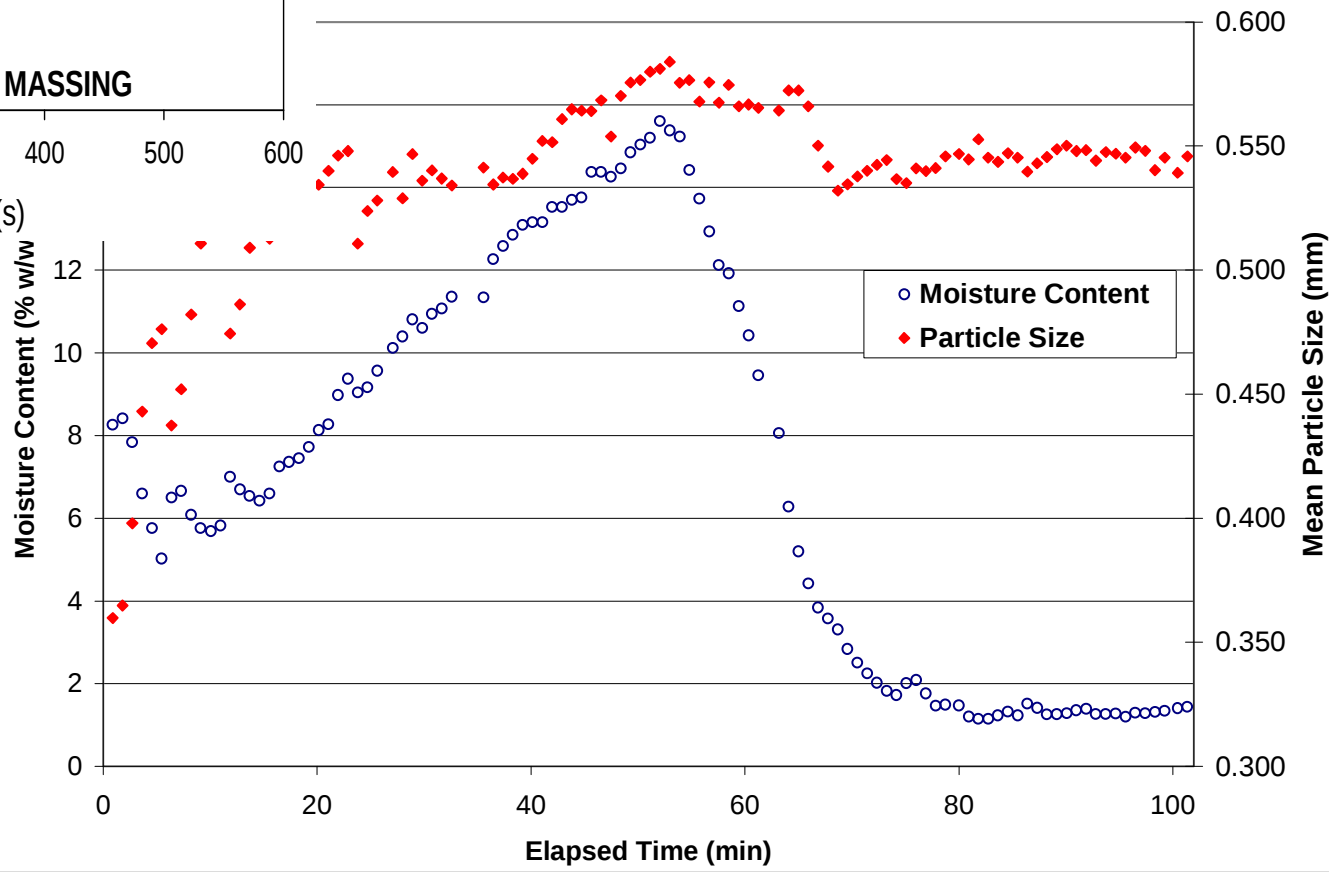
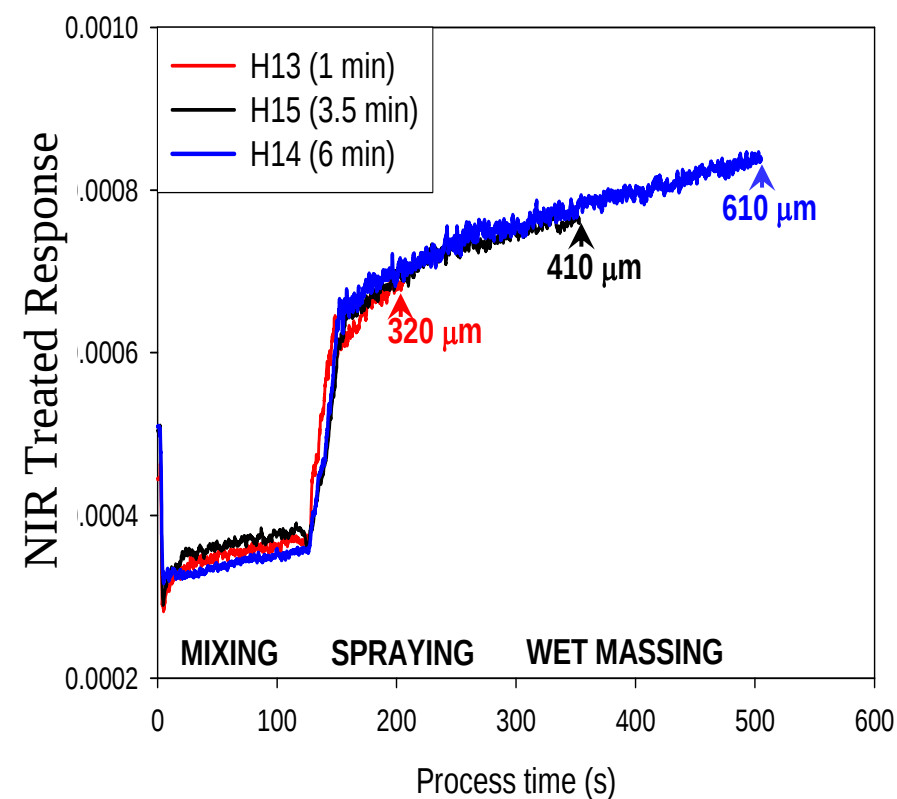
Explain: Outcome up to now

- Identification of critical material and process parameters using prior knowledge, FMEA, DOE)
 - Model the effect of the critical process parameters on product quality (e.g. particle size)(DOE)
 - The above studies contribute to gaining product and process understanding passive
 - However we also need **real time control of the process**
- 
- Design a **process measurement system** to allow on-line or at-line monitoring of critical quality attributes
- And**
- Design a **control system** that will allow adjustment of critical quality attributes

Explain: NIR spectroscopy for online monitoring

- NIR fast and non destructive analytical technique → often used for on-line monitoring
- NIR measures the light reflected from the solid sample
- General Principles:
 - » All organic molecules are held together by covalent bonds
 - » Each bond vibrates at a set frequency
 - » The strength of the bond varies according to the elements involved and the nature of adjacent groups
 - » Thus the chemical nature of a molecule gives a “fingerprint” when all the absorption bands are displayed
 - » In NIR band the overtones are strongly influenced by hydrogen bonding.
- NIR spectroscopy is often used to monitor online the particle size growth during wet granulation

Monitoring and Modeling of Wet Granulation



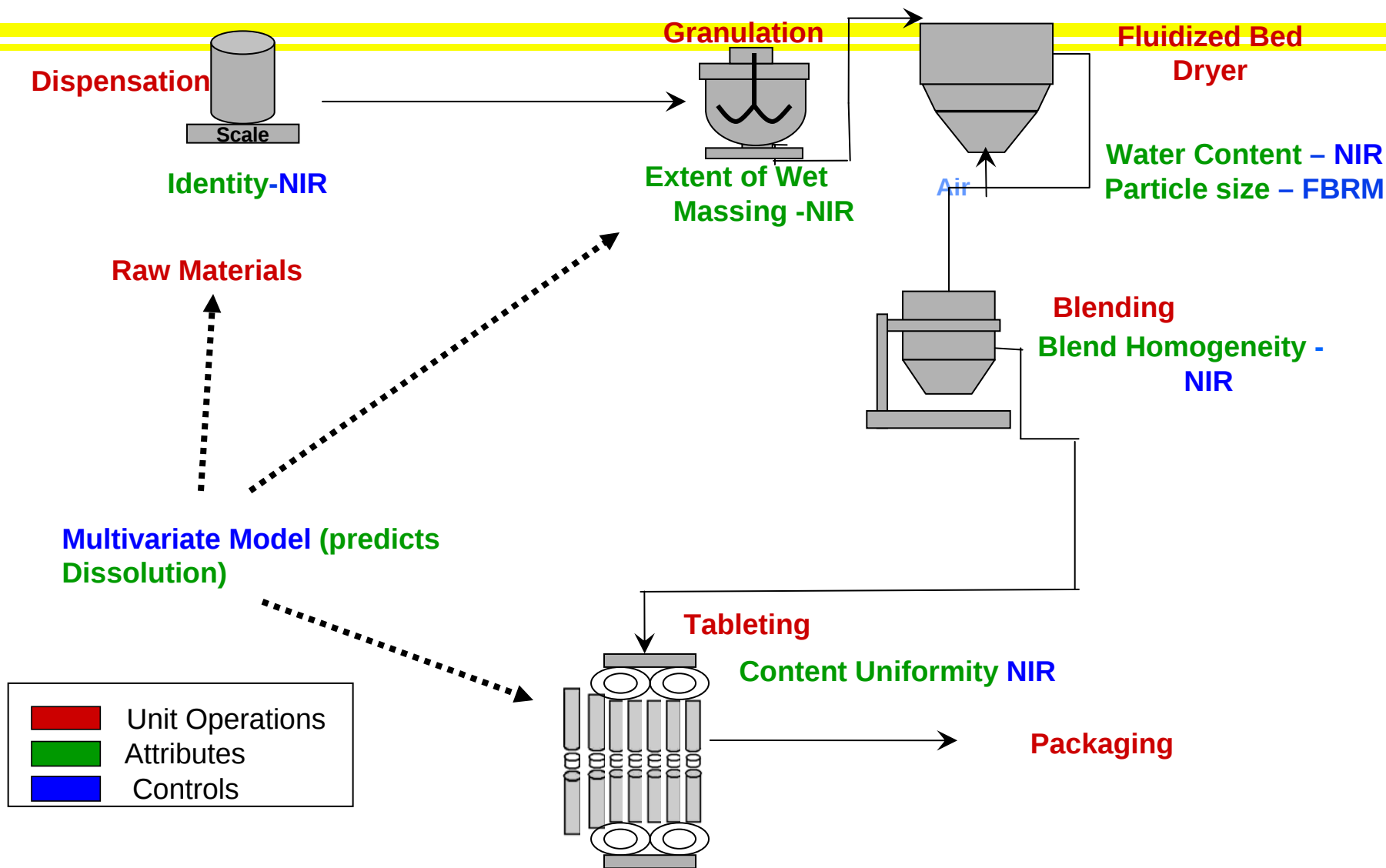
Explain: Outcome for granulation step

- Identification of critical material and process parameters using prior knowledge, FMEA, DOE)
- Model the effect of the critical process parameters on product quality (e.g. particle size)(DOE)

AND

- Design a **process measurement system** to allow on-line or at-line monitoring of critical quality attributes (NIR)

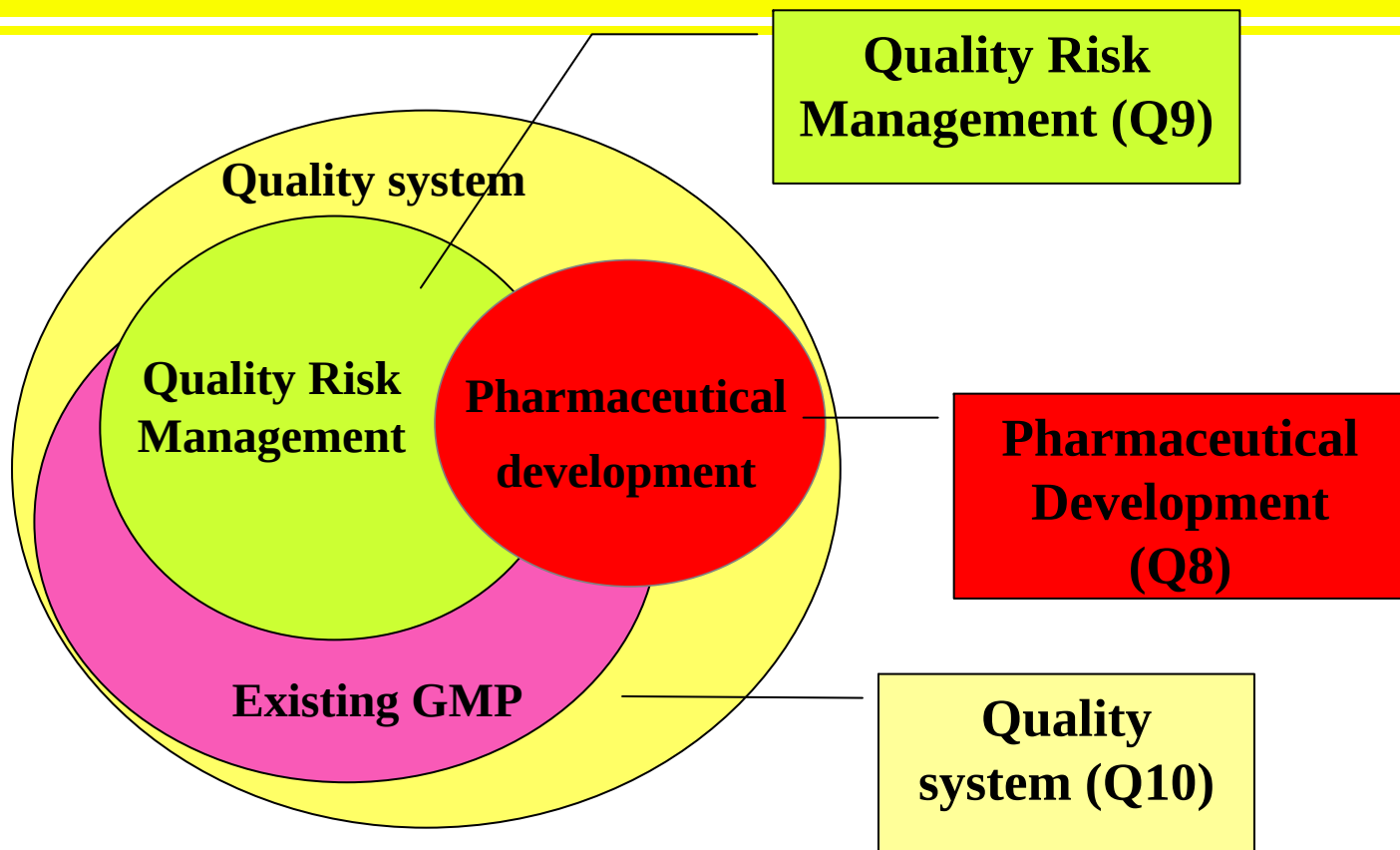
Exampmain: Control Strategy



Explain: Conclusions

- In depth understanding and online in process monitoring is achieved, but,
- Is it always needed? Too cumbersome...
- Level of development work depends on complexity of the product and process
- However, if a more systematic approach to development is chosen like the one presented in the example there are possibilities for regulatory flexibility

ICH Regulatory toolkit to support the new Quality Paradigm



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”

Pharmaceutical Development

- “Quality cannot be tested into products; quality should be built-in by design”
- Introduces a new (optional) development paradigm, **Quality by Design (QbD)**, a systematic approach to pharmaceutical development.

ICH Q8: DS and PAT

ICH Q8 also introduces some new terms:

- **Design Space (DS)**
- **Process Analytical Technologies (PAT)**

What is Design Space?

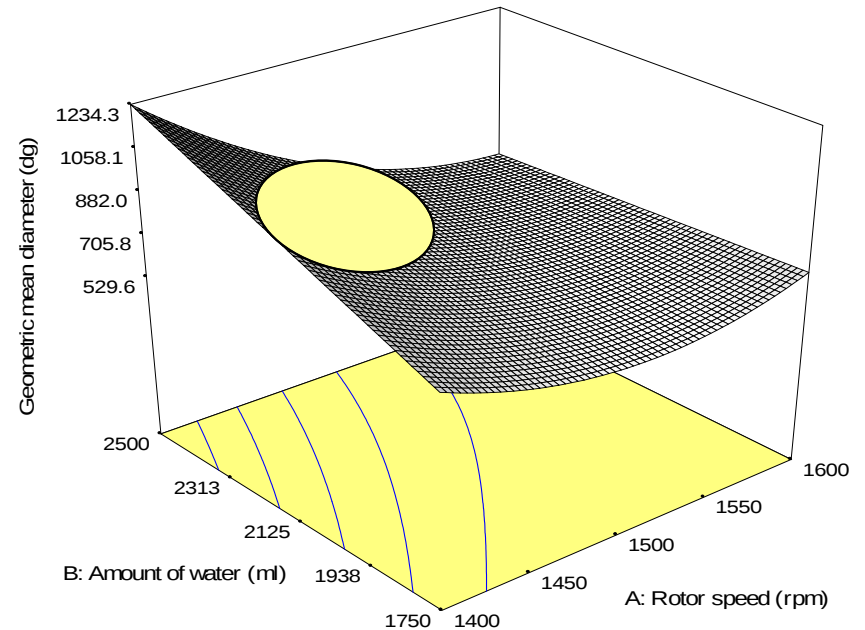
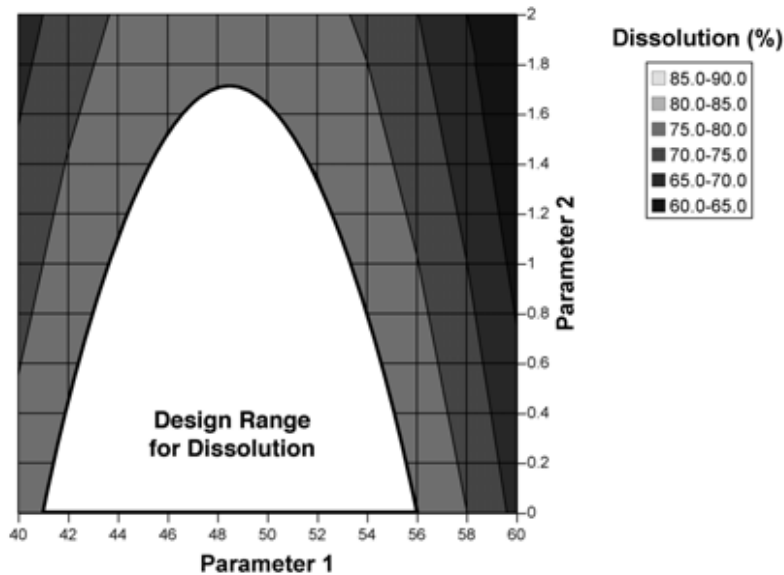
ICH Q8 definition:

“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)

Tools used to develop a DS:

Prior knowledge, Risk assessment, DOE, MVDA

Examples of a Design Space





Design Space vs Proven acceptable ranges

- Design space is established in a multivariate manner. Allows insight in interactions between factors
- Proven acceptable ranges are established univariately

Implications of Design space

- **Increased process and product understanding**
- **Increased assurance to Regulators → regulatory flexibility**
 - » Working within the design space is not considered as a change
 - » Movement out of the design space is a change and would normally initiate a regulatory post approval change process
 - » The review of Variations Regulation and the revised Variations Classification Guideline has taken into account QbD submissions to enable easier updates of the dossier

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

! The focus is on **Process/ Product Understanding**
not on advanced online monitoring of the process

MAAs with QbD and PAT elements in CP*

- Avamys (EMA/H/C/770)
- Toricel (EMA/H/C/799)
- Tykerb (EMA/H/C/795)
- Norvir X-91
- Exjade II/14
- Exjade II/16
- Revolade (EMA/H/C/1110)
- Patorma (EMA/H/C/1141)

*Not exhaustive list

Assessing QbD / PAT dossiers-

Points to consider

- **A DS may cover**
 - » one or multiple unit operations for the finished product and/or active substance
- **Not all unit operations must have a DS**
 - Unit operations without a DS will obviously not achieve the regulatory benefits (i.e. ability to move within DS)
- **DS changes post approval**
 - » Changes to an approved DS are subject to the variations regulation in force at the time of the application
- It's preferable, when **a DS is complemented by an appropriate control strategy**
- DS may be accompanied by a **real time release** proposal for some of the attributes (e.g. dissolution release based on particle size control, and disintegration test)

Assessing QbD / PAT dossiers-

Points to consider

- **Amount of data in the dossier**
 - » FMEA
 - » Evaluation of DoEs
 - » Evaluation of chemometric methods
- **Design Space scale-up**
- **Design Space verification and model maintenance throughout the product lifecycle**
 - » How to ensure that development data are valid at production scale and during the lifecycle? need for confirmatory runs at production scale and appropriate control strategy.
- **Process validation vs continuous process verification**
 - » Is there a need for the traditional 3 validation batches approach?
- **Real time release**
 - » Is there a need for parallel testing at least in the beginning? Is there a need for skip-lot testing?
- **Large sampling sizes vs Ph. Eur acceptance criteria (e.g. for content uniformity)**
- **Requests for inspection**

Useful Guidance

- ICH Q8,9, 10
- Draft NIR Guideline
- Draft parametric release guideline
- New d80 Quality AR templates to be published in March 2010

Advice may also be requested from the

- EMEA PAT Team

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 (as part of the peer-review process)
- Input to the IWG for ICH Q8-9-10
- 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, or at scientific advice
- Q&A document published on the EMEA website

Conclusions

- ICH Q8-9-10 concepts are still relatively new
- Issues keep arising as experience is gathered
- Guidance documents are being drafted/revised
- New paradigm requires closer collaboration between Assessor and Inspector
- Assessors are requested to evaluate new types data –Need for appropriate expertise
- Need to strike the balance on the type and level of information that is requested
- Need for harmonised approach in evaluation
- Assessors are encouraged to contact the EMEA PAT team during the assessment of MAAs, as this will help towards the harmonisation goal.

Thank you for your attention!

Questions ?

Evdokia Korakianiti

Email: Evdokia.Korakianiti@emea.europa.eu