Quality by Design (QbD): a quick start guide

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A new Quality paradigm

- ICH discussions in July 2003 (Brussels) agreed a consensus vision:
  - «Develop a harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to risk management and science»

What is Quality by Design?

- Quality by Design (QbD) is:
  - «A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and Process control, based on sound science and Quality Risk Managment»

ICH Q8(R2)

Key characteristics of QbD

- A tool for focused & efficient drug development
- Is a dynamic and systematic process
- Relies on the concept that Quality can be built in as a continuum
- Is applicable to Drug Product and Drug Substance development (chemicals / biologics)
- Is applicable to analytical methods
- Can be implemented partially or totally
- Can be used at any time in the life cycle of the Drug
- Is encouraged by Regulators (EMA & FDA)

QbD: Regulatory tools (1/3)

Date	Guideline Reference	Scope
Aug. 2009	ICH Q8(R2)	Pharmaceutical Development
Nov. 2005	ICH Q9	Quality Risk Managment
June 2008	ICH Q10	Pharmaceutical Quality System
Jan 2011	FDA	Process validation. General principles and practices
Dec 2011	ICH Q8/Q9/Q10 (R2)	Guide for implementation
March 2012	EMA/CHMP/QWP/ 811210	Real Time Release Testing (formerly GL on parametric release)
March 2012	EMA/CHMP/CVMP/QWP/70278 (**draft**)	Process validation
May 2012	ICH Q11	Development & Manufacture of Drug Substances

QbD: Regulatory tools (2/3)

- EMA/FDA Pilot project started in April 2011
- QbD highly expected for Generics in the US (as of January 2013)
  - To support generic manufacturers, the Office of Generic Drugs (OGD) has published a 161 page example of a fictitious modified release tablet formulation

QbD: Regulatory tools (3/3)

- EU-PAT Team (Process Analytical Technology)
  - A forum of dialogue between Quality Assessors and Inspectors
  - Pharmaceutical companies are regularly invited to PAT team meetings
  - PAT organizes various trainings relative to QbD
  - Has issued Q&A and reflection papers
  - It is highly recommended to organize a Scientific Advice with PAT prior to MAA submission

Roadmap for QbD

- Define the Quality Target Product Profile
- Identify the Quality Attributes
- Perform a Risk (Assessment) Analysis
- Perform experiments
- Determine the Critical Quality Attributes and Critical Process Parameters
- Determine the Design Space
- Identify a Control Strategy

Quality Target Product Profile

Definition

«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»

ICH Q8(R2)

Example

- Oral administration
- Immediate release tablet
- Stable at room temperature at least 3 years
- Single tablet dosed three times daily
- Bioavailable
- Safe
- Efficacious

Critical Quality Attribute

Definition

"*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*".

ICH Q8(R2)

Drug Substance
(chemical)

- Appearance
- Particle size
- Morphic forms
- Water content
- Residual solvents
- Organic impurities
- Inorganic impurities
  - Heavy metals
  - Residue on ignition
- Assay

Drug product
(tablet)

- Appearance
- Identification
- Hardness
- Uniformity of dosage
- Physical form
- Dissolution
- Degradation products
- Water content
- Assay
- Microbiological limits

Design Space

Definition

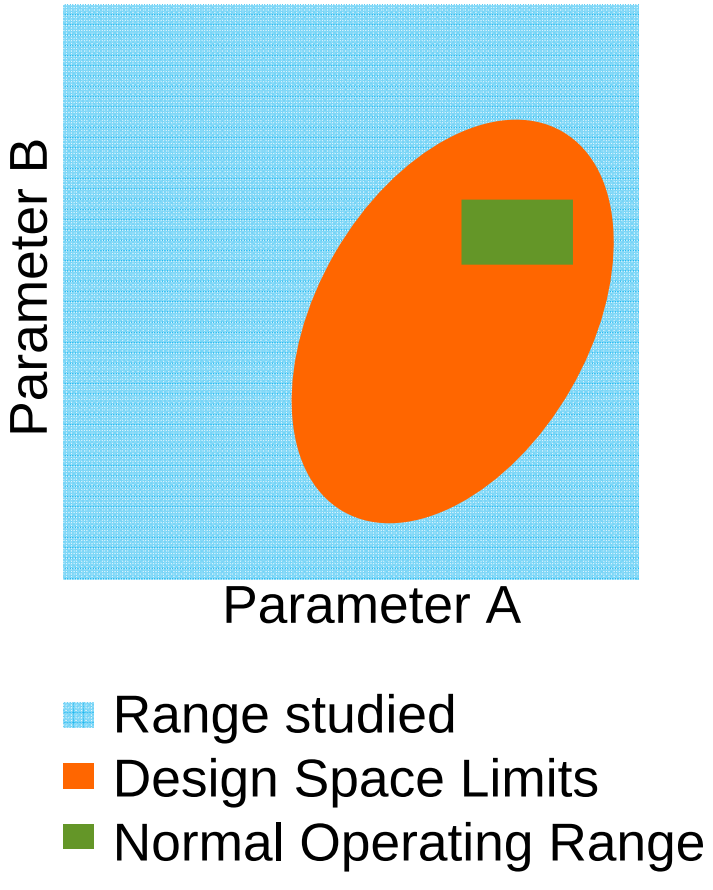
"Multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Working within the design space is not considered as a change".

Movement outside of the Design space is considered to be a change and would normally initiate a regulatory post approval change

ICH Q8(R2)

Concept (2 parameters)



Impact of QbD on control strategy

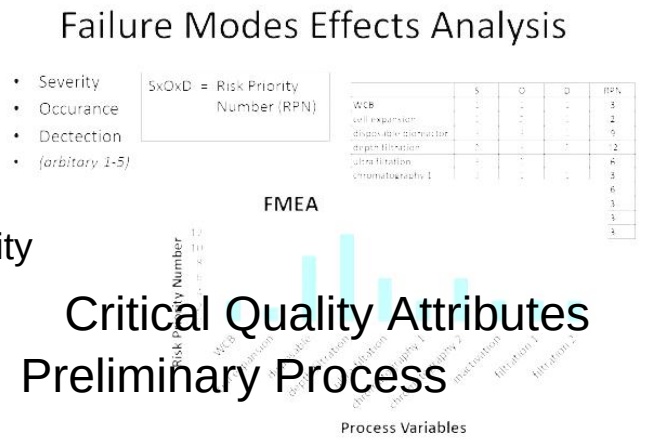
- Risk-based approach
- Quality Control may be shifted upstream
- May allow reduced end product testing
- Allows real-time testing
  - *«The ability to evaluate and ensure the quality of in-process and/or final product based on process data which typically include a valid combination of measured material attributes and process controls»* ICH Q8(R2)

Biopharmaceutical case study

Gene Therapy: Adenoviral Vector

Quality Target Product Profile

Physicochemical Quantity Purity Activity

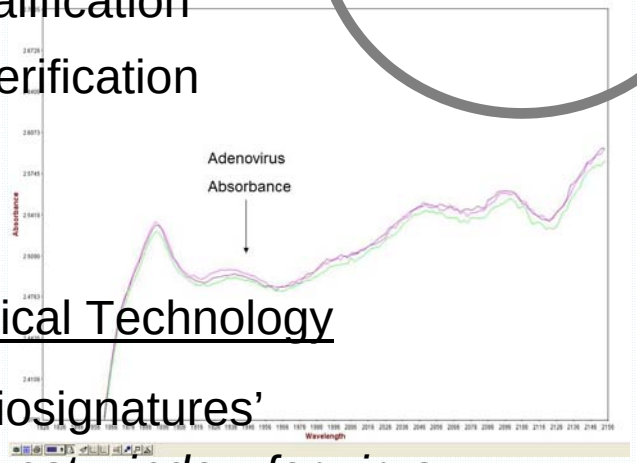


cGMP phase 1

Engineering batch

Pilot Process qualification

Product quality verification



Critical Quality Attributes

Preliminary Process

Criticality Analysis /FMEA)

Critical Process &
Product Parameters

Viral Harvest

<u>Process Analytical Technology</u>

NIR process 'biosignatures'

Pinpoint of harvest window for virus

Operational Design Space

DoE

Scale down process model

QbD in MAA - Tips

- Explain in detail the QbD approach in the Module 3 (S.2 and P.2)
- Take the «D80 Critical Assessment Report» as a guide

http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004808.pdf

- Use ICH terminology
- Explain in detail how criticality is ranked
- Describe the parameters (critical or not critical) in S.2.2 and P.3.3
- Insert tables, graphs and figures
- Provide Design Space depictions & NOR

Benefits of QbD

- Better understanding of the process
- Enhanced process monitoring
- Reduce end-product testing
- Speed-up release decision
- Facilitate continuous improvement
- Facilitate Change managment
- Reduction of post-approval submissions to Competent Authorities