

Case Study on Quality First : Driving Critical Process Parameters to Fulfill Critical Quality Attributes

*Designing Quality, Efficiency and Sustainability into
Pharmaceutical Processes – Bologna, 11 May 2010*

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Agenda

- ✓ *How to define a TPP*
- ✓ *How to identify CQA's*
- ✓ *How to deduce and implement CPP's*
- ✓ *Impact of Risk Assessment*
- ✓ *Definition and implementation of a successful Control Strategy*
- ✓ *Process Validation under the QbD paradigm*
- ✓ *Performance review and continual improvement*
- ✓ *Economic return*

Background & Scope

- *QbD Perspective*
- *Simplistically, QbD means that there's a systematic approach to drug development, starting with pre-defined objectives; a comprehensive understanding of the product/process is achieved and continuously improved in order to assure that product meeting true patient needs is consistently produced; Quality Risk Management is used throughout the product life-cycle; relevant information is appropriately conveyed in regulatory filings*
- *Reference documents : ICH Q8, Q9, Q10, etc.*

How to define a TPP - Definition



Early Development

- *The TPP is a mechanism for identifying the customer requirements (VOC) and some key business requirements that must be delivered by the market formulation:*
 - *Patient Safety, Efficacy, Convenience*
- *TPP is the beginning of specification setting process*
 - *ID's which Quality targets are clinically relevant, ie, linked to formulation (clinical) performance*

“The target product profile forms the basis of design for the development of the product.”

ICH Annex to Q8: Pharmaceutical Development (2007)

How to define a TPP - Example

General Section

Parameter	Characteristics/Requirements	Quality Profile
Type	NCE, 1° in therapeutic class	na
Indication	Sleep Disorder	na
Mechanism		na
Treatment	Chronic	na
Route of Admin	Oral	na
Dosage Form	IR Solid	na
Dose Frequency		na
Biopharmaceutics Classification System (BCS) Class	II (High Permeability, Low Solubility)	na
Special Population	Elderly, Taking multiple medicines	na

How to define a TPP - Example

Safety/Efficacy/Other Requirements

Parameter	Characteristics/Requirements	Quality Profile
PK Performance		in vivo and in vitro tests
Likely Dose	10-30 mg	Identity, Assay, Uniformity
Expected Therapeutic Range	1-90 mg	Identity, Assay, Uniformity
Purity	Impurities < ICH Degradates < ICH	Manufacturing process
Stability	Degradates < ICH	Time-dependent chemical degradation
Subjective Properties	Taste masking	na
Size/Image	< 500 mg, round	Appearance, elegance
Food or Drug Interaction	Lack of food effect desirable	na

How to define a CQA - Definition



Early Development

A CQA is 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 (purity, safety, efficacy, stability etc). CQA's are used to guide the product and process development. Potential CQA's can be identified from the TPP.

How to define a CQA - Example

Quality Attributes of a Drug Product (tablet)

Attribute	Test	Critical	Control
Identification	ID tests	yes	Quality Systems
Appearance	Physical state, Color	yes	Process and material
Integrity	Hardness, Thickness, Friability	yes	Process
DU/Assay	Content Uniformity, Weight Uniformity	yes	Process and API
Purity	Organic Impurities	yes	API
Dissolution	Disintegration, Dissolution	yes	API
Microbial Count	Total viable aerobic count, Pathogens	yes	Process, material environment
Manufacturability	Blend flowability	yes	Process and API

How to deduce and implement CPP's



Early/Late Development

Risk assessments can serve as the means to identify where to focus development efforts and justify what parameters will not be evaluated during process development and will not deserve close scrutiny during manufacturing (e.g. those low risk process parameters having low likelihood of occurrence, little expected impact and high detectability). Raw material attributes and process parameters can be linked to CQA's by means of formal risk assessments.

How to deduce and implement CPP's – Example (DC, CU)

Process Step	Parameters	Parameter Control Scenarios	In-Process CQA Monitoring or Control Scenarios
Dispensing	API quantity	Weights, scale	Achievement of right dispensing operations : Weight controls, procedural controls
	Excipient quantity	Weights, scale	
	Method of addition	Procedures, facility design (options like pneumatic conveying that could affect raw materials properties, e.g. PSD) or losses in addition	
Blending/ Lubrication	Raw material properties	Supplier qualification, COA review, ID test, compendia testing, property comparison against design space	Achievement of blend uniformity : RTR(T), e.g. on-line NIR – endpoint or parameter set points, e.g. #revolutions, blending speed. Traditional, e.g. slug thief sampling – off-line HPLC and/or parameter set points, e.g. #revolutions, blending speed
	Material order/method of addition	Procedures	
	Operational parameters, e.g. # of revolutions, blending speed	Automated recipes, procedures	
	Particle motion/stress	Blender design and size	
	Fill volume of blender	Batch size	

How to deduce and implement CPP's – Example (DC, CU)

Process Step	Parameters	Parameter Control Scenarios	In-Process CQA Monitoring or Control Scenarios
Compression	Lubricated blend properties	Controlled by prior processing steps	Achievement of content uniformity: RTR(T), e.g. at/on-line NIR for concentration and/or on-line automated systems for tablet weights. Traditional, e.g. off-line HPLC or for high drug load – off-line weight uniformity;
	Tooling parameters	Design specifications (geometry factors that could affect consistency of fill weight into the dies)	
	Tablet press operation parameters	Automated recipes /procedures and based on equipment capability	
	Compression equipment configuration	Facility design (all that can affect formulation flow and/or segregation, e.g. feed chutes venting)	

Impact of Risk Assessment

The ICH Q9 outlines expectations, and offers a systematic approach to quality risk management. Some key points: 1) "Quality risk management supports a scientific and practical approach to decision making. It provides documented, transparent and reproducible methods to accomplish steps of quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk" 2) "Evaluation of risk should be based on scientific knowledge and ultimately link to the protection of the patient" 3) "The amount of effort used for risk control should be proportional to the significance of the risk"

Impact of Risk Assessment – When to perform it

- **Early development** - Identification of variables potentially affecting CQA's (example: for BCS II compound, it is highly likely that API particle size will affect dissolution) in order to prioritize the development strategy
- **Late Development** - Includes rationale how CPP's have been chosen, how they are controlled and monitored

!!! Input from manufacturing site

- **Manufacturing Site** – Ensures knowledge transfer from the development studies and regulatory submission to on-site manufacturing documentation and covers site specific risks

How to define/implement a Control Strategy - Definition

ICH Q8/Q10 : “A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and associated methods and frequency of monitoring and control.”

When to define/implement a Control Strategy

- **Late development** - Using Late Phase Risk Assessment as an input, all functions pull together recommendations for high level control strategy to meet objectives.

!!! Input from manufacturing site

- **Pre-Filing** – Using all data available at the end of Development, the Control Strategy is updated and finalized.

!!! Input from manufacturing site

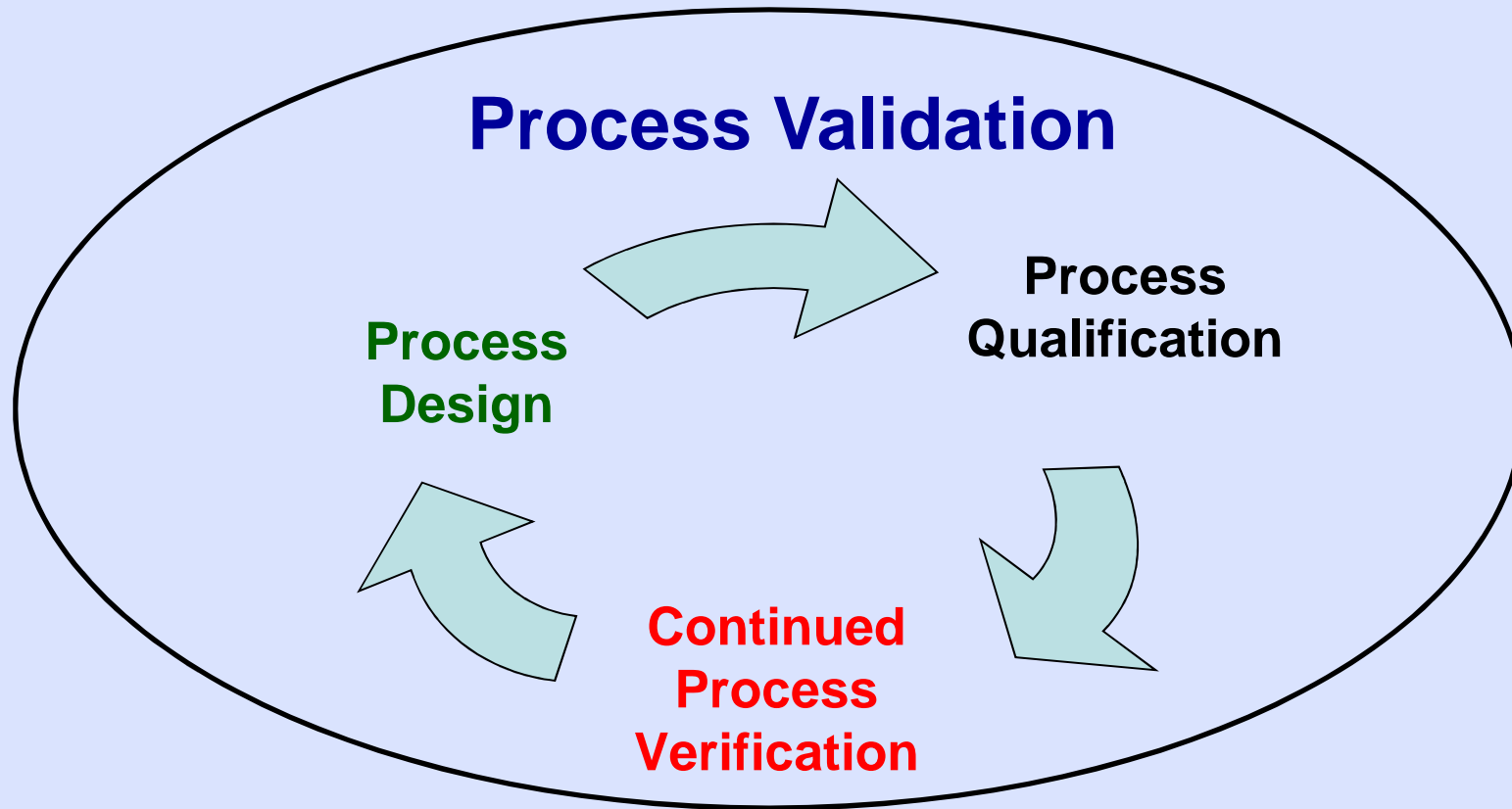
- **Manufacturing Site** – Site Quality Systems are modified as needed; new skills are adequately built; site SOP's are updated

Process Validation – QbD approach



Supply Phase
!!! Input from development

FDA Draft Guidance on Process Validation, November 2008
EMA Concept Paper on the Revision of the Guideline on Process Validation, February 2010



Process Validation – QbD approach - FDA

“the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products”

Process Design : the process is defined based on knowledge gained through development and scale-up

Building and Capturing Process Knowledge and Understanding; Establishing a Strategy for Process Control

Process Qualification : the process design is confirmed as being capable of reproducible commercial manufacturing

Design of a Facility and Qualification of Utilities and Equipment; Performance Qualification

Continued Process Verification : ongoing assurance is gained during routine production

Process Validation – QbD approach - EMA

- *Problem statement : The current guideline does not reflect the recent regulatory developments on PAT, QbD, RTRT*
- *“The main objective of process validation remains that a process design yields a product meeting its pre-defined quality criteria. ICH Q8, Q9, Q10 provide a structured way to define product CQA’s, design space, the manufacturing process and the control strategy”*
- *Reference to the FDA Draft Guidance*

Performance Review and Continual Improvement

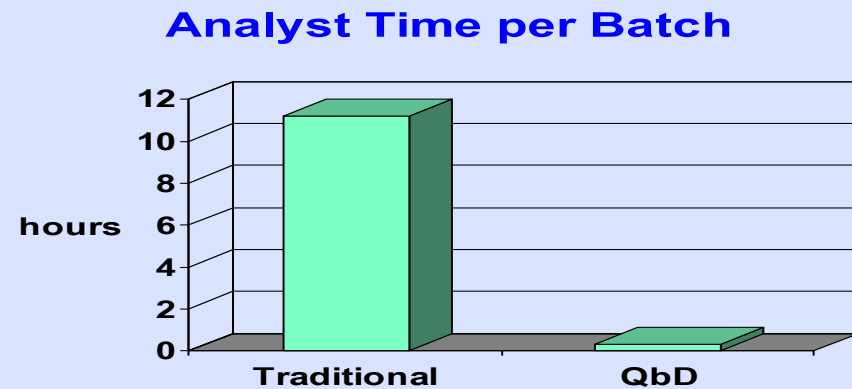
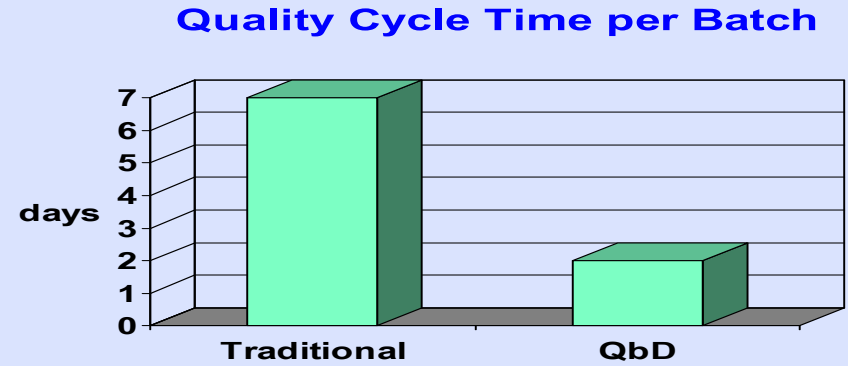
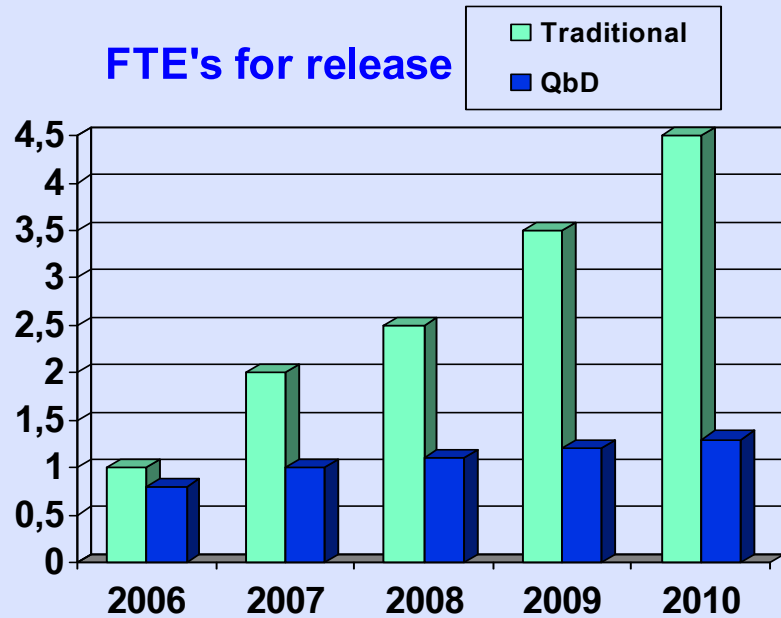


Supply Phase

!!! Feedback to development

- ***Linked to Risk Assessment & Control Strategy***
- ***Goal : the process remains in a state of control (the validated state)***
- ***Detection of process drifts (ongoing statistical analysis)***
- ***Sources of variability not previously anticipated***
- ***Manufacturing experience (e.g. complaints, OOS, deviations, etc)***
- ***Human errors***

Economic Return



**Cost of Inventory -
With shorter cycle time could
avoid 0.5 MOC on a rolling basis**