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How the PQS supports a QbD Approach, including RTRt

Georges France
Pfizer, Maidenhead, UK
Vice President, Global Quality Strategy,
georges.france@pfizer.com

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Overview

- Development Quality Systems: 'Fit-for-Purpose'
  - Case study: Process validation
- How Q10 supports Product Realisation
  - Inhaler Case Study: Use of CAPA and QRM
- How ICH Q10 enablers support RTRt implementation
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Development Quality System - Proportionate Application of Elements

1.6.2 Quality Risk Management

Quality risk management is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality. It facilitates continual improvement of process performance and product quality throughout the product lifecycle. ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.

1.7 Design and Content Considerations

(a) The design, organisation and documentation of the pharmaceutical quality system should be well structured and clear to facilitate common understanding and consistent application.

(b) The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the different goals and knowledge available for each stage.

(c) The size and complexity of the company's activities should be taken into consideration when developing a new pharmaceutical quality system or

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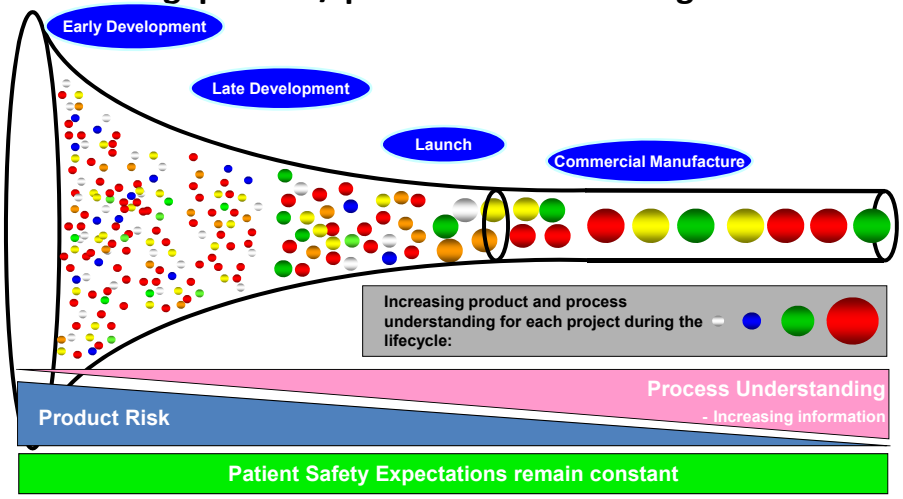
Foundation for Fit-for-Purpose Quality System Elements: Increasing product/ process understanding



Flexibility - Regulatory expectations for IMP's

FDA Phase I guidance	Annex 13 Manufacture of IMP's
'Some manufacturing controls, and the extent of manufacturing controls needed to achieve appropriate product quality differ not only between investigational and commercial manufacture, but also among the various phases of clinical trial '	*'Procedures need to be flexible to provide for changes as knowledge of the process increases and appropriate to the stage of development of the product'* *'In clinical trials there may be added risk to participating subjects compared to patients treated with marketed products'.*

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Development to Commercial…the differences

- Development and Technology Transfer
  - Continuous learning so that variables and their impact on patients are understood, managed and controlled
  - Evaluation of effects of scale, equipment changes etc.
  - Knowledge incomplete
    - e.g. Target Value vs Proven Acceptable Range or Design Space
    - Continuous 'real-time' evaluation of application of GMP principles
- Commercial:
  - Regulatory commitments for formula, process description, specs, methods etc.
  - Well-established GMP requirements
  - Formal change management with continual improvement

What can vary across the lifecycle?

- Product and process knowledge increases through product lifecycle
  - Proportionate application of Q10 elements: Fit-for-Purpose
- Consider phase-appropriate approaches to:
  - Raw Material qualification
  - Handling changes, deviations
  - Calibration, Qualification and Validation
  - Manufacturing documentation
  - Analytical methods and Specifications
  - etc.

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Examples for Fit-for-Purpose PQS Elements

	Pre-clinical	Phase I	Phase II	Phase III	Commercial
Documentation	Lab Notebooks, Operational Records	Begin Batch Records evaluate minimal use of Notebooks (flexibility for QA prior approval)	Batch Record (flexibility for QA prior approval)	Batch Record (transition to QA prior approval)	Batch Record with Formal Change Control and Regulatory impact evaluation
Analytical Method Qualification/ Validation	Reliable Data	Scientifically Sound Data	Qualified Methods	ICH Method Validation	Validated Method Changes

Case Study – Process Validation approaches

- Clinical supplies
  - Powder for Oral Solution for bioequivalence study
  - Pre-Manufacturing Risk Assessment
    - Limited product/process knowledge of filling behaviour on automated equipment
  - Risk mitigation
    - Manual bottle filling process selected
  - Non-validated process
    - Verification: record all fill weights
- Commercial manufacture
  - Fully validated automated filling operation

Validation approach is appropriate to quality requirements and lifecycle stage

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Achieve Product Realisation

1.5 ICH Q10 Objectives

Implementation of the Q10 model should result in achievement of three main objectives which complement or enhance regional GMP requirements.

1.5.1 Achieve Product Realisation

To establish, implement and maintain a system that allows the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers.

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Corrective Action and Preventive Action System

3.2.2 Corrective Action and Preventive Action (CAPA) System

The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring. A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9. CAPA methodology should result in product and process improvements and enhanced product and process understanding.

Table II: Application of Corrective Action and Preventive Action System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Product or process variability is explored. CAPA methodology is useful where corrective actions and preventive actions are incorporated into the iterative design and development process.	CAPA can be used as an effective system for feedback, feedforward and continual improvement.	CAPA should be used and the effectiveness of the actions should be evaluated.	CAPA should continue after the product is discontinued. The impact on product remaining on the market should be considered as well as other products which might be impacted.

Inhaler Case Study – Use of CAPA and QRM

- New Metered Dose Dry Powder Inhaler
- Supplies manufactured for Phase III clinical study
- Three deviations identified
  1. Out of target content uniformity result at disc assay stage
  2. Inhaler exceeding the actuation force specification
  3. Inverted disc assembled into an inhaler
- Investigations opened

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Inhaler Case Study – Investigation 1

- Out of target result for content uniformity for pre-metered dosage units
  - Provides indication of blend uniformity and disc filling
  - Actual performance measured using uniformity of emitted dose
- Comprehensive investigation by cross-functional team of SMEs
  - Two batches
  - Manufacturing operation
  - Technology transfer
  - Process characterisation
  - Formulation
- Outcome
  - Aggregation of API identified as root cause
- CAPA
  - Manufacturing process change

Inhaler Case Study – Investigation 2

- Inhaler exceeded actuation force limit
  - Difficulty or failure to operate inhaler
  - 100% inspection of inventory
- Outcome
  - Root cause identified as misalignment of component
- CAPA
  - Engineering on assembly modified to prevent recurrence

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Inhaler Case Study – Investigation 3

- Dose carrier assembled into inhaler inverted
  - Drug would not be emitted when inhaler actuated
- Outcome
  - Only a single example identified
  - Difficult to inspect out of inventory
- CAPA
  - Assembly jig modified to eliminate possibility of incident recurring

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Case Study – QbD Product X

- Product Background
  - BCS* Class 1 compound (High Water Solubility, High Permeability)
  - Immediate Release Tablets
  - Potent, low dose compound, low drug load
- Launched from small-scale containment manufacturing facility
  - Initial approval featured robust, but traditional, control strategy
- Potential for Real Time Release Testing
  - Increased demand – need to increase efficiency
    - More information in real-time

* Biopharmaceutical classification system

Change Management System -
Implementation of RTRt on a commercial product

The change management system should include the following, as appropriate for the stage of the lifecycle:

(a) Quality risk management should be utilised to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk;

(b) Proposed changes should be evaluated relative to the marketing authorisation, including design space, where established, and/or current product and process understanding. There should be an assessment to determine whether a change to the regulatory filing is required under regional requirements. As stated in ICH Q8, working within the design space is not considered a change (from a regulatory filing perspective). However, from a pharmaceutical quality system standpoint, all changes should be evaluated by a company's change management system;

(c) Proposed changes should be evaluated by expert teams contributing the appropriate expertise and knowledge from relevant areas (e.g., Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs and Medical), to ensure the change is technically justified. Prospective evaluation criteria for a proposed change should be set;

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Using Q10 Enablers to develop RTRt

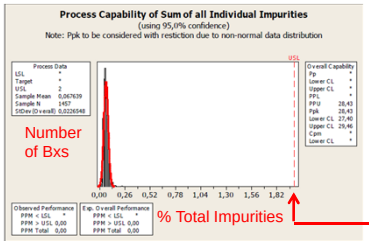
1.6 Enablers: Knowledge Management and Quality Risk Management

Use of *knowledge management* and quality risk management will enable a company to implement ICH Q10 effectively and successfully. These enablers will facilitate achievement of the objectives described in Section 1.5 above by providing the means for science and risk based decisions related to product quality.

1.6.1 Knowledge Management

Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding. Knowledge management is a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components. Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and *change management* activities.

Using QRM to Develop Control Strategy: Data-Driven evaluation for Impurity Testing



Specification Limit

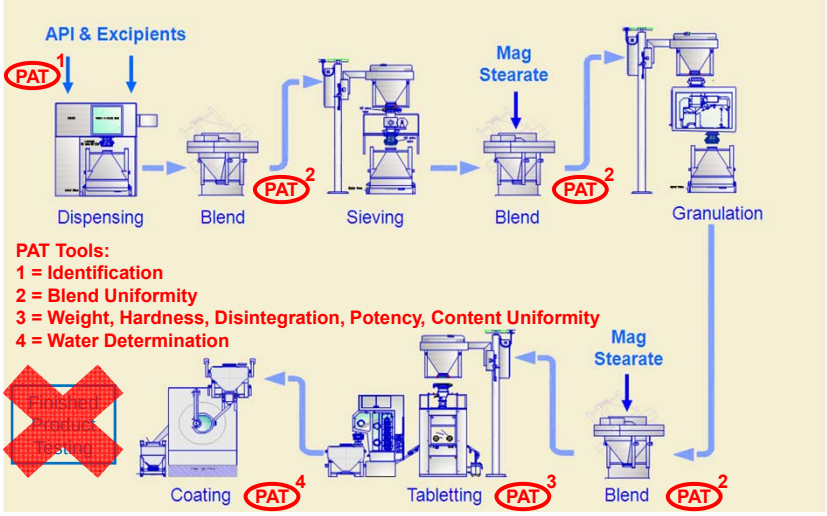
- Scientific understanding of mechanisms of impurity formation (hydrolysis)
  - Dry process limits potential for impurity formation
- Commercial batch data (>1000 bxs) shows very high process capability

Conclusion:
Routine Finished Product Impurity Test not required

KM to support RTRt Implementation

- Feeding back Manufacturing Information
  - Several hundred batches manufactured after approval
  - Process capability (Ppk values) and general experience demonstrated robust manufacturing process
  - Established good correlation between e.g. HPLC assay and NIR assay
  - Enhanced understanding supported RTRt submission
- Organization and Communication
  - Special cross-functional “Limited Duration Team” established
  - Site-wide QbD Training
  - Quality system elements revised
- Ongoing Knowledge Management
  - Operator experience with PAT tools fed back to Development

Product X Manufacturing Process



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Evolution of Control Strategy

'Traditional' → RTRt

Methods for conventional QC Release Testing	Methods for Real Time Release Testing
Appearance (Visual)	Appearance (Visual)
Identity (TLC / HPLC)	Identity (NIR)
Assay / CU (HPLC)	Assay / CU (NIR + Weight)
Dissolution (Dissolution Tester)	Disintegration (Disintegration Tester)
Water Determination (Karl Fischer)	Water Determination (NIR)
Impurities (HPLC)	Not Tested routinely - due to process capability and understanding
Microbial Quality (Microbiology)	Not Tested routinely - due to process capability and understanding

For RTRt these controls shifted upstream in process

Conclusion from Risk Assessment: Routine Finished Product Testing not required

Note: Real Time Release Testing does not mean less testing!

PP&PQM System and RTRt

3.2.1 Process Performance and Product Quality Monitoring System

Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained. An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement. The process performance and product quality monitoring system should:

(a) Use quality risk management to establish the control strategy. This 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 the associated methods and frequency of monitoring and control. The control strategy should facilitate timely *feedback / feedforward* and appropriate corrective action and preventive action;

(b) Provide the tools for measurement and analysis of parameters and attributes identified in the control strategy (e.g., data management and statistical tools);

(c) Analyse parameters and attributes identified in the control strategy to verify continued operation within a state of control;

(d) Identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation;

(e) Include feedback on product quality from both internal and external sources, e.g., complaints, product rejections, non-conformances, recalls, deviations, audits and regulatory inspections and findings;

(f) Provide knowledge to enhance process understanding, enrich the *design space* (where established), and enable innovative approaches to process validation.

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Impact on Quality Systems

- Quality Systems
  - Evolution, not revolution, of existing quality systems
  - Use of Q10 with Quality Risk Management & Knowledge Management
- 'Proactive quality'
  - Planned responses to these problems defined in procedures etc
  - Quality System elements that may be revised could include:
    - Deviations
    - Change Management
    - Validation
    - Knowledge Management
    - Product Quality Review
- Personnel
  - Cross-functional teams for QRM
  - Training on revised SOPs and PAT/QbD
- Outsourced Activities
  - Quality agreements – e.g. may need special consideration for design space
  - Knowledge Management

Batch Disposition

- Batch disposition
  - Batch disposition process and decision to accept or reject the batch is still needed when Real Time Release testing is used (Ref. ICH IWG Q&A)
- Batch disposition decision may be facilitated by
  - Use of electronic batch records and exception reporting systems (flag deviations) to provide information in real time
  - Product/process monitoring systems (e.g. Statistical Process Control) can provide real time assessment of process performance
- Certificate of Analysis
  - Values from online testing may be reported on CoA
- Impact on Qualified Person
  - Release process essentially unchanged with QbD and/or RTRt
  - Need to understand systems supporting the disposition decision
  - Continue to rely on robust Quality System

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Summary – Take Away Messages

- Quality System in Development
  - Provides framework for confidence in the scientific data
- Q10 elements can be applied proportionately during Product Development phase of Product Lifecycle
  - 'Fit-for-purpose' quality system in Development
- Successful RTRt
  - Foundation is appropriate development of product and process understanding
  - Robust control strategy
  - Quality system provides the backbone for implementation

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