Implementation of ICH Q8, Q9, Q10

Key messages

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICH

Content

- ***Design Space***
- ***Control Strategy***
- ***Pharmaceutical Quality System***
- ***Quality Risk Management***

ICH

Disclaimer

The information within this presentation is based on the ICH Q-IWG members expertise and experience, and represents the views of the ICH Q-IWG members for the purposes of a training workshop.

Acknowledgement

This presentation has been developed by members of the ICH Quality Implementation Working Group (Q-IWG)

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Implementation of ICH Q8, Q9, Q10

Breakout A
Design Space

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

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Introduction

- Structure of this session
  - Discussion of key messages on Design Space
  - Examples from the Case Study
  - Wrap up
    - Feedback on barriers to implementation
    - Feedback on issues where further clarification is required
  - Breakout report

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Introduction

- There are no regulatory requirements to have a Design Space
- Quality Risk Management approaches need to be considered to ensure the robustness of the Design Space
- Design space can illustrate understanding of parameter interactions and provides manufacturing flexibility
  - Proven acceptable range alone is not a design space
- Design space can include critical and non-critical parameters
- Design space should be verified and opperational at full scale
  - No requirement to develop a design space at the full manufacturing scale
  - Many options exist for how (and where) to present a design space

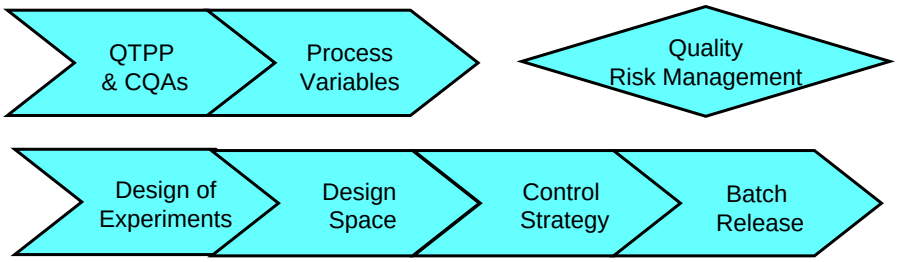
Training Objectives

- Design Space development
  - Steps in Development of Design Space
  - Prior knowledge
  - QRM
  - DOE & modeling
  - Process Parameter and Quality Attribute as factors in Design Space development
- Implementation of Design Space
- Presentation of Design Space in regulatory submission

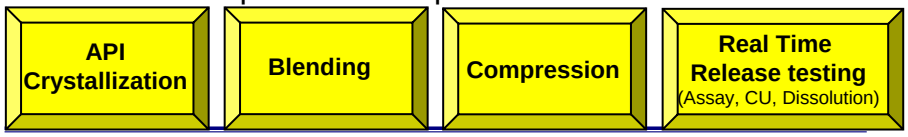
Steps in Development of Design Space

- Consider QTPP in establishing the Design Space
- Initial determination of CQAs
- Assess prior knowledge to understand variables and their impact
  - Scientific principles & historical experience
- Perform initial risk assessment of manufacturing process relative to CQAs to identify the high risk manufacturing steps (->CPPs)
- Conduct Design of Experiments (DoE)
- Evaluate experimental data
- Conduct additional experiments/analyses as needed

QbD Story per Unit Operation



Illustrative Examples of Unit Operations:



DS development - Prior knowledge

- Key messages
  - Prior knowledge may include :
    - internal knowledge from development and manufacturing
    - External knowledge: scientific and technical publications (including literature and peer-reviewed publications)
  - Citation in filing: regulatory filings, internal company report or notebook, literature reference
  - No citation necessary if well known and accepted by scientific community

DS development - Prior knowledge

- What might be applicable sources of Prior Knowledge ?
- Identify other type of prior knowledge that can be used in DS development

Example from Case Study : Crystallization of the drug substance

- Particle size control needed during crystallization
- Prior knowledge/1st principles shows that other unit operations (Coupling reaction, aqueous workup, filtration and drying) have low risk of affecting purity or PSD.
  - > Knowledge from prior filings
  - > Knowledge from lab / piloting data, including data from other compounds using similar “platform” technologies
  - > First principles knowledge from texts/papers/other respected sources

DS development - QRM

- Risk assessment is based on prior knowledge and relevant experience for the product and manufacturing process
  - **Gaps** in knowledge could be addressed by further experimentation
  - Assignments of risk level must be appropriately justified
- Risk assessments/control will **iterate** as relevant new information becomes available
  - Final **iteration** shows control of risks to an acceptable level

DS development - QRM

- Training questions
  - If the risk acceptance criteria (conclusions) are different than scientific theory/prior knowledge would indicate, then is further explanation provided to justify unexpected conclusions?
  - If there are gaps in the information then what would the plan be to make adjustments to further reduce risk?

Case Study Example

Illustration from the Case Study - Risk Assessment for PSD Control

What is the **Impact** that ---------- will have on purity? 1) minimal 5) moderate 9) significant
What is the **Probability** that variations in ---------- will occur? 1) unlikely 5) moderately likely 9) highly likely
What is our **Ability to Detect** a meaningful variation in ---------- at a meaningful control point? 1) certain 5) moderate 9) unlikely

Unit Operation	Parameter	IMPACT	PROB.	Detect	RPN	Comments
Crystallization	Feed Temperature	1	5	1	5	
Crystallization	Water content of Feed	1	5	5	25	
Crystallization	Addition Time (Feed Rate)	9	5	9	405	Change in addition time is easy to detect, but rated high since there is no possible corrective action
Crystallization	Seed wt percentage	9	5	5	225	
Crystallization	Antisolvent percentage	1	1	1	1	Yield loss to crystallization already low (< 5%), so reasonable variations in antisolvent percentage (+/- 10%) will not affect the percent of batch crystallized, and will not affect PSD
Crystallization	Temperature	9	5	9	405	Change in crystallization temperature is easily detected, but rated high since no possible corrective action (such as, if seed has been dissolved)
Crystallization	Agitation (tip speed)	9	5	5	225	Prior knowledge indicates that final PSD highly sensitive to Agitation, thus requiring further study.
Crystallization	Seed particle size distribution	9	1	1	9	Seed PSD controlled by release assay performed after pin milling.
Crystallization	Feed Concentration	1	1	1	1	Same logic as for antisolvent percentage

To be investigated in DOE

Detailed working documents like this would likely not be included in the submission

DS development – DOE & Modeling

- Target the desired quality attribute range from QTPP
- Determination of edge of failure is not required
- Modeling is not required to develop a Design Space
- Models need to be verified, updated and maintained

DS development – DOE & Modeling

- Does the DOE results, as presented in the case study, provide sufficient information to define a design space?
- Describe which parameters are addressed by univariate vs. multivariate DOEs and how these are factored into the design space
- Model implementation: Describe how variability due to the process operations and/or analytical method is considered in use of the model
- Describe the process for maintenance & updating of the model

DS development – Process parameter & quality attributes

- **Design space presentation in the submission could include critical and non-critical parameters**
  - Critical parameter ranges/model are considered a regulatory commitment and non-critical parameter ranges support the review of the filing
  - Critical parameter changes within design space are handled by the Quality System and changes outside the design space need appropriate regulatory notification
- **Non-critical parameters would be managed by Quality System**

DS development – Process parameter & quality attributes

- Illustration & training questions
  - Has the model for PSD Control (next slide) been demonstrated to be scale and equipment independent?
  - Is a mathematical model always needed to have a design space?
  - How to evaluate the impact of changing non-critical process parameters when included in the design space ?
    - Technical evaluation of a change of non-critical is the same scientific principle as for critical

Illustration from case study : QTPP and CQAs

QTPP

Dosage form and strength	Immediate release tablet containing 30 mg of active ingredient.
Specifications to assure safety and efficacy during shelf-life	Assay, Uniformity of Dosage Unit (content uniformity) and dissolution.
Description and hardness	Robust tablet able to withstand transport and handling.
Appearance	Film-coated tablet with a suitable size to aid patient acceptability and compliance. Total tablet weight containing 30 mg of active ingredient is 100 mg with a diameter of 6 mm.

CQAs derived using Prior Knowledge
(e.g. previous experience of developing tablets)

CQAs may be ranked using quality risk assessment.

Drug Product CQAs
- •Assay
- •Content Uniformity
- •Dissolution
- •Tablet Mechanical Strength

Breakout A: Design Space

API Crystallization: Design Space & Control Strategy

Particle Size	Crystallization	Temperature	20 to 30°C	Control between 23 and 27°C
Particle Size	Crystallization	Feed Time	5 to 15 hours	Control via flow rate settings
Particle Size	Crystallization	Agitation	1.1 to 2.5 m/s	Quality system should ensure changes in agitator size result in change to speed setting
Particle Size	Crystallization	Seed Wt%	1 to 2 wt%	Controlled through weigh scales and overcheck
Hydrolysis Degradate	Distillation / Crystallization	Water Content	< 1 wt%	Control via in process assay (e.g. < 0.5%)

Breakout A: Design Space

Implementation of Design Space

- **What PQS element need to be considered ?**
  - How DS is captured in batch documentation and batch release ?
  - How DS knowledge used in managing changes in the manufacturing process?
- **What information would be transmitted to the manufacturing site?**

Presentation of Design Space in regulatory submission

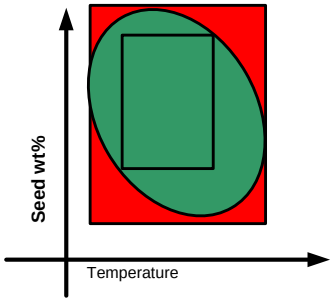
- **Design Space need to be clearly presented and justified in regulatory submission**
  - Design Space need to be described in sufficient details in regulatory filing
    - Description could include critical and non critical parameters to assure complete understanding
  - Designation of criticality need to be justified in regulatory submission based on QRM and/or experimental results

Presentation of design space in regulatory submission

- What is needed in the manufacturing process description in the filing to demonstrate the implementation of the Design Space?
- What is the appropriate level of detail to present DOE and it's conclusions in regulatory submissions ?

Breakout A: Design Space

Illustration from the case study : Options for Depicting a Design Space



- In the idealized example at left, the oval represents the full design space. It would need to be represented by an equation.
- Alternatively, the design space can be represented as the green rectangle by using ranges
  - a portion of the design space is not utilized, but the benefit is in the simplicity of the representation

Large square shows the ranges tested in the DOE
Red area shows points of failure
Green area shows points of success.

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Implementation of ICH Q8, Q9, Q10

Breakout B
Control Strategy

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Introduction

- Structure of this session
  - Discussion of key messages on Control Strategy
  - Examples from the Case Study
  - Wrap up
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  - Breakout report

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Key Messages - Definitions

- '**Control Strategy** is 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 the associated methods and frequency of monitoring and control.' (ICH Q10)

Key Messages - Definitions

- **Critical Quality Attribute (CQA):**

  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 (Q8(R2))

- **Critical Process Parameter (CPP):**

  A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality (Q8(R2))

Key Messages - Definitions

- **In-Process Control (or Process Control):**

  Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications (Q7)

  Applies similarly to the drug product

- **In-Process Tests:**

  Tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release (Q6A)

ICH Quality Implementation Working Group - Integrated Implementation Training Workshop
Breakout B: Control Strategy

Key Messages - Definitions

- '**Real time release testing (RTRT)**

  is 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' (Q8(R2))

- **Process Analytical Technology (PAT):**

  A system for designing, analyzing, 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 (Q8(R2))

Key Messages 1/5

- Control strategy derives from management of risk and should lead to assurance of consistent quality of product in alignment with the Quality Target Product Profile (QTPP)
- Control strategy is:
  - Not a new concept
  - Not just specifications
  - Based on product and process understanding and risk management
  - While space is optional, control strategy is not.

Key Messages 2/5

- Every process and product has an associated control strategy.
  - There is one overall control strategy for a given product.
  - There are control strategies for unit operations
  - It could include some site specific aspects
- For a given product, different approaches for the control strategy are possible (e.g. in-process testing, RTRT, end product testing)
- Specifications for API and drug product are still needed for stability testing, regional regulatory testing requirements, etc.

Key Messages 3/5

- Control strategy and batch release should not be confused.

  Control strategy is a key component, but not the only element needed for the batch release decision.

- Scale-up, technology transfer and manufacturing experience can lead to refinements of the control strategy under the PQS considering regulatory requirements

Key Messages 4/5

- **Process for defining the control strategy**
  - What are the quality criteria (QTPP)
  - Initial design of specific product & process
  - Assess prior knowledge to understand materials, process and product with their impact
    - Experience with different approaches to control
  - Risk assessment for process steps and variables
    - Assure all CPPs are identified during QRA
  - Development to further determine what type of controls are appropriate for each variable
  - Consider design space, if submitted
  - Specifications
- **Scale-up considerations**
- **Quality system requirements of control strategy**
  - Implementation, maintenance and updating

Key Messages 5/5

- Industry selects control approach based on multiple factors
  - Factors may include analytical testing sensitivity, equipment limitations, etc.
- Regulators evaluate the control strategy and whether the risk has been adequately controlled
- Inspector reviews the implementation of the control strategy at site, including adaptation at scale up, and the adequacy of the site quality system to support it

Examples from the Case Study

- Review of QTPP and Drug Product Risk Assessment
- Blending Process Control Options
  Decision on conventional vs. on-line testing
- Tablet weight control during compression

Breakout B: Control Strategy

Quality Target Product Profile (QTPP) Safety and Efficacy Requirements

Sakura Tablet	Characteristics / Requirements	Translation into Quality Target Product Profile (QTPP)
Dose	30 mg	Identity, Assay and Uniformity
Subjective Properties	No off-taste, uniform color, and suitable for global market	Appearance, elegance, size, unit integrity and other characteristics
Patient Safety – chemical purity	Impurities and/or degradates below ICH or to be qualified	Acceptable hydrolysis degradate levels at release, appropriate manufacturing environment controls
Patient efficacy – Particle Size Distribution (PSD)	PSD that does not impact bioperformance or pharm processing	Acceptable API PSD Dissolution
Chemical and Drug Product Stability: 2 year shelf life (worldwide = 30ºC)	Degradates below ICH or to be qualified and no changes in bioperformance over expiry period	Hydrolysis degradation & dissolution changes controlled by packaging

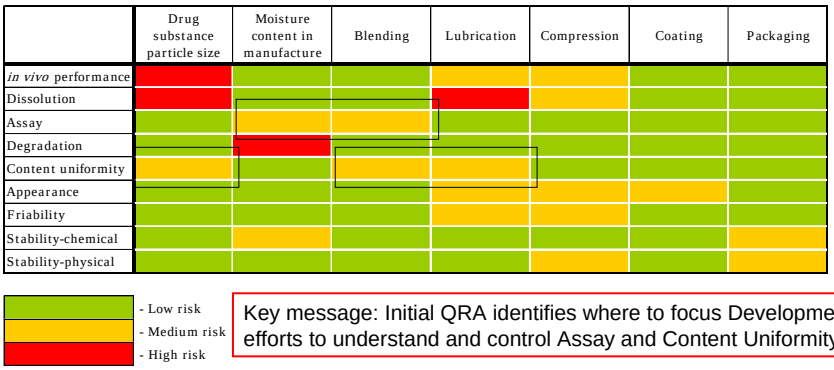
QTTP may evolve during lifecycle – during development and commercial manufacture – as new knowledge is gained e.g. new patient needs are identified, new technical information is obtained about the product etc.

Breakout B: Control Strategy

Quality Risk Assessment

Impact on Assay and Content Uniformity CQAs

- QRA shows API particle size, moisture control, blending and lubrication steps have potential to affect Assay and Content Uniformity CQAs
  - Moisture is controlled during manufacturing by facility HVAC control of humidity (GMP control)



Key message: Initial QRA identifies where to focus Development efforts to understand and control Assay and Content Uniformity CQAs

Blending Process Control Options

Decision on conventional vs. RTR testing

Control strategy 1: Control items		Control strategy 2: Control items
• Blending time • Blending speed • Equipment • Scale • Drug substance particle size	Process understanding	• Control of blending end point by NIR • Drug substance particle size

Figure 2.3.P.2.3-7 Control Strategy for Blending Process

Note) In the case of employment of control strategy 1, it is possible that drug substance partcle size as an input variable is combined with process parameters of blending time and blending speed to construct and present a three dimensional design space.

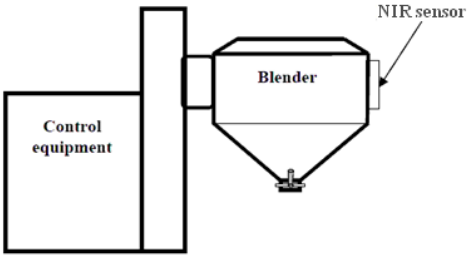
Key message: Both approaches to assure blend uniformity are valid in combination with other GMP requirements

Process Control Option 2

Blend uniformity monitored using a process analyser

- Control Strategy to assure homogeneity of the blend
  - Control of blending end-point by NIR and feedback control of blender
  - API particle size

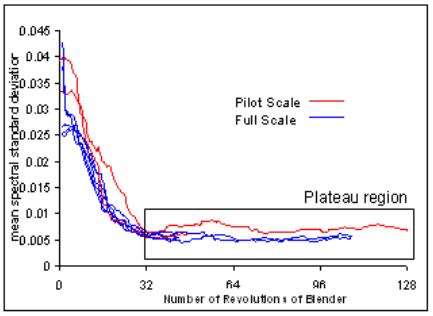
Equipment: XXXXX
Location of sensor attachment: Side position of the blender
Wavelength: XXXX cm^{-1} (Range of wave number: XXX to XXX cm^{-1})
Spectral Acquisition mode: diffuse reflectance



In this case study, the company chooses to use online NIR to monitor blend uniformity to provide efficiency and more flexibility

Process Control Option 2: Blend uniformity monitored using a process analyser (ctd)

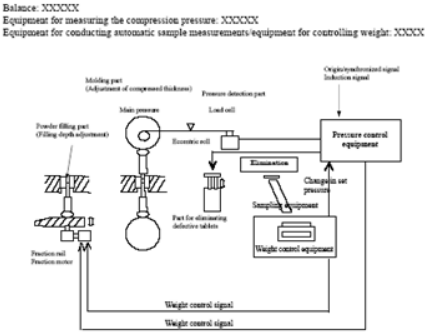
- On-line NIR spectrometer used to confirm scale up of blending
- Blending operation complete when mean spectral std. dev. reaches plateau region
  - Plateau may be detected using statistical test or rules
- Feedback control to turn off blender
- Company verifies blend does not segregate downstream
  - Assays tablets to confirm uniformity
  - Conducts studies to try to segregate API



Data analysis model will be provided
Plan for updating of model available

Acknowledgement: Adapted from Paul Stott (AZ) – ISPE PQLI Team

Tablet Weight Control in Compression Operation



Conventional automated control of Tablet Weight using feedback loop:
Sample weights fed into weight control equipment which sends signal to filling mechanism on tablet machine to adjust fill volume and therefore tablet weight.

Control strategy: Assay assured by control of weight of tablets made from a uniform powder blend that has acceptable API content by HPLC

RTRT of Assay and Content Uniformity

- Finished Product Specification – *use for stability, regulatory testing, site change, whenever RTR testing is not possible*
  - Assay acceptance criteria: 95-105% of nominal amount (30mg)
  - Uniformity of Dosage Unit acceptance criteria
  - Test method: HPLC
- Real Time Release Testing Controls
  - Blend uniformity assured in blending step (online NIR spectrometer for blending end-point)
  - API assay is analyzed in blend by HPLC
  - Tablet weight control in compression step
- No end product testing for Assay and Content Uniformity (CU)
  - Would pass finished product specification for Assay and Uniformity of Dosage Units if tested because assay assured by combination of blend uniformity assurance, API assay in blend and tablet weight control (if blend is homogeneous then tablet weight will determine content of API)

Topics to discuss using this Case Study

- What are the steps in building the control strategy elements for content uniformity?
  - Does this connect with the control strategy elements for another CQA (e.g. potency)?
  - How does this fit into the overall control strategy of the product CQA's?
- What are the benefits in this blending example of the different control strategy options?
- Is this control strategy adequate to assure assay and content uniformity of the final product? Can it replace end product testing for these CQA's?
- What could be alternative approaches to the proposed control strategy?

Additional discussion questions

- What could the drug product specification be presented in the application file when RTRT is employed?
- What might a certificate of analysis look like for a product that is released via RTRT?

Implementation of ICH Q8, Q9, Q10

Breakout C Pharmaceutical Quality System (PQS)

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Introduction

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Learning Objectives

- To review the key aspects of ICH Q10
- To understand the role and responsibilities of senior management
- To determine the practical application of ICH Q10 throughout the product lifecycle
  - New products
  - Legacy products
- To demonstrate how Continual Improvement can be used to improve both product quality and the PQS itself

Key Message: What is ICH Q10?

- **ICH Q10 is a guideline on the essential elements of a PQS throughout the product life cycle**
- **ICH Q10 complements Q8 and Q9**
  - ICH Q8 - strengthens the link between development and manufacturing
  - ICH Q9 - as an enabler of the PQS
- **Implementation of PQS should provide enhanced assurance of product quality**
- **GMP is applicable to the Manufacturing part of the life cycle**
  - Manufacturing of Investigational (medicinal) Product
  - Manufacturing of commercial products

Key Message: What is ICH Q10?

- A ICH Q10 type PQS reinforces/introduces some elements e.g.
  - Link manufacturing and development (incl. feedback)
  - Continual improvement
    - Products
    - Processes
    - PQS itself
  - Role and Responsibilities of Senior Management
  - Quality Risk Management and Knowledge Management
  - Product Lifecycle
    - Development through to Discontinuation
  - Management of outsourcing and purchasing material

Key messages

- Building quality into the product during development is fundamental
- ICH Q10 is a harmonised model of a PQS based on ISO Quality Management Systems (ISO 9000 series) which reinforces GMP and introduces some elements beyond GMP
- No intent to create new regulatory expectations
- Applies to e.g.
  - Drug Substance (small molecule & biotech)
  - Drug Product
  - Enhanced and Traditionally Developed Products

Key Messages: Knowledge Management and PQS

- The company should capture and use knowledge gained during development and manufacturing using a systematic approach
  - For continual improvement of the current products as well as future products
  - Each company should consider how this is achieved
- Examples
  - QTPP may evolve during lifecycle – during development and commercial manufacture - as new knowledge is gained
  - The Control Strategy is refined during product transfer and commercial manufacturing
  - Use of prior knowledge of similar products at the manufacturing site

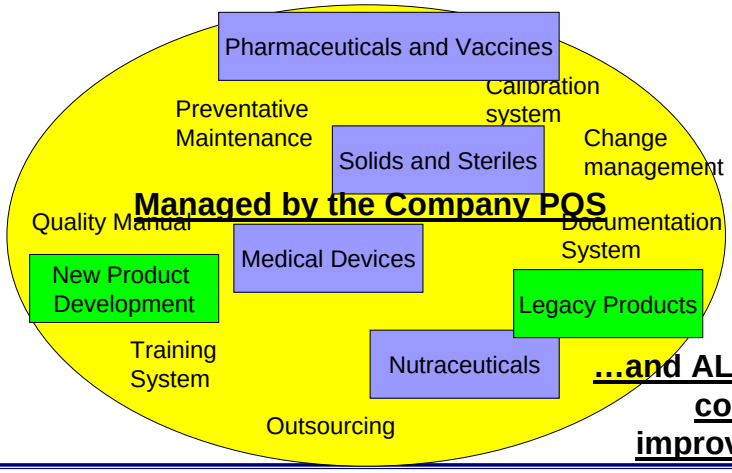
Key Message: The PQS should be fit for purpose

- Applied in a structured and consistent manner that is appropriate and proportionate to each of the product lifecycle stages
- Implementation of PQS/Q10 type take into account the size and complexity of the company's activities (incl. products)
- The vision, objectives, design and the implementation should be pragmatic, clear and therefore understood
  - The PQS must be linked to real practices and integrated into daily work

Different Types of Products

At Different Stages of Product Lifecycle

All need 'relevant' supporting processes



…and ALL need continual improvement

Key message on Pharmaceutical Quality System as proposed by ICH Q10

- Introduces the involvement and role of senior management
- Introduces a product life cycle perspective
- Quality Risk Management and Knowledge Management are enablers for the PQS

Details will follow

- Implementation of PQS should provide enhanced assurance of product quality

Implementation of ICH Q8, Q9, Q10

PQS Breakout Sub-Group Work

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Role and Responsibilities of Senior Management

- The decision to have enhanced development approaches (QbD) reinforces the need for a strong link between quality systems in development and manufacturing
- Senior management demonstrates commitment to the PQS by :
  - Granting adequate resources to implement, support and manage the PQS
  - Communicating the importance of the PQS
  - Ensuring strong interfaces between all relevant functions e.g. Development, manufacturing, Quality Unit (QA, QC, QP), engineering, supply chain and management of outsourced activities
  - Participation in the system through the conduct of management review (including process performance), product quality reviews and the PQS itself

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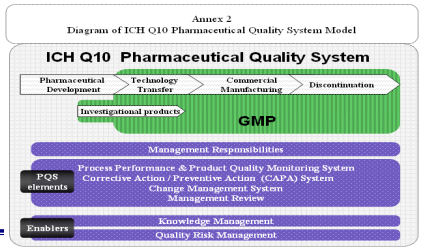
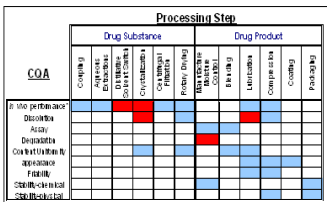
Concept of Product Lifecycle Covered by PQS

- The development of a product is done under the framework of a PQS that is appropriate and proportionate e.g.
  - This PQS should be a general system (encompassing all products) such as organisation, quality policy, general documentation e.g. procedures, records, decisions, archiving
  - At a product specific level facilitates a comprehensive understanding of development that feeds into manufacturing



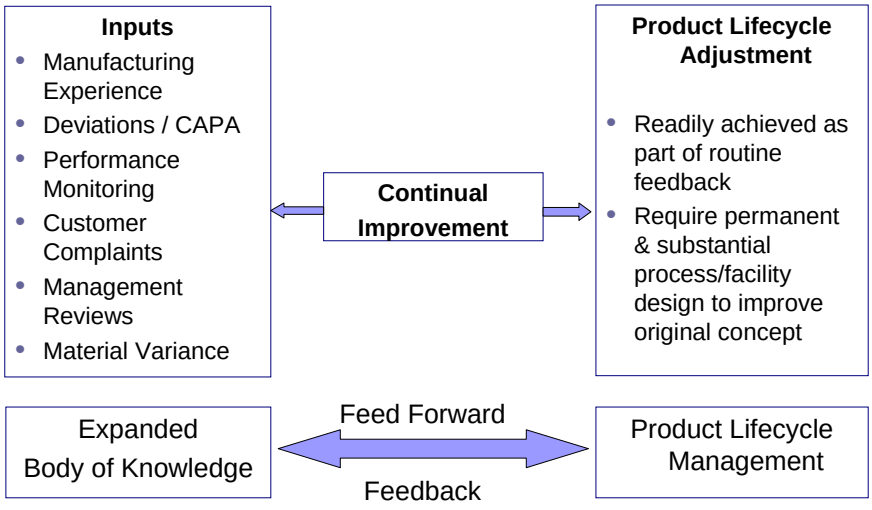
PQS and Product Lifecycle
Example from case study

- Using QRM as an enabler the PQS ensured
  - The Quality Risk Management processes were performed at key stages by involvement of the right technical disciplines
  - Selection of appropriate tools respecting the different aspects of the QRM process and appropriate training
  - Defined and documented processes as required in the PQS
  - Appropriate management review
- The knowledge gained during the development process was captured and shared with manufacturing



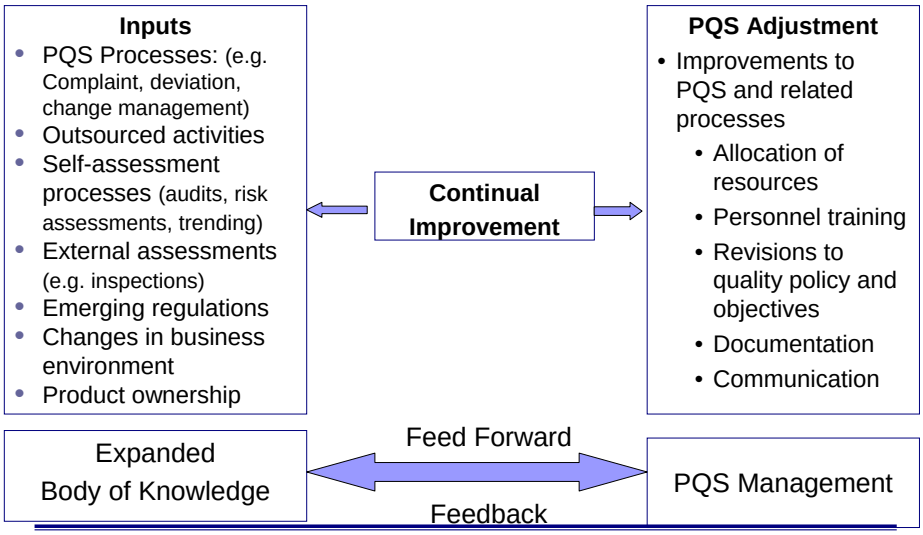
Breakout C: Pharmaceutical Quality System

Continual Improvement of the Product



Breakout C: Pharmaceutical Quality System

Continual Improvement of the PQS



Continual Improvement of Legacy Products

- ICH Q9 and Q10 can on their own bring advantages to legacy products
  - Traditionally developed, and extensive QC laboratory testing
- Most companies/sites manufacture legacy products and there are significant advantages to continually improve
  - Principles of ICH Q8, Q9, Q10 can be equally applied to these
    - To improve products and process understanding
    - To improve product quality and reduce waste (e.g. rejects)
    - To reduce process variability
    - To include RTRT to reduce lead times and QC testing
- There are challenges of introducing and new technologies (e.g. RTRT) to older products
  - More data = possible risk of uncovering problems/issues

Continual Improvement of Legacy Products

- However, industry must be encouraged to improve legacy products and processes
  - No sense to stay working with old technology and ways of working
  - PQS has to be able to deal with the knowledge gained from Continual Improvement of legacy products
- Industry can work with regulators to consider and control the risks
  - The regulators will encourage and support companies who want to improve legacy products and processes
  - Dialogue will be welcomed

Topics to discuss (1)

- Is a PQS mandatory? Is ICH Q10 mandatory?
- What is the added value for a company in implementing an ICH Q10 type PQS across the life cycle?
- What modifications to a company's existing PQS is envisaged to meet ICH Q10 intentions?
- How can Q10 type PQS facilitate in handling an enhanced development approach?
- How might a PQS support continual improvement?
- What do you see as the top 3 'high risk' elements that are managed by a PQS?
- Are there any barriers to practical implementation of an ICH Q10 type PQS?

Topics to discuss (2)

- Which PQS elements do you think are most useful in a development site?
- Is it necessary to describe PQS elements in regulatory submission (Q-CTD)?
- What is important in a PQS at the global/corporate level and at the local/site level?
- What are the key elements to settle before designing a PQS ?

Implementation of ICH Q8, Q9, Q10

Breakout D
Quality Risk Management

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICH

Introduction

- Structure of this session
  - Discussion of key messages on QRM
  - Examples from the Case Study
  - Wrap up
    - Feedback on barriers to implementation
    - Feedback on issues where further clarification is required
  - Breakout report

ICH

Goals of this Breakout

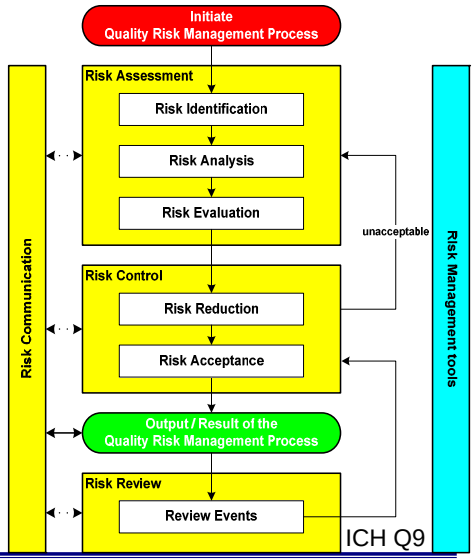
- Facilitate understanding of the QR**Management** process
  - Using example of the case study describe the QRM process
  - Ability to use the QRM process cycle in your organisation i.e. Development, Assessment, Manufacturing, Inspections / Audit
- Facilitate understanding of the linkage between QRM and knowledge management
- Feedback to Q-IWG

Key Message - Why use QRM?

Use of QRM can improve the decision making processes from development, technical transfer, manufacturing, post approval changes and throughout the entire product life cycle

Key Messages

- Quality Risk Management is the full process
- Quality Risk Assessment, Control, Review etc. represent only individual steps



Key Messages

- QRM is an iterative process and not a one off activity
- Utilisation of QRM activities should lead to a greater assurance of quality through risk control
  - Facilitate the awareness of risks
  - Risk does not go away
  - Risk can be predicted, prevented and controlled
- QRM processes should
  - Focus on what is important to establish the manufacturing process and controls and maintain them over the life cycle
  - Be integrated in Pharmaceutical Quality System elements

Key Messages

- QRM **used by company** can provide regulators with greater assurance of a company's product and process understanding and the ability to assure quality of manufactured products

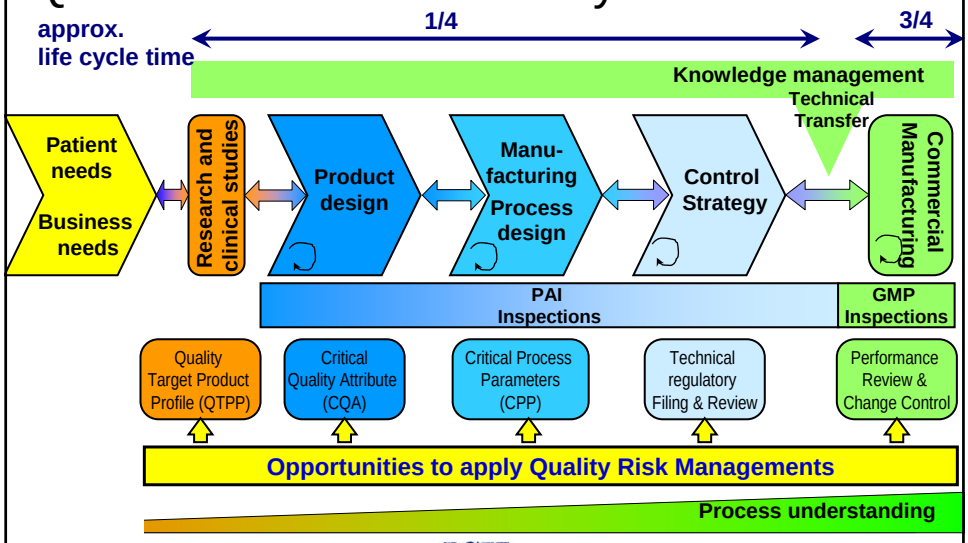
- QRM should be **used by regulators** (both assessors and inspectors) to guide regulatory activities independent of the industry utilisation of QRM

Key Messages

- **Regulators** should use QRM methods appropriately to reach rational and justified regulatory decisions e.g.

  - Risk based regulatory decisions (suspected quality defects etc.)
  - Assessment of regulatory filing
  - Planning and conducting of inspections
  - Prioritisation of inspection findings

QRM in the Product Life Cycle



Key Messages

Two **primary principles** of QRM are

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk

ICH Q9

Key Messages

- **Reduce subjectivity of implementing QRM by making sure the right people are at the table**
  (e.g. multi-discipline, include respective stakeholders, as applicable)
- **Use QRM methods appropriately and present the conclusions and justifications clearly**
  - Be clear and consistent in wording / terms used based on internationally agreed definitions
  - Transparency on the logic of the methodology and the decision making
  - QRM can not be used to justify failure
- **Use QRM proactively for increasing the knowledge of your product and processes**

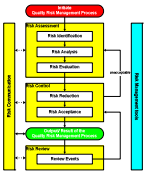
Linkage between QRM and Knowledge Management

Definition on Knowledge Management

Systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components

(ICH Q10)

Linkage between QRM and Knowledge Management



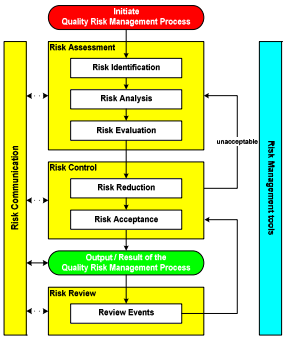
- Risk assessment as part of QRM in relation to knowledge management can be linked to
  - Identifying data to be collected (risk identification)
  - Analysing raw data (risk analysis)
  - Evaluating the results from measurement will lead to information (risk evaluation)
- New information should be assessed and the risk control decision captured (risk review and risk control)
- Knowledge management facilitates risk communication among stakeholders

Linkage between QRM and Knowledge Management

- In conjunction with QRM, Knowledge Management as systematic activity can facilitate e.g.
  - Usage of prior knowledge (including from other similar products)
  - Development, implementation and maintenance of the Design Space and Control Strategy
  - Technology transfer
  - Continual improvement of the product and manufacturing processes across its life cycle
  - Continual improvement of Quality System elements (including documentation)

Exercise

- Which QRM step the following examples belongs to?
  - You will see examples from the case study
  - Please discuss and suggest which steps of the QRM process those belong to



Which QRM step this example belongs to?

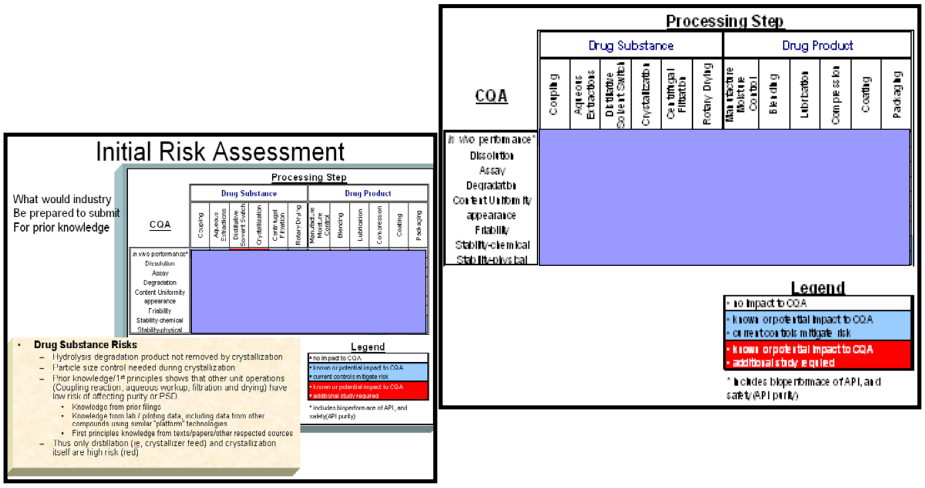
Design Space/Control Strategy
Parameter controls & Testing

CQA	Unit Operation	Parameter	Design Space	Comments
Particle Size	Crystallization	Temperature	20 to 30C	Control between 23 and 27C
Particle Size	Crystallization	Feed Time	5 to 15 hours	Control via flow rate settings
Particle Size	Crystallization	Agitation	1.1 to 2.5 m/s	Quality system should ensure changes in agitator size result in change to speed setting
Particle Size	Crystallization	Seed Wt%	1 to 2 wt%	Controlled through weigh scales and overcheck
Hydrolysis Degradate	Distillation / Crystallization	Water Content	< 1 wt%	Control via in process assay (e.g. < 0.5%)

Particle size will be tested in this example, since the result is included in the model used for dissolution.

Design space, but not normal operating parameter ranges, included in submission. Normal operating parameters free to move within design space to respond to business drivers

Which QRM step these examples belongs to?



On which step of the QRM process
you do not find an example in the case study?

Which QRM step this example belongs to?

Risk Assessment (FMEA): Purity Control

What is the **Impact** that ---------- will have on purity? 1) minimal 5) moderate 9) significant
What is the **Probability** that variations in ---------- will occur? 1) unlikely 5) moderately likely 9) highly likely
What is our **Ability to Detect** a meaningful variation in ---------- at a meaningful control point? 1) certain 5) moderate 9) unlikely

Unit Operation	Parameter	IMPACT PROB. Detect RPN	Comments
Distillative Solvent Switch	Temperature / Time, etc.		Distillation performed under vacuum, at low temperature, minimizing risk of hydrolysis
Distillative Solvent Switch / Crystallization	Water content at end of Distillation (Crystallization Feed)		Higher water = higher degradation In process control assay should ensure detection and
Crystallization -- API Feed Solution	Feed Temperature		Higher temperature = higher degradation Temperature alarms should enable quick detection and control
Crystallization -- API Feed Solution	Addition Time		Longer time = higher degradation Detection of prolonged addition time may occur too late to prevent some degradation
Crystallization	Seed wt percentage		This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.
Crystallization	Antisolvent percentage (charge ratio)		This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.
Crystallization	Crystallization temperature		Temperature is low enough that no degradation will occur.
Crystallization	Other crystallization parameters		These parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.

Which QRM step these examples belongs to?

Dissolution: Control Strategy

- **Controls of input material CQAs and CPPs**
  - API particle size
    - Control of crystallisation step
  - Magnesium stearate specific surface area
    - Specification for incoming material
  - Lubrication step blending time
    - Automated equipment timer
  - Compression force (or tablet hardness)
    - Tablet press force-feedback control system
    - (At-line weight-hardness-thickness testing)
- **Prediction Algorithm**
  - Use of algorithm potentially allows process to be adjusted for variation in API particle size, for example, and assure dissolution performance

Be sure that we have confirmed this approach with actual data

Key message: Control strategy for Dissolution CQA includes controls for raw material attributes and process parameters at multiple steps in the Drug Product and Drug Substance manufacturing processes

Batch Release Strategy

- Finished product not tested for lab tests for assay, CU and dissolution
- **Input materials** meet specifications and are tested
  - API PSD
  - Magnesium stearate specific surface area
- **Assay calculation**
  - Verify (API assay of blend by HPLC) X (tablet weight)
  - Tablet weight by automatic weight control (feedback loop)
    - For 10 tablets per sampling point, <2% RSD for weights
- Content Uniformity
  - On-line NIR criteria met for end of blending (blend homogeneity)
  - Tablet weight control results checked
  - Compression force is within the design space
- Dissolution
  - Predictive model using input and process parameters for each batch calculates dissolution meeting acceptance criteria
  - Input and process parameters used are within the filed design space
- Water content – NMT 3% in finished product (not covered in this case study)

Which QRM step this example belongs to?

Batch Release for API

- Test the final API
  - Hydrolysis degradate levels by HPLC
  - Additional quality tests not covered in case study
  - No particle size testing
    - In the case of the following drug product, it will be necessary to test since the particle size result is included in the model used for dissolution
- Verify that the crystallization parameters are within the design space
  - Temperature = 20 to 30 C
  - Seed charge = 1 to 2 wt%
  - Agitation = 1.1 to 2.5 m/s
  - Feed Rate = 5 to 15 hr

Which QRM step these examples belongs to?

Risk Assessment (FMEA): Purity Control

What is the **Impact** that ---------- will have on purity? 1) minimal 5) severe 9) significant
What is the **Probability** that variations in ---------- will occur? 1) unlikely 5) occasional 9) highly likely
What is our **Ability to Detect** a meaningful variation in ---------- at a meaningful control point? 1) certain 5) uncertain 9) unlikely

Unit Operation	Parameter	Impact	Probability	Detect	RPN	Comments
Distillative Solvent Switch	Temperature / Time, etc.	1	5	1	5	Distillation performed under vacuum, at low temperature, minimizing risk of hydrolysis
Distillative Solvent Switch / Crystallization	Water content at end of Distillation (Crystallization Feed)	9	5	1	45	Higher water = higher degradation In process control assay should ensure detection and
Crystallization -- API Feed Solution	Feed Temperature	9	5	1	45	Higher temperature = higher degradation Temperature alarms should enable quick detection and control
Crystallization -- API Feed Solution	Addition Time	9	1	5	45	Longer time = higher degradation Detection of prolonged addition time may occur too late to prevent some degradation
Crystallization	Seed wt percentage	1	1	1	1	This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.
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Crystallization	Crystallization temperature	1	5	1	5	Temperature is low enough that no degradation will occur.
Crystallization	Other crystallization parameters	1	1	1	1	These parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.

API Crystallization: Design Space/Control Strategy

- Control Strategy should address
  - Parameter controls (example below)
    - Include control of unstudied "high impact / low probability" parameter from risk assessment, since the risk assessment implies that the parameter is easily controlled
  - Testing
    - Final API will be tested for hydrolysis degradate with limit of NMT 0.3%
    - In this case, no routine testing of particle size since it is consistently controlled by the process parameters
- Batch release
- Quality systems (to be discussed in detail later)
  - Should be capable of managing changes within design space
  - Program lifecycle can result in future design space changes

Design space, but not normal operating parameter ranges, included in submission. Normal operating parameters free to move within design space to respond to business drivers.

Topics to Discuss

1. What is the benefit using QRM in development, assessment, manufacturing and/or inspection?
2. What are the expectations of the level of training and understanding for regulators and industry in order to use the methods appropriately?
3. How to link quality risk management to knowledge management?
4. What level of detail on QRM need to be included in a submission (general / case by case)?

Topics to Discuss

A. How can industry demonstrate the robustness of a QRM process?
   Aa) In regulatory filing?
   Ab) In manufacturing operations?

B. How does an assessor independently evaluate the company's risk management conclusion?

C. How could inspectors use QRM principles to align risk based decisions?

Feedback to ICH Q-IWG

- Are we clear with the key messages? Yes / No
- Are there practical concerns on implementation? (e.g. on harmonisation among regions needes, by region/local issue)
- Where is more clarification required for practical harmonised implementation?

Did we meet the goals?

- Facilitate understanding of the QR**Management** process
  - Using example of the case study describe the QRM process
  - Ability to use the QRM process cycle in your organisation i.e. Development, Assessment, Manufacturing, Inspections/Audit
- Facilitate understanding of the linkage between QRM and knowledge management
- Feedback to Q-IWG

Implementation of ICH Q8, Q9, Q10

Breakout D - Back up Quality Risk Management

Suggested answers on examples

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

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Which QRM step this example belongs to?

Design Space/Control Strategy

Parameter controls & Testing

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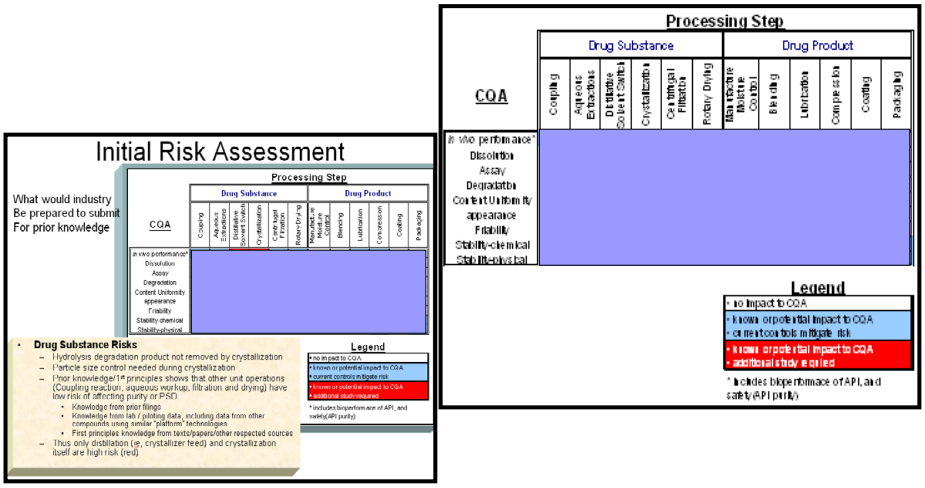
ICH *Risk reduction as part of risk control*

Which QRM step these examples belongs to?



ICH

Risk identification as part of risk assessment

On which step of the QRM process
you do not find an example in the case study?

Risk review
It should be in PQS elements and it's review
No risk review may lead to reactive Change Management topics

ICH

Which QRM step this example belongs to?

Risk Assessment (FMEA): Purity Control

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ICH

Risk analysis as part of risk assessment

Which QRM step these examples belongs to?

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ICH

Risk communication
External: submission
Internal: technical transfer process

Which QRM step this example belongs to?

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