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

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.

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

Goals of this Breakout

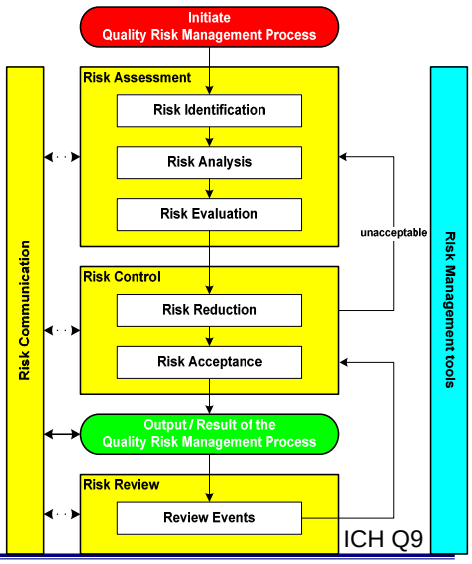
- Facilitate understanding of the QR**Management** process
  - Using example of the case study describe the QRM process
  - Ability to use the QRM process cycle in your organisation i.e. Development, Assessment, Manufacturing, Inspections / Audit
- Facilitate understanding of the linkage between QRM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

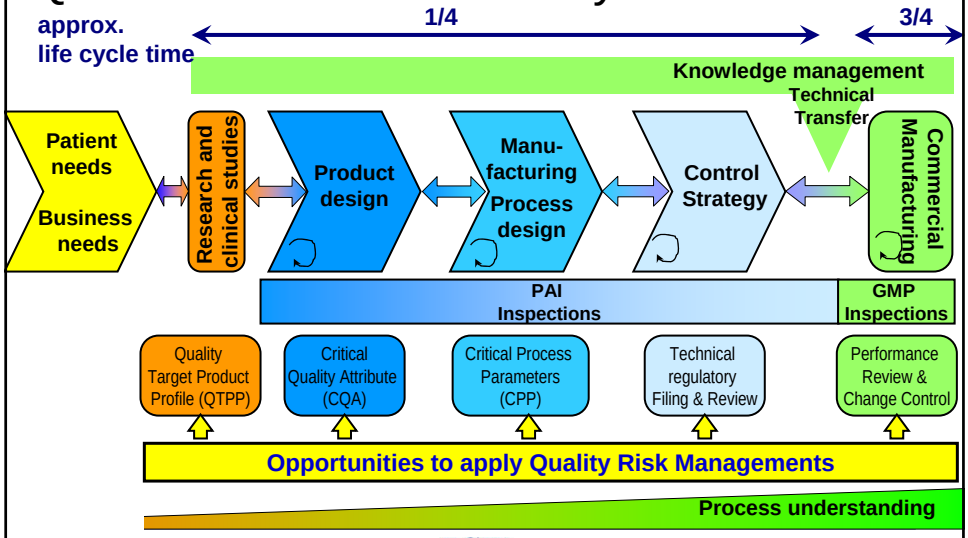
Key Messages

- 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**

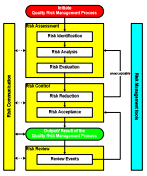
Linkage between QRM and Knowledge Management

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



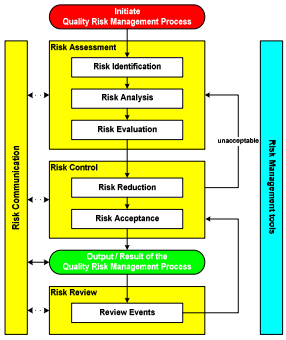
- Risk assessment as part of QRM in relation to knowledge management can be linked to
  - Identifying data to be collected (risk identification)
  - Analysing raw data (risk analysis)
  - Evaluating the results from measurement will lead to information (risk evaluation)
- New information should be assessed 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?

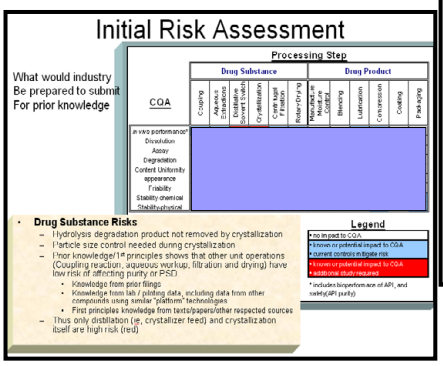
Design Space/Control Strategy
Parameter controls & Testing

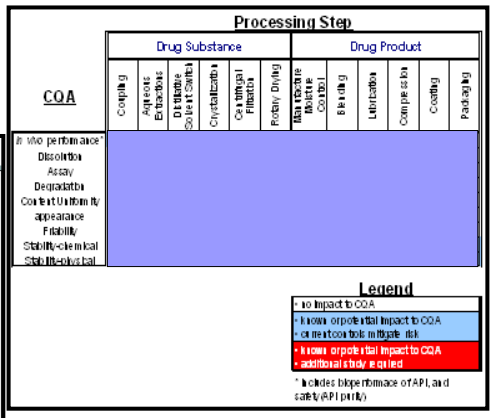
CQA	Unit Operation	Parameter	Design Space	Comments
Particle Size	Crystallization	Temperature	20 to 30C	Control between 23 and 27C
Particle Size	Crystallization	Feed Time	5 to 15 hours	Control via flow rate settings
Particle Size	Crystallization	Agitation	1.1 to 2.5 m/s	Quality system should ensure changes 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.
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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

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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

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 D - Back up Quality Risk Management

Suggested answers slide 17-23

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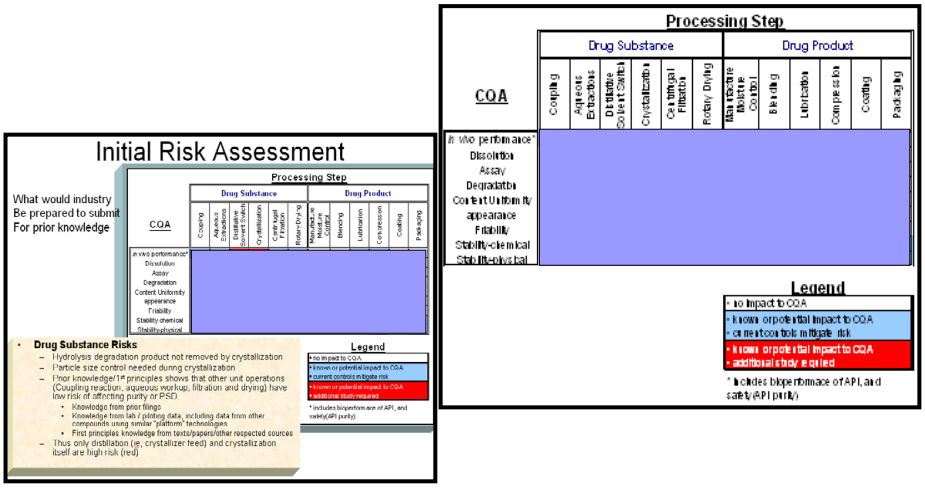

Risk identification as part of risk assessment

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

Which QRM step this example belongs to?

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Risk analysis as part of risk assessment

Which QRM step these examples belongs to?

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Risk communication
External: submission
Internal: technical transfer process

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ICH *Risk acceptance as part of risk control*

Which QRM step these examples belongs to?

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ICH *Risk evaluation as part of risk assessment*

Implementation of ICH Q8, Q9, Q10

Breakout: D
Quality Risk Management Discussions

Stephan Rönninger
Diana Amador-Toro

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

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  - Douglas Kovacs
  - Sharon Thoma
- Industry:
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  - Brett Duersch
  - Emabelle Ramnarine
  - Jeff Huth

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Disclaimer

General on this presentation

- Feedback from the facilitated discussions
- See it as a brainstorming from the breakout discussions

Principal feedback

- **Cultural change needed**
  - New paradigm not yet fully implemented
  - The evolution from training to education on the new paradigm
  - Ongoing collaborative dialog between all stakeholders (e.g. regulator & industry, assessors & inspectors, development and manufacturing)
  - Balance level of detail in submissions while enabling trust between regulators and industry

Principal feedback

- **Both regulator and industry are on a learning curve**
  - Regional differences between and within regulatory agencies and industry in terms of guidance vs. expectation
  - Best practice sharing / Case study / Guidance helpful
    (e.g. what to submit so that industry and regulator work to the same expectations)
- **QRM focuses on patient harm** including product availability
  - There are also other types of non-quality risk management activities e.g. business, EH&S etc.

Are we clear with the key messages? Yes / No

Mostly

- The level of implementation experience with QRM is increasing
- However approx. 60 % have little experience with using QRM methodologies *(Tallinn)*
- Open issues around QRM:
  Need to be clear what 'risk review' is *(Tallinn)*

How to deal with QRM in submissions?

- **Little experience overall**
- **Misalignment of "perceived" expectations: Not clear on level of detail expected**
  - QRM during development vs.QRM tools
- **Consistency needed**
  - Discussions for common understanding
    (e.g. training, discussions, internal harmonization of tools)
- **Need enough information to 'tell the story' behind the decisions and convey process understanding**

How to deal with QRM in submissions?

Specifics: What is the level of documentation required?

- Will a robust /scientific/patient focused "good job" suffice?
- If something unusual / does not follow normal expectations, then it needs a detailed explanation
- Do we just submit knowledge rich submissions/ files, or in the case of QRM do we need to submit more data?
- What goes in the file, what should be available at site for review during inspection?
- In a country that adopts ICH guidance and in a country that does not follow ICH guidance
- More clarity required as to where QRM information is placed in the submission - In which part of the CTD?
- If a legacy product has a change (using QRM)?
- Prior Knowledge Summary in the submission?
- Should the Risk Assessment approach be described?
- Some assessors seem to require a full FMEA within the submission, others do not (regional concern)?
- "Worst case" information to be included?
- What type of risk assessment changes require resubmission (if part of the dossier)?

Are there **practical concerns** on implementation?

(e.g. on harmonisation among regions needed, by region/local issue)

Open issues around QRM

- How can QRM be included within the company's PQS elements?
- Will approvals or inspections get more difficult by adding QRM approaches?
- How can QRM knowledge be communicated to the right stakeholders in a consistent and timely manner?
- What is the difference between Risk Reduction and Control Strategy? *(Tallinn)*

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Breakout D: Quality Risk Management

Are there **practical concerns** on implementation?

(e.g. on harmonisation among regions needed, by region/local issue)

Open issues around QRM techniques

- Early interactions between development, manufacturing and other disciplines as applicable during the QRM process
- Integrate QRM as part of Business Management Systems (not PQS only) or it will become a burden
- Implementation is resource intensive
  (concern for smaller companies)
  - Resource allocation for QRM activities
  - Consider long term benefits

Are there **practical concerns** on implementation?

(e.g. on harmonisation among regions needed, by region/local issue)

Open issues around QRM techniques

- **How to implement knowledge management?**
- **Converting data -> information -> knowledge -> understanding**
  - How to capture this in written instructions (PQS)
- **Tools for knowledge management**
  - How to capture (prior) knowledge and assumptions in risk assessments?
  - Older IT systems do not support knowledge management
- **Time sensitivity around knowledge sharing**

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Breakout D: Quality Risk Management

Are there **practical concerns** on implementation?

(e.g. on harmonisation among regions needed, by region/local issue)

Open issues around QRM techniques

- **Regardless of the risk assessment tool focus on the justification for the QRM decision**
  - Rank order is more important than the actual score
  - Rationale for the risk acceptance decision needed
- **Options on selection of other appropriate QRM tools beside FMEA**
  - Pros and Cons on individual tools might help
  - Qualitative tools may be better suited in some cases

Are there **practical concerns** on implementation?

(e.g. on harmonisation among regions needed, by region/local issue)

- **Senior management support is critical for QRM implementation**
  - Allocation of necessary resources
  - Understanding and buy-in for QRM
  - Link QRM application to financial benefits and other risk management procedures
- **Level of documentation and rationale for 'non-critical' (?) parameters**
- **Cumulative impact of changes to multiple non-critical parameters**

Where is more **clarification required** for practical harmonised implementation?

- **QRM expectations**
  - How to apply to legacy products?
  - Case studies for application to different product types (e.g. biotech)
  - Is there a different 'lower' expectation of QRM for generic industry / generic products? *(Tallinn)*
- **Balance of data / information / knowledge / understanding needs to be understood and defined for submissions**

Where is more **clarification required** for practical harmonised implementation?

- **Interface and responsibility for regulators**
  - Accessibility and communication of information between inspectors and assessors
  - Assessor / Inspector: Who decides what? *(Tallinn)*
  - Having a reviewer at the pre-approval inspection can be very helpful *(Washington)*
- **Working near the "edge of failure" (high risk)**
  - Is a more robust control strategy needed than when working in the core of the design space? *(Tallinn)*

ICH Quality Implementation Working Group - Integrated Implementation Training Workshop
Breakout D: Quality Risk Management

Where is more **clarification required** for practical harmonised implementation?

- **Implementation of QRM for contractors / suppliers when they support different companies**
  - Difference in access to information / knowledge at contractors versus suppliers
- **Variability in risk acceptance decisions**
  - Severity dominates risk acceptance decisions
  - Inconsistency in acceptability of residual risks

Where is more **clarification required** for practical harmonised implementation?

- **Consistency in training and application**
  - e.g. Investigators and reviewers / assessors among the different regulatory agencies
  - Several examples of QRM tool application by different regulatory agencies (e.g. FDA, PIC/S, MHRA etc.)
- **More descriptive, but not prescriptive**
  - Guidance versus allowing flexibility of interpretation

Best practice

- **QRM may be used as a systematic process**
  - Independent of enhanced development approaches as an integral part of the PQS
- **Feedback regarding expectations**
  - Pre-meetings between assessors and industry will be useful to facilitate understanding of the needs for specific products
- **Sharing experience and lessons learned within and between industry and regulators is desired**
  - Use of experienced QRM facilitators avoids wasted effort
  - Workshops like the ICH Q-IWG training