Implementation of ICH Q8, Q9, Q10

Quality Risk Management

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

Introduction

- Structure of this session
  - Goal & Key messages
    - 15 min
  - Discussion in sub groups
    - 80 min
  - Breakout report
    Clarity on key messages, Concerns, Need for clarification, Feedback
    - 25 min

Goals of this Breakout

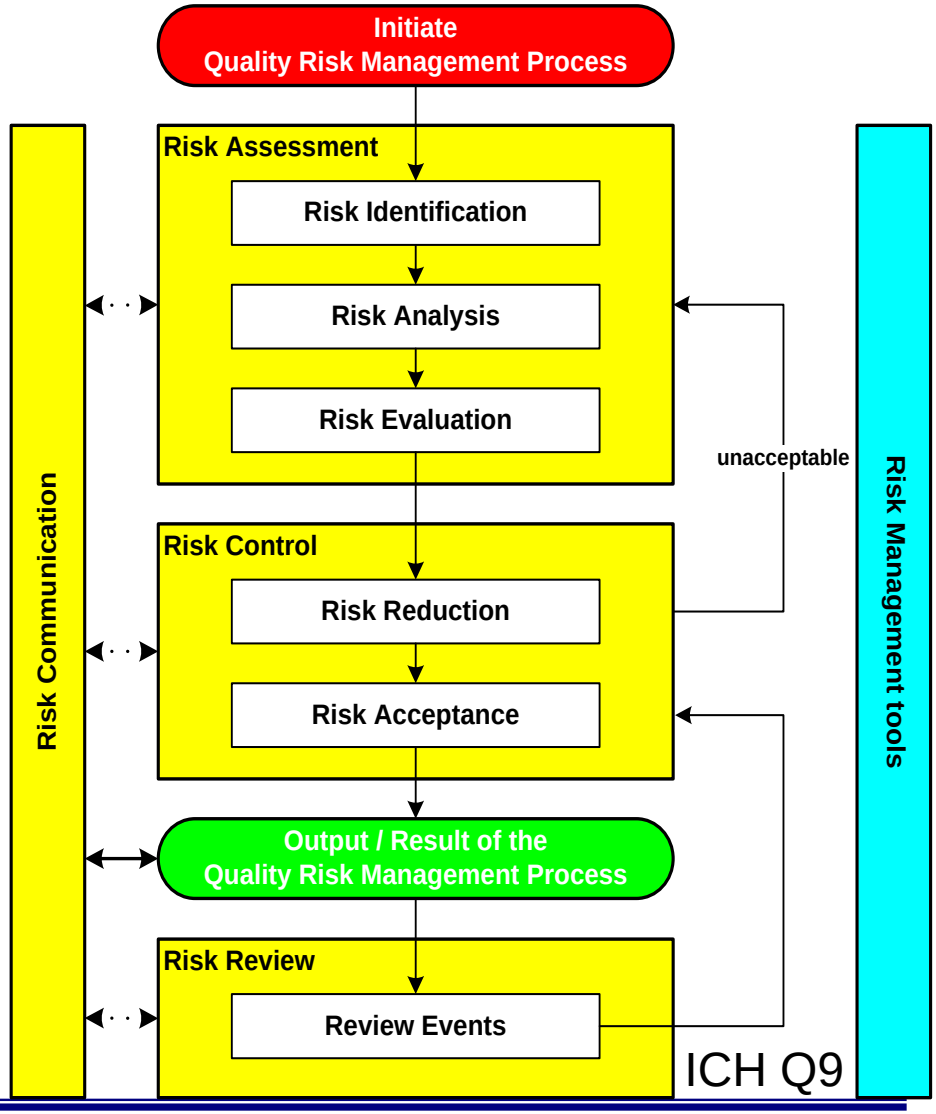
- Facilitate understanding of the QR**Management** process
  - Using example of the case study describe the QRM process
  - Ability to use the QRM process cycle in your organisation i.e. Development, Assessment, Manufacturing, Inspections / Audit
- Facilitate understanding of the linkage between QRM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

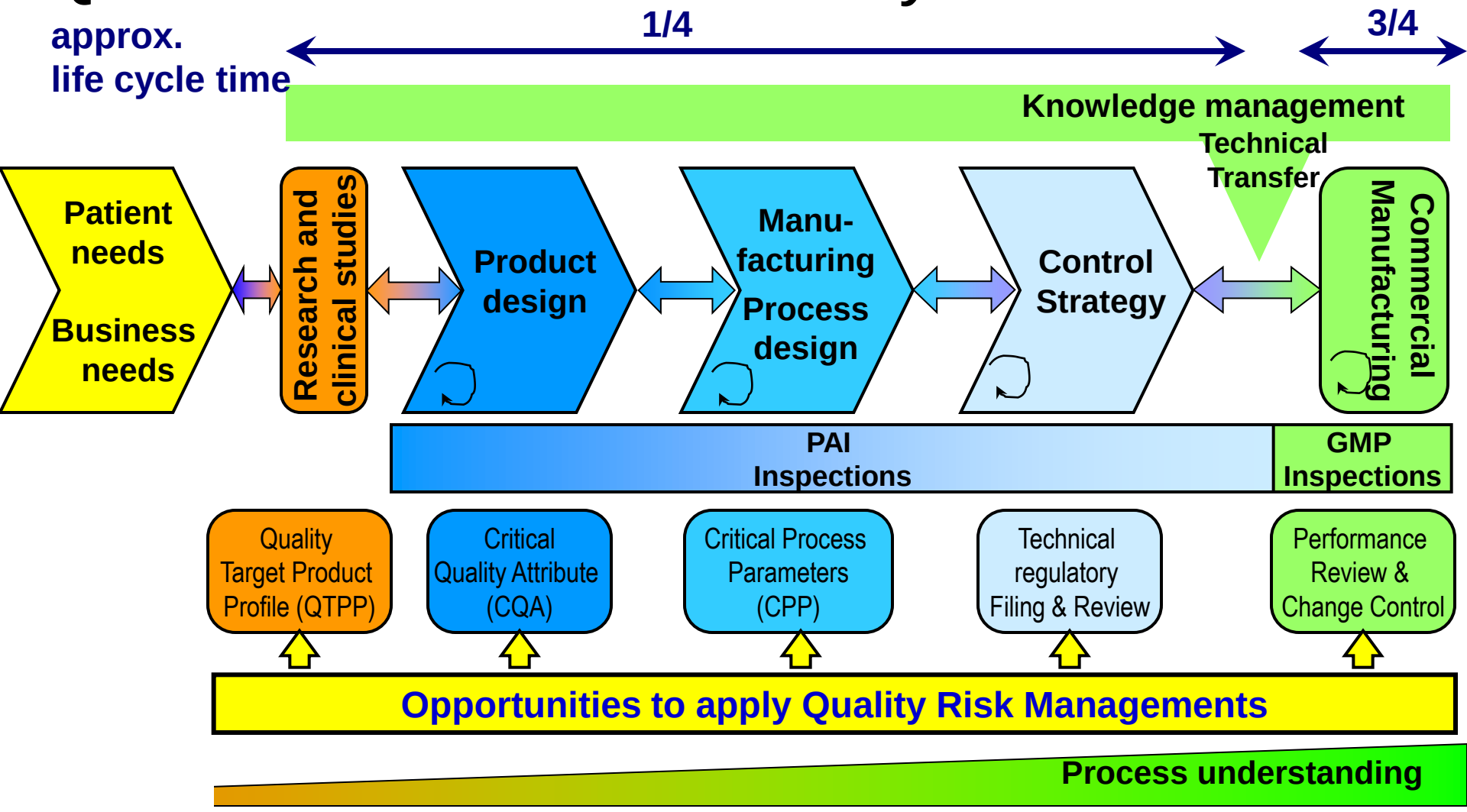
- QRM **used by company** can provide regulators with greater assurance of a company's product and process understanding and the ability to assure quality of manufactured products

- 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**

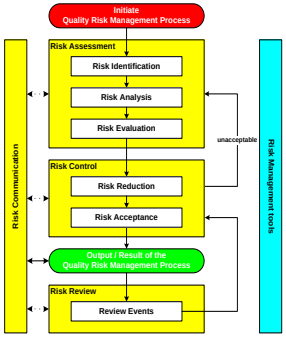
Linkage between QRM and Knowledge Management

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)

Breakout in sub-teams

- Assessors
- Inspectors
- Manufacturing
- Development
- Others

Topics to discuss in the sub teams

- Introduce yourself and tell your expectation for this QRM breakout

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.

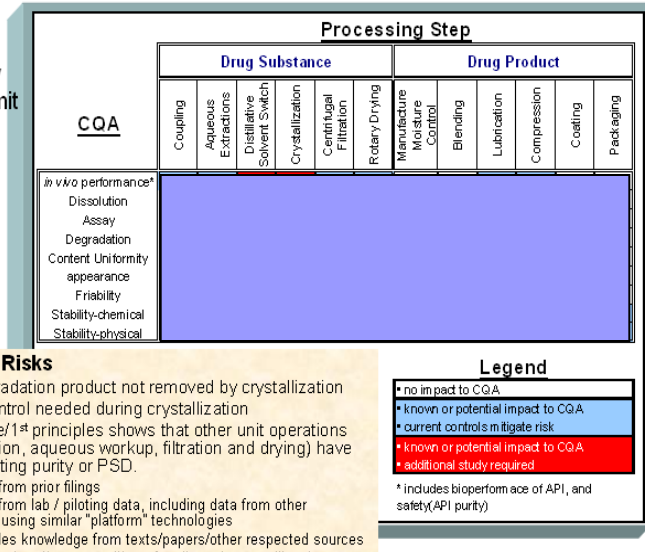
Design space, but not normal operating parameter ranges, included in submission. Normal operating parameters free to move within design space to respond to business drivers

Breakout D: Quality Risk Management

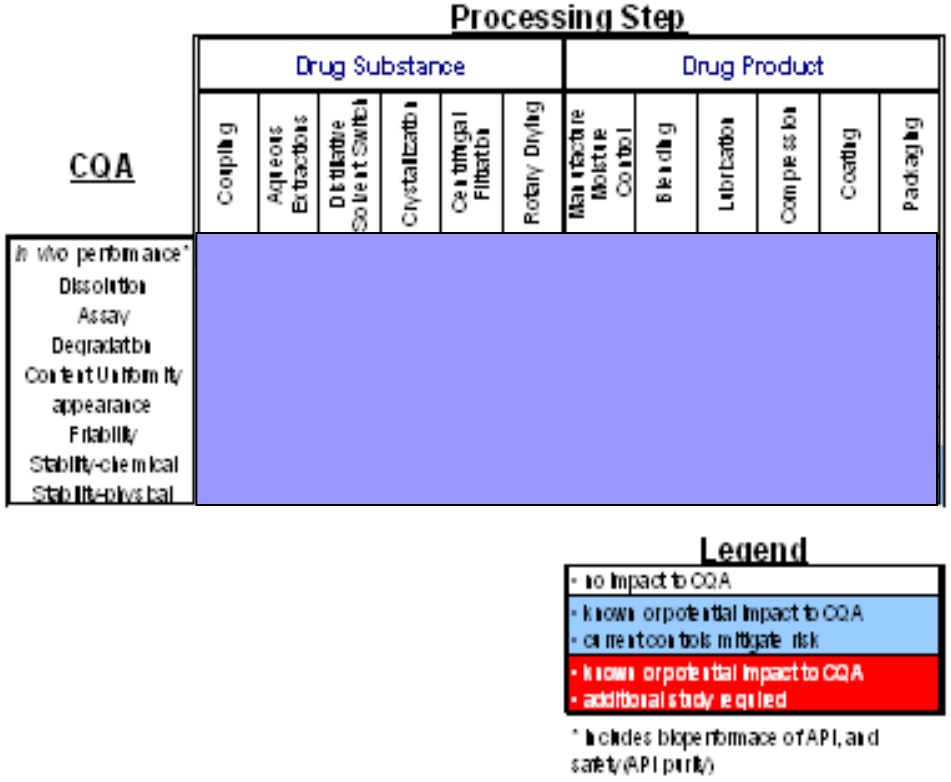
Which QRM step this example belongs to?

What would industry
Be prepared to submit
For prior knowledge

Initial Risk Assessment



- **Drug Substance Risks**
  - Hydrolysis degradation product not removed by crystallization
  - 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
  - Thus only distillation (ie, crystallizer feed) and crystallization itself are high risk (red)



Breakout D: Quality Risk Management

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

Which QRM step this example 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 this example belongs to?

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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 is 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 companies 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 needed, 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
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