Quality Risk Management in the Manufacture of Advanced Therapy Medicinal Products

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Quality Risk Management

ICH Q9 Guideline

- Manufacturing and use of medicinal products necessarily entails some degree of risk
- Commonly understood that risk is defined as the combination of the probability of occurrence of harm and the severity of that harm
- Protection of patients by managing quality risks is of prime importance
  - Maintain quality attributes throughout the lifecycle of a medicinal product consistent with those used in the clinical studies
  - Risk to its quality is just one component of the overall risk
- Achieving shared understanding of risk management among diverse *stakeholders* is challenging
  - Different perceptions of potential harms
  - Different perception of probability of each harm occurring
  - Attribute different severities to each harm

Quality Risk Management

ICH Q9 Guideline

- Effective quality risk management contributes to ensuring medicinal product quality
  - Proactive means to identify and control potential quality issues during development and manufacturing
  - Improve decision making in the event that a quality problem arises
  - Provide regulators with greater assurance of a company's ability to deal with potential risks
  - Beneficially affect extent and level of direct regulatory oversight
- Not always appropriate or necessary to use formal risk management processes (recognized tools, SOPs)
  - Informal risk management (empirical tools/ internal procedures) can also be acceptable
- Appropriate use of quality risk management can facilitate compliance but does not obviate regulatory requirements or replace appropriate communication with regulators

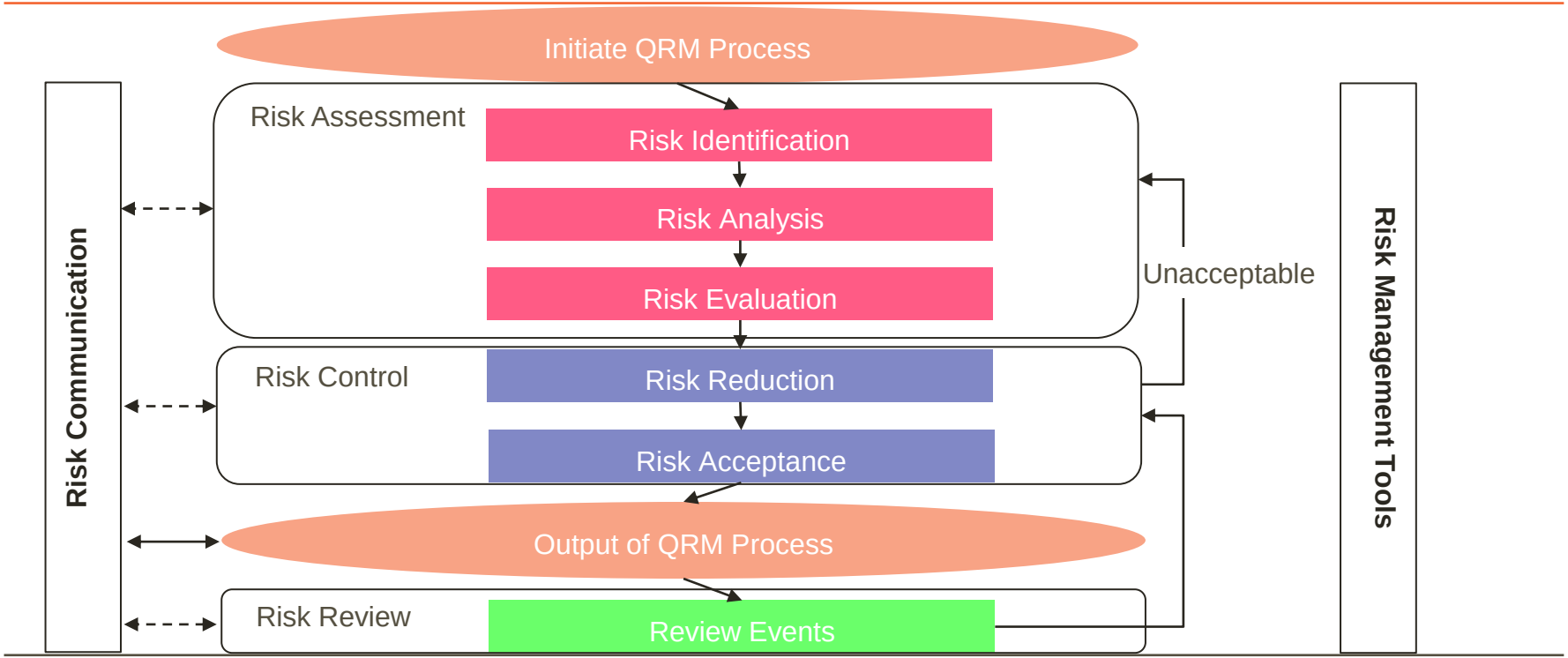
Quality Risk Management

ICH Q9 Guideline

- Two primary principles of quality risk management are:
  - Evaluation of risks 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
- Quality risk management is a systematic process to assess, control, communicate and review risks to quality of the medicinal product across the product lifecycle

Quality Risk Management

ICH Q9 Guideline



Quality Risk Management

ICH Q9 Guideline

- QRM activities usually undertaken by multidisciplinary teams
  - E.g quality, engineering, regulatory affairs, production operations, sales, legal, statistics and clinical
  - The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk
- Decision makers
  - Coordinating QRM across functions/ departments
  - Assure that a QRM process is defined, deployed, reviewed and resourced
- Steps taken include
  - Define the problem/ risk question, including pertinent assumptions identifying the potential for risk
  - Assemble background information on potential hazard, harm or human health impact
  - Identify a leader and necessary resources
  - Specify timeline, deliverables and decision making for the risk management process

Risk Assessment

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- Identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards
- Begin with a well-defined problem description or risk question
  - When the risk in question is well defined, appropriate risk management tools and information needed to address the risk question will be more readily identifiable
- Three fundamental questions are often helpful
  - What might go wrong?
  - What is the likelihood (probability) it will go wrong?
  - What are the consequences (severity)?

Risk Identification
Risk Analysis
Risk Evaluation

Risk Control

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- Decision making to reduce and/ or accept risks
- The purpose is to reduce the risk to an acceptable level
- Focus on the following questions:
  - Is the risk above an acceptable level?
  - What can be done to reduce or eliminate risks?
  - What is the appropriate balance among benefits, risks and resources?
  - Are new risks introduced as a result of the identified risks being controlled?
- **Risk reduction** focuses on processes for mitigation or avoidance of quality risk when it exceeds an acceptable) level
- **Risk acceptance** can be a formal decision to accept residual risk or a passive decision in which residual risks are not specified

Risk Communication and Review

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- **Risk communication** is the sharing of information about risk and risk management between the decision makers and stakeholders
  - Regulators and industry, industry and the patient, within a company, industry or regulatory authority
- The output/result of the quality risk management process should be appropriately communicated and documented
- Information communicated might include existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality
- **Risk Review** quality management process should be ongoing and include a mechanism to review or monitor events
  - Planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall)
- Output/results of the risk management process should be reviewed to take into account new knowledge and experience
- Frequency of any review based on level of risk

Risk Management Tools

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- Risks to quality assessed and managed in a variety of informal ways
  - Empirical and/ or internal procedures
  - Compilation of observations and trends
  - May support topics such as handling of complaints, quality defects, deviations and allocation of resources
- Additional recognized risk management tools may be employed
  - Basic risk management facilitation methods (flowcharts, check sheets etc.)
  - Failure Mode Effects (and Criticality) Analysis (FMEA)/FMECA List individual failure modes and score according to effect on process (severity, probability)
  - Fault Tree Analysis (FTA) hierarchy of causes that individually or jointly determine failure modes
  - Hazard Operability Analysis (HAZOP) identify deviations in highly industrialised processes
  - Preliminary Hazard Analysis (PHA) characterized by semi-quantitative criticality judgments
  - Risk ranking and filtering
  - Supporting statistical tools

ATMP Manufacture

Application of Risk Based Approach

- ATMPs are complex products with risk differing according to product type
  - Nature/ characteristics of the starting materials
  - Level of complexity of the manufacturing process
- Variability in finished product due to the use of biological materials and/or complex manipulation steps
  - Cell culture
  - Manipulations that alter function of the cells
- Strategies implemented to ensure quality of autologous/ donor matched allogeneic ATMPs must account for constraints in manufacturing process
  - Limited batch sizes
  - Inherent variability of starting materials

ATMP Manufacture

Application of Risk Based Approach

- ATMPs are innovative products addressing high unmet need, often requiring new manufacturing models to ensure supply
  - Development in hospital/academic setting with different quality systems to those used for conventional medicinal products
  - Decentralised manufacture of autologous cell therapies (particularly short shelf-life products)
- Require a certain level of flexibility in order to implement control measures appropriate to the characteristics of the manufacturing process and product
- Knowledge of products and manufacturing processes in clinical development is often limited
  - Flexibility is therefore even more important for investigational ATMPs

ATMP Manufacture

Application of Risk Based Approach

- The risk-based approach (“RBA”) is applicable to all type of ATMPS and permits the manufacturer to design the organisational, technical and structural measures that are put in place to ensure quality
  - According to the specific risks of the product and the manufacturing process
  - RBA allows flexibility, but manufacturer is responsible for control measures necessary to address the specific risks of the product and the manufacturing process
- Principles of ICH Q9 applicable
  - Evaluation of the risks and the effectiveness of the control/mitigation measures should be based on current scientific knowledge and accumulated experience
  - Level of effort and documentation commensurate with the level of risk
  - RBA can facilitate compliance but does not obviate obligation to comply with requirements and demonstrate adequate management of risk to product/ process
  - Does not replace appropriate communication with authorities

Risk Based Approach

Authorised vs Investigational ATMPs

- Quality control of investigational ATMPs intended to protect clinical trial subjects and ensure reliability of clinical trial results
  - Ensure quality and consistency of the product
  - Ensure results of the clinical trial are not affected by unsatisfactory manufacturing
  - Ensure changes to the product during development are adequately documented
- Also ensures that data obtained from early phases of a clinical trial can be used in subsequent phases of development
- Product quality to be ensured from start of development
  - Acknowledged that there is a gradual increase in the knowledge of the product
  - Corresponding level of effort to ensure quality will step up gradually; control methods are expected more refined during later stages of clinical trials
- Responsibility for application of RBA is that of manufacturer
  - Agency advice should be sought regarding implementation (pre-submission dialogue as needed)
  - Clinical trial authorisation application should explain quality strategy when RBA is applied

Risk Based Approach

Authorised vs Investigational ATMPs

- For authorised ATMPs application of RBA should be consistent with terms of the marketing authorisation
  - Description of manufacturing process/ process controls in license application account can account for specific characteristics of the product/ process
  - Justify deviation from standard expectations
- Strategy to address specific limitations in manufacturing process should be agreed as part of license application and may include:
  - Control of raw and starting materials, facilities and equipment, tests and acceptance criteria, process validation, release specifications, stability data
- For aspects not specifically covered by the CTA/ license, manufacturer documents reasons for the approach implemented when RBA applied
  - Justifies measures are adequate to ensure product quality

Example of RBA Application

Raw Materials

- Requires understanding of role of raw material in the manufacturing process and of the properties of raw materials key to the manufacturing process and final product quality
- Account for risk of raw material due to its intrinsic properties
  - Growth factors *vs* basic media
  - Culture media containing cytokines *vs* basal media without cytokines
  - Raw material from animal origin *vs* autologous plasma
- Account for risk of raw material use in the manufacturing process
  - Higher risk if raw material comes into contact with the starting materials
- Assess whether control sufficient to eliminate risks or mitigate to an acceptable level
  - Qualification of suppliers
  - Performance of suitable functional testing

Example of RBA Application

Testing Strategy

- In some cases it may not be possible to perform release tests on the active substance or the finished product
  - Product needs to be administered immediately after completion of manufacturing
  - Amount of available product is limited to the clinical dose
- In such cases alternative testing strategies considered
  - Testing of key intermediates instead of finished product
  - In-process controls instead of release testing, if relevance to CQAs of finished product demonstrated for these tests
  - Real time testing of short shelf-life products
  - Increased reliance on process validation (which may require enhanced validation approach)
  - Completion of release testing after product administration (may require additional mitigation, for example when applied to sterility testing)
  - Waive elements of ongoing stability testing for short shelf-life products

Example of RBA Application

Minimal Manipulation

- Manufacturing processes of ATMPs may not involve substantial manipulation of cells/tissues
  - Lower risk than the manufacture involving complex substantial manipulations
- Cannot infer that processes that not qualified as “substantial manipulation” are risk-free
  - E.g processing of cells entails long exposure to the environment
- Analysis of risks of the specific manufacturing process should be performed to identify appropriate product quality control measure
- Facilities validated to process cells/tissues for transplantation purposes in accordance with appropriate standards (e.g EU blood/tissue directives) need not being validated again
- Elements of GMP not specifically addressed under other legislative frameworks still apply
  - Product characterisation, setting adequate specifications, process validation

Additional Considerations

Investigational ATMPs

- Additional adaptations in the application of GMP may be justified for investigational ATMPs, whilst ensuring quality, safety and traceability of the product in clinical trials
- During early (phase I and I/II) clinical studies when the manufacturing activity is very low, calibration, maintenance and inspection of facilities and equipment should be performed at appropriate intervals
  - May be based on risk-analysis
  - Suitability for of all equipment should be verified before use
- Formality and detail of documentation can be adapted to stage of development
  - The traceability requirements should be implemented in full
- During clinicial studies specifications can be based on wider acceptance criteria
  - Taking account of the current knowledge of risks and as approved by the competent authority