COMBINATION PRODUCTS SUMMIT

FT. WORTH, TX • NOVEMBER 28–30, 2023

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Combination Products Risk Management

Integration of ICH Q9(R1) & ISO 14971:2019

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AFDO RAPS HEALTHCARE PRODUCTS COLLABORATIVE

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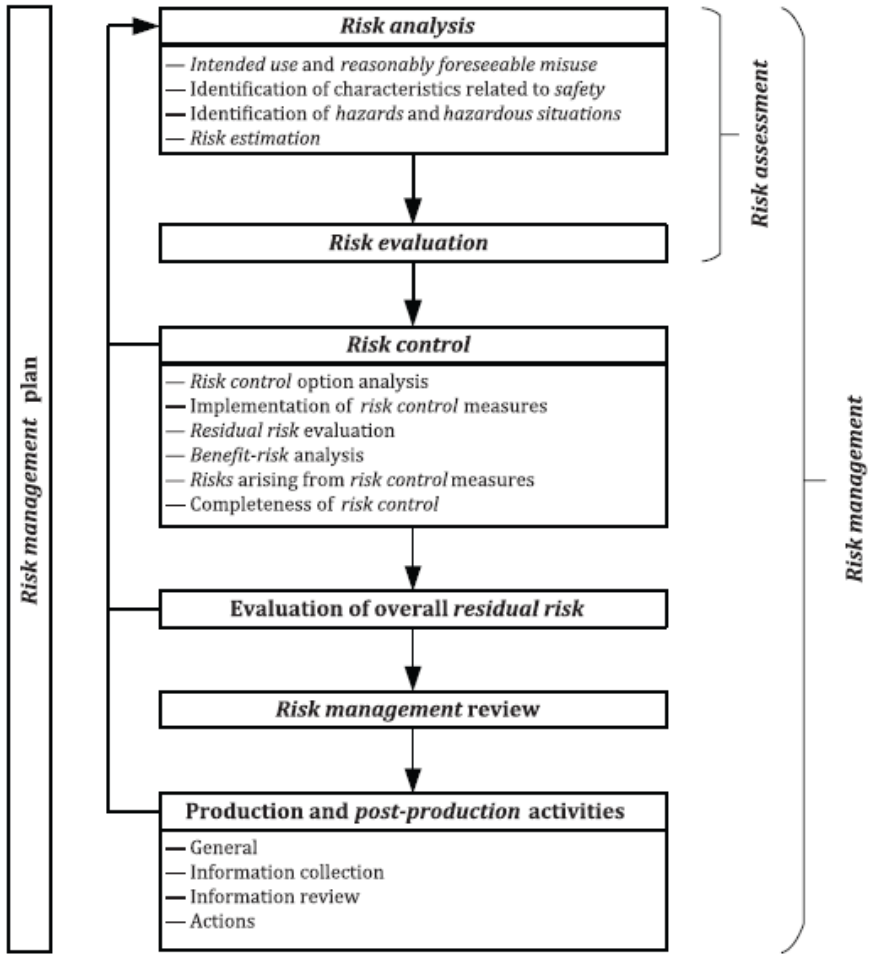
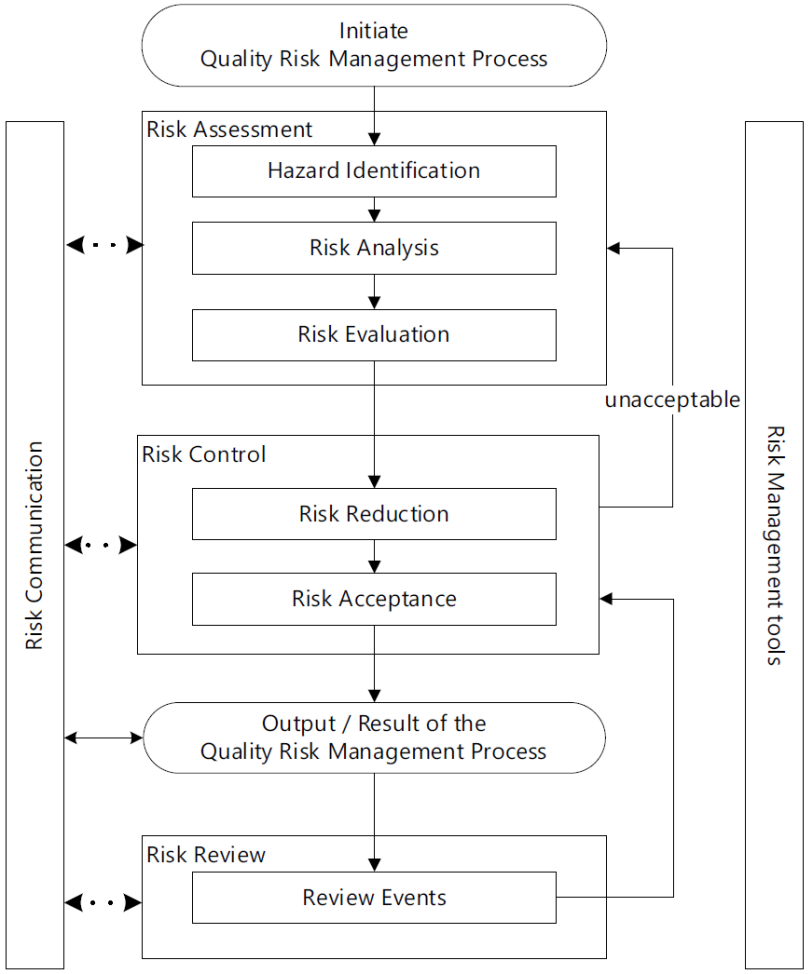
ISO 14971:2019 *vs.* ICH Q9(R1)

Similarities, Nuances & Differences

Overview



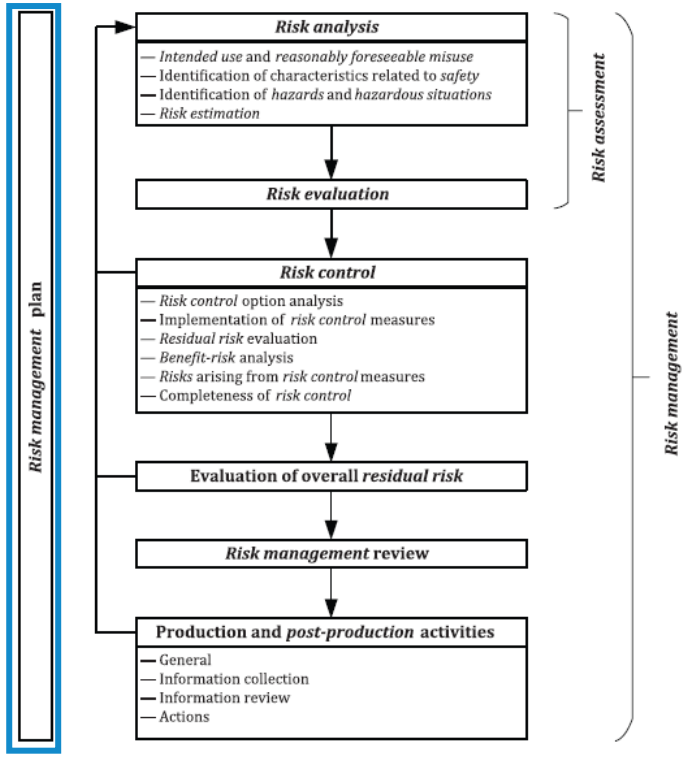
ISO 14971:2019

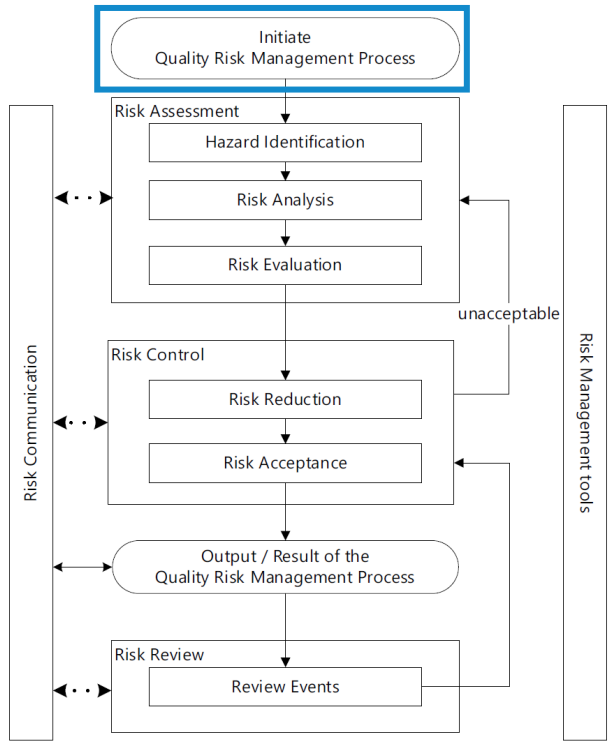


ICH Q9(R1)

Planning

- Requires a risk management plan.
  - Scope of planned activities
  - Assignment of responsibilities & authorities
  - Method of evaluating and criteria for acceptability of overall residual risk
  - Verification activities
  - Activities related to collection and review of production & post-production information
- Retained in Risk Management File.



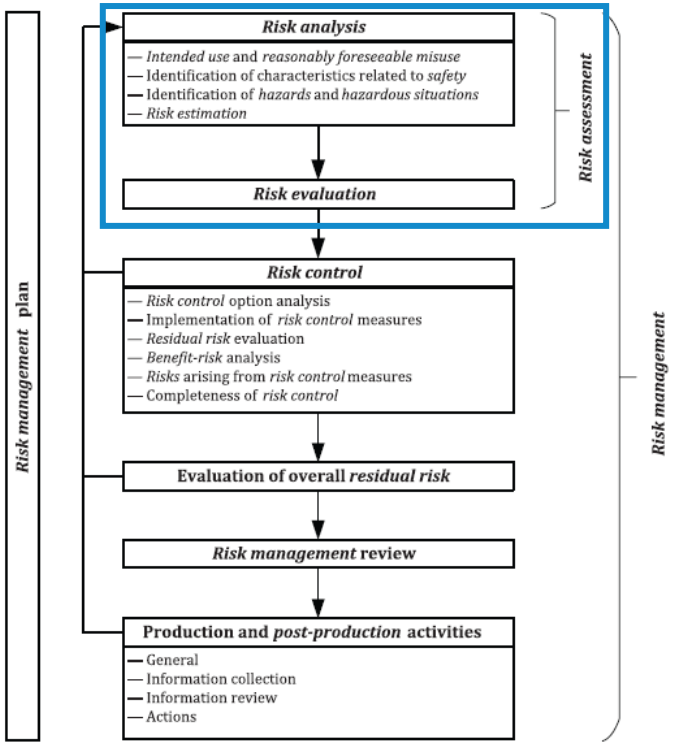


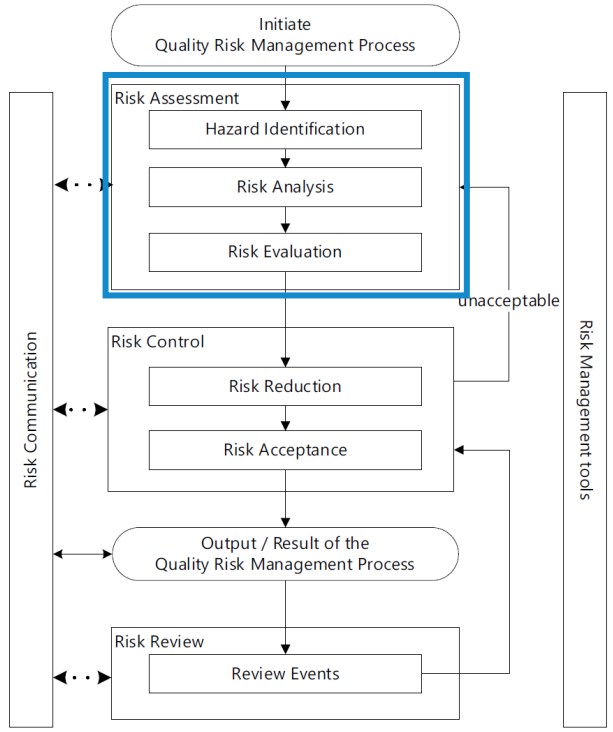
- Does not require plan as process step.
- Process starts with defined problem or question.
- Assessment of formality required.
- No requirement for Risk Management File.

- Scope of risk management activities documented.
- Definition of risk criteria and specification of acceptable levels.

Risk Assessment

- Document intended use, characteristics affecting safety & reasonably foreseeable misuse.
- Identification of hazards in normal & fault modes.
- Hazardous situation defined as a term.
- Probability of occurrence can be decomposed into P1 and P2.



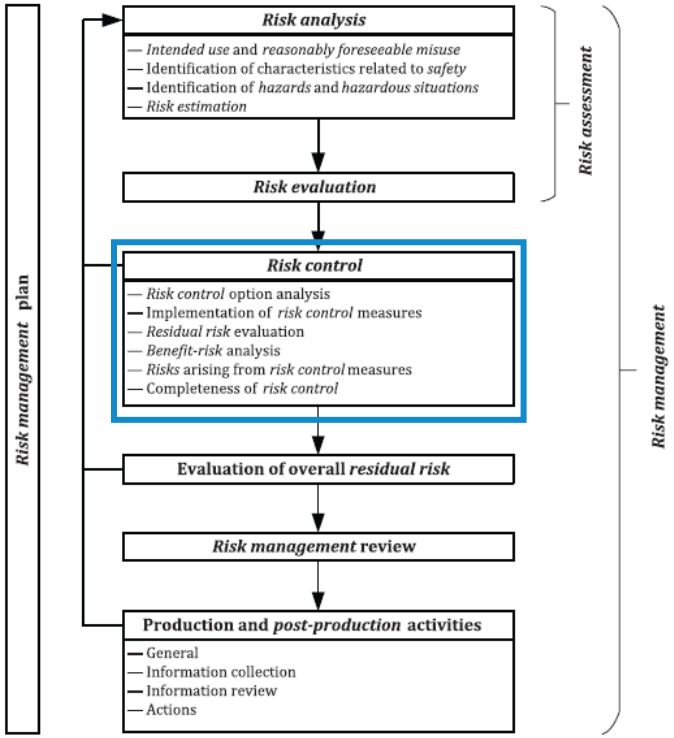


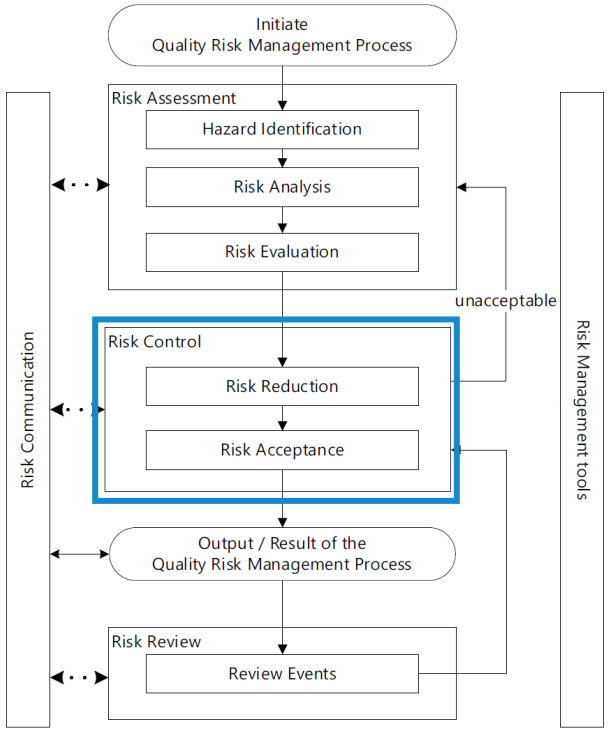
- Requires well-defined problem description or risk question. What might go wrong?
- No use of the term hazardous situation.

- Identification of hazards.
- Evaluation of risks associated with exposure to hazards.
- Severity and occurrence used as factors to determine the level of risk
- Level of risk evaluated against documented criteria.

Risk Control

- Risk control option analysis.
  - Inherent safety by design
  - Protective measures
  - Information for safety
- Verification of implementation of risk control measures.
- Verification of effectiveness of risk control measures.
- Specification of individual residual risks.
- Benefit risk analysis.



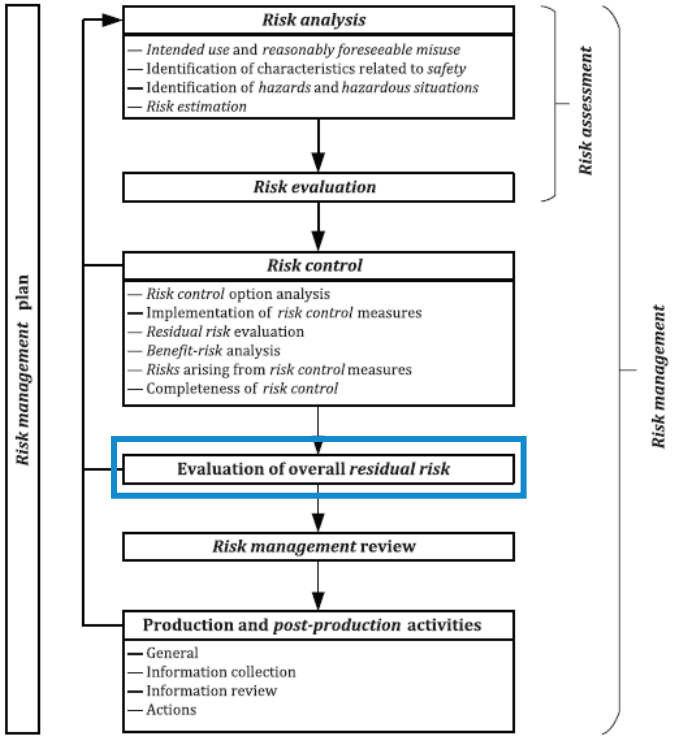


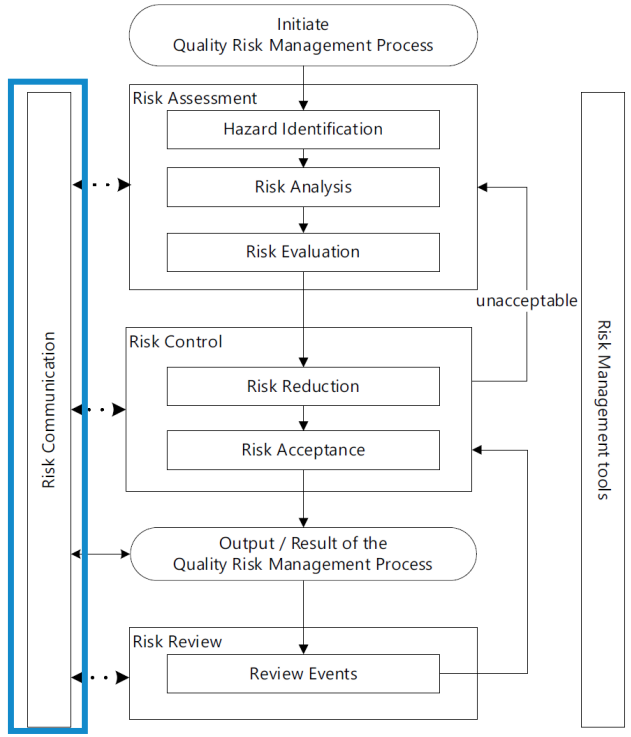
- Focus on decision making to reduce and accept risks.
- Effort to reduce risk proportional to the level of risk.
- Acceptance of risk can be formal or passive.

- Reduction of severity and occurrence.
- Assessment of whether risk control measures lead to further risks or significance of existing risks.
- Reduction of risk to an acceptable level.

Overall Residual Risk & Risk Communication

- Determination of benefit/risk ratio.
  - Benefits of intended use
  - Contribution of residual risks
  - Risk control hierarchy
  - Clarity of IFU
  - Results of Design Validation, Clinical Evaluation etc.
  - Literature
  - Generally acknowledged start of the art
- Generation of Risk Management Summary Report.



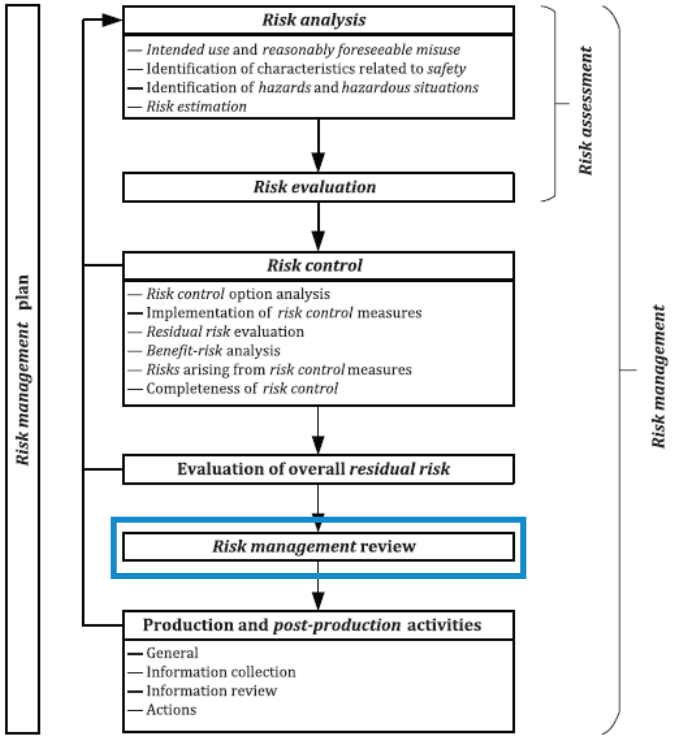


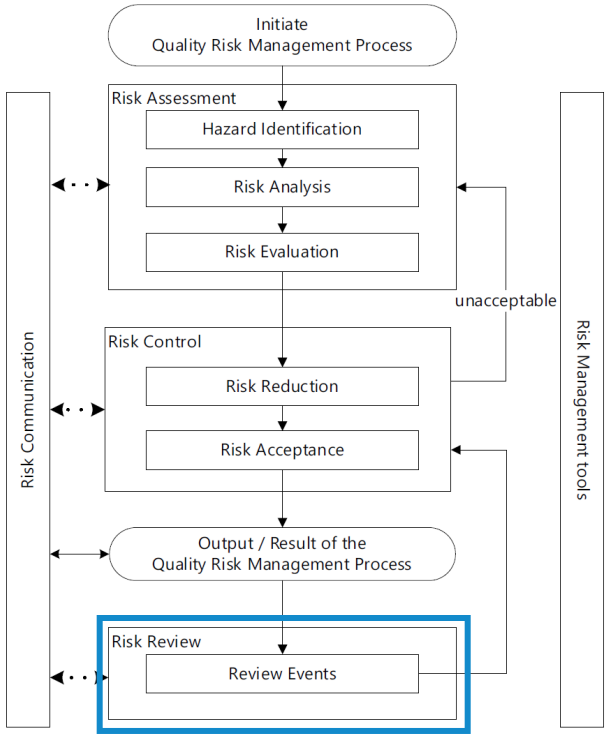
- Effort to reduce risk proportional to the level of risk.
- Acceptance of risk can be formal or passive.
- Focus on balance between benefits, risks and resources.
- Communication of information to decision makers.

- Output of risk management process appropriately documented.
- Disclosure of residual risks to regulators and the patient/user.

Risk Management Review

- Review of the execution of the Risk Management Plan prior to commercial launch.
- Agree on acceptance of overall residual risk.
- Agreement of methods to collect and review production and post-production information.



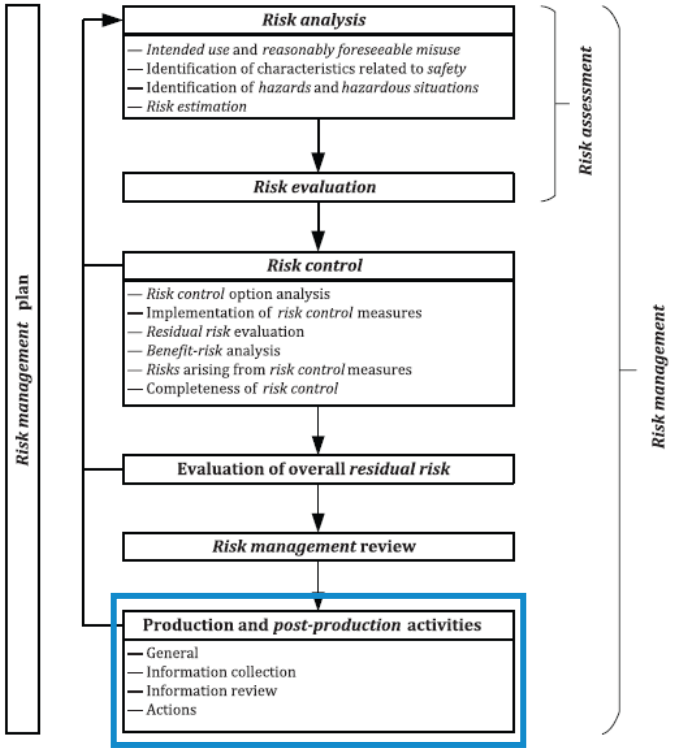


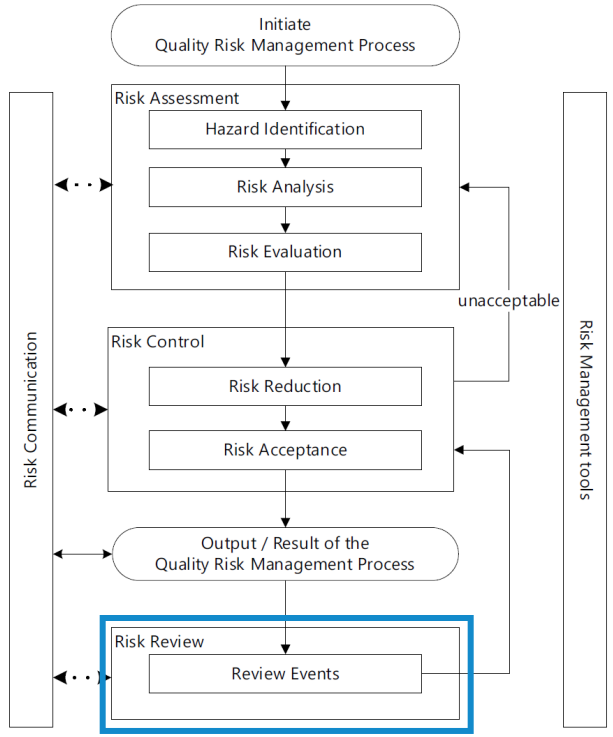
- Outputs of QRM process communicated in individual reports.
- Frequency of review determined based on level of risk.
- May involve reconsideration of original acceptance decision.

- Outputs of risk management reviewed and monitored as new knowledge about and experience with risks are gained.

Production & Post-Production Activities

- Requirements for information collection, information review and follow on actions.
- Need to be in place prior to commercial launch.





- Statement on use of QRM process for events on original decision.
  - Planned
  - Unplanned

- Review of risks over the lifecycle of the product.
- Methods for review of risks need to be implemented.
- Periodic monitoring of the acceptance of risk levels.

Merging The Two Approaches

Combination Product Risk Assessments

AAMI TIR105:2020 Approach

ISO 14971 – Medical Devices – Application of Risk Management to Medical Devices

AAMI TR105 – Risk Management Guidance for Combination Products

ICH Q9(R1) – Quality Risk Management

Risk Management Plan

Risk Analysis
- Intended use and reasonably foreseeable misuse.
- Identification of characteristics related to safety.
- Identification of hazards and hazardous situations.
- Risk estimation.

Risk Evaluation

Risk Control
- Risk control option analysis.
- Implementation of risk control measures.
- Residual risk evaluation.
- Benefit-risk analysis.
- Risks arising from risk control measures.
- Completeness of risk control.

Evaluation of Overall Residual Risk

Risk Management Review

Production and Post-Production Activities
- General.
- Information collection.
- Information review.
- Action.

Risk Assessment

Drug Device Interaction Risks
- Dose delivery.
- Effect of delivery device on drug product CQAs.
- Effect of drug product on delivery device.
- Minimization of medication errors.

Risk Communication

Initiate Quality Risk Management Process

Risk Assessment
- Hazard Identification
- Risk Analysis
- Risk Evaluation

Risk Control
- Risk Reduction
- Risk Acceptance

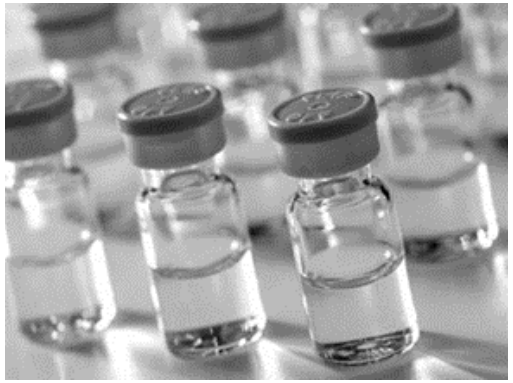
Unacceptable

Output/Result of the Quality Risk Management Process

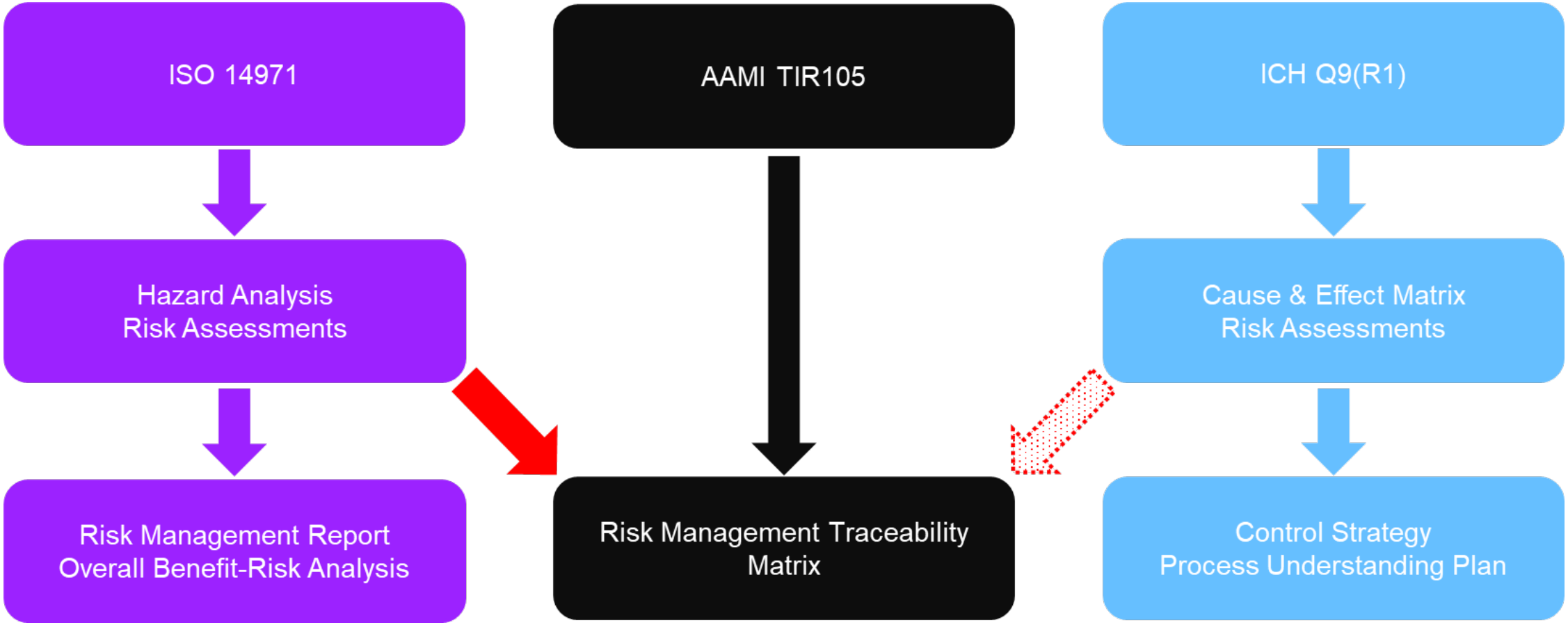
Risk Review
- Review Events

Risk Management Tools

Risk Management Traceability Matrix



Current Situation



Linking Drug & Device Risk Assessments

Attribute Score	
Score	**Description**
10	**Established or expect a direct impact on safety and/or efficacy of product.**
7	Moderate or indirect impact on safety and/or efficacy. Direct impact on efficiency.
5	Low or unlikely impact to product safety and/or efficacy. Moderate or indirect impact efficiency.
1	No impact to product safety and/or efficacy. Low or unlikely to impact efficiency.

Common terms	Possible description
Catastrophic / Fatal	Results in death
Critical	Results in permanent impairment or irreversible injury
Serious / Major	Results in injury or impairment requiring medical or surgical intervention
Minor	Results in temporary injury or impairment not requiring medical or surgical intervention
Negligible	Results in inconvenience or temporary discomfort

ISO 14971:2019 – Medical Devices – Application of Risk Management to Medical Devices

Hazard	Hazardous Situation	Harm	Severity of Harm
Chemical & Biological Hazards			
Biological Agents (Bacteria, Viruses, Fungi & Parasites)	Administration of biological agent into the patient.	Death.	Catastrophic (S5)
		Systemic infection (sepsis), permanent impairment or life-threatening/irreversible injury.	Critical (S4)
		Localized infection, abscess, systemic effects, requiring medical/surgical intervention.	Serious (S3)
		Localised infection, not requiring medical intervention.	Minor (S2)

Hazard Analysis

Cause & Effect Matrix

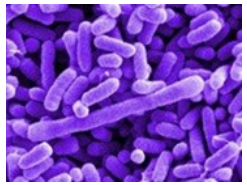
Critical Quality Attributes
Critical Process Parameters

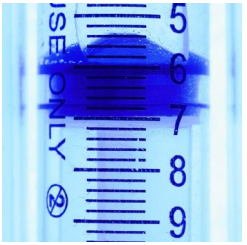
Process FMEA

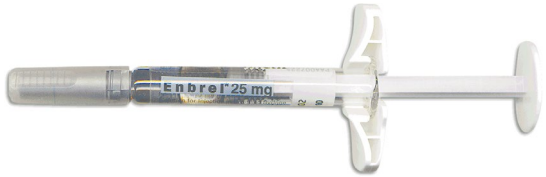
Risk Management
Traceability Matrix

Relationship Score	
Score	**Relationship**
10	**Known of expected strong relationship.**
5	Known or expected medium or low relationship.
1	Known that there is no relationship.

CQA	Hazard
Visible Particles	Chemical Agents - Particles
Subvisible Particles	
Concentration	Delivery - Quantity
Sterility	Biological Agents
Immunogenicity	Immunological Agents – Allergenic Substances
Deliverable Volume	Delivery - Quantity
Potency	Functionality – Critical Performance



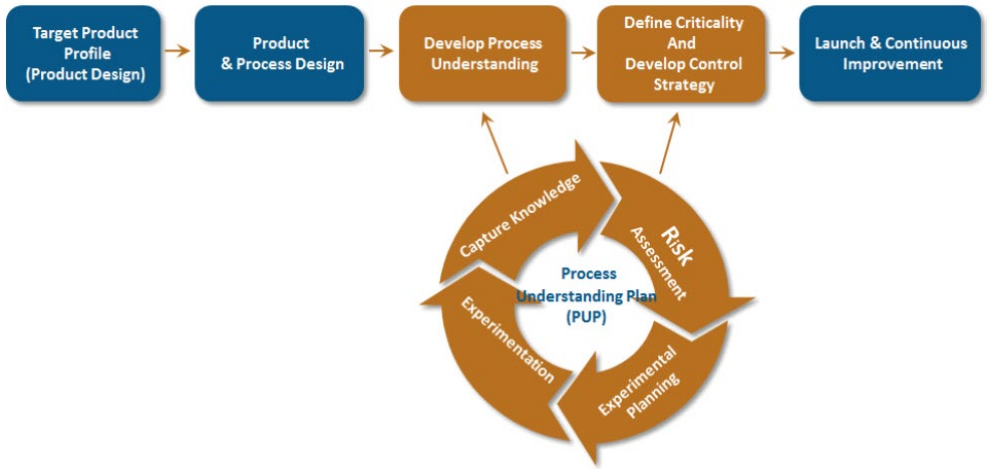


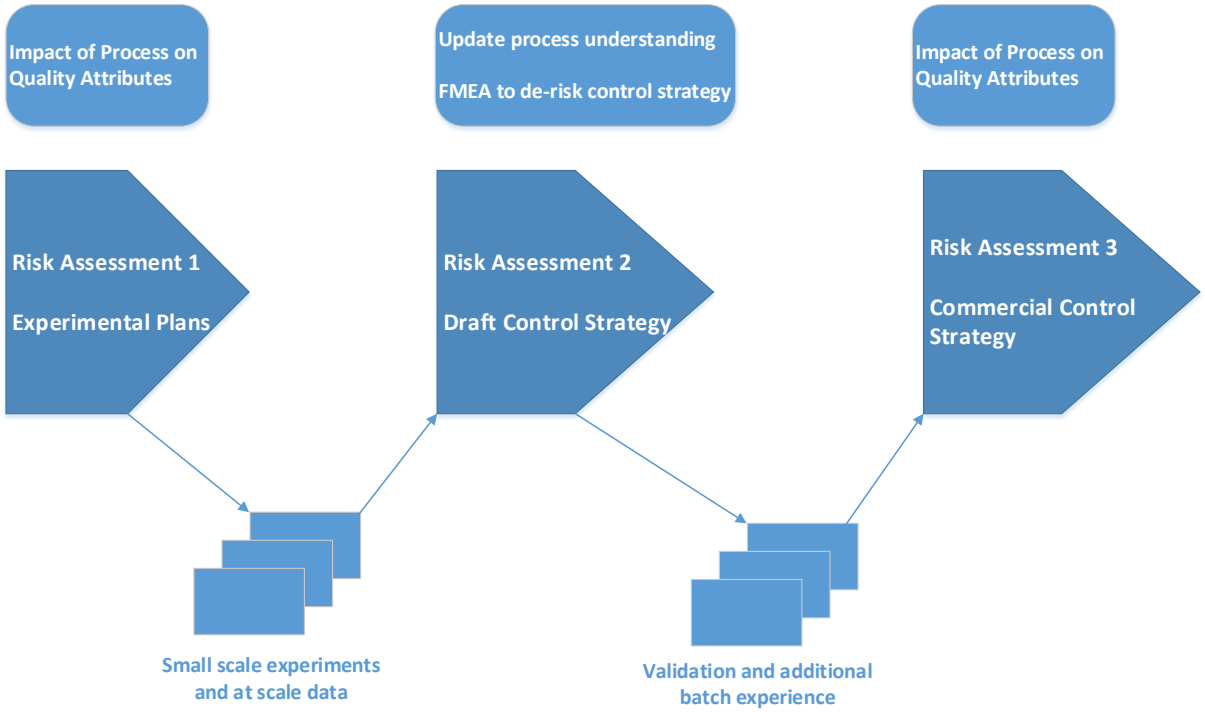


Identification of DP Hazards & Hazardous Situations

DP Critical Quality Attribute	Equivalent Hazard	Hazardous Situation
Bioburden	Biological Agents	Administration of biological agent into the patient
Sterility	Biological Agents	Administration of biological agent into the patient
Immunogenicity	Immunological Agents – Allergenic Substances	Administration of allergenic substance
Deliverable Volume	Delivery – Quantity	Partial dose
Potency	Functionality – Critical Performance	Administration of drug product that is not fully homogenized

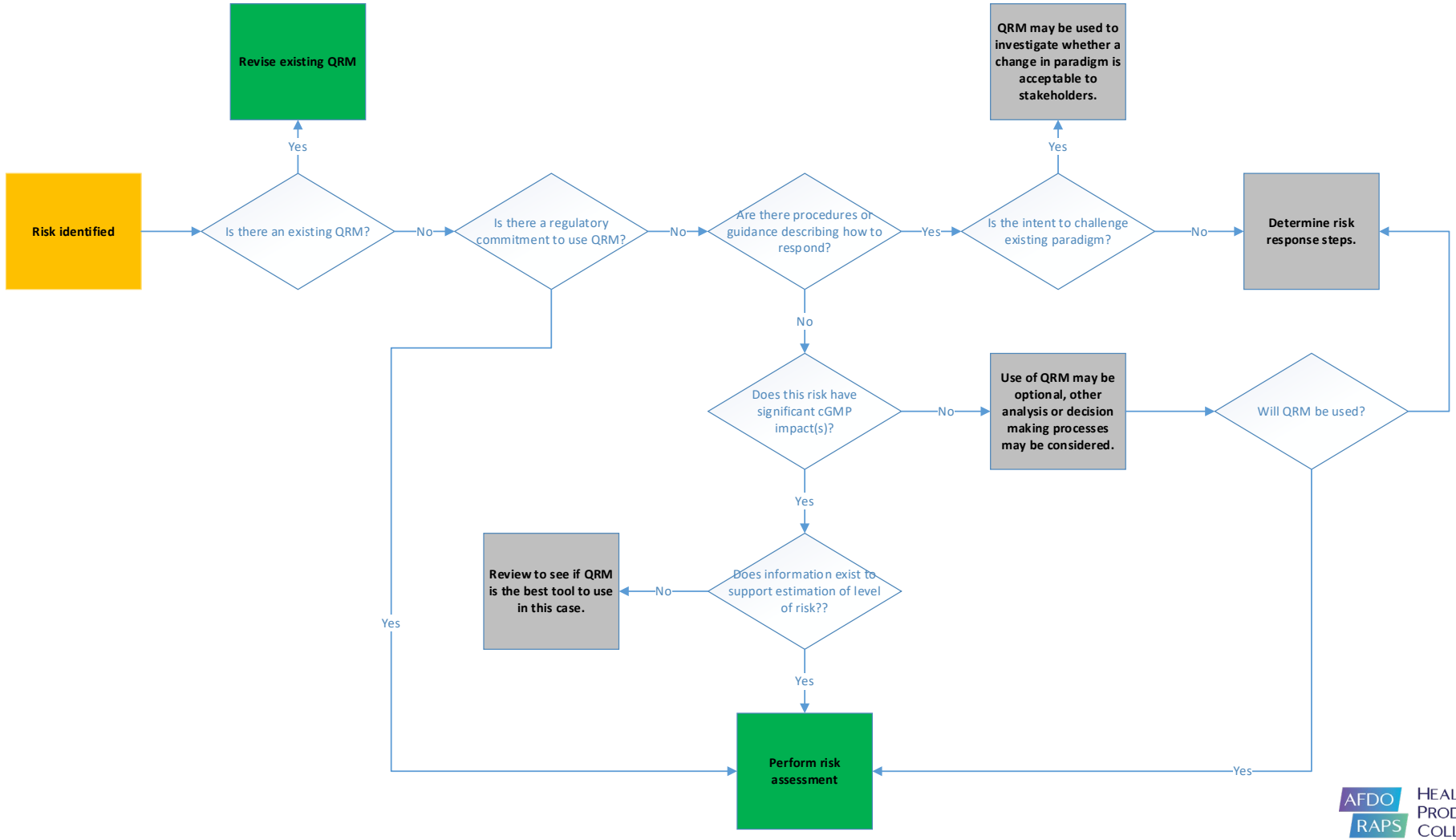
Flavors of ICH Q9(R1) – Control Strategy



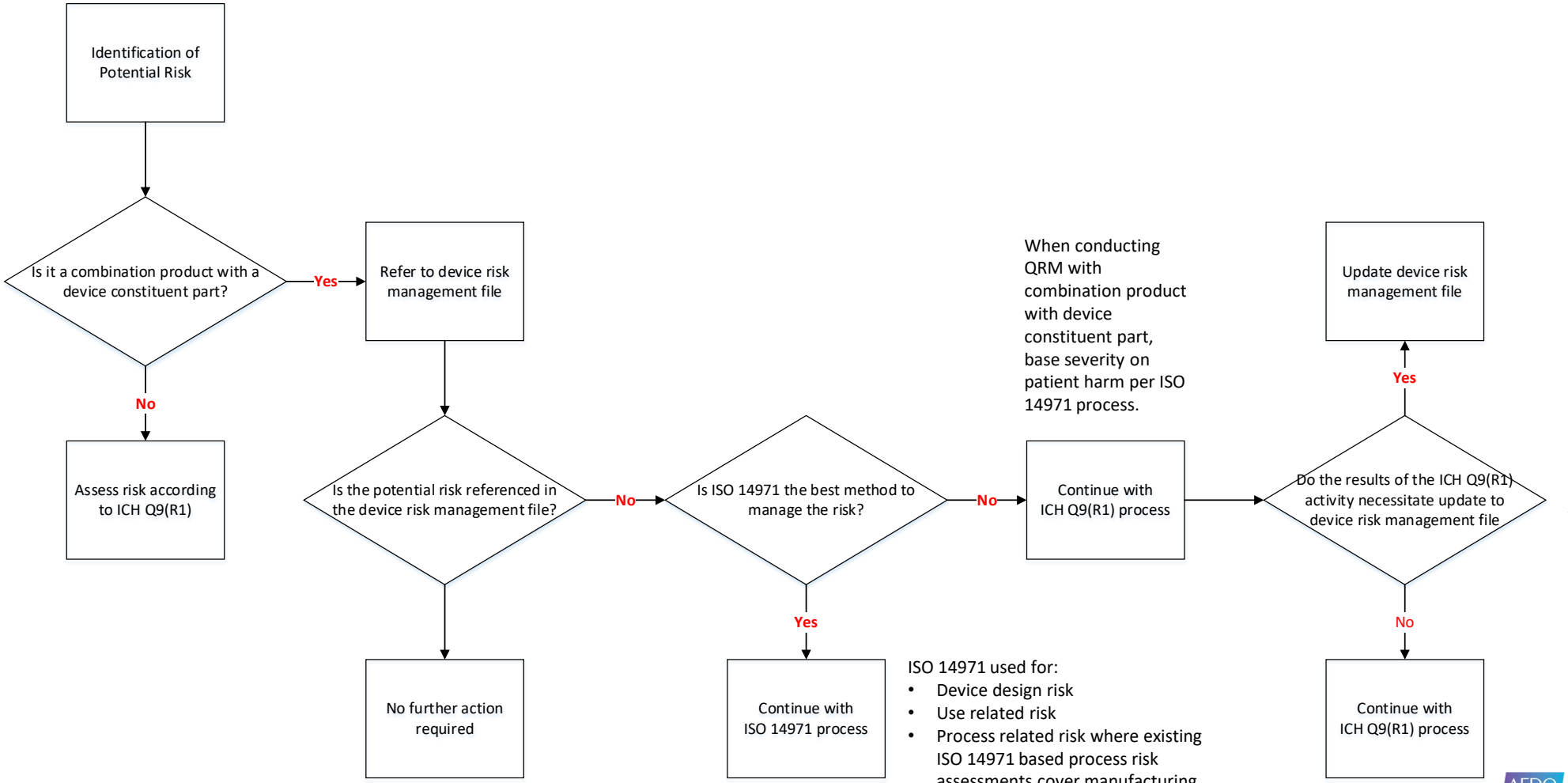


Quality Target Product Profile	Prior Knowledge	Product / Process Development	Product / Process Design Space	Control Strategy	Regulatory Flexibility
Definition of **product, intended use**, and predefinition of **quality** targets (with respect to clinical relevance, efficacy, and safety).	Summary of **prior scientific knowledge** (drug substance, excipients; similar formulations and processes). **Initial risk assessment.**	Overview of **Quality By Design**, key actions and decisions taken to develop **new scientific knowledge**, e.g., DoE, **risk assessment**, and **risk control.**	Summary of **scientific understanding of product and process**. Justification and description of **multidimensional space that assures quality** (interrelationships and boundaries of **clinical relevance**)	Definition of **control strategy** based on design space leading to **control of quality** and **quality risk managment** (process robustness).	Proposal of **regulatory flexibility** based on product and process, scientific knowledge, and **quality risk management** (materials, site, scale, etc.).

Flavors of ICH Q9(R1) – Single Risk Assessment



Decision Tree for ICH Q9(R1) *vs.* ISO 14971:2019



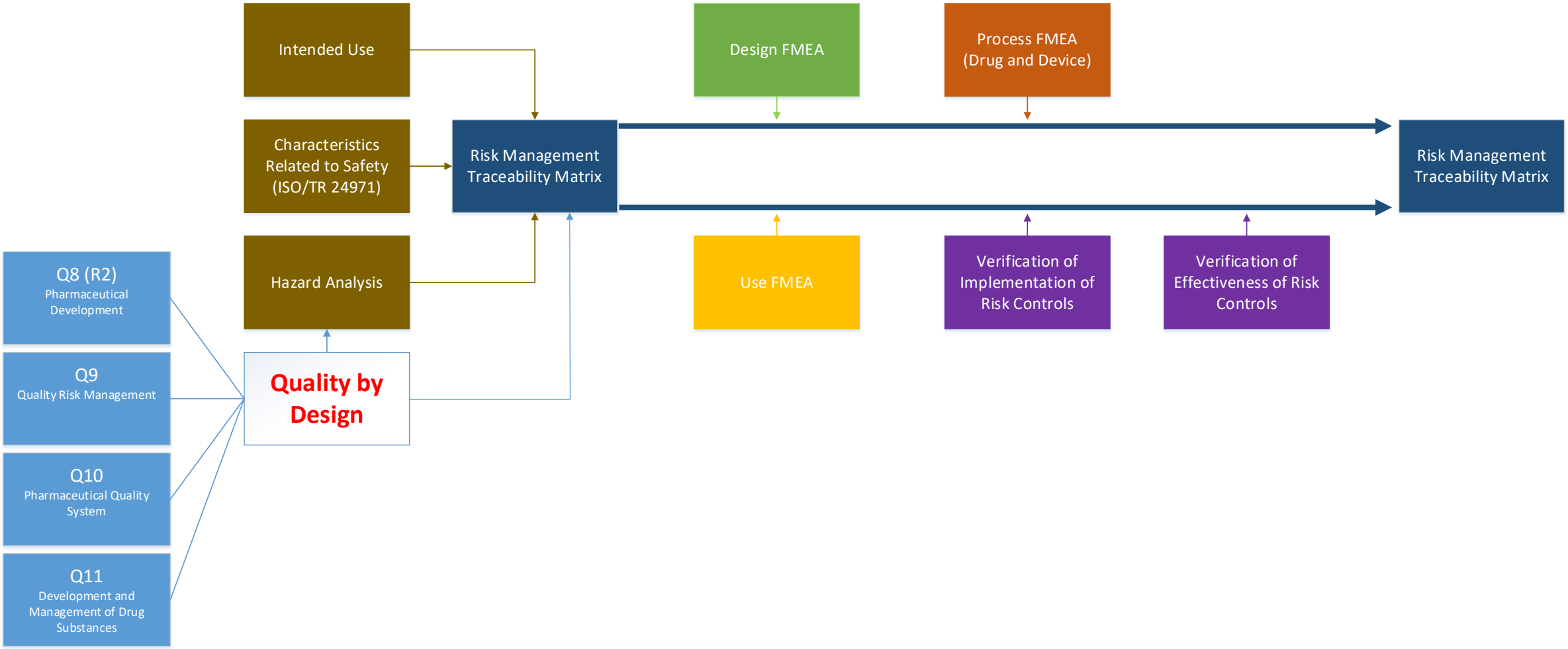
ISO 14971 used for:

- Device design risk
- Use related risk
- Process related risk where existing ISO 14971 based process risk assessments cover manufacturing process in question

Update to device risk management file required if:

- A new risk, hazard, hazardous situation or harm identified
- If P1 for an existing risk changes

Inputs to Risk Management Traceability Matrix



Thank You!