Quality Risk Management across Product Life Cycle

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“Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science” by applying

- Q8 (R2): Pharmaceutical Development Revision
- **Q9: Quality Risk Management**
- Q10: Pharmaceutical Quality System
- Q11: Development and Manufacture of Drug Substance

Quality: A new Paradigm for ICH

Main message:

Science is no longer isolated; it is living across the lifecycle of the product/process within a Quality Management System

Quality: A new Paradigm for ICH

New Paradigm emphasize:

- Quality must be mainly built in and it will not only improve by additional testing and inspection.
- Better utilization of modern science throughout product life cycle
- **QRM is a key enabler throughout product lifecycle**
- Robust Pharmaceutical Quality System (PQS), with appropriate knowledge management, assures quality throughout product life cycle
- An integrated approach to development, manufacturing and quality for both industry and regulators

SCOPE & Principals-ICH Q9

SCOPE:

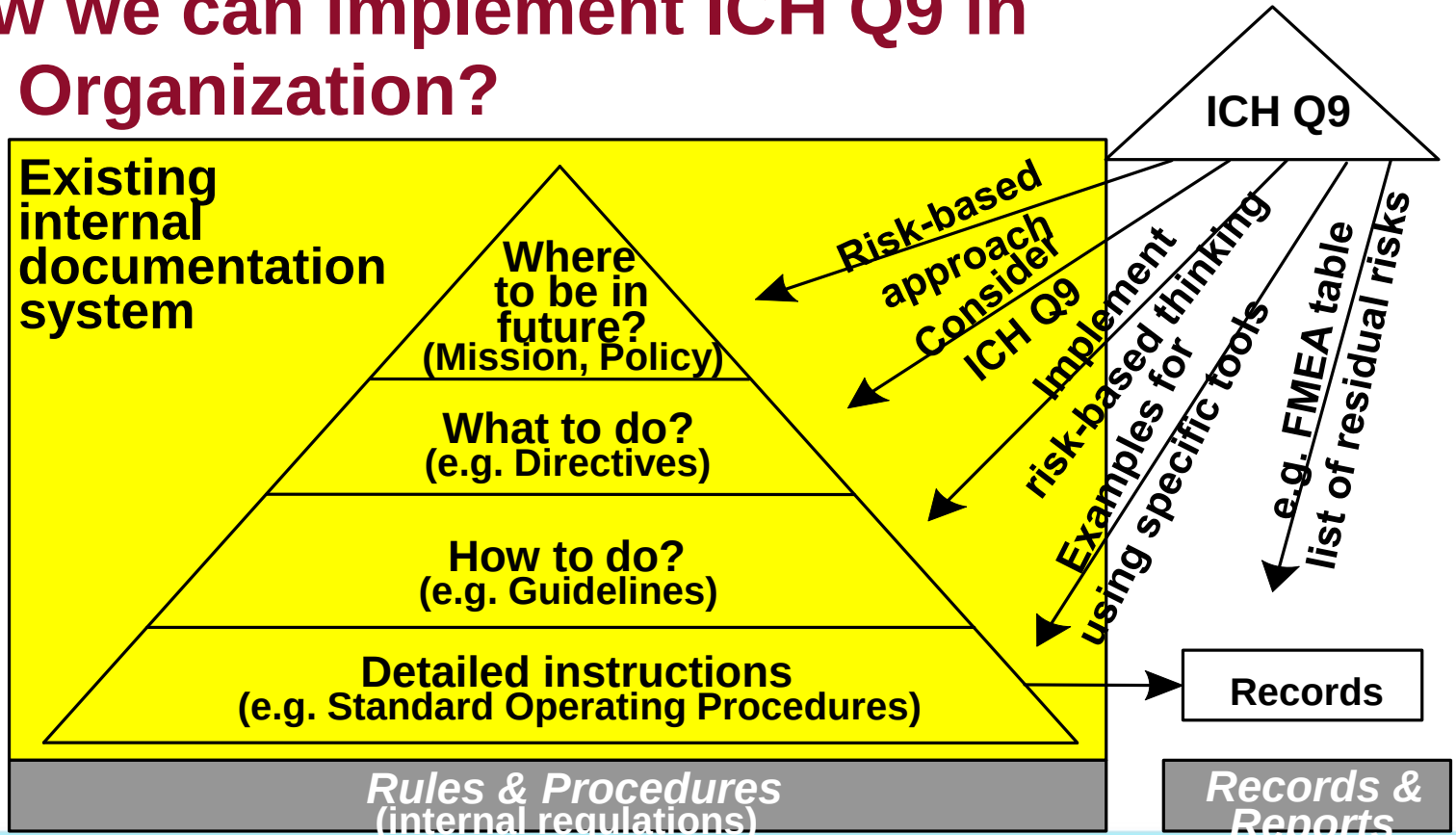
- Provides tools for Quality Risk Management that can be applied different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug products, and biologics.

PRINCIPALS:

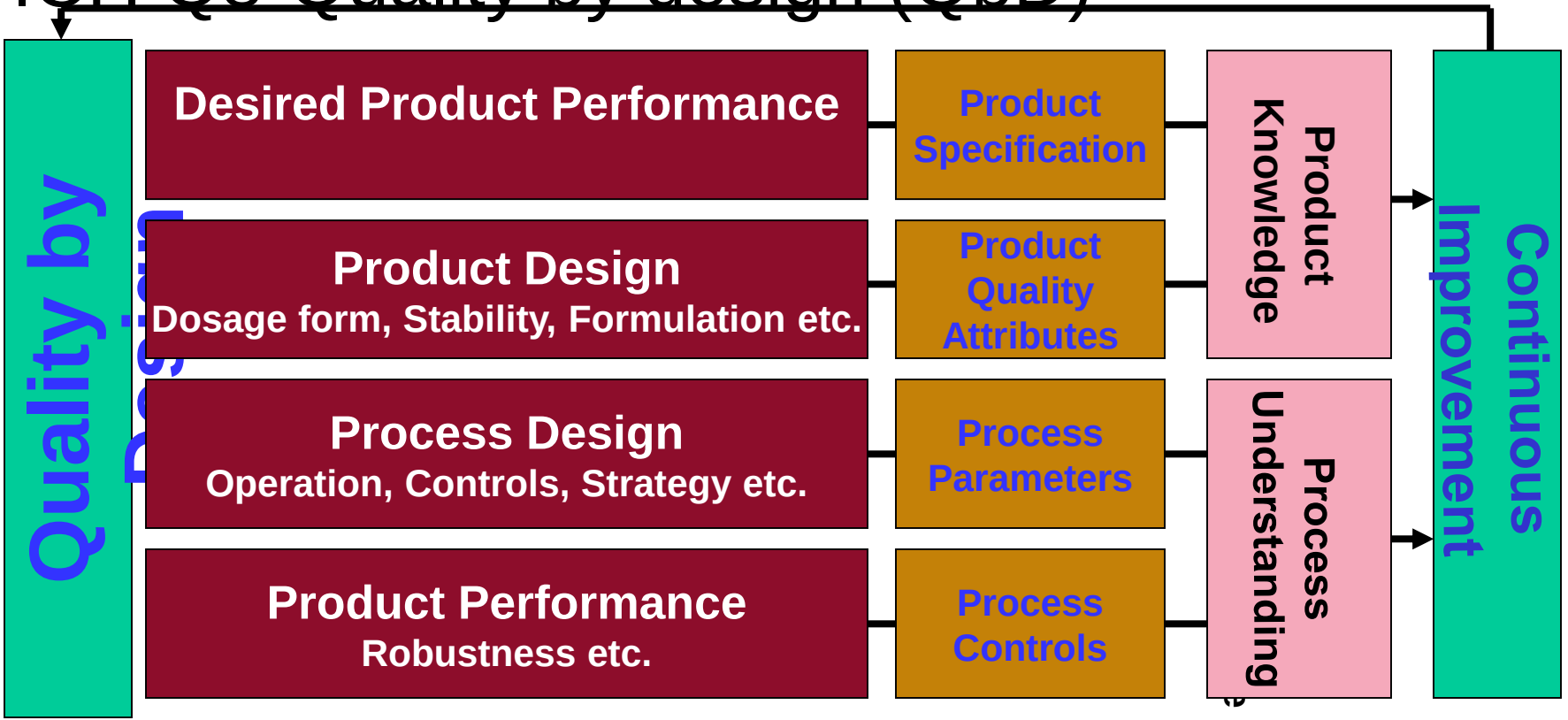
- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and

- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk

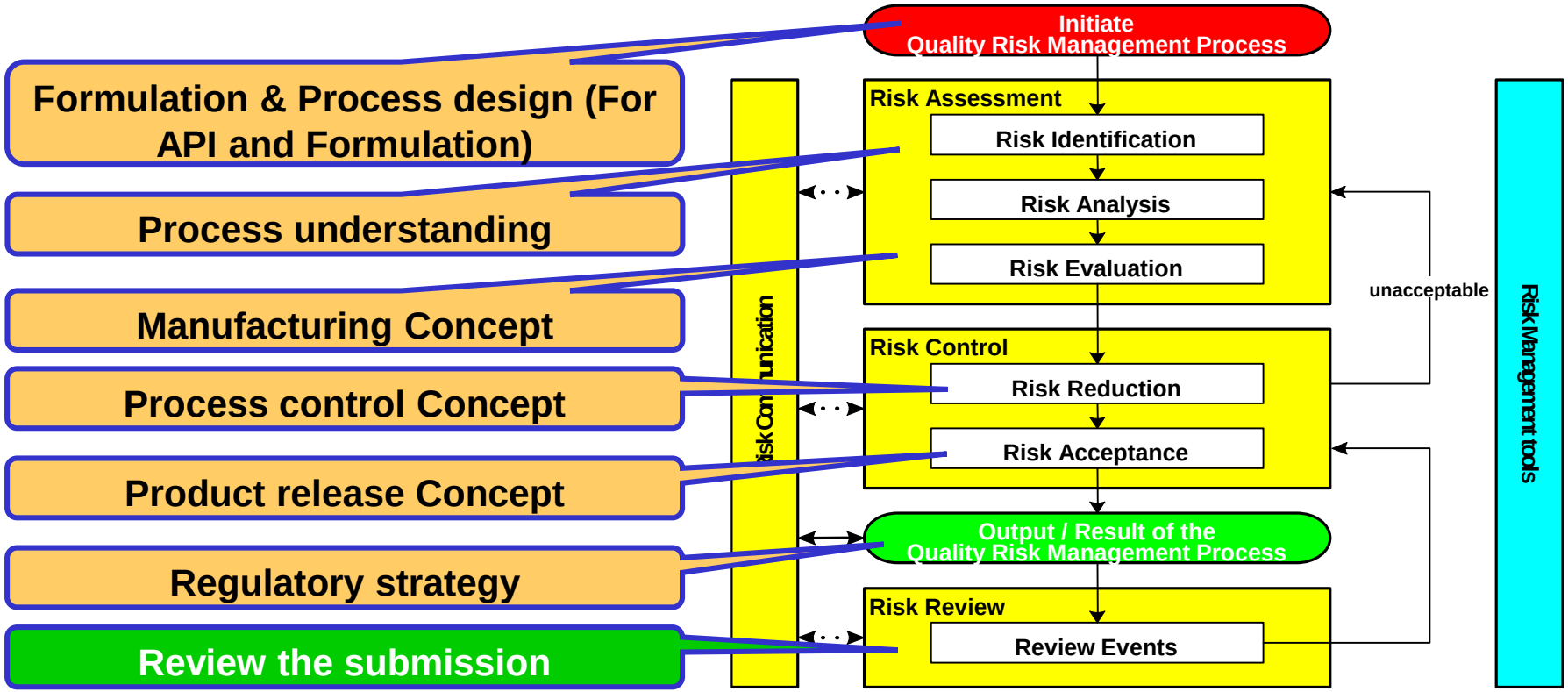
How we can implement ICH Q9 in my Organization?



ICH Q8-Quality by design (QbD)



Quality Risk Management Process



Basics of Risk Assessment

Risk Assessment

- What might go wrong?-**Risk Identification**
- What is likelihood (probability) it will go wrong?-**Risk Analysis (Detectability)**
- What are the consequences (Severity)?-**Risk Evaluation**

Risk Control

Risk reduction and risk acceptance four fundamental questions:

1. Is the risk above an acceptable level
2. What can be done to reduce or eliminate risks
3. What is the appropriate balance among benefits, risks and resources
4. Are new risks introduced as a results of the identified risks being controlled

Basics of Risk Assessment

Risk Review

It is a follow up and final evaluation of the incident

Risk Communication

Most important aspect of the risk assessment. Which includes:

1. Selection appropriate team
2. Selection of appropriate risk management tool
3. Pin-point the area of greatest risk
4. Potential source of problem

Risk Management methodology

Basic risk management facilitation methods

Failure Mode Effects Analysis (FMEA)

Failure Mode, Effect and Criticality Analysis (FMECA)

Fault Tree Analysis (FTA)

Hazard Analysis and Critical Control Points (HACCP)

Hazard Operability Analysis (HAZOP)

Preliminary Hazard Analysis (PHA)

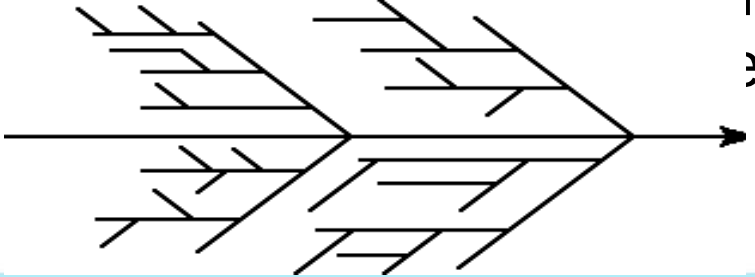
Risk ranking and filtering

Basic risk management facilitation methods

Cause and Effect Diagrams (Ishikawa / fish bone)

- To associate multiple possible causes with a single effect
- Constructed to identify and organize possible causes for it

- Primary branch: represents the effect
- Major branch: corresponds to a major cause
- Minor bran e detailed causal factors



What is an “acceptable risk”

- This has to be decided in the context of each specific risk management problem
- If you put in precise and definite data, you will receive a clear answer. This enables decision makers to make good and transparent decisions
- Accept residual risk, where further effort to reduce a risk is disproportional to the protection of the patient

Residual Risk

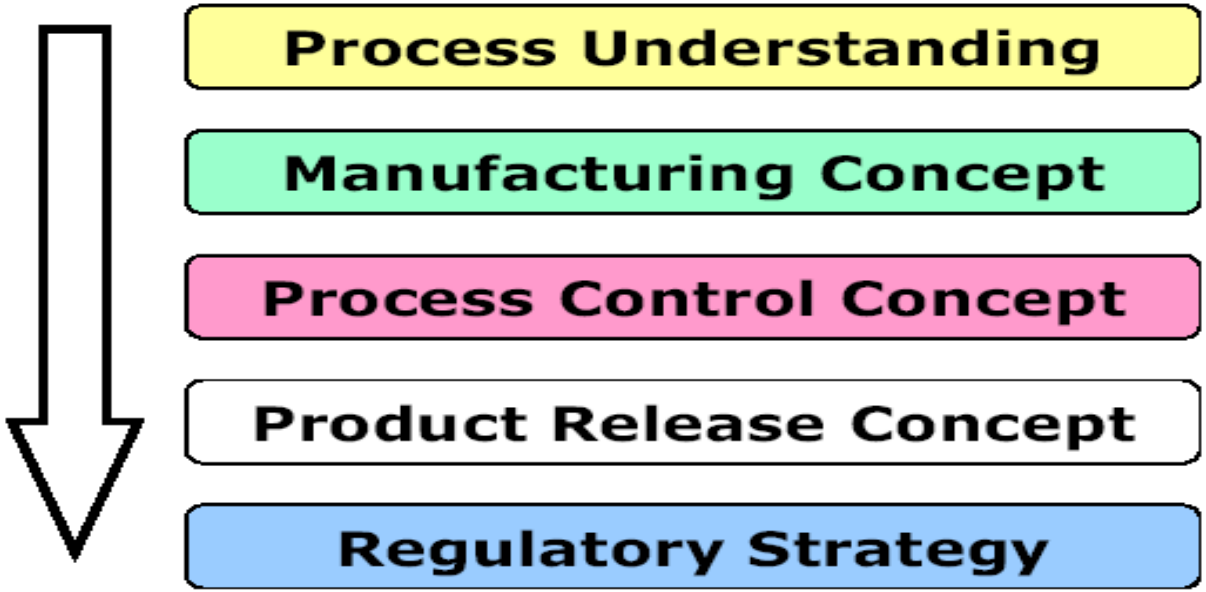
Residual risk addresses hazards that

- Have been assessed and risks that have been accepted
- Have been identified but the risks have not been correctly assessed
- Have not yet been identified
- Are not yet linked to the patient risk

Is the risk transferred to an acceptable level?

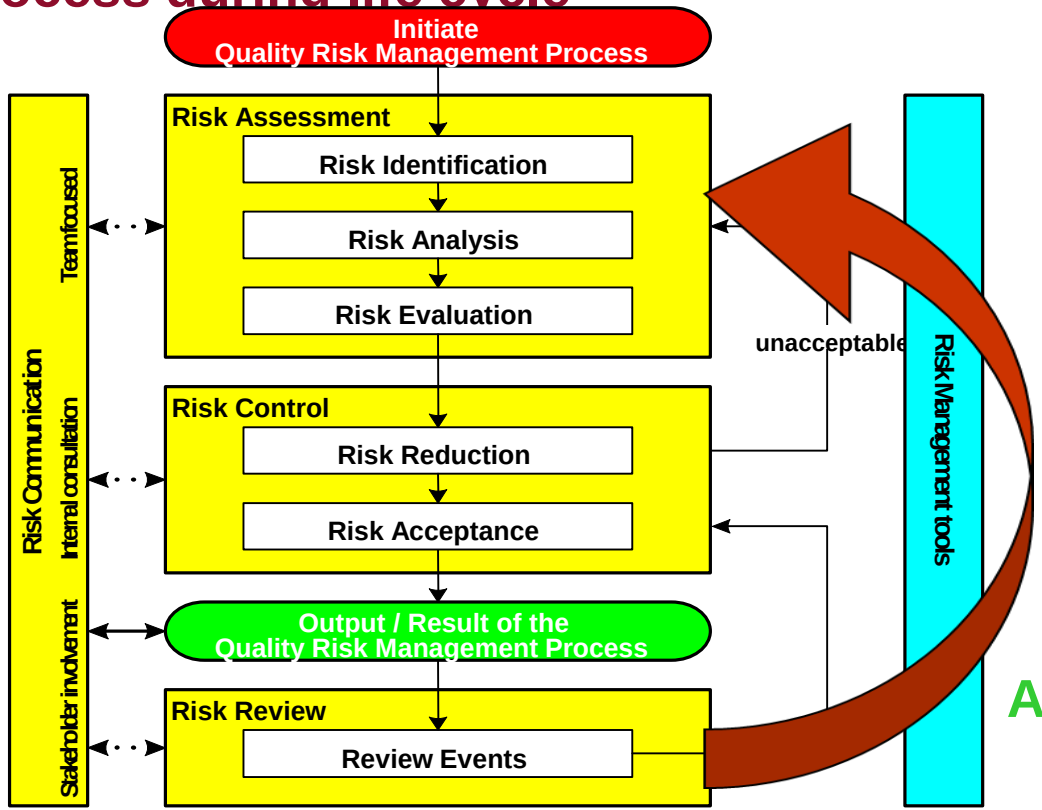
- Consider current scientific knowledge & techniques

QRM as part of regulatory strategy



Regulatory process during life cycle

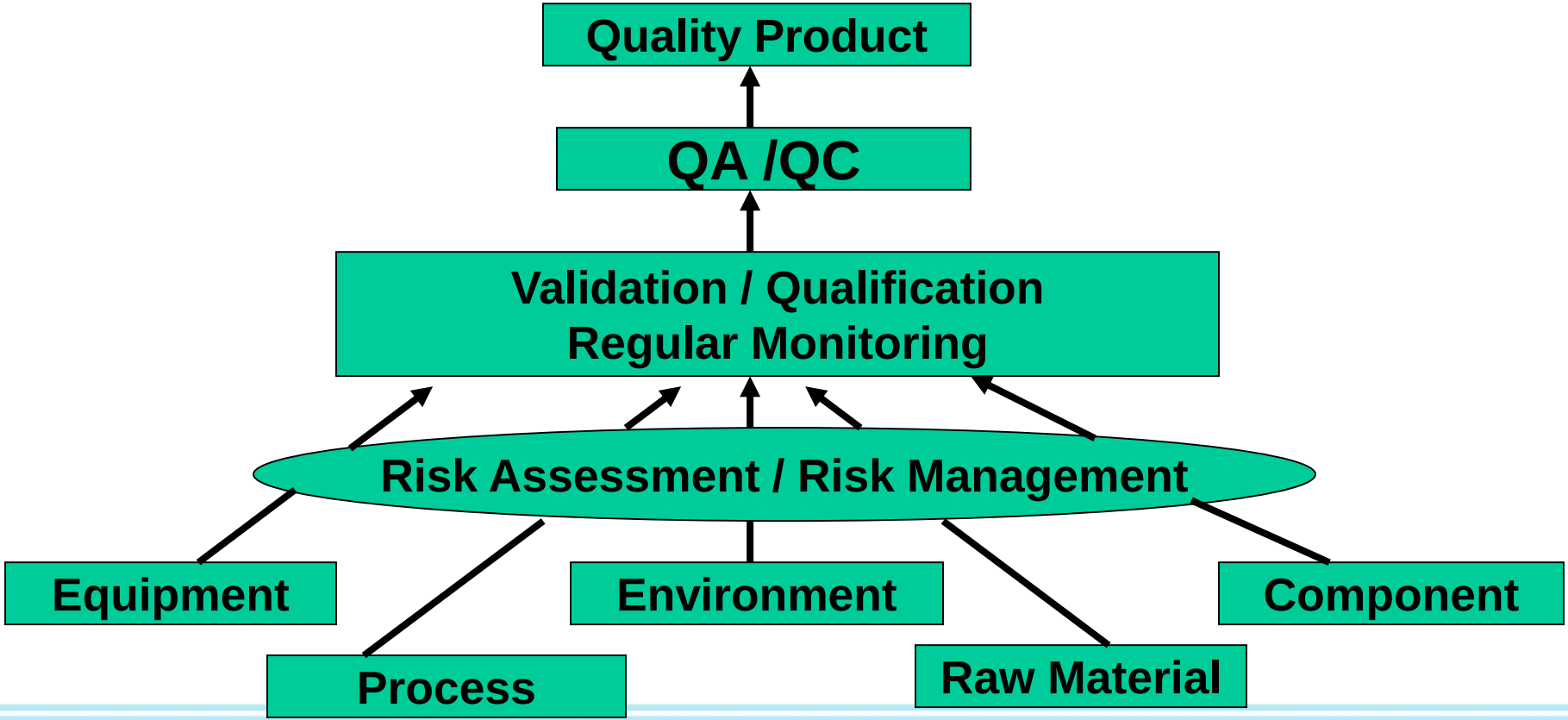
Industry



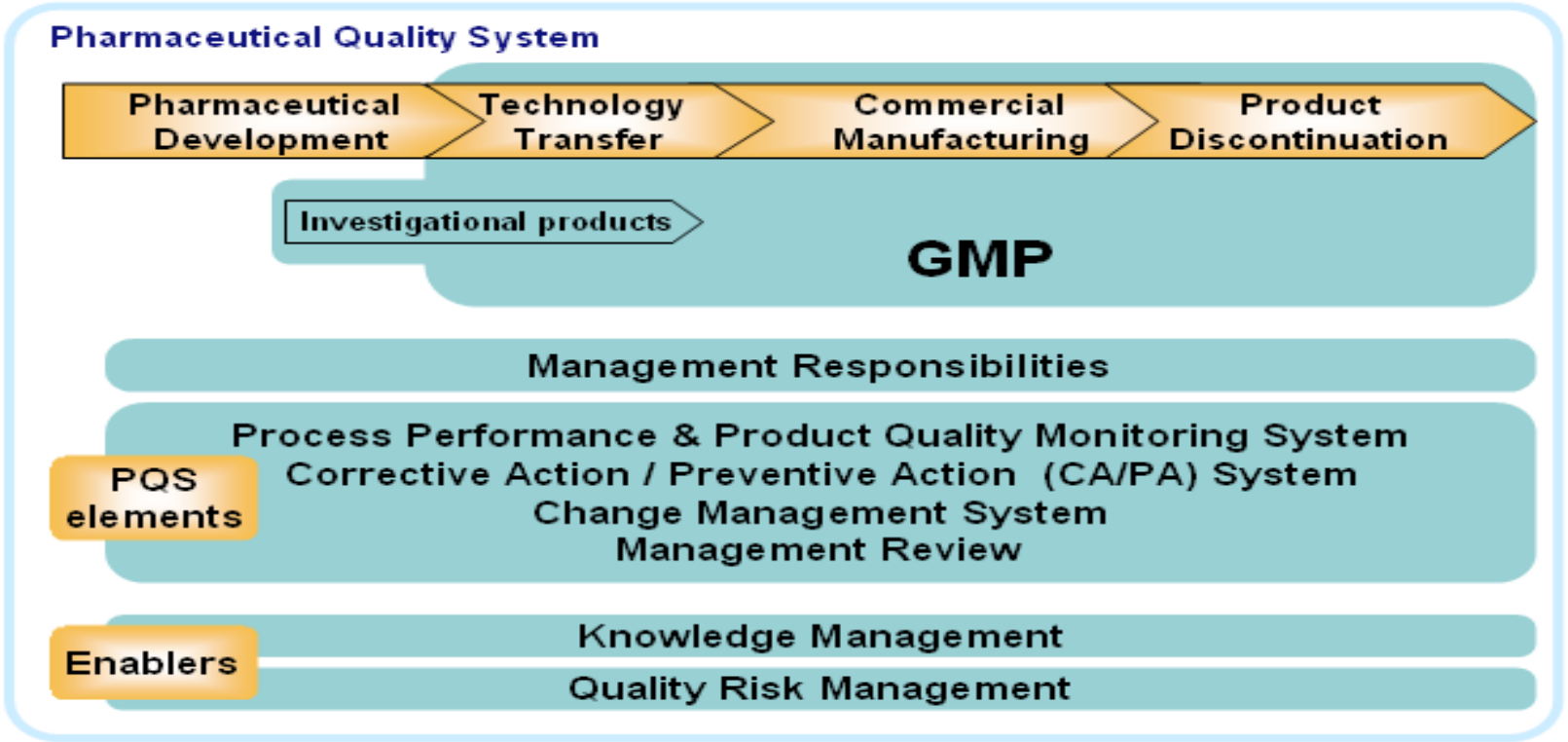
B) Inspectorates

A) Reviewers

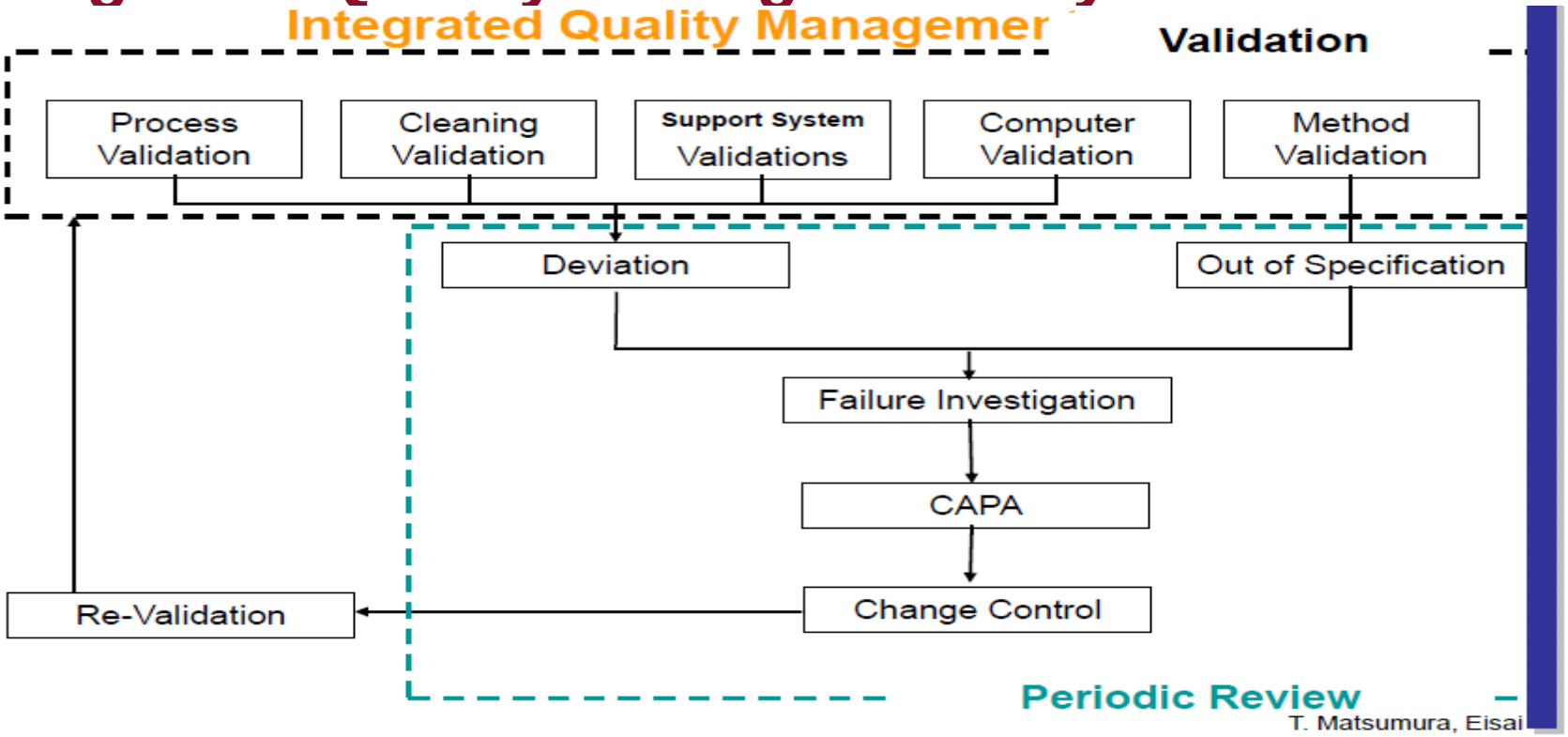
Quality Product responsibility



ICH Q8, Q9, Q10 and Q11 used for Risk assessment during product life cycle



Integrated Quality Management System

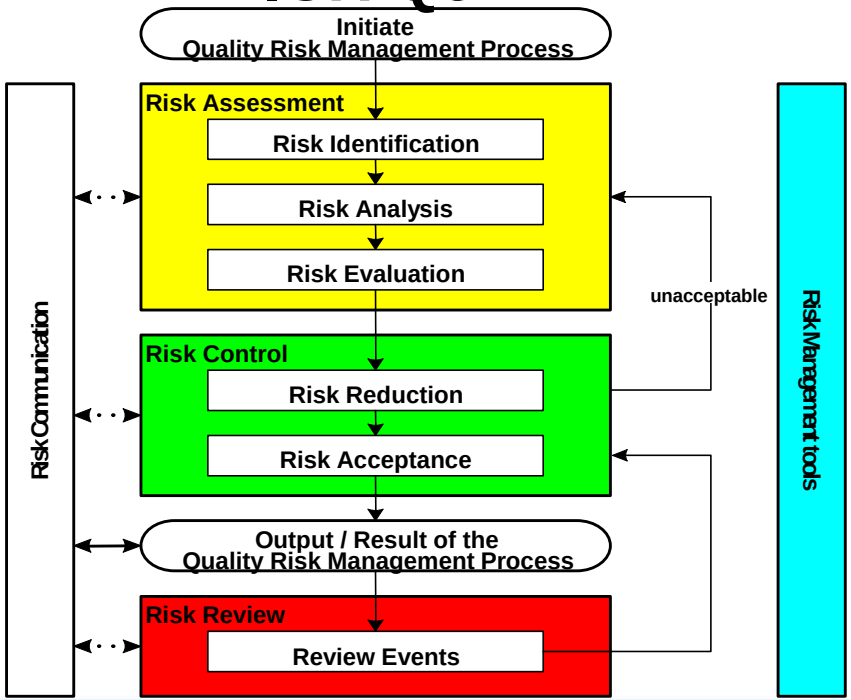


Risk assessment during late phase development and after commercialization

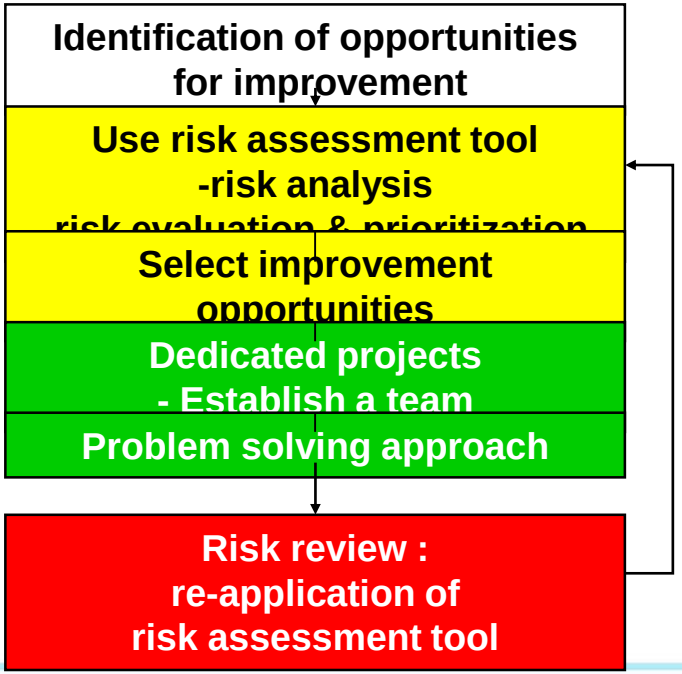
	ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
Commercial Scale Manufacturing for Drug Product	• Definition of commercial process design • Commercial scale runs to verify process design, with additional sampling to verify understanding • Implementation of on-line measurement technologies	• Development of a control strategy for commercial manufacturing, including in-process controls, end-product testing, raw material controls and change control • Check procedures in the PQS regarding risk from Process specific procedure (e.g., sampling plans, design space and model verification, change control for movement within design space)	• Process-specific operating procedures (e.g. sampling plans, design space etc.) • Documentation to support on-line testing methods • Validation to demonstrate process and analytical method reproducibility • Storage of development reports, risk assessments
Continual Process Verification and Continual Improvement	• On-going analysis and trending of process data, (multivariate SPC, etc.) • Evaluation of process changes and associated effect on intermediates and products	• Manage risks of process or material attribute change (including changes within or outside of design space) • Review risks in audits/inspections and implement risk-based CAPAs	• Procedures on process monitoring and action limits • Change control procedures including how and when to do risk assessment for process changes and evaluation of the change • Maintenance and update of knowledge management

Assess the history of known quality defects

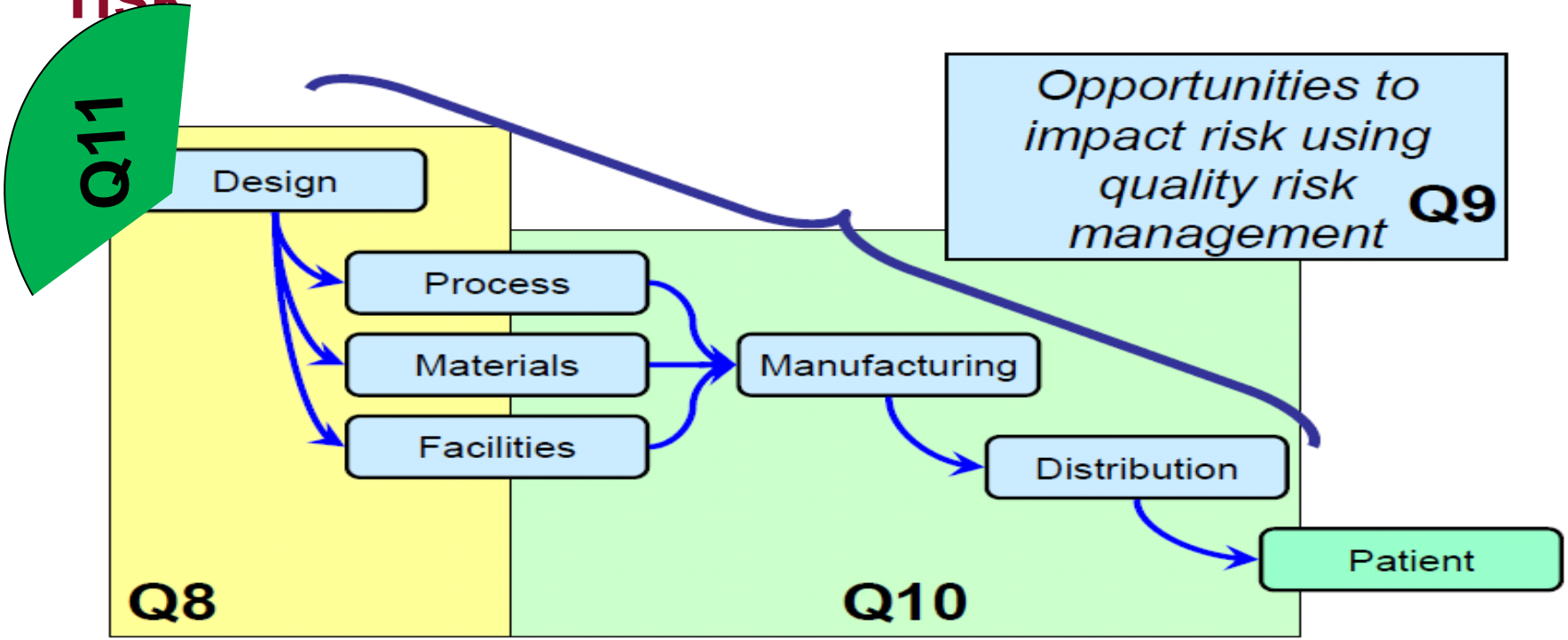
ICH Q9



Site approach



ICH Q8, Q9, Q10 & Q11 Goal: To reduce patient risk



Why risks are high in Pharmaceutical Products

Facility, Manufacturing and Controls

- Inadequate process validation design and data-fails to establish scientific evidence that a process is consistently capable of delivering quality product
- Inadequate understanding of critical and important process details from validation and development and scope for capturing enough information in the Batch records
- Control of variability commensurate with the risk

Integrated Risk Management

Risk assessment: Risk analysis

Assessment of effects of the discrepancy
Examples if applicable:

- Product quality
- Drug safety
- Registration files / Marketing authorisation
- Systems in place
- Availability of goods:
potentially insufficient stock levels

Analytical Laboratory role in ICH Q8, Q9 and Q10 environment

- To determine the scope and extent of verification, qualification and modern validation activities-Analytical methods and cleaning methods
- To determine the extent for follow-up activities-Sampling, monitoring and revalidation of analytical methods
- To evaluate the frequency and extent of in-process control testing
- Evaluation and justification of process analytical technique (PAT) In conjunction with parametric and real time release
- Deviation / Out of specification results: To identify potential root cause and corrective actions during the investigation
- Retest period / expiration date: To evaluate adequacy of storage and

Analytical Laboratory role in ICH Q8, Q9 and Q10 environment

May require more real time testing

Switch from traditional sampling concept, traditional sampling requires discrete sampling size-which is a minimal sampling expectation

More statistical and scientifically sound sampling approach- More number of samples for assurance

More scientific database required for real time testing-e.g. creation of NIR library etc.

Analytical Laboratory role in ICH Q8, Q9 and Q10 environment

- Development of alternate method or monitoring approaches-In case of breakdown of on-line / in-line test or monitoring equipment
- Validation of alternate method-Alternate method should be provided in the product application
- More effective / extensive, training / qualification and it's management for continuous improvement for product life cycle
- More statistical data generation and analysis
- Establish mechanism to demonstrate Pharmaceutical Quality System across the product life cycle-An easily understandable way for management, staff and regulatory inspectors (quality manual

Analytical Laboratory role in ICH Q8, Q9 and Q10 environment

Knowledge Management (ICH Q10): All the department need to share product knowledge / information to understand product which can add value to SPC.

Some knowledge source indicated in ICH Q10 are:

1. Prior knowledge from similar process
2. Pharmaceutical development studies
3. Mechanism of action
4. Structure / function relationship
5. Technology transfer activities
6. Process validation studies
7. Manufacturing experience
8. Change management activities, deviations etc
9. Adverse event reports
10. Stability reports

Regulatory application of ICH Q9

- There have already references been made to the use of ICH Q9 principles in recent regulatory documents by USFDA through QbR. This indicates the awareness and commitment to ICH Q9 in some competent authorities. QbR is also extended as requirement by FDA for Drug substance, which is biggest challenge now for API Industry

- There are some existing and proposed regulations which do not fully recognise OR request for the use of ICH Q9 principles. It is the hope and expectation that soon all ICH countries will soon make this as requirement for regulatory submission in line to USFDA.

- Competent authorities will check if the science used for the quality risk management process is acceptable

- Competent authorities may not accept the outcome of the risk management process if it is not satisfactory in terms of science

Will ICH Q9 activity inspected?

- **Inspections/audits already focus on QRM activities e.g.**
  - **How the problems have been solved?**
  - **What corrective and preventive measures have been taken?**

- **Inspectors/Audits might review/inspect:**
  - **Whether the quality risk management performed is integrated in the Quality System of the organization**
  - **Traceability, transparency**
  - **How was the decision made?**
  - **Was a (risk) problem / question defined?**
  - **Did the process performed answer this question?**

Future Benefits

- Real time release testing may eliminate end point testing-if quality is assured by product specific designed in-process monitoring and testing of material

- Facilitated robustness of the manufacturing process, through facilitation of continual improvement through science and risk based post approval change process

- High level confidence of quality by manufacturer and Regulatory bodies

Thank You