Implementation of ICH Q8, Q9, Q10

How ICH Q8, Q9, Q10 guidelines are working together throughout the product life cycle

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

Outline

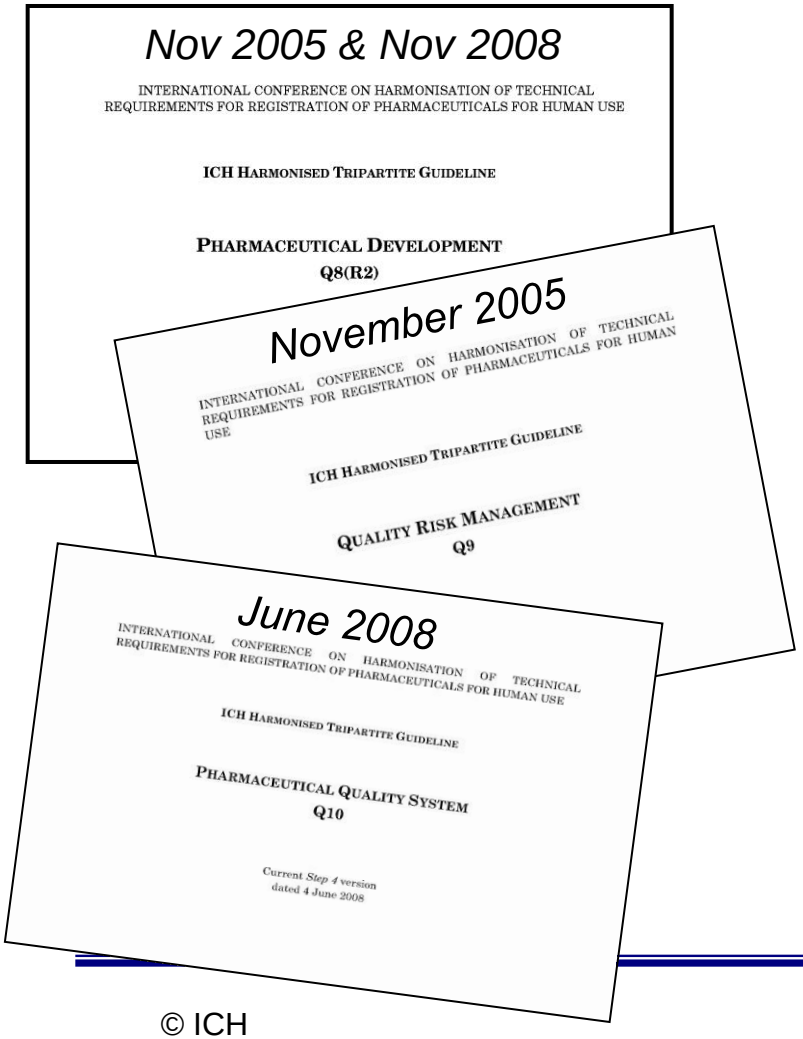
- Workshop Goals and Objectives
- ICH Q8, Q9 & Q10
- How the guidelines are working together throughout the product life cycle
- Utility of ICH Q8, Q9 & Q10
- Key messages
- Conclusion

Workshop Goals and Objectives

- This presentation is intended to outline the linkage between Q 8,9 &10 and how the guidelines are working together
- This presentation is **NOT** intended to outline regulatory expectations (assessment and/or inspection)
- This workshop will:
  - Provide training on the integrated implementation of Q 8, Q9 and Q10
  - Allow participants to share implementation strategies and experiences
  - Seek participants' input and identify implementation issue and concerns

How ICH Q8, Q9, Q10 guidelines are working together throughout the product life cycle

ICH Q8, Q9 and Q10



- High level guidances (not prescriptive)
- Science and risk-based
- Encourages systematic approaches
- Applicable over entire product lifecycle
- Intended to work together to enhance pharmaceutical product quality

Pharmaceutical Development - Q8(R2)

- Describes science and risk-based approaches for pharmaceutical product and manufacturing process development
- Introduced concepts of design space and flexible regulatory approaches
- Introduced concepts of Quality by Design (QbD) and provided examples of QbD development approaches and design space

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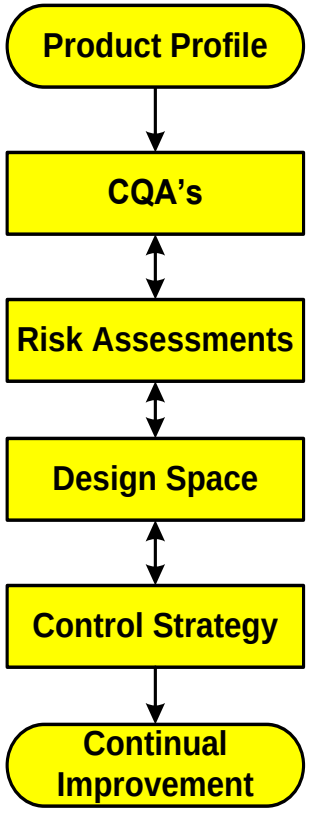
Q8(R2) - Example QbD Approach



- Quality Target Product Profile (QTPP)
- Determine "potential" critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space (*optional and not required*)
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

How ICH Q8, Q9, Q10 guidelines are working together throughout the product life cycle

Quality Risk Management – Q9

- Describes systematic processes for the assessment, control, communication and review of quality risks
- Applies over product lifecycle: development, manufacturing and distribution
- Includes principles, methodologies and examples of tools for quality risk management
- Assessment of risk to quality should:
  - Be based on scientific knowledge
  - Link to the protection of the patient
  - Extend over the lifecycle of the product

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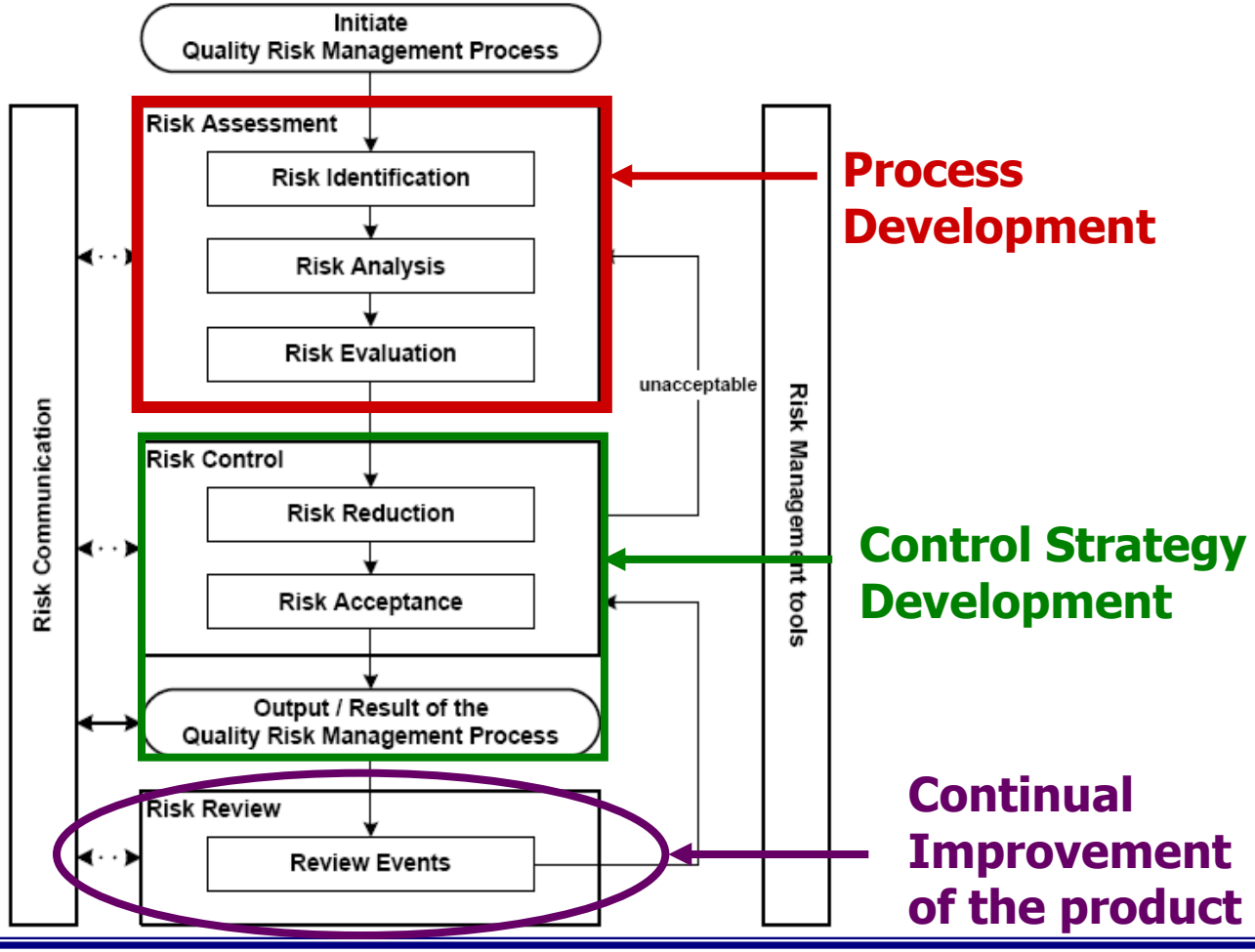
Quality Risk Management Process - Q9



How ICH Q8, Q9, Q10 guidelines are working together throughout the product life cycle

Pharmaceutical Quality System - Q10

- Describes key systems that facilitate establishment and maintenance of a state of control for process performance and product quality
- Facilitates continual improvement
- Applies to drug substance and drug product throughout product lifecycle
- Sound pharmaceutical development (Q8R(2)) in combination with a robust PQS (Q10) provide opportunities for flexible regulatory approaches. Relevant PQS elements include systems for:
  - Track and trend product quality
  - Maintain and update models as needed
  - Internally verify that process changes are successful

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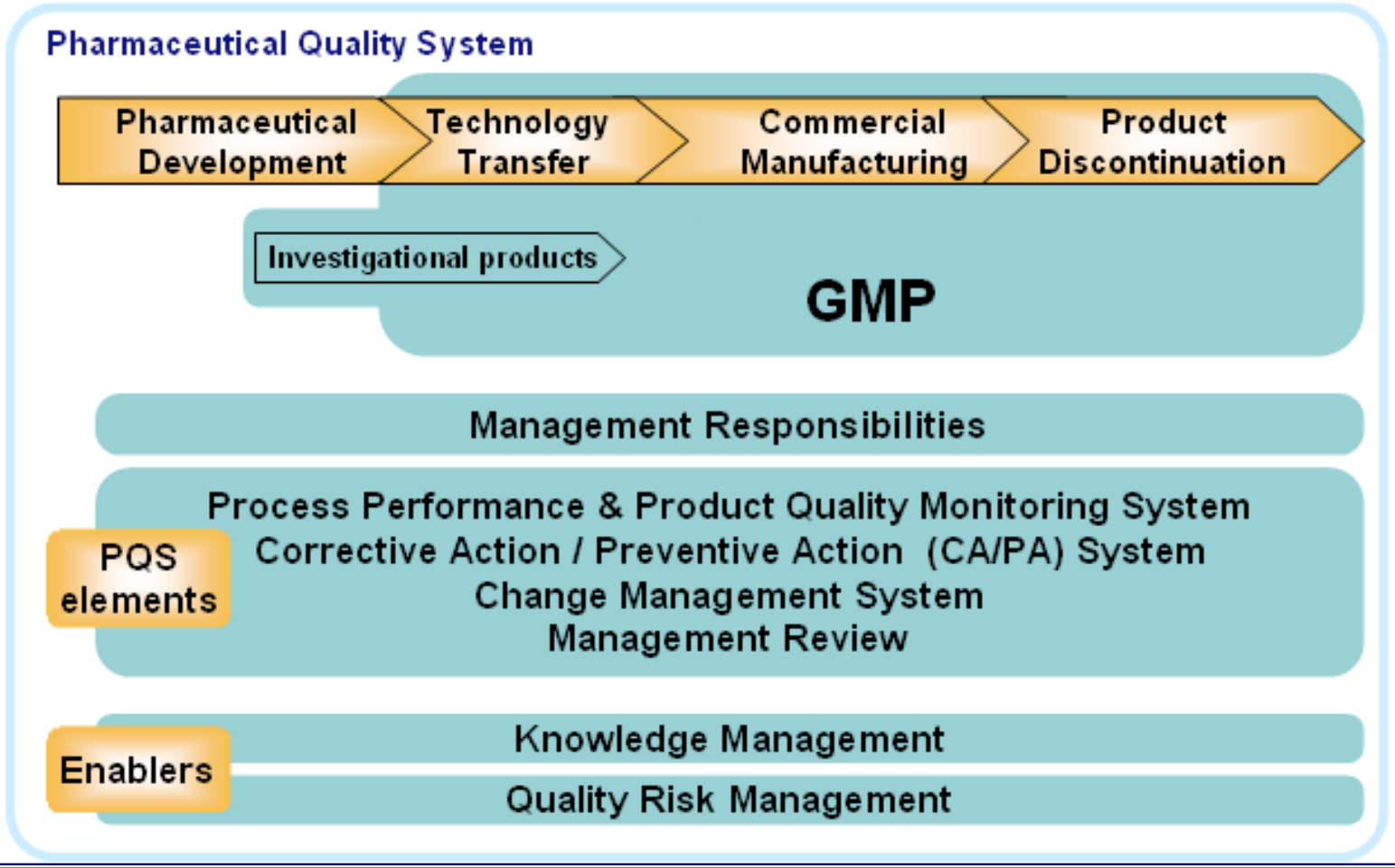
Pharmaceutical Quality System - Q10



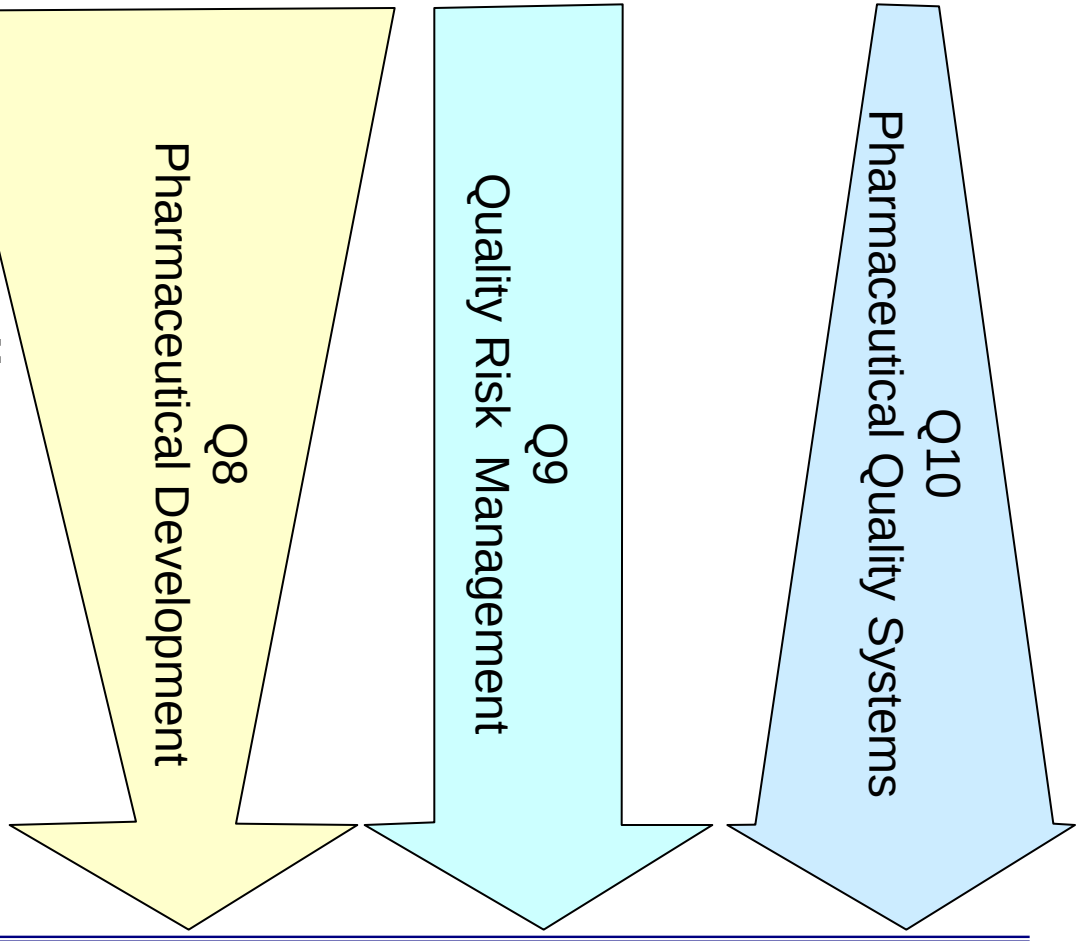
How ICH Q8, Q9, Q10 guidelines are working together throughout the product life cycle

ICH Q8, Q9 and Q10 Working Together

Formulation Activities:
- QTPP Definition
- Pre-Formulation Studies
- Formulation Screening
- Optimization & Selection

Process Development Activities:
- Process Screening
- Lab Scale Development
- Scale-Up Studies

Manufacturing Activities:
- Commercial Scale Manufacturing
- Batch Release
- Continual Verification & Improvement



How can the three guidelines work together

- The following four slides (slides 14-17) are intended to show how Q8, Q9, Q10 can work together at different stages of the product lifecycle

- It is important to note that they are NOT intended to show complete activities at each stage **NOR** to show the exact timing (stage) for those activities

How ICH Q8, Q9, Q10 guidelines are working together throughout the product life cycle

Formulation Development Activities

	ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
Quality Target Product Profile (QTPP)	• Clinical and non-clinical studies on drug substance: bioavailability, PK/PD, and safety	• Informal and/or formal risk assessment to evaluate patient needs and potential medication risks	• Knowledge Management / Prior Knowledge (relevant information to support the understanding, risk assessment and scope of DOE) - Laboratory note book documentation - Development report - Etc…
Pre-Formulation Studies	• Characterization of drug substance (physical properties) • Chemical stability of drug substance, degradation and potential formulation interactions • Development of analytical tests	• Determine failure modes and risk factors for drug substance physical and chemical stability	
Formulation Screening	• Excipient compatibility • Dissolution method development • Screening DOEs	• Determine failure modes and risk factors for excipient interactions	
Formulation Optimization and Selection	• Excipient and drug substance material property & characterization • DOEs for excipient amounts • Stability of drug product and storage conditions • Develop IVIVC relationships	• Opportunities for formal risk assessment	

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Process Development Activities

	ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
Process Screening	• Exploration of unit operations • Characterization of process intermediates	• Determine failure modes, risk factors for unit operations and rank risk	• Batch records and operational guidelines for manufacturing • Tech Transfer report • Identification and selection of suppliers that meet raw material needs
Process Development and Optimization (Lab Scale)	• DOEs for process parameters and interactions with material attributes • Development of Design Space • Operational ranges for scale-independent parameters • understanding of critical process operations	• Screening risk assessment to determine potential parameters impacting product quality (e.g., Ishikawa) • Determine critical process steps, process parameters and material attributes (e.g., FMEA) • Potential issues of scale	
Process Development and Optimization (Pilot Scale)	• Pilot to verify lab scale knowledge • DOE and modeling effects of scale • Development of design space • Development of on-line measurement technologies	• Development of control strategy to control risks incl. for scale up	

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Technology Transfer

ICH Q8(R2) – Pharmaceutical Development Related Activities	ICH Q9 – QRM Related Activities	ICH Q10 – PQS Related Integrated Activities
• Gain product and process knowledge • Knowledge supports transfer between development and manufacturing to achieve product realization	• Forms the basis for the manufacturing process • Improves effectiveness of control strategy • Contributes to processes validation and ongoing continual improvement	• Advance understanding through scale-up activities • Provide preliminary indication of process performance and successful integration into manufacturing • Gain knowledge from transfer and scale up activities to enhance the basis for the control strategy

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Commercial Manufacturing Activities

	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

The Utility of ICH Q8, 9 &10

- The implementation of Q8, 9 &10 is valuable for all drug products, pharmaceutical development approaches and regulatory systems
  - New/innovator, marketed/legacy and generics
  - Simple and complex dosage forms
  - Small molecule and biotech
  - Traditional development and QbD
  - Within and outside ICH regions
- Good scientific development (Q8) in combination with QRM (Q9) and PQS (Q10) will improve drug quality and efficiency of pharmaceutical manufacturing
  - Quality is important for all drug products throughout product lifecycle (new, legacy and generics)

Key Messages

- ICH Q8, Q9 and Q10 are linked together to provide a systematic, modern risk- and science- based approach to pharmaceutical manufacturing and development
- Comprehensive implementation of the three guidelines together is essential to achieve ICH Quality Vision
  - Guidelines are applicable over entire product lifecycle
- Guidelines can be utilized by all stakeholders
  - Industry and regulators
  - Assessors and inspectors are expected to incorporate QRM during regulatory processes

How ICH Q8, Q9, Q10 guidelines are working together throughout the product life cycle

Key Messages

- Traditional development approaches, as outlined in ICH Q8(R2) part I, are acceptable
  - Enhanced approaches (QbD) provide higher assurance of product quality and additional opportunities for manufacturing efficiency and flexibility
- The use of quality risk management process, methodologies and tools (Q9) is beneficial regardless of development or manufacturing approaches used
- Pharmaceutical Quality Systems (Q10) applies to drug substance and drug product throughout product lifecycle and provide tools to facilitates continual improvement

Conclusions

- Workshop materials, plenary presentations, and breakout discussions will provide useful information to facilitate pharmaceutical development and manufacturing, and related regulatory aspects
  - Training materials provide only illustrative examples
  - Training materials are not intended to serve as templates for pharmaceutical development, manufacturing, regulatory assessment or inspection
  - Depending of the pharmaceutical product, other approaches might be appropriate

Conclusions

- The main goal of this workshop is to provide training on the comprehensive implementation of Q8, Q9 and Q10

- Workshop feedback will be utilized by IWG to further improve the implementation for the new paradigm of pharmaceutical quality