Implementation of ICH Q8, Q9, Q10

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

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ICH Q8, Q9, and Q10

ICH Quality Implementation Working Group - Integrated Implementation Training Workshop

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ICH Q8, Q9, and Q10 guidelines are high level guidances (not prescriptive), science and risk-based, encourage systematic approaches, applicable over the entire product lifecycle, and intended to work together to enhance pharmaceutical product quality.

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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

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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

- Initiate Quality Risk Management Process
  - Risk Assessment
    - Risk Identification
    - Risk Analysis
    - Risk Evaluation
  - Risk Control
    - Risk Reduction
    - Risk Acceptance
  - Output / Result of the Quality Risk Management Process
- Risk Review
  - Review Events

Process Development
Control Strategy Development
Continual Improvement of the product

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

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

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

#### Process Development Activities

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</thead>
<tbody>
<tr>
<td><strong>Process Screening</strong></td>
<td>• Exploration of unit operations • Characterization of process intermediates</td>
<td>• Determine failure modes, risk factors for unit operations and rank risk</td>
</tr>
<tr>
<td><strong>Process Development and Optimization (Lab Scale)</strong></td>
<td>• DOEs for process parameters and interactions with material attributes • Development of Design Space • Operational ranges for scale-independent parameters • Understanding of critical process operations</td>
<td>• 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</td>
</tr>
<tr>
<td><strong>Process Development and Optimization (Pilot Scale)</strong></td>
<td>• Pilot to verify lab scale knowledge • DOE and modeling effects of scale • Development of design space • Development of on-line measurement technologies</td>
<td>• Development of control strategy to control risks incl. for scale up</td>
</tr>
</tbody>
</table>
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Technology Transfer

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<tbody>
<tr>
<td>• Gain product and process knowledge</td>
<td>• Forms the basis for the manufacturing process</td>
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<tr>
<td>• Knowledge supports transfer between development and manufacturing to achieve product realization</td>
<td>• Improves effectiveness of control strategy</td>
<td>• Advance understanding through scale-up activities</td>
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<td></td>
<td>• Contributes to processes validation and ongoing continual improvement</td>
<td>• Provide preliminary indication of process performance and successful integration into manufacturing</td>
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<td>• Gain knowledge from transfer and scale up activities to enhance the basis for the control strategy</td>
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Commercial Manufacturing Activities

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