Pharmaceutical Development: ICH Q8/Q(8)R

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Food and Drug Administration (FDA)

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Outline

- Recent ICH and FDA Guidances
- ICH Q8 and Q8(R)
- Quality by Design (QbD)
  - Example Approach to QbD
  - QbD for APIs
- FDA Experience with QbD
  - ONDQA QbD Pilot Program
- Challenges of Implementing QbD
- Concluding Remarks
Recent ICH & FDA Guidances

ICH Q8/Q8(R) - Pharmaceutical Development

FDA PAT Guidance

ICH Q9 – Quality Risk Management

ICH Q10 – Pharmaceutical Quality Systems
ICH Q8 Guidance

- Provides guidance on the contents of Section 3.2.P.2 (Pharmaceutical Development)
- Describes good practices for pharmaceutical product development
- Introduces concepts of
  - Design space
  - Flexible regulatory approaches
  - Quality Risk Management (Q9)
- Does not discuss QbD
QbD Definition (ICH Q8(R))

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.
Why QbD?

- Higher level of assurance of product quality
- Cost saving and efficiency for industry
  - Increase efficiency of manufacturing process
  - Minimize/eliminate potential compliance actions
  - Provide opportunities for continual improvement
  - Facilitate innovation
- More efficient regulatory oversight
  - Enhance opportunities for first cycle approval
  - Streamline post approval manufacturing changes and regulatory processes
  - More focused PAI and post approval cGMP inspections
ICH Q8R

- Annex to ICH Q8
- Describes principles of QbD vs. minimal approach
- Provides further clarification of key concepts of Q8
- Provides illustrative examples

*Details provided in the next Presentation - Brian Withers, Abbott Laboratories*
ICH Q8(R) Update

- Reached Step 4 in Brussels, November 11, 2008

- Only a few minor step 4 revisions:
  - Quality Target product Profile
    - QTPP forms the basis of design for development
  - Design space versus proven acceptable ranges
    - combination of PARs doesn’t constitute design space
  - Real Time Release Testing (RTRT)
    - To distinguish between RTRT and batch release
ICH Q9 and Q10

- Key enablers
- Assure correct implementation of QbD (Development & manufacturing throughout product life cycle and supply chain)
- Both will be discussed in more details tomorrow
ICH Q9: Quality Risk Management

- A systematic process for the assessment, control, communication and review of risks to the quality of the drug product
- Guidance includes principles and examples of tools for quality risk management
- Evaluation of risk to quality should:
  - be based on scientific knowledge
  - link to the protection of the patient
- Applies over product lifecycle: development, manufacturing and distribution
Role of Quality Risk Management in Development & Manufacturing

Product Development
- Product/prior Knowledge
  - Risk Assessment
    - Excipient & drug substance design space
- Process Understanding
- Risk Assessment
- Process design space

Process Development
- Risk Control
- Product quality control strategy

Process Scale-up & Tech Transfer
- Process History
  - Risk Review
    - Continual improvement

Manufacturing

Quality Risk Management
ICH Q 10: Why Focus on PQS?

The regulatory flexibility provided with a design space approach requires effective change management at the manufacturing site.

- Track and trend product quality
- Respond to process trends before they become problems
- Maintain and update models as needed
- Internally verify that process changes are successful
Example QbD Approach (ICH Q8R)

- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement
Quality Target Product Profile

“Begin with the end in mind”

- Summary of the quality characteristics of a drug product to ensure safety and efficacy
- Includes, but not limited to:
  - Dosage form
  - Route of administration
  - Pharmacokinetic characteristics
    - e.g., dissolution, aerodynamic performance
  - Quality characteristics for intended use
    - e.g., sterility, purity
Critical Quality Attributes (CQAs)

- Physical, chemical, biological or microbiological property or characteristic
- Drug product, drug substance, intermediates, and excipients can possess CQAs
  - Directly affect product quality
  - Affect downstream processability
- Drug product CQAs affect product quality, safety, and/or efficacy
  - Attributes describing product purity, potency, stability and release
  - Additional product specific aspects (e.g., adhesive force for transdermal patches)
Risk Assessment (ICH Q9)

- **Tools for parameter screening**
  - Examples: Ishikawa diagrams, What-if analysis, HAZOP analysis

- **Tools for risk ranking**
  - Examples: FMEA/FMECA, Pareto analysis, Relative ranking

- **Experimental tools for process understanding**
  - Examples: Statistically designed experiments (DOE), mechanistic models
Design Space (ICH Q8)

- **Definition**
  - The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality

- **Regulatory flexibility**
  - Working within the design space is not considered a change

- **Important to note**
  - Design space is proposed by the applicant and is subject to regulatory assessment and approval
Design Space Determination

- First-principles approach
  - combination of experimental data and mechanistic knowledge of chemistry, physics, and engineering to model and predict performance

- Non-mechanistic/empirical approach
  - statistically designed experiments (DOEs)
  - linear and multiple-linear regression

- Scale-up correlations
  - translate operating conditions between different scales or pieces of equipment

- Risk Analysis
  - determine significance of effects

- Any combination of the above
Describing Design Spaces

- Linear Ranges of Parameters
- Mathematical Relationships
- Time-dependent functions
- Combinations of variables
  - e.g., Principle components of multivariate model
- Scaling Factors
- Single or multiple unit operations

The applicant decides how to describe and present the design space
• Design space can be described as a mathematical function or simple parameter range
• Operation within design space will result in a product meeting the defined quality attributes
Design Spaces Example #2

Dissolution

Friability

Design space for multiple attributes
Quality control strategy encompasses process controls and specifications, based on process understanding.
Continual Improvement

- Flexibility for movement within design space
  - Wider range of material attributes or process parameters
  - No reporting if moving operating range within design space
  - Potential scale or equipment change without supplement (subject to regional regulatory requirements)

- Post-Approval Management Plan (CMC-PMP)
  - A mechanism for applicant to propose a regulatory strategy specific to a product and/or process
  - Currently under development by FDA
QbD Concepts in Development and Manufacturing of API

- It may be simpler to apply QbD concepts to drug substances than drug product.
- Mixing and transport within liquids and slurries better understood than for dry particles.
- Well-established modeling techniques:
  - Reaction kinetics
  - Cell growth
  - Crystallization nucleation and growth
  - Scale-up correlations
- Readily available in-line and on-line measurement techniques
- Laboratory equipment for parallel experiments and automated analysis
Example Risk Assessment for Batch API Synthesis Step

<table>
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<th>Category</th>
<th>Process Parameter</th>
<th>Severity S (1-5)</th>
<th>Occurrence O (1-5)</th>
<th>Detection D (1-5)</th>
<th>Risk priority number S<em>O</em>D</th>
<th>Risk Ranking/Prioritization</th>
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<td>4</td>
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<td>Nucleation time</td>
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<td>3</td>
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<td>24</td>
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<td>Anti-solvent addition rate</td>
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<td>3</td>
<td>2</td>
<td>30</td>
<td>4</td>
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</table>

Risk ranking helps focus research and development efforts.
ONDQA’s QbD Pilot Program

- **Objectives**
  - To provide participating firms an opportunity to submit CMC information demonstrating QbD
  - To enable FDA to implement new QbD concepts

- **Status**
  - 9 original and 3 supplemental NDAs accepted
  - 11 submitted to date: 9 approved, 2 under review

- **Common factors**
  - Submission of design space
  - Use of risk assessment
  - Proposals of regulatory flexibility under firm’s quality system
Examples of Design Space in Recent NDAs

- **Excipient attributes**
  - Degree of polymer substitution
  - Viscosity/molecular weight distribution
  - Particle size distribution

- **Drug substance attributes**
  - Particle size distribution

- **Process parameters**
  - Drug substance unit operations
  - Drug product unit operations
  - Effect of scale-up considered
  - Effect of equipment type understood
Most applications included a design space for drug product; some for drug substance

Most included design spaces for process parameters; some included formulation component properties

Methods for determining design space included:

- One variable at a time experiments
- Statistically designed experiments (DOE’s)
- Modeling approaches
CMC Pilot Program – Control Strategy Examples

- Certain tests for drug substance CQAs moved upstream to the control points
- On-line analyzers (non-PAT) used for intermediates
- In-process testing (in lieu of end-product testing) for
  - Identification and assay using at-line NIR
  - Dose uniformity by on-line weight variation
- Real-time release testing
Several applications presented risk assessments

- Linking of process parameters to CQAs
- Identification of relevant parameters for design space
- Weighting of processing risks and experimental priorities
- Tools used included Ishikawa (fishbone) diagrams, FMEA analysis, Pareto analysis
Findings from ONDQA Pilot Program

- Provided valuable experience for industry and FDA in implementing QbD
  - Elements of QbD in submissions
    - Risk assessments
    - Design spaces
    - Proposals for flexible regulatory approaches
  - Risk-based regulatory decisions were enabled
- Pointed out gaps
  - Learning from pilot applied to ICH Q8 (R)
  - Demonstrated the need for:
    - Harmonized implementation (ICH IWG)
    - Post-Approval Management Plan (CMC-PMP)
Challenges of Implementing QbD

- **FDA**
  - Communicating new concepts
  - Providing regulatory flexibility while assuring product quality
  - Integration of review and inspection under the new ICH quality paradigm

- **Industry**
  - Management support
  - Communication across business units
  - Global acceptance and implementation

- **FDA and industry**
  - Cultural changes needed
  - More resources needed initially (Investment)
  - Learning and experience needed for new approaches
Concluding Remarks

Quality by Design has moved into the implementation phase

- New guidelines are in place to facilitate
- Recent NDAs (incl. ONDQA pilot program) have provided opportunities for implementing QbD

Full implementation of QbD is a win-win-win situation

- Manufacturers – Better understanding of product/process, more efficient process, reduced regulatory burden
- Regulators – providing regulatory flexibility without sacrificing quality
- Patients – increased assurance of product quality
Pathway to the Desired State

**The Desired State:**
A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.

**Quality Risk Management (ICH Q9)**

**Quality by Design Highway**

**Product and Process Understanding (ICH Q8/Q8R)**

**Pharmaceutical Quality Systems (ICH Q10)**