ICH Q8/Q8R – Pharmaceutical Development

Christine M. V. Moore, Ph.D.
Deputy Director for Research and Policy
Office of New Drug Quality Assessment
CDER/FDA
Outline

• Background on ICH Q8/Q8R
  – Quality by Design (QbD)
• FDA experience with QbD
  – Examples from CMC Pilot
  – Recent ONDQA experience
• Remaining challenges
• Concluding comments
ICH Q8 - History

• ICH Quality Vision – July 2003 (Brussels)
  Develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to risk management and science

• Q8 Step 2 (draft for comment) – Nov 2004
• Q8 Step 4 (finalized) – Nov 2005
• Q8 Annex Step 2 (draft for comment) – Nov 2007
• Q8(R1) Step 4 (final) – Nov 2008
• Q8(R2) Revision for editorial errors – Aug 2009
ICH Q8 Core Document - Content

• 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 Quality by Design
Key Points from ICH Q8 Core Document

• Quality cannot be tested into products, it should be built in by design

• Pharmaceutical development provides the scientific understanding to support the establishment of design space, specifications and manufacturing controls

• Aspects of pharmaceutical development include:
  – Components of Drug Product
  – Drug Product Development
  – Manufacturing Process Development
  – Container Closure System
  – Microbiological Attributes
  – Compatibility
ICH Q8(R2) - Content

• Defines and describes principles of Quality by Design (QbD)

  Quality by Design is 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

• Provides further clarification of key concepts of Q8

• Provides illustrative examples
Key Points
from ICH Q8 Annex Document

• Minimal Approach
  – Defining the quality target product profile
  – Identify potentially critical quality attributes of drug product
  – Determine critical quality attributes of the drug substance and raw materials
  – Selecting an appropriate manufacturing process
  – Defining a control strategy

• Enhanced (QbD) Approach
  – Systematic evaluation and understanding of the formulation and manufacturing process
  – Using the enhanced understanding with risk management to establish an appropriate control strategy
  – Can support flexible regulatory approaches
Example QbD Approach - ICH Q8(R2)

- 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
  - Patient needs – elderly, children
  - Amount of drug per dose
  - Desired dosing schedule
  - Route of administration
  - Safety requirements
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)
Defining CQAs Example: In Vitro – In Vivo Correlations

In Vivo Response
(Plasma Conc. Profile)

In Vitro/In Vivo Correlation

In Vitro Release
(Dissolution Profile)

Predictive Model

Formulation and Manufacturing Process

Reference: Medscape, 2002
Risk Management

- A systematic process for the assessment, control, communication and review of risks to the quality of the drug product

- Evaluation of risk to quality should:
  - be based on scientific knowledge
  - link to the protection of the patient
  - Extend over the lifecycle of the product

- Typically conducted with an integrated group of experts, including development and manufacturing
Risk Assessment Example #1
Ishikawa Diagram

Tablet Compression

Machines
- Pre and Main Compression
- Material Addition Method
- Drop Height

Methods
- Press Speed
- Feeder Speed
- Cam Size/Tooling
- Machine set-up
- SOPs
- Batch records
- SOPs
- Precompression Force
- Main Compression Force

Measurements
- Weight
- Thickness
- Metal Check
- Turret RPM
- Cylindrical fill height

Materials
- Drug Substance
  - Age
  - P.S. LOD
  - ID
- Diluent
  - P.S. LOD
  - Batch Size
- Other Excipients
  - Quantity
  - Properties

Personnel
- Operators
  - Experience
  - Training

Environment
- Manufacturing Suite
  - Internal Temp
  - Humidity
  - External Temp
## Risk Assessment Example #2
### Failure Mode and Effects Analysis

#### Moisture Sensitive Crystalline Product

<table>
<thead>
<tr>
<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>Criticality rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalliztn</td>
<td>Residual solvent</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>60</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Induction time</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Anti-solvent addition time</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Mixing</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Isolation/drying</td>
<td>Temperature during crystal drying</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Solids transfers</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Washing effectiveness</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Handling/storage</td>
<td>Relative humidity</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>45</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Inerting</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>24</td>
<td>6</td>
</tr>
</tbody>
</table>
Design Space

- **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 as a change

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

**Inputs:**
- M1
- M2
  - Material Attributes
- P1
- P2
- P3
  - Process Parameters

**Outputs:**
- CQA1
- CQA2
- CQA3
  - Critical Quality Attributes

**Relationships:**
- CQA1 = function (M1)
- CQA2 = function (P1, P3)
- CQA3 = function (M1, M2, P1)
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
  – a semi-empirical approach to translate operating conditions between different scales or pieces of equipment

• Risk Analysis
  – Determine significance of effects

• Any combination of the above
Example - Establishing Design Space

Pilot Scale DOE

Commercial Scale Confirmatory Experiments

Dissolution Response (Design Space)

Input Variables: Polymer concentration, Roll gap, Roll force

Responses: Porosity, Compressibility, Dissolution, Hardness
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
Example – Describing Design Spaces

- 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
Control Strategy

- A planned set of controls, derived from current product and process understanding, that assures process performance and product quality (ICH Q10)

- Control strategy can include
  - parameters and attributes related to drug substance and drug product materials and components
  - facility and equipment operating conditions
  - in-process controls
  - finished product specifications
  - associated methods and frequency of monitoring and control
Design Space and Quality Control Strategy

Design Space

Input Materials

Process (or Process Step)

Input Process Parameters

Monitoring of Parameters or Attributes

Process Controls/PAT

Product (or Intermediate)

Reduced Product Variability

Process Variability

Reduced Product Variability
Real Time Release Testing

• The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls
  
  ICH Q8(R2)

• Manufacturing flexibility
  – Increased manufacturing efficiency
  – Measure and control in real-time

• Increased assurance of quality
  – Science based release criteria
  – More representative of process

A more modern approach to manufacturing and control
Control Strategy Example – Real Time Release

- **Raw materials & API dispensing**
  - Specifications based on product

- **NIR Monitoring**
  - Blend Uniformity

- **Laser Diffraction**
  - Particle Size

- **NIR Spectroscopy** (At-Line)
  - Identity
  - Assay
  - API to Excipient ratio

- **Dispensing**
- **Blending**
- **Sifting**
- **Roller compaction**
- **Tablet Compression**
- **Pan Coating**
Continual Improvement

- Lifecycle risk management
  - Use development information as starting point
  - Update as experience gained
- Process tracking and trending
  - Statistical process control
  - Adjust trends before they become problems
- Knowledge management
- Model maintenance and updating
FDA Review Office Programs

- Office of New Drug Quality Assessment (ONDQA)
  - Pharmaceutical Quality Assessment System (PQAS)
  - 2005 CMC Pilot program

- Office of Biotechnology Products
  - 2008 Biotechnology Pilot Program

- Office of Generic Drugs
  - Question Based Review (QBR)
  - Workshops on QbD for generic drugs
ONDQA’s CMC Pilot Program

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

• Status – complete
  o First announced June 2005
  o 9 original and 2(3) supplemental NDAs accepted
  o 11 approved, 1 withdrawn for non-CMC reasons

• Common factors
  o Submission of design space
  o Use of risk assessment
  o Proposals of regulatory flexibility under firm’s quality system
CMC Pilot Observations

• Wide variety of design spaces proposed:
  o Most included drug product, some included drug substance
  o Most included process parameters, some included formulation components
  o Developed using varied experimental techniques & mathematical models
  o Several utilized risk assessment in development

• Wide variety of control strategies utilized, including
  o On-line analyzers
  o In-process testing in lieu of end-product tests
  o Real time release testing using PAT
Findings from CMC Pilot Program

• Provided valuable experience for industry and FDA in implementing QbD
  o Elements of QbD in submissions
    • Risk assessments
    • Design spaces
    • Proposals for flexible regulatory approaches
  o Risk-based regulatory decisions were enabled
• Learning has been incorporated into ICH Q8R
• Refinement of concepts still ongoing
  o QbD applications within and outside of pilot program
Recent QbD Experiences-Outside the CMC Pilot

• Number of QbD meetings and applications have been increasing

• Number of submissions containing QbD elements received in 2008 & 2009 outside of pilot
  – 12 NDAs
  – 6 supplemental NDAs

• New proposals have contained challenging regulatory approaches

• Additional experience is helping to coalesce review approaches
Challenges for QbD

- **Culture challenges**
  - Move from prescriptive approach
  - More sharing of scientific and risk information

- **Business Challenges**
  - Business justification
  - Management Support
  - Budgeting silos across business units

- **Implementation Challenges**
  - Collaboration between functions
  - Experience with new concepts
  - Workload and resource limitations

- **International harmonization**
Potential Costs & Benefits of QbD

**Increased Resources**
- Development costs
- Organizational planning

**Decreased Expenses**
- Manufacturing Costs
- Compliance Costs
- Regulatory Filings
- Reduced inventories

- **Initiate QbD Efforts**
- **QbD Fully Realized**

**QbD Implementation Progress**
Concluding Thoughts

• FDA and ICH quality initiatives are enabling a fundamental paradigm shift in pharmaceutical manufacturing:
  – Quality control strategies based on product knowledge and process understanding
  – A more scientific and risk-based regulatory oversight

• 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
Thank you!

Questions, comments, concerns:
NewDrugCMC@fda.hhs.gov