The Role of Quality Risk Management in New Drug Development and Manufacturing

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Outline

- Quality by Design
- Risk Management
- Risk Management Tools
- Risk Management in a CMC Review
- Summary
Definition of Quality by Design

- Systematic approach to development
- Begins with predefined objectives
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management

*From ICH Q8(R), Nov. 2008*
The Desired State

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

— Janet Woodcock
FDA View on QbD

Product & process design and development

Define desired product performance upfront; identify product CQAs

Design formulation and process to meet product CQAs

Continually monitor and update process to assure consistent quality

Identify and control sources of variability in material and process

Understand impact of material attributes and process parameters on product CQAs

Risk assessment and risk control
Risk Management in QbD

• Risk assessment and control as part of process design and development
  – Aids in identifying and linking material attributes and process parameters to CQAs
  – Enables early identification of risk to guide development efforts
  – Employed to quantify the severity of harm and likelihood of occurrence
  – Updated, as needed, through process modifications or additional understanding to reduce risk
Principles of Quality Risk Management (ICH Q9)

• A systematic process for the assessment, control, communication and review of risks to assure the quality of the drug product across the product lifecycle

• Evaluation of risk to quality should:
  – be based on scientific knowledge
  – be linked to the protection of the patient

• The effort and documentation should be commensurate with the level of risk
Quality Risk Management Process

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

Design of Control Strategy

Continual Improvement
Role of Quality Risk Management in Development & Manufacturing

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

Process Development
- Process Understanding
  - Risk Assessment
  - Process design space

Process Scale-up & Tech Transfer
- Process Design Space
  - Risk Control
  - Product quality control strategy

Manufacturing
- Process History
  - Risk Review
  - Continuous improvement

Quality Risk Management
Example of Risk Assessment Tools in Product & Process Development

• Qualitative Tools for parameter screening
  – Examples: Ishikawa Diagrams, What-if Analysis, HAZOP Analysis

• Quantitative Tools for risk ranking
  – Examples: FMEA/FMECA Analysis, Pareto Analysis, Relative Ranking

• Experimental Tools for process understanding
  – Examples: Statistically Designed Experiments, Mechanistic Models
Ishikawa (Fishbone) Diagrams

- Also known as Fishbone or Cause & Effect Diagram
- Includes all the potential inputs that effect a desired output (CQA)
- Effective for initial brainstorming of potential design space parameters
Failure Mode Effects Analysis (FMEA)

- Cross-functional evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance
- Relies on product and process understanding
- Used to prioritize risks and monitor the effectiveness of risk control activities.
- Output/results can be used as a basis for design of experiment or further analysis
- Quantitative assessment of risk
  - Risk = Severity x Likelihood x Detectability
Experimental Approach for Identifying Parameters - Example

Design of Experiments (DOE): an efficient method to determine relevant parameters and interactions

1. Choose experimental design
   (e.g., full factorial, d-optimal)

2. Conduct randomized experiments

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Factor A</th>
<th>Factor B</th>
<th>Factor C</th>
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<tr>
<td>1</td>
<td>+</td>
<td>-</td>
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<td>-</td>
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<td>4</td>
<td>+</td>
<td>-</td>
<td>+</td>
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</table>

3. Analyze Data
Determine significant factors

Pareto Chart of the Standardized Effects
(response is Strength, Alpha = .05)
Risk Assessment Benefits

• Systematic approach to identifying and classifying parameters in the design space
• Useful in process development, monitoring, improvement, and troubleshooting
• Increased assurance of quality:
  – Process variability is identified and its linkage to product CQAs understood
  – Process and product controls reduce impact of variability
  – Quality product will continue to be made when movement within the design space occurs in the future
• Communication tool between different organizations and groups
  – Development and manufacturing
  – Industry and regulators
  – Multiple manufacturing sites
Risk Assessment
ONDQA QbD Pilot Program

Outline
– Observations
– Risk Assessment in CMC Review
  • Utility of Risk Assessment
  • Detectability
– Risk Assessment and Design Spaces
– Examples
– Points to Consider
– Reviewer Feedback
Risk Assessment – Observations to Date

• Several applications presented risk assessments, especially for drug product, linking input/process variables to CQAs
  – Tools used included Ishikawa (Fishbone) diagrams, FMEA, FMECA, Pareto analysis, DOE, Britest
  – Identification of relevant parameters for design space
  – Weighting of processing risks and experimental priorities
  – Linking input/process variables to CQAs
  – Failure mode analysis during development and scale-up
Risk Assessment in CMC Review

Utility of Risk Assessment

• Preferred for applicant to include Risk Assessment in NDA
  – Focus on CQAs that impact safety and efficacy
  – Consider developmental knowledge
  – Provide more information for risk in critical operations

• If not provided, CMC reviewer may perform a risk assessment during the review
  – Similar principles as applicant was used
  – Risk was always considered as part of review process
  – More formal process and uniform language per Q9
Detectability

- Will an adverse impact on safety or efficacy be detected by routine testing?
  - Yes: lowers risk from reviewer’s perspective
  - No: depending on severity and probability, may raise level of risk

- If detectability is low, reviewer may need to understand how risk is handled by overall quality control strategy
  - Assurance that applicant recognizes and controls the risk
  - Details need not always be in the application
Risk Assessment & Design Space

• Some Pilot applications include summary information on FMEA, etc that were used to select parameters to study
  – Reviewers found this very informative

• Valuable to use Detectability, Severity and Probability to select parameters of Design Space for regulatory interaction per Q8
Examples of Risk Assessment

• Example 1
  – Parameter screening for tablet manufacturing

• Example 2 & 3
  – Parameter screening and risk ranking for tablet manufacturing

• Example 4
  – Impurity mapping
Risk Assessment – Example 1
Ishikawa Diagram for Tablet Hardness

Identify input/process variables that affect CQAs
## Risk Assessment – Example 2

### Failure Mode and Effect Analysis (FMEA) (truncated)

#### Risk Prioritization

- Rating (1-10)
  - Probability
  - Severity
  - Detectability

- Semi-quantitative values assigned using knowledge management
  - Multidisciplinary expert teams
  - Prior knowledge
  - Development experiments

### Semi-quantitative rating of Risk Factors

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Select process parameter</th>
<th>Polymer Concentration</th>
<th>API Particle Size</th>
<th>Roll Gap</th>
<th>PSD of Intragranular Blend</th>
<th>Compressing Force</th>
<th>Weighted Average</th>
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<tbody>
<tr>
<td>Dissolution</td>
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<td>4</td>
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<td>1</td>
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<tr>
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<td>5</td>
<td>5</td>
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<td>1</td>
<td>9</td>
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<tr>
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<tr>
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</table>
Risk Assessment – Example 3

Pareto Analysis

Relative importance of inputs based on FMEA
Risk Assessment – Example 4

Impurity Mapping

<table>
<thead>
<tr>
<th>Spike level</th>
<th>Stage1</th>
<th>Stage2</th>
<th>Stage3</th>
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<tr>
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<td>&lt; 0.05</td>
<td>&lt; 0.05 *</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

- Appropriate controls in starting materials
- Similar knowledge on the origin and fate of all other impurities
Risk Assessment: Points to Consider

- Utilize a systematic approach to risk analysis
  - Consider effect of raw materials, process steps, and process parameters on product quality
  - Use over entire product lifecycle
- Discuss the comprehensive control strategy reduces risks to product quality
- Discuss controls in place to reduce potential risks to product quality upon process changes inside or outside the design space
- Detectability, Severity and Probability of effect all important from reviewer’s perspective
Reviewer Feedback – Pilot Program

• Risk analysis
  – Highly useful, but not systematically applied
  – Risk reduction through process and material controls often not integrated
  – Missing “big picture” of how quality is assured
    • At launch and with continual improvement
  – Application to change control sometimes unclear

• Risk assessment is highly valuable for reviewing CMC applications
Summary
Risk Assessment

• A valuable science-based method used in quality risk management
• Aids in identifying which material attributes and process parameters have an effect on product CQAs.
• Typically performed early in the risk management process
• Repeat as information and greater knowledge become available.
Thank you

• Acknowledgements
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