Pharmaceutical Quality – Current Challenges and Future Opportunities

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Outline

• Background on Quality and FDA’s Quality Initiatives
• Challenges and Opportunities
  – Product Understanding
  – Process Understanding
  – Process Control
  – Integration and Collaboration
• Concluding Thoughts
What is Pharmaceutical Quality?

- The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength and purity (ICH Q6A)
- The degree to which a set of inherent properties of a product, system or process fulfills requirements (ICH Q9)
Holistic View of Pharmaceutical Quality

Patient

Process

Product

Clinical Outcome

Critical Quality Attributes

Material Attributes & Process Parameters
What is Quality by Design (QbD)?

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

*From ICH Q8(R2)*
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

QbD Approach

Understand the Product

Understand the Process

Control the Process Over the Product Lifecycle
Understanding the Product

Product understanding questions include:
- What defines “good” quality drug substance?
- How do the formulation components interact during and after processing?
- How does the drug product interact with the container closure?
- How does the drug become available at the site of action?
- How might the patient incorrectly use or misuse the drug product?
Examples of Traditional Studies for Product Understanding

• Drug substance properties selection
  – Polymorph screening
  – Particle size evaluation

• Formulation selection
  – Excipient selection and compatibility
  – Container closure leachables and extractables

• Drug distribution within the body
  – Pharmokinetic/Pharmodynamic (PK/PD) studies
  – Bioequivalence studies to previous formulations

Challenges in Product Development

• Traditional approaches to product development often have been:
  – Focused on optimization and not robustness
  – Developed with little or no input from manufacturing
  – Performed without understanding the relevance to bioavailability
  – Not performed with the patient use in mind
Some Challenges Related to Product Understanding

- Effects of excipient variability on product performance
- Solid state of drug substance within the drug product
- Variability in complex molecules – biotech or naturally derived products
- Complex delivery systems – transdermal patches, inhalation products
- Potential for patient misuse or abuse
  - Residual drug in transdermal patches
  - Alcohol related dose dumping
  - Tablet splitting

Opportunities for Product Understanding

- Application of formal Quality Risk Assessment early in development
  - Involve of all stakeholders
  - Define potential failure modes
  - Include patient use factors
- Understand how variability of excipients and raw materials affects product performance
- Integrate biopharmaceutics into product development
- Use of advanced analytics for complex molecules or products
Example Patient Use Factors: Alcohol Induced Dose Dumping

- Some modified release solid oral dosage forms can contain drugs or excipients that are highly soluble in ethanol (EtOH).
- Ingestion of alcohol could lead to dangerously high drug exposure - Either intentionally or unintentionally
- Dose dumping should be considered when designing modified release formulations

Example of Understanding Excipient Variability: Artificial Neural Network Example

- **Problem:** Dissolution is highly dependent on polymer properties

- **Method:** ANN dissolution model developed from from pilot and commercial batches

- **Results:** Dissolution properties successfully predicted based on excipient attributes
Approach for Product Understanding: Biopharmaceutics Studies

- The science and study of the ways in which drugs influence their pharmacodynamic and pharmacokinetic behavior
  - Typically uses plasma concentrations as biomarker for safety and efficacy
- Strives to relate in vivo performance of a drug to in vitro measurements
  - Enables development of clinically relevant specifications
  - Understand the impact of manufacturing process variables
- Supports control strategy development through setting clinically meaningful dissolution specifications to assure consistent therapeutic benefit

Example In vitro/In vivo Correlation (IVIVC) Approach

In Vivo Response (Plasma Conc. Profile)  \[\text{In Vitro Release (Dissolution Profile)}\]  \[\text{In Vitro/In Vivo Correlation} \]

Formulation and Manufacturing Process  \[\text{Predictive Model} \]

Reference: Medscape, 2002
Example – Bioequivalence without IVIVC

- Multiple batches are produced with widely varied dissolution rates
- Clinical relevance is assured within established range
- Assures product robustness, and can achieve a wider dissolution specification

![Graph showing drug release over time for Forms A, B, C, and clinical trials, indicating bioequivalence without IVIVC.]

**Std approach dissolution spec:**
Q= 80 at 30 min.

**BE approach dissolution spec:**
Q= 80 at 45 min
Understanding the Process

• Process understanding can include:
  – What process parameters can affect product quality?
  – What ranges of process parameters produce acceptable quality?
  – How do intermediate material attributes relate to final product quality?
  – What is the effect of atypical operations on quality - excess hold times, environmental effects, excursions?
Challenges with Process Development

- Traditionally, process development studies have often:
  - Not systematically approached
  - Focused on reproducibility (i.e., 3 validation batches) and not robustness
  - Focused on optimization and not robustness
  - Not considered interactions between parameters (e.g., one variable at a time experiments)
  - Looked at each step or unit operation in isolation
  - Not evaluated potential failure modes

Opportunities for Process Understanding

- Risk assessment approaches
  - Narrows down important variables
  - Prioritizes work for greater efficiency
  - Examines potential failure modes

- Modeling approaches
  - Empirical Models
    - Design space experiments for parameter range finding and interactions
  - Mechanistic Models
    - Utilizes knowledge of physical system and equations describing the underlying chemistry and physical phenomena
    - Often uses computational modeling for more complex systems
  - Semi-empirical Model
    - Scale-up relationships
Risk Assessment Example

Ishikawa Diagram for Tablet Compression

Risk Assessment Example - FMEA

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>
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<tbody>
<tr>
<td>Crystallization</td>
<td>Residual solvent</td>
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<td>4</td>
<td>3</td>
<td>60</td>
<td>1</td>
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<tr>
<td></td>
<td>Induction time</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>24</td>
<td>6</td>
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<tr>
<td></td>
<td>Anti-solvent addition time</td>
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<td>3</td>
<td>2</td>
<td>30</td>
<td>4</td>
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<tr>
<td></td>
<td>Mixing</td>
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<td>2</td>
<td>1</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Isolation/ drying</td>
<td>Temperature during crystal drying</td>
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<td>4</td>
<td>2</td>
<td>32</td>
<td>3</td>
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<td></td>
<td>Solids transfers</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td></td>
<td>Washing effectiveness</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>15</td>
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<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>
Empirical Modeling – Design of Experiments (DOE)

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>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
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<td>2</td>
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</tr>
<tr>
<td>4</td>
<td>+</td>
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<td>+</td>
</tr>
</tbody>
</table>

3. Analyze Data
Determine significant factors

Example Mechanistic Model of Crystallization

- Controlled crystallization with seeding
- Processing occurs entirely in thermodynamically favored regime

Highly reproducible particle size distribution
Laboratory experiments indicated an impurity level was mixing dependent. Computational Fluid Dynamics model showed that adequate mixing will be attained at all settings at commercial scale.
Control Strategy

• 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

• An effective and efficient control strategy relies upon integration of product and process understanding

Challenges with Product Manufacturing Control Strategies

• Traditionally, product manufacturing has often:
  – Focused on ability to “pass validation”
    • Reproducibility vs. Robustness
    • Limited data collection – fear of too much data
  – Defined quality solely based on ability to meet release specifications
    • Not measurement and analysis of potential process signals
    • Inability to make timely process corrections
  – Processes are fixed or “frozen”
    • Process changes reactive, not for continual improvement
Opportunities for Manufacturing Controls

- Incorporate product and process understanding into regulatory control strategy
  - Design space to allow more flexible operation
- Measure process intermediates in real time
  - Active controls (e.g., feed-back, feed-forward)
  - Can lead to real time release testing approach
- Actively monitor process parameters
  - Correct trends before they become problems
- Update product and process knowledge over lifecycle
  - Knowledge management
  - Risk management

Example Approach for Defining Design Space

Adapted from ICH QIWG training slides, Washington DC, October, 2010

Multi-factorial DOE to study factors affecting dissolution

Factors: API particle size
MgSt surface area
Lubrication time
Tablet hardness

Response: % dissolved in 20 min

Design space represented as a contour space on the basis of DOE data

Prediction algorithm:

\[ \text{Diss} = 108.9 - 11.96 \times \text{API} - 7.556 \times 10^5 \times \text{MgSt} - 0.1649 \times \text{LubT} - 3.783 \times 10^2 \times \text{Hard} - 2.557 \times 10^5 \times \text{MgSt} \times \text{LubT} \]
Example - In-Process Measurement for Blend Uniformity

Uniformity of excipients and blend determined by on-line process monitoring by NIR

Real Time Release Testing - ICH Q8(R2)

- The ability to evaluate and ensure the quality of in-process and/or final product based on process data
  - Typically include a valid combination of measured material attributes and process controls 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 Testing (RTRT)

- **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

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Conceptual Example of Control Strategy for Continuous Manufacturing

- **Receiving**
- **Continuous Blending**
- **Continuous Granulation**
- **Particle Size Distribution**
- **Weight & Hardness**
- **Compression**
- **Continuous Film Coating**
- **At-line Chemical Properties**
- **Physical Properties**
- **Dissolution Model (release)**
- **Digital Imaging**
- **Concentration & Uniformity** (Multi-component)
- **Real-time Release Testing**

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Example of Multivariate Statistical Process Control

A multivariate statistical process control model was constructed for tablet compression
  • Built from multiple batches that made acceptable quality product
  • Data from additional batches projected on to the model to demonstrate conformance

Integration and Collaboration (Industry and Regulators)
• Traditionally, little integrated communication between organizations
• Different goals in different organizations (timelines, budgets, priorities - process robustness vs. yield)
Traditional Approach for Industry

Integrated Approach for Industry
• Traditionally, little integrated communication between organizations
• Different goals in different organizations (timelines, priorities)
Integrated Approach for Regulators (FDA)

Reviewer

Compliance Officer

Investigator

Information Flow

Collaborative Working Environment

No silos

No gatekeepers

Open Information
Sharing and Teamwork

Applies to both Industry and Regulators
Collaborative Working Environment to Support Pharmaceutical Quality

- Understand and respect the roles and needs of colleagues
- Engage in open and early communication
- Collaboratively develop risk assessment and management plans
- Develop, maintain and utilize a system for knowledge retention
- Anticipate and plan for problems
- Develop a “Culture of Quality”

Benefits of Integration - Industry

Potential for:
- More robust processes, fewer deviations in manufacturing
- Less product variation
- Smoother start-ups and transitions with less errors
- Reduced need for redevelopment
- Faster implementation
- Monetary savings

*Increased efficiency and effectiveness*
Benefits of Integration - Regulators

• More risk focused inspections
  – Reviewer knowledge shared with investigator to facilitate quick understanding of product and process related risks
  – Compliance knowledge shared with investigator to facilitate understanding of facility related risks
  – Participation of reviewers and/or compliance officers in more inspections

• Better informed review
  – Better understanding by reviewers of how PQS supports product quality
  – Feedback from field related to product quality issues
  – Better ability to understand firm’s approaches to changes in supplements

*Increased efficiency and effectiveness*

Concluding Thoughts

• Challenges remain, but opportunities abound for ensuring pharmaceutical quality
  – Focus on product understanding, process understanding, and process control

• Use a science and risk based approach
  – Both industry and regulators
  – Continue efforts for international harmonization

• Engage in open and early communication
  – Communication within an organization (no silos)
  – Communication between regulators and industry
Thank you!

Questions, comments, concerns:
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