Assurance of Pharmaceutical Quality through Utilization of Science Based Approaches

Workshop on “Operational Excellence: A Lifecycle Approach to Assuring Product Quality”
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Outline

• Background on Quality and FDA’s Quality Initiatives
• Product Understanding
• Process Understanding
• Process Control
• Remaining Gaps and Challenges
What is Pharmaceutical Quality?

- The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as 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).

Linking Process - Product - Patient

- Critical Quality Attributes
- Material Attributes & Process Parameters
- Clinical Outcome
The Patient Cannot “See” Pharmaceutical Quality

Which product is subpotent?

![Low Concentration](image1.png)  
![High Concentration](image2.png)

- Poor quality can lead to:
  - Lack of safety and/or efficacy (often difficult to detect)
  - Product recalls, withdrawals, shortages

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
Examples of Studies for Product Understanding

- Drug interactions and stability
  - Polymorph screening
  - Excipient compatibility
  - Container closure leachables and extractables
- Drug distribution within the body
  - Bioequivalence studies
  - Pharmokinetic/Pharmodynamic (PK/PD) studies
- Potential for misuse or abuse
  - Residual drug in transdermal patches
  - Alcohol related dose dumping

Product Understanding: Extractables and Leachable Studies

- Used to screen for and monitor presence of toxic materials from container closure system (CCS)
  - Usually related to plastic components of the CCS
- A risk-based approach can be used to:
  - Determine likelihood and identity of leachables, based on prior knowledge and experimentation
  - Consider risk to patient, based on route of administration (e.g., parenteral, topical, ophthalmic) and toxicity of leachables
- Understanding of the potential risks can be the basis for an effective process control strategy
Extractables Studies

- Extraction with solvents of multiple polarities
- Estimate daily exposure, and safety concern threshold
- Involve toxicologists in assessment

Extractables and Leachables

- Not all extractables are leachables
- Not all leachables are extractable
- When possible, develop a correlation between extractables and leachables
- Control and/or characterize the non-correlatable leachables

Anthony Grilli, Leachables and Extractables Testing, A Primer on Regulations and Methods
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

In vitro/In vivo Correlations (IVIVC)

Formulation and Manufacturing Process

In Vivo Response (Plasma Conc. Profile)

In Vitro Release (Dissolution Profile)

In Vitro/In Vivo Correlation

Predictive Model

Reference: Medscape, 2002
Alcohol Related 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

Approaches to Process Understanding

- Risk assessment approaches
  - Narrows down important variables
  - Prioritizes work for greater efficiency
- Modeling approaches
  - Mechanistic Models
    - Exact solution for simple system
    - Computational modeling for more complex systems
  - Empirical Models
    - Data driven (input vs. output)
    - Typically do not have physical basis; cannot extrapolate
  - Semi-empirical Model
    - Combination of mechanistic equations and empirical (fit) data
Risk Assessment Example #1
Conceptual Mechanistic Approach

Ishikawa Diagram for Tablet Compression
Risk Assessment Example #3 - 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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<tr>
<td>Crystallization</td>
<td>Residual solvent</td>
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<td>4</td>
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<td></td>
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<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>
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<td>Isolation/drying</td>
<td>Temperature during crystal drying</td>
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<td>2</td>
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<td>3</td>
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<tr>
<td></td>
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<td>1</td>
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<td>Washing effectiveness</td>
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<td>Handling/storage</td>
<td>Relative humidity</td>
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<td>3</td>
<td>45</td>
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<tr>
<td></td>
<td>Inerting</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>24</td>
<td>6</td>
</tr>
</tbody>
</table>

Example Mechanistic Model of Crystallization

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

Highly reproducible particle size distribution
Example Mechanistic Model of Mixing

Laboratory experiments indicated an impurity level was mixing dependent.

Computational Fluid Dynamics Model

Model showed that adequate mixing will be attained at all settings at commercial scale.

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

3. Analyze Data
Determine significant factors
Example Model for Defining Design Space

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

Design space for dissolution in terms of a regression correlation

Prediction algorithm:
\[
\text{Diss} = 108.9 - 11.96 \times \text{API} - 7.556 \times 10^5 \times \text{MgSt} - 0.1849 \times \text{LubT} - 3.763 \times 10^2 \times \text{Hard} - 2.557 \times 10^5 \times \text{MgSt} \times \text{LubT}
\]

Example Model for Scaling Up

Process parameters for high shear granulation represented by a dimensionless number:

**Spray Flux**: Measure of area wetted by drops from spray nozzle to powder flux through spray zone

Multivariate DOE to study granulation at pilot scale:

**Inputs**: amount of granulation liquid, impeller speed, granulation time

Analysis of DOE data used to define a scale invariant design space in terms of range of **Spray Flux**

**Acceptable Spray Flux**
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
Feed-forward Control Example
Artificial Neural Network

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

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

- **Results:** Dissolution properties successfully predicted based on excipient attributes

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Endpoint Control Example
Chemometric Model 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_
Conceptual Example of Control Strategy for Continuous Manufacturing

- Receiving
- Continuous Blending
- Continuous Granulation
- Compression
- Continuous Blending
- Weight & Hardness
- Continuous Film Coating
- Digital Imaging
- Dissolution Model (release)
- Real-time Release Testing

At-line Chemical Properties
Physical Properties
Concentration & Uniformity (Multi-component)
Particle Size Distribution

Multivariate Statistical Process Control

- Process variables often track together
- Reducing the dimensionality of the process into principle components (combined variables) can simply fault diagnosis
- Multivariate approach can identify some quality issues that univariate analysis might not detect

(adapted from T. Kourti, PAT, 1 (1), p. 13-19)
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

Scientific Gaps in Implementing QbD

• Understanding the link from product to patient
  – Integration of biopharmaceutics into QbD
• Understanding complex products and processes
  – Examples: biotech products, transdermal patches
• Uncertainty in design space
  – Modeling and statistical approaches to evaluate
• Modern control strategies
  – Instrumentation and control
  – Model maintenance and improvement
  – Continual process improvement
Culture and Organization Gaps

• Cultural change
  – Level of detail included in application
  – Better integration of industry scientists in regulatory discussions with FDA
  – Increased collaboration and communication between industry and FDA

• Business challenges
  – Remove communication silos across business units
  – Remove budgeting silos across business units (e.g. higher cost of development to achieve lower manufacturing cost over entire lifecycle)
  – Management Support

Bridging the Gaps

• Keep the science first!
  – Both industry and regulators need to use science and risk based approaches
  – Continue efforts for international harmonization
  – Drive cultural and organizational changes

• Share information and experience in an open dialogue
  – Within an organization (no silos)
  – Between industry, regulatory agencies and academia
Thank you!

Questions, comments, concerns:
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