Quality by Design and Analytical Methods

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Outline

• Introduction to Quality by Design (QbD)
• Analytical methods for QbD in product and process development
• In-process measurements for process control and real time release testing (RTRT)
• Use of QbD approaches to develop robust analytical methods
• Concluding thoughts
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)*

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**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 and Analytical Methods

• ICH Q8(R) does not specifically discuss QbD related to analytical methods
• However, the concepts of using a science and risk based approach can be logically extended to analytical methods

Analytical Methods | Quality By Design

QbD and Analytical Methods

• Analytical Methods used to support product and process development under a QbD paradigm
  – Measurement of Critical Quality Attributes (CQAs) of products, intermediates and raw materials
  – Support risk assessment
• Advanced analytical methods used to enhance manufacturing control under a QbD paradigm
  – Basis of Process Analytical Technology (PAT) and Real Time Release Testing (RTRT)
  – Process monitoring and continual improvement
• Use the QbD approach to apply a science and risk based approaches applied to analytical methods
  – Developing a “analytical method design space”
Analytical Methods to Support QbD Approaches for Product and Process Development

Role of Analytical Methods in QbD Approach

- Quantify Target Product Profile
- Measure product CQAs and process intermediates
- Provide in-process measurements and controls
- Provide data for tracking, trending and continual improvement
### Use of Analytical Methods in Control Strategy

<table>
<thead>
<tr>
<th>Testing</th>
<th>Description</th>
</tr>
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</table>
| **Raw Material Testing**      | • Specification based on product QTPP and CQA  
• Effect of variability, including supplier variations, on process is understood                                                |
| **In process Testing**        | • Real time (at-, on-, or in-line) measurements  
• Enable manufacturers to actively control process to minimize product variation  
• Set acceptance criteria based on multivariate process understanding                                                               |
| **Release Testing**           | • Confirm the control of material attributes and process inputs (Design Space)  
• Specification based on patient needs (quality, safety, efficacy, performance)  
• Specification is only part of the quality control strategy                                                                              |
| **Stability Testing**         | • Predictive models at release minimize stability failures  
• Monitor desired product performance w/time                                                                                           |

### Analytical Method and Risk Management

**Risk Factor = Severity x Occurrence x Detectability**

- **Severity = Effect on Patient**  
  - Related to safety or efficacy (CQAs)  
  - Different than impact of a manufacturing failure
- **Likelihood of Occurrence = Chance of Failure**  
  - Related to product and process knowledge and controls  
  - Includes uncertainty for new processes or process changes
- **Detectability = Ability to Detect a Failure**  
  - Appropriateness and capability of analytical method  
  - Sampling considerations
Analytical Testing and Continual Process Improvement

In a QbD paradigm, process learning does not stop at product launch!

- **Product and Process Tracking and Trending**
  - Find and correct process drifts before they become problems
  - Can include both routine and non-routine analysis

- **Non-routine analysis**
  - Evaluation of product quality on periodic and/or risk basis (e.g. upon process changes)
  - Can use non-traditional analytical techniques not typically used for routine release testing (e.g., LC-MS)
  - Performed under firm’s quality system

In-process Measurement to Support QbD Approaches for Pharmaceutical Manufacturing
Why In-Process Measurements?

• Provides real time or near real time data to understand and control the process
• Enables process analytical technology (PAT) approaches for real time measurement and control
• Enable real time release testing approaches

A more modern approach for manufacturing

Near Infrared (NIR) Spectroscopy

• Currently, Near Infrared (NIR) is the common spectroscopy method for in-process measurements in pharmaceutical manufacturing
  – Used to support RTRT and PAT approaches
  – Measurements are rapid and simple for operator
  – Can measure multiple components simultaneously
  – Complex, multivariate models are needed
Where and how can NIR be used?

- Anywhere in process
  - Raw materials, starting materials, intermediates
  - Drug substance, drug products
  - In-line, on-line, at-line measurements
- Quantitative analysis
  - Concentration (Assay)
  - Variation/Distribution (Content or Bulk Uniformity)
- Qualitative analysis/classification
  - Identification

What has ONDQA seen to date?

<table>
<thead>
<tr>
<th>NIR Approach</th>
<th>Number of Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>17</td>
</tr>
<tr>
<td>Drying monitoring and end-point</td>
<td>5</td>
</tr>
<tr>
<td>Water content</td>
<td>4</td>
</tr>
<tr>
<td>Blending monitoring and/or endpoint</td>
<td>9</td>
</tr>
<tr>
<td>Assay and Content Uniformity</td>
<td>12</td>
</tr>
</tbody>
</table>

As of January 2012
How is NIR different than “traditional” analytical methods?

• Analyte(s) measured within the sample matrix
  – Little or no sample preparation
  – Other components or physical properties can affect the measurement of the desired compound
• Calibration samples and model are typically needed
  – Calibration set needs to be carefully chosen to include potential variations
• Complex multivariate models (chemometrics) are used
  – Models require maintenance and periodic update

NIR Method Lifecycle

Different Types of Multivariate Models

• Identification methods
  – Differentiate between other compounds or product
  – Include variability between multiple lots

• Quantitative methods
  – Used for assay or concentration measurements
  – Calibration based on a reference method
  – Standard error cannot be lower than reference method

• Rate of change methods
  – Sometimes used for end-point determination (e.g., blending, drying)
  – Non-calibration method, based on change of variance
  – Probe location can be critical (e.g., scale-up)

Considerations for Multivariate Model Development

• Include as many sources of variability as possible

• Understand robustness of model
  – Data preprocessing type should have a scientific/physical basis
  – Avoid over-fitting the model
  – The lowest error is not always the best model!

• Validate using independent data set
  – Examine internal vs. external fit of data
Maintaining and Updating Calibration

- Process changes or drifts can introduce new sources of variability
- Evaluate consistency with calibration model (e.g., residual error of fit)
- Investigate cause of outliers
- As needed, add to model any data representing new acceptable variation
- Monitor and maintain calibration under a robust pharmaceutical quality system (ICH Q10)

Other Uses for Multivariate Models - Process Signatures

- Many batch processes are path dependent
  - Arriving at the same endpoint does not assure the same quality product
- Controlling to a process signature can improve product and process reproducibility
Other Uses for Multivariate Models - Characterizing Complex Products

- Characterization of complex / heterogeneous products can be difficult
  - Identity, purity
- Chemometrics allows extraction of information from analytical methods
  - Ability to handle multidimensional data
  - Can be used to simultaneously evaluate data from multiple analytical methods
- May lead to discovery of “hidden/unexpected” patterns
  - “Fingerprint” approach
  - May be used to identify trace contaminants
- Extending methodologies to botanical products


QbD Approaches to Support Development of Robust Analytical Methods and Regulatory Flexibility
QbD Approaches for Analytical Methods

Example QbD for Drug Product:
- Target Product profile
- CQAs
- Risk assessment
- Design space
- Control strategy
- Continual improvement

Example QbD for Analytical Methods:
- Target Measurement Output
- Select Technique
- Risk assessment
- Analytical Method w/ Design Space
- Control strategy
- Continual Improvement

Analytical Method Understanding

- Understand how variation in input parameters affects analytical results
- Examine multivariate relationships
  - Across instrument, laboratory, analyst, sample and method parameters
- Employ mechanistic understanding
  - Based on chemical, biochemical and physical characteristics
- Incorporate prior knowledge of techniques and methods
Analytical Method Variation

- Variability in instrument, sample, method or choice of model can affect the analytical results
  - both traditional or non-traditional methods
  - more complex models and interactions for non-traditional methods

Can Design Space be Defined for Analytical Methods?

- Yes, but not much experience by industry or regulators
  - Method Operable Design Range “MODR” term being used by some companies
- Based on a science and risk based approach, considering
  - Risk related to intended use of method
  - Understanding of method
  - Quality system to support changes
“Analytical Method Design Space”

- Typically DoE (Design of Experiment) used to find region of successful operation including
  - Instrument operating parameters
  - Sample preparation variations
- Can be conducted together with method validation
- When approved, movements within the “Analytical Method Design Space” are not considered regulatory changes
- Allows continual improvement throughout the life cycle of the product, within the approved ranges

Interchanging Analytical Techniques

- Most analytical development efforts are specific to the analytical technique
- Alternative, or back-up methods, require additional development and validation efforts
- Approach is more appropriate for lower risk analytical tests
Current Status

- FDA has approved some NDA applications applying QbD approach to analytical methods (e.g. HPLC, UV)
- Regulatory flexibility has been granted for movement within the defined analytical method “Design Space”

Regulatory Considerations for “Analytical Method Design Space”

- Applicants should clearly define intent and any non-standard terminology used
- Sufficient statistical power to support proposal
- Consider potential risks to product quality
- For change in type of method (e.g., HPLC to NIR) submission of supplement or comparability protocols is recommended
Concluding Remarks

- Analytical methods play an essential role under QbD paradigm
  - Supports product and process development
  - Enables advanced strategies like PAT and RTRT
- Regulatory flexibility is achievable by applying QbD approach to design of analytical methods, but requires
  - High degree of understanding
  - Robust quality systems
- Applicants are encouraged to discuss novel QbD implementation approaches with the FDA prior to submission

Questions?
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