Quality by Design Approaches to Analytical Methods
-- FDA Perspective

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Outline

• What is Quality by Design (QbD)
• Role of Analytical Methods Under QbD Paradigm
• Applying QbD Approach to Analytical Methods
  – Current status
  – Regulatory considerations
• Concluding Remarks
What is “Quality by Design”?

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

--ICH Q8 (R), Step 2
What is “Quality” and “Quality by Design”?

- **Quality**
  - “Good *pharmaceutical quality* represents an acceptably low risk of failing to achieve the desired *clinical attributes.*”

- **Quality by Design (QbD)**
  - “Means that *product and process performance characteristics* are scientifically *designed* to meet specific objectives, not merely empirically derived from performance of *test* batches.”

  --Janet Woodcock (2004)
- Role of Analytical Methods under QbD Paradigm
  - Provide information about process understanding, process control, and product quality

**Product profile**
- CQAs

**Process Understanding**
- Risk assessment
- Design space
- Control strategy

**Lifecycle Management**
- Provide data to better understand the process and for continual improvement
- **Confirm** success of process changes
  -- can use non-traditional methods

- Prior knowledge used in initial risk assessment
- Material quality assessment
- Perform in-process testing for timely process control decision
  -- adjust process before failures occur
- **Confirm** product quality
  -- quality is not determined solely by product specification
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
Control Strategy Includes:

- Process parameters and material attributes related to drug substance and drug product manufacturing
- Components, facility and equipment operating conditions
- In-process controls, finished product specification, and the associated methods and frequency of monitoring and control
# Use of Analytical Methods in Control Strategy

| 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  
|                      | • Active control of process to minimize product variation  
|                      | • Criteria based on multivariate process understanding |
| Release Testing      | • Quality attributes predictable from process inputs (Design Space)  
|                      | • Specification is only part of the quality control strategy  
|                      | • Specification based on patient needs (quality, safety, efficacy, performance) |
| Stability Testing    | • Predictive models at release minimize stability failures  
|                      | • Specification set on desired product performance w/timeas |
Role of Process Analytical Technology (PAT)

- Provide real time information (at-, on- and in-line testing) for process control and improvement
- Non-traditional analytical techniques (e.g. NIR) have been used in these areas:
  - identification, drying, blending, assay, and content uniformity
- Need reliable reference information to establish calibration models
  - Need to maintain calibration models
  - Sampling effect on model calibration and validation
Analytical Method and Continual Process Improvement

• Routine analysis
  – Provides data for tracking and trending
  – Quantitative results are more useful than PASS/FAIL

• Non-routine analysis
  – Evaluation of product quality on periodic basis for higher quality assurance
  – Reassessment of process or product upon process changes
  – Can use non-traditional analytical techniques that are not typically applied to routine release testing
  – Performed under firm’s quality system
QbD Approach for Analytical Methods

- ICHQ8(R2) doesn’t explicitly discuss analytical method development.
- However, concepts apply:
  - Application of Science and Risk based methodology
  - Systematic approach that includes: risk assessment, defining a design space, control strategy and continual improvement to increases method robustness and understanding
QbD Approach to Analytical Methods

- **Target Measurement**: Determine what to measure and where/when to measure it. Develop measurement requirements based on product QTPP and CQA.
- **Select Technique**: Select appropriate analytical technique for desired measurement. Define method performance criteria.
- **Risk assessment**: Assess risks of method operating parameters and sample variation. Can use risk assessment tools (e.g. FMEA).
- **Method Develop/ Val**: Examine potential multi-variate interactions (DoE and design space). Understand method robustness and ruggedness.
- **Control strategy**: Define control space and system suitability, meet method performance criteria.
- **Continual Improvement**: Monitor method performance; update as needed as process and analytical technology evolves.
QbD Approach to Analytical Methods

- Allow continual feedback and feed-forward interactions among all steps.
- Meet and maintain method performance criteria
Variation of Analytical Method

Many Factors can affect analytical results.

e.g. variations in instrument, sample, method, choice of model
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 “Design Space”

• A science and risk based and multi-variate approach to evaluate effects of various factors on method performance
• Typically DoE* (Design of Experiment) is used to find ranges for instrument operating parameters, to understand sample preparation variations and variations of method precision.

  * Example terminology for design space: MODR (method operable design range)

• Method performance criteria are response factors
• Can be conducted together with method validation
Benefits of Application of QbD Approach to Analytical Methods

- Development of a robust method
- Applicable throughout the life cycle of the product
- Regulatory flexibility
  - Movements within “Design Space” are not considered a change in method
Current Status

• FDA has approved some NDA applications applying QbD approach to analytical methods (e.g. HPLC and UV)

• Regulatory flexibility has been granted for movements within the defined analytical method “Design Space”
Regulatory Considerations

• Define intended use of the analytical method (e.g. RTRT (real time release testing) or endpoint testing)
• Not all analytical techniques are inter-changeable
  – Example: from HPLC to NIR
    ▪ Require additional development and validation efforts
    ▪ Submission of comparability protocols is recommended
• Need sufficient statistical power to support analytical “Design Space”
• Applicants need to clearly define terminologies
• Proposal for regulatory flexibility should consider potential risk to product quality
Concluding Remarks

• Analytical techniques and methods play an essential role in QbD paradigm
• Real time release testing and non-traditional testing techniques provide valuable information for in-process control and improvement
• Regulatory flexibility is achievable by applying QbD approach, but requires
  – High degree of process, product and analytical method understanding
  – Robust quality systems
• Applicants are encouraged to discuss ‘novel’ QbD implementation approaches with the agency prior to submission
Thank You!

Questions?
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