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

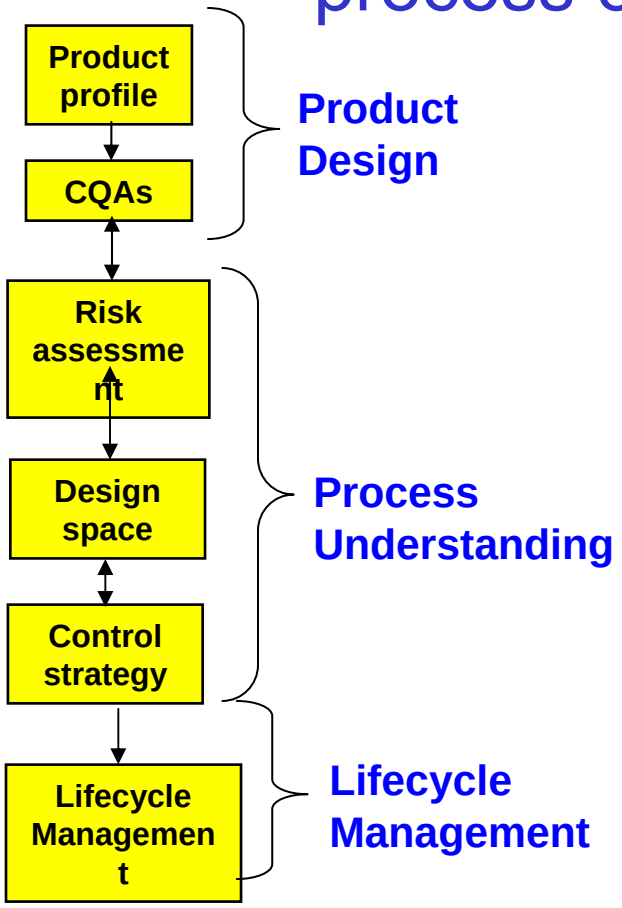
What is "Quality" and "Quality by Design"?

- **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



- 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

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

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 Method and Control Strategy

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/time

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

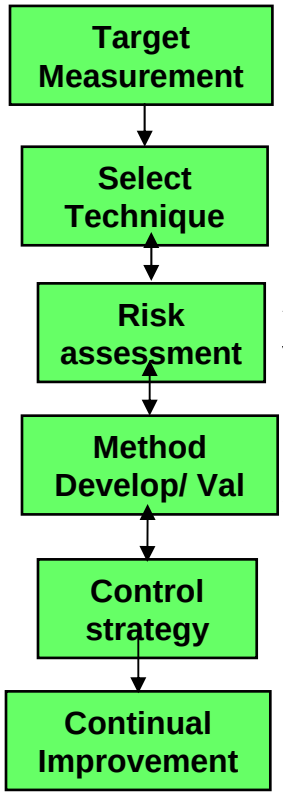
Analytical Method and Continual Process Improvement

- 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



Determine what to measure and where/when to measure it. Develop measurement requirements based on product QTPP and CQA.

Select appropriate analytical technique for desired measurement. Define method performance criteria.

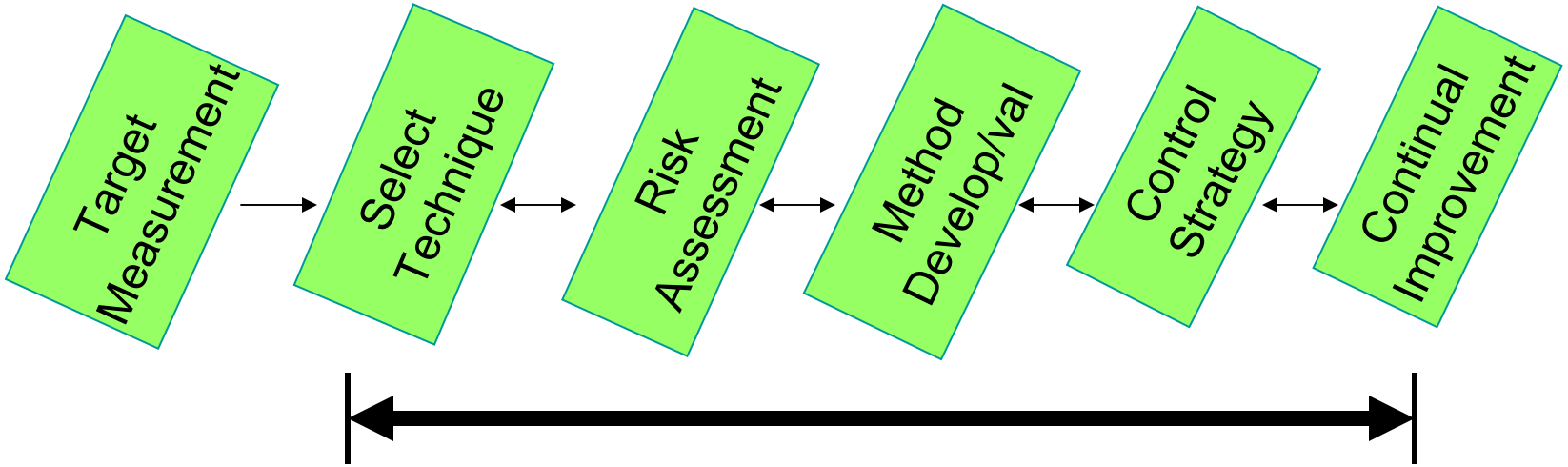
Assess risks of method operating parameters and sample variation. Can use risk assessment tools (e.g. FMEA)

Examine potential multi-variate interactions (DoE and design space). Understand method robustness and ruggedness

Define control space and system suitability, meet method performance criteria

Monitor method performance; update as needed as process and analytical technology evolves

QbD Approach to Analytical Methods

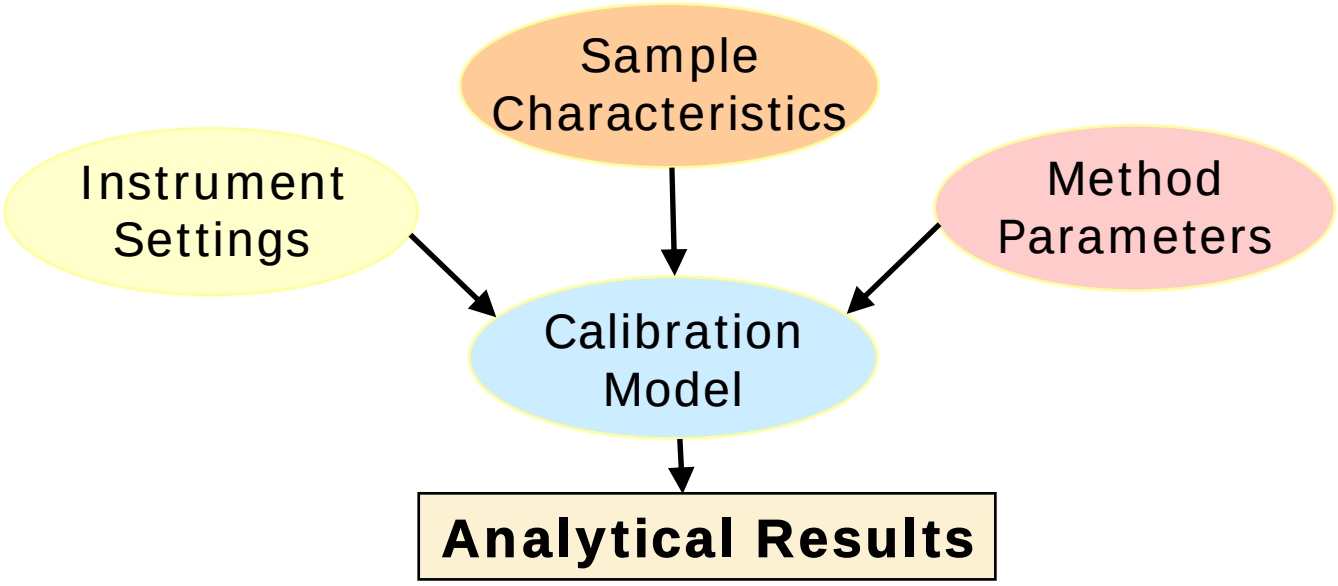


- Allow continual feedback and feed-forward interactions among all steps.
- Meet and maintain method performance criteria

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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