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

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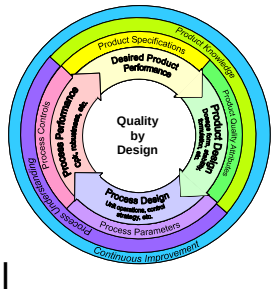
What is Quality by Design (QbD)?

- 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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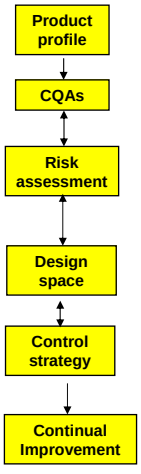
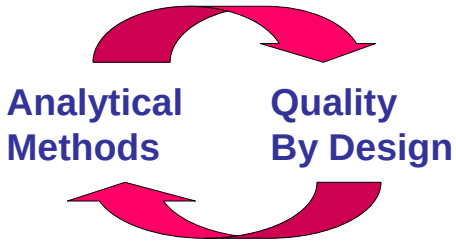
Example QbD Approach - ICH Q8(R2)



- 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



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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”

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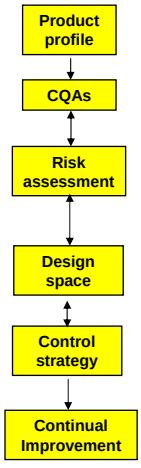
Analytical Methods to Support QbD Approaches for Product and Process Development

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

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

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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

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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

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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

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What has ONDQA seen to date?

NIR Approach	Number of Applications
Identification	17
Drying monitoring and end-point	5
Water content	4
Blending monitoring and/or endpoint	9
Assay and Content Uniformity	12

As of January 2012

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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

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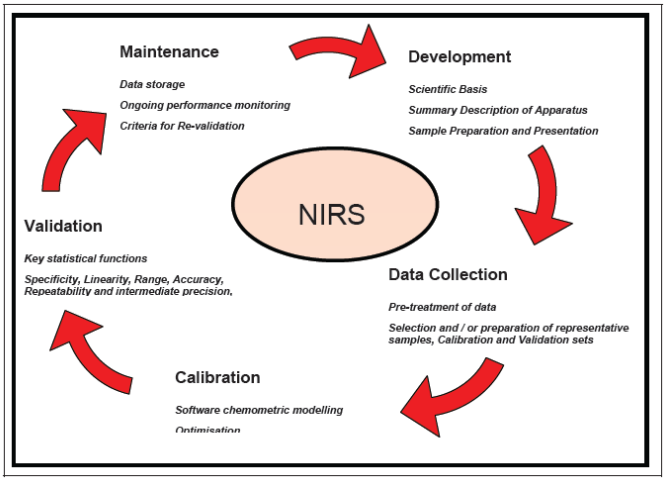
NIR Method Lifecycle



EMA Draft "Guideline on the Use of Near Infrared Spectroscopy by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations," 2/09.

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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)

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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

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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)

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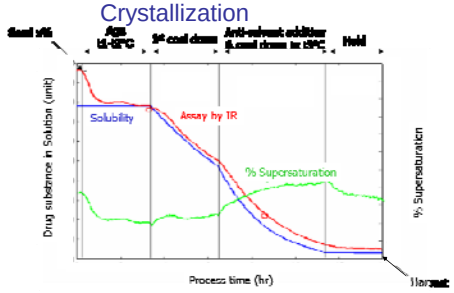
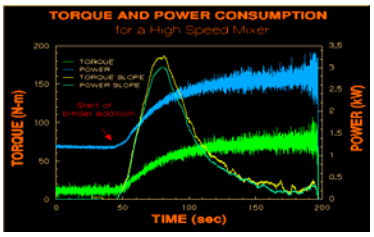
Other Uses for Multivariate Models - Process Signatures

Crystallization



Wet Granulation



http://www.mcc-online.com/granulation.htm

- 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

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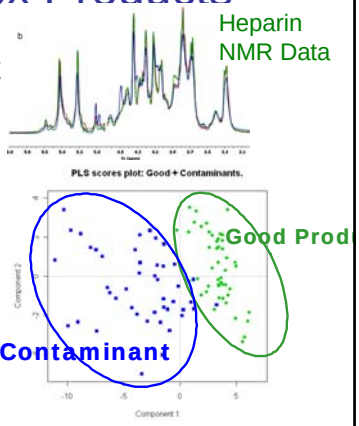
Other Uses for Multivariate Models - Characterizing Complex Products

- 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

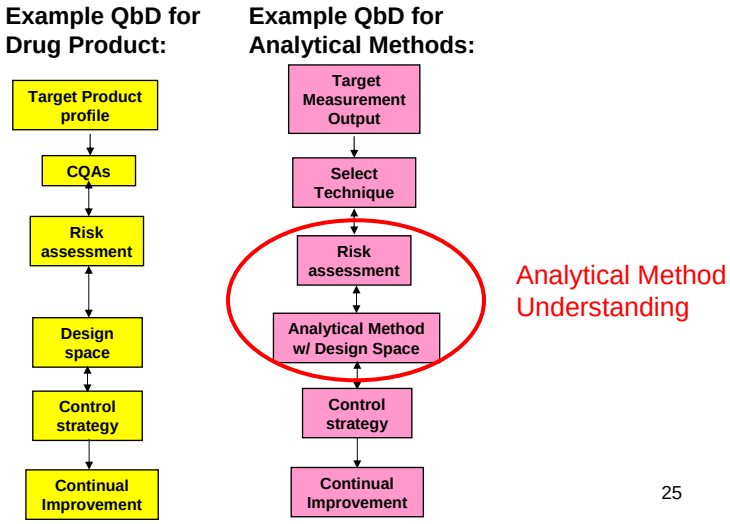
Expert Analyst → Expert System



Reference: Q.Zang, et. al, J.Pharm.Biomed.Anal.(2011), doi:10.1016/j.jpba.2010.12.008

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

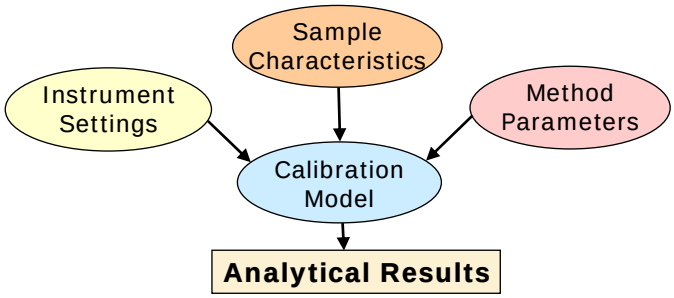
QbD Approaches for Analytical Methods



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

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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

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"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

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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

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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

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Thank You!

Toda!

Shukran!

Questions?
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