



# **A Regulatory Perspective on NIR Method Robustness**

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# Outline

- Role of NIR Method under QbD Paradigm
- What are the Challenges?
- Regulatory Considerations
- Concluding Remarks

# NIR Spectroscopic Method and QbD

- NIR Spectroscopy is a widely used process analytical technology (PAT) as part of QbD paradigm.
- NIR analytical method is developed for critical quality attribute (CQA) measurements and for in-process control
  - Provides real time information via at-, on- and in-line testing for process control and improvement
  - NIR analysis has been used in the areas of identification, drying, blending, assay, and content uniformity

# Differences Between NIR and Traditional Analytical Procedures

- Use of chemometrics and development of multivariate model
- Statistically relevant samples for model development and comparable samples for model validation
- Reliable and suitable software for data analysis

# Where Are Challenges in Attaining a Robust NIR Analytical Procedure?

- Sufficient number of samples and appropriate sampling locations, esp.
  - on- and in-line sampling
  - for RTRT measurement
- Integrating variations in calibration model development,
  - not all sources of variations are known
  - lack of thorough understanding of known variations
- Method transfer issues

# Regulatory Perspective on Method Validation

- Method validation is the **process** of demonstrating that analytical procedures are suitable for their intended use.
- The method validation process **begins with the planned and systematic** collection of the validation data.

--- *US FDA Guidance for Industry:  
Analytical Procedures and Method Validation (08/2000)*

# Method Robustness

## -- ICH Q2(R1) Definition

The robustness of an analytical procedure is a **measure of its capacity to remain unaffected** by small, but deliberate **variations** in method parameters and provides an indication of its reliability during normal usage.

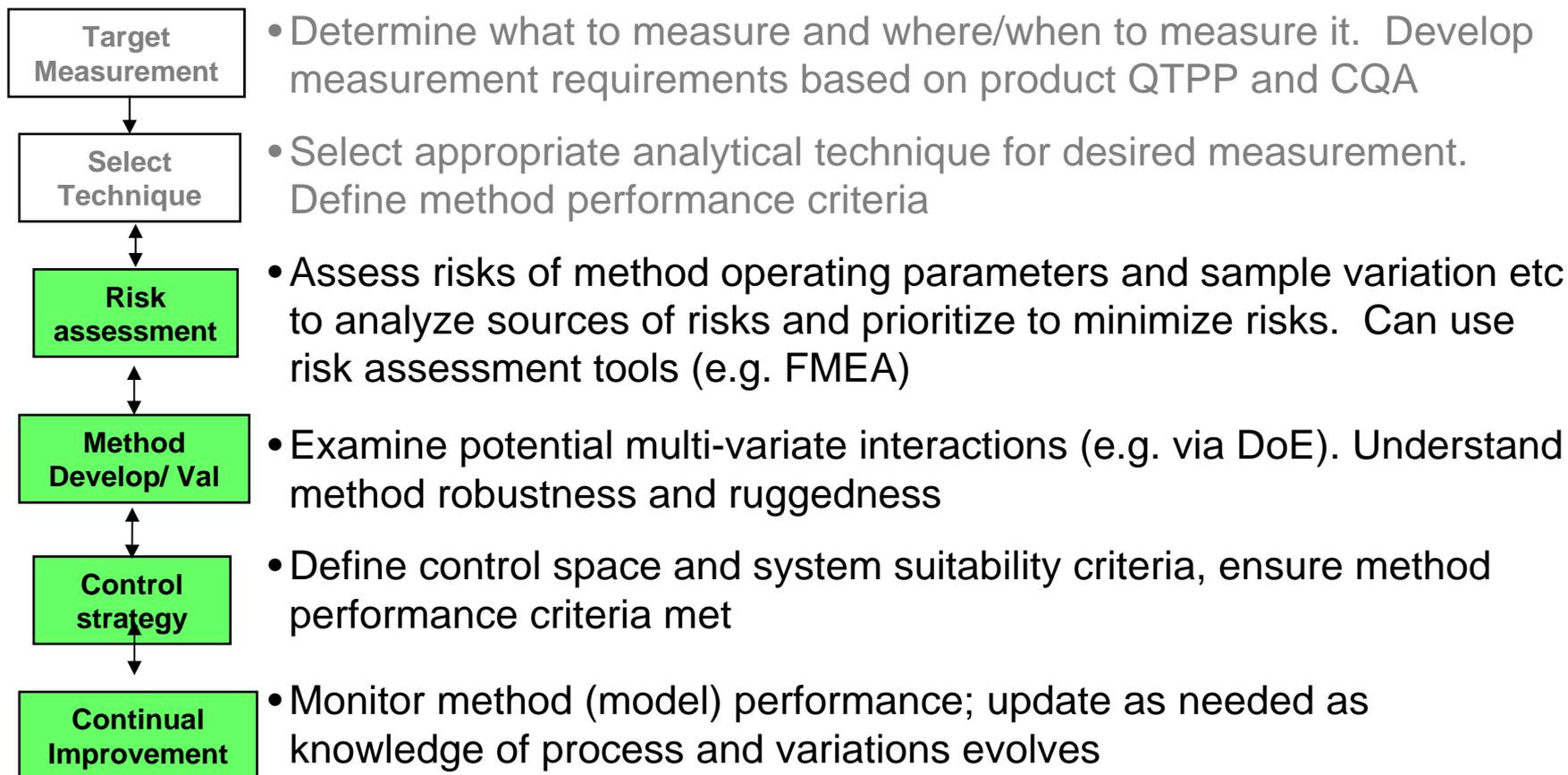
# Potential Factors that Impact NIR Model Performance

- Environmental (temperature, humidity, vibration)
- Process related (solvation state, lot-to-lot variation, excipient variability, water content)
- Physical (polymorphism, particle size/shape)
- Instrument/computer (21 CFR11 compliance, IQ/PQ/PV for hardware and software)
- Sampling (location, temperature, frequency)
- Samples (temperature, homogeneity, age, source)
- Data pre-processing approach
- Reference method (technology, validity, robustness)

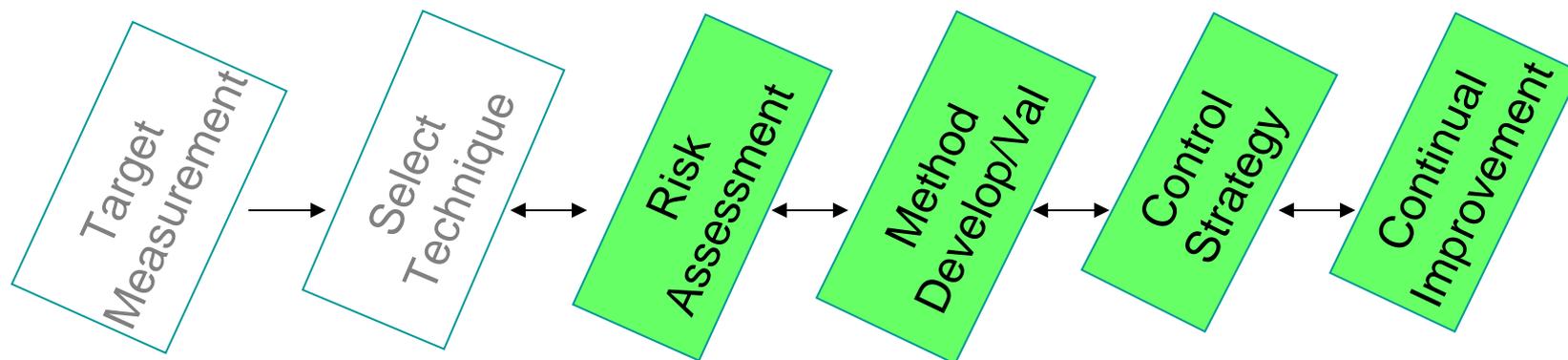
# NIR Method Robustness Study

- Systematic and holistical approach to understand how an NIR method (calibration model) is affected by unavoidable/ inherent variations.
- Information of the study should be used to define operative settings for a given NIR method.

# QbD Approach to NIR Method Robustness



# QbD Approach to NIR Method Lifecycle



- Allow continual feedback and feed-forward interactions among all steps and throughout NIR method lifecycle

- Meet method/model performance criteria and maintain performance

- Continuously evaluate the appropriateness of method/model for its intended use

# Considerations for NIR Method Sampling/Samples

- Statistically relevant/sufficient samples and consistent sampling approaches
- Appropriate acceptance criteria for at-, on- and in-line samplings
- Independent sample sets for model development and validation
- DoE study including all critical variables and span the range of variations
- Same representative samples used for both NIR and reference methods

# Special Considerations for On- and In-line NIR Methods

- Adequate sample size, e.g. for blend uniformity,
  - sample size comparable to size of unit dose
  - sample remains relatively static in front of acquisition window during measurement
- Adequate stability of sample/probe interface
- Sample representative of processes

# Other Considerations for Robust NIR Analytical Method

- Select an appropriate number of latent variables for calibration model
- Deliberately change certain critical parameters to test the sensitivity of your model
  - Develop a model that is least sensitive, i.e. least RMSEP, to method parameter variations.
  - Identify triggers for model maintenance

# Other Considerations

- **Software (Chemometrics) Reliability**
  - Typically off-the-shelf products are used, sometime with modification
  - Evaluate suitability (e.g. design objective/specification; data treatment process)
  - Computer system requirement
  - Vendor's cGMP awareness and vendor's lifecycle support
- **User training and readiness**
  - NIR and other chemistry fundamentals
  - Chemometrics and data processing knowledge
  - Instrumental /software familiarity and re-familiarity

# Benefit of Robustness Study

- A requirement for any regulatory analytical procedure
- Provides thorough understanding of an NIR method and its role in control of a process and product quality.
- Proactive risk-management for undesired events,  
e.g. NIR equipment failure

# Considerations for NIR Method Maintenance

- SOPs including technical details are typically managed by manufacturer's internal quality system
- High level overview of methodology can be provided in regulatory submission to aid reviewers, esp. for RTRT and for other novel applications of NIR
  - planned maintenance events
  - monitoring, trending and action taken
    - model updating, re-validation, re-built
  - risk management plan, e.g. readiness of alternate analytical procedure
  - approach to NIR method transfer (next)

# Consideration for NIR Method Transfer to a New Location

- Global calibration model approach
  - be cautious of model over-fitting
- Alternatively, update calibration model by bias adjustment
- Impacts on sampling/sample, e.g.
  - change in equipment
  - change in probe location or probe type
- Equivalent NIR spectroscopic hardware and software

# Concluding Remarks

- NIR method is an important PAT tool used in QbD paradigm
  - been used for CQA measurement
  - provides real time measurements
  - offers ample process information.
- NIR method is non-traditional analytical procedure
  - chemometric model development, validation and maintenance
- NIR method robustness study should be a systematic process that
  - begins at method development phase
  - considers software suitability/reliability
  - Includes user training
- A robust NIR method is critical to product quality, esp. for real time measurements.



# Thank You!

*Questions?*  
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