# Regulatory Considerations for Utilization of Near-Infrared (NIR) Spectroscopy in Process Monitoring and Control

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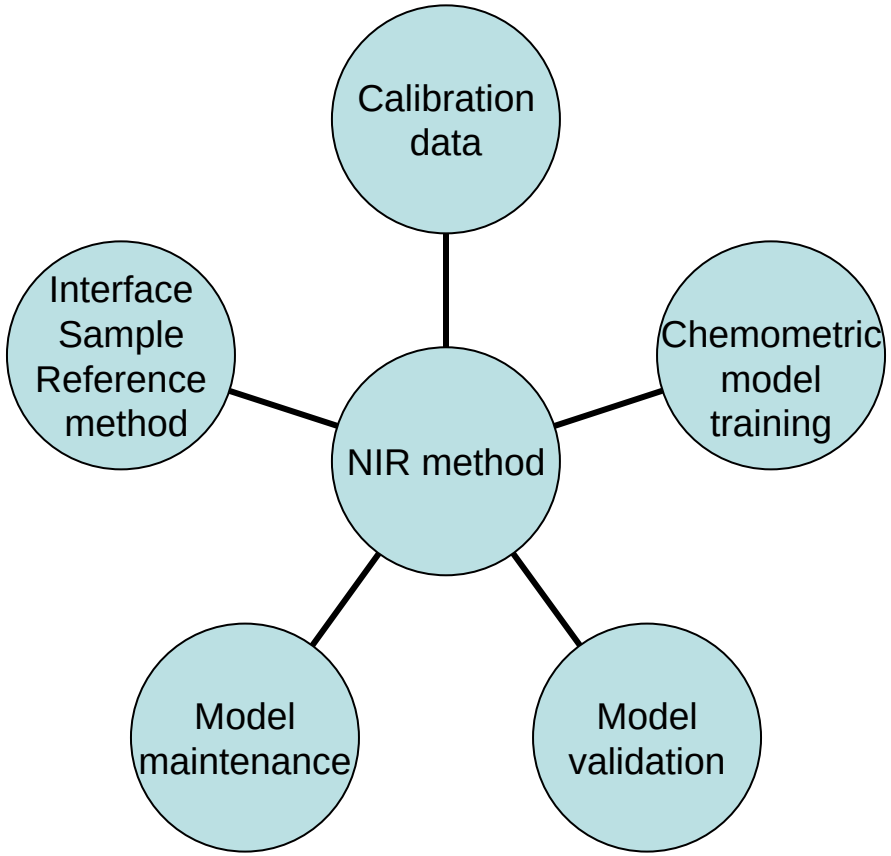
# Outline

- Introduction
- Discussion of key elements of NIR methods
  - Interface
  - Calibration set selection
  - Spectral pretreatment
  - Model development
  - Model validation
- Submission details
- Model update and maintenance
- Summary

# Introduction

- Near-Infrared (NIR) spectroscopy is a well-established method for pharmaceutical analysis
- NIR has become increasingly popular as an a method for in-process control and testing in pharmaceutical manufacturing
- The Agency has received and approved multiple submissions including NIR measurement in pharmaceutical manufacturing for identification, drying, blending, assay, and content uniformity

# NIR Method Components



# Elements of Successful NIR Method (1)

- Appropriate sample/probe interface
- Calibration spectra
  - representing sample population
  - including sources of variance
  - covering design space
- Spectral pre-treatment
  - physical basis for pretreatment is preferred
- Model fitting
  - statistical justification for number of factors

# Elements of Successful NIR Method (2)

- Model validation
  - internal validation
  - external validation using independent validation set
- Acceptance criteria for method
  - absolute measure
  - rate of change
- Model maintenance and update

# Interface/Sample Considerations

- Assure that different interfaces or instrumentation provide equivalent spectra
- Test samples collected in a similar manner (in space and time) to reference samples
- Determine volume (mass) of sample exposed to the NIR beam for powder blends
  - Usually estimated by the combination of the window area, powder density, and depth of NIR penetration into powder
  - Acquisition time frame short enough to ensure that the blend is stationary in front of the window during acquisition

# Interface/Sample Possible Problems

- Spectra can vary with temperature
  - Differences between laboratory and in-process measurements
- Positioning of sample and/or probe
- Probe or window may get contaminated (blocked) during the operation
  - Fouling of window or probe
  - Condensation on window

# Calibration Set Considerations

- Include sources of variance
- Span the entire design space
  - Scale considerations
  - Variation of non-critical process parameters
- Obtain uniform distribution of spectra over the analysis range
- Collect spectra from multiple analyzers

# Spectral Pre-treatment and Model Development

- Standard set of pre-treatments (e.g., derivatives, standard normal variate method) typically included in operating software
- Preferred to have scientific/physical basis
- Optimization (search for the best set of wavelength ranges) can cause over fitting

# Considerations for Model Development

- Number of factors is a key parameter of a model
  - Too many factors cause over fitting
  - Statistical analysis can aid in determining number of factors
- Standard methods for finding the number of factors include:
  - Predicted Residual Sum of Squares (PRESS) vs. rank plot
  - Variance-based F-test
  - More robust than performance-based approach

# Model Validation Considerations

- Internal validation
  - Uses subset(s) of calibration data
  - Confirms the proper selection of model parameters, and estimates the method error
- External validation
  - Compare predictions of NIR and reference method to “simulate” future analysis
  - Confirms method error
  - Independent validation set
    - Splitting a single pool of spectra into calibration and external validation sets is not truly independent!

# Considerations for "Rate of Change" Methods

- Applies mostly to blending
- Probe location representative of entire vessel
- Calculation of statistical parameter(s) on a moving block of data
  - The parameter(s) stay below a limit for a pre-determined time
  - Calculation basis is an integral part of the NIR method
- Uses end-point criteria
- Confirmation (validation) for full-scale batches

# Considerations for Identification Methods

- Differentiate between tested material and other compounds or product
  - Uses a spectral library with multiple products
  - PCA models often used
  - Developed and validated separately from quantitative methods
- Include variability between multiple lots for increased robustness
- If measured in process, evaluate risk of post-measurement errors

# Considerations for Quantitative Methods

- Used for assay or concentration measurements
  - Often PLS method
- Calibration based on a reference method
  - Standard error cannot be lower than reference method
  - Requires a robust reference method
- Can be coupled with weight of tablets for content uniformity determination

# Considerations for Regulatory Documentation

- Principles of ICH Q2(R1) are mostly applicable to NIR methods
  - Calibration model instead of “linearity”
  - Include reference method details
  - Discuss how samples were obtained
- Procedures for model maintenance and update under quality system at manufacturing site
  - Address how will the model be evaluated and updated to assure continued performance

# Model Update and Maintenance

- NIR models may change with time as new sources of variability are introduced
  - New raw material suppliers
  - Changes in process parameters, not previously included in the model calibration
  - New data added to increase robustness or prevent false negatives
  - Results of periodical evaluation

# Detection of Outliers

- Allows detection of bad spectra, interface problems, or changes in the process
- Usually implemented through a distance to the model or residuals
  - Threshold normally established during model development
- Part of model implementation and maintenance

# Considerations for Model Update and Maintenance

- Frequency and methods of periodical model evaluation
- Actions resulting from OOS, new suppliers, process changes, new data, failed evaluation (level of change)
- Depth of validation done on updated model, depending on level of change
- If the method includes end-point criteria, they should be re-evaluated to reflect performance of the new model

# Summary

- NIR is becoming a staple for advanced control and monitoring in pharmaceutical manufacturing
- Good scientific and mathematical practices should be applied to NIR method development and implementation
- ONDQA encourages discussion of approaches for NIR models prior to submission

# Thank you!

*Questions?*
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