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 in-process control and testing method 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

- Calibration data
- Chemometric model training
- Model maintenance
- Model validation
- Interface Sample Reference method
- NIR method
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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