Multivariate Tools for Modern Pharmaceutical Control – FDA Perspective

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Outline

• Introduction to Multivariate Analysis (MVA)
• Utilization of MVA
  – Chemical Analysis - Spectroscopy
  – Identity of Complex Products
  – Process Monitoring and Control
  – Real Time Release Testing
• Considerations for MVA Models
• Concluding Remarks
Multivariate Analysis

• Multivariate Analysis Definition (MVA) - Any statistical technique analyzing the relationship of simultaneous and combined effects of more than two variables

• Examples of Multivariate Analysis Methods
  – Multiple Linear Regression
  – Principal Component Analysis (PCA)
  – Partial Least Squares (PLS)
  – k-Nearest Neighbor (kNN)
  – Artificial Neural Networks (ANN)
Multivariate Analysis

• Features of Multivariate Analysis
  – Uncover inherent patterns in data
    • Discover similarities and differences in data
    • Identify features that explain the patterns and outliers
  – Build models to predict for classification or quantitation

• Limitations of Multivariate Analysis
  – Requires calibration, often using a reference method
  – Data driven model – does not reveal underlying mechanisms
  – Valid only within the ranges/conditions studied
Data Exploration & Clustering

Classifying & Discrimination

Quantitative Prediction & Correlation

Example Uses

Example Methods
Chemometric Analysis

• Chemometric methods for spectroscopy are the most common MVA method seen in pharmaceutical regulatory filings

• Useful in support of in-process measurements for Process Analytical Technology (PAT) and/or Real Time Release Testing (RTRT)

• Potential uses include:
  – Identification of materials (raw materials, finished products)
  – Determination of water or residual solvents
  – In-process blending analysis
  – In-line/at-line determination of assay and content uniformity
Quantitative Assay – Determination of Number of Factors

Assay by Near Infra Red (NIR) analysis.
Regression Models for Predicting Impurities

Analysis of Dermatan Sulfate (DS) in heparin samples using NMR.

**Regression Models**
- Multiple Variable (MLR)
- Ridge Regression (RR)
- Partial Least Squares (PLS)
- Support Vector (SVR)

All Regression Models Performed Equally Well
Rate of Change Measurement – Blend Uniformity Example

Uniformity of excipients and blend determined by on-line process monitoring by NIR
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
Classification of “Good” Heparin Samples

Heparin NMR Data

Botanical samples

Different plant parts distinguished by fingerprinting analysis

PCA by UPLC fingerprints
Role of Multivariate Statistical Process Control (MSPC)

• Routine monitoring
  – consistency checking
  – identification of atypical operation

• Part of RTRT approaches
  – Used to assure that operation is within ranges previously studied
  – Potential to use as a surrogate as part of RTRT control strategy
  – Potential to support reduced testing approach
Multivariate Statistical Process Control

- Process variables often track together
- Reducing the dimensionality of the process into principle components (combined variables) can simply fault diagnosis
- Multivariate approach can identify some quality issues that univariate analysis might not detect in RTRT approach

Many batch processes are path dependent
  - Arriving at the same endpoint does not assure the same quality product
  - Often important physical or chemical attributes are not measured routinely but can affect downstream product performance
Example: Routine Monitoring of High Shear Granulation

Aim of MSPC model is to understand current state of the process and ‘flag’ deviations.
Real Time Release Testing

• Real Time Release Testing (RTRT) is the ability to evaluate and ensure the quality of in-process and/or final product based on process data
  – Typically include a valid combination of measured material attributes and process controls

ICH Q8(R2)
Example: Surrogate Dissolution Model in RTRT

- Process Data
- Raw Material Data
- Multivariate Model (e.g., MSPC)
- Calibration Data
- Manufacturing Data
- Quantitative Prediction by PLS
- Measured vs. Predicted
Considerations for MVA Development and Implementation

- Training data selection
- Model development
- Validation
- Implementation

*The principles of model building are the same regardless of the use of the model!*
MVA Model Development Considerations

- Calibration data
  - Include potential sources of variance (e.g., operating conditions, raw materials, scale)
  - Cover intended areas of operation/design space
  - Appropriate distribution of samples over the analysis range

- Model development
  - Data pre-treatment / scaling
  - Selection of parameters/spectra
  - Number of model factors justified (avoid overfitting)

- Model validation
  - Internal validation using subsets of calibration data
  - External validation using an independent data set
  - Ability to detect “bad” material/batches

- Robust and representative reference method
MVA Model Maintenance and Update Considerations

- Model results may change as new sources of variability are introduced
  - Changes in raw material, process or analyzer

- Evaluation of outliers as part of maintenance
  - Can detect atypical trends with process and/or analyzers
  - Usually implemented through examination of residuals
  - Outliers do not imply a failed batch!

- Develop and document procedures on how to evaluate and update the calibration model
  - Done under the manufacturer’s quality system
  - Include frequency and methods of periodical model evaluation

- Depth of validation done on updated model, depending on level of change
Considerations for Setting Acceptance Criteria for MSPC RTRT models

• Based on scientific rationale
• Allowable deviation from the historical process average
  – What is the highest deviation experienced so far?
• Address risk of accepting marginal batches and rejecting good batches
  – Use historical knowledge and information from development
Future Growth Opportunities for MVA

• Identity of complex molecules
• Routine use of MSPC as part of continual process verification
• Monitoring in support of RTRT
• Integration of multiple sensors for control of entire process
  – Implementation of feed-back or feed-forward control
  – Control to a process signature
  – Control of continuous manufacturing
• Further development of data management tools
Considerations for Submission of Models

- Level of detail in submission should depend on the importance of the model to the overall control strategy
- Low Impact Model (e.g., models for development)
  - General discussion of how model was used to make decisions during process development
- Medium Impact Model (e.g., design space models)
  - More detailed information about model building, summary of results and statistical analysis
  - Discussion of how the model fits into the control strategy
- High Impact Model (e.g., RTRT models)
  - Full description of data collection, pretreatment and analysis
  - Justification of model building approach
  - Statistical summary of results
  - Verification using data external to calibration set
  - Discussion of approaches for model maintenance and update
Interactions with FDA

• Request meeting according to guidance
  “Formal Meetings Between the FDA and Sponsors or Applicants”
  – Clearly state as CMC meeting for RTRT
  – Both CMC and GMP questions can be included

• End of Phase II or Pre-supplement submission is a good time to start dialogue
  – Initially, not all details or data are expected to be available
  – Discuss desired or expected approach
  – Ask specific questions

• Additionally, a Pre-Operational Review (or Pre-Operational Visit, POV) can be requested
Communicate Early and Often!
Concluding Remarks

• Multivariate models can be used for a variety of ways in pharmaceutical manufacturing
  – Assay or uniformity measurements by spectroscopy
  – Identity of complex products
  – Monitoring and/or control of routine production
  – Support of RTRT

• Mathematics and model building approaches are similar for all approaches

• FDA supports implementation of MVA using a science and risk based approach
  – Recommend discussions with the Agency before implementation of novel approaches
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