Independence and Dependence in Calibration: A Discussion FDA and EMA Guidelines

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Professor, you have nice academic ideas, but FDA will never approve a NIR method
Continuous Manufacturing Has a Strong Impact on Drug Quality

Posted on April 12, 2016 by FDA Voice

By: Lawrence Yu, Ph.D.
How does it all come together?

A Procedure for Developing Quantitative Near Infrared (NIR) Methods for Pharmaceutical Products

Rodolfo J. Romañach, Andrés D. Román-Ospino, and Manel Alcalà

Guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations

- “This guideline describes the regulatory requirements for marketing authorization applications and variation applications submitted for medicinal products for human or veterinary use, which include the use of NIRS”
- “NIRS for non-regulatory purposes, such as generating process knowledge, is out of the scope of this guideline”

Page 6, European Medicines Agency, Guideline on the use of Near Infrared Spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new submissions and variations. 2014; p 28.
Development and Submission of Near Infrared Analytical Procedures
Guidance for Industry
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
March 2015
Pharmaceutical Quality/CMC

Progress

- The two documents provide a much needed reference in terms of terminology.
- In chemometrics we have too many terms for the same concept – idea.
- I don’t fully agree with the terms in the two documents, but I can say “As per the EMA guideline ..... is defined as: ”
27 January 2014
EMA/CHMP/CVMP/QWP/63698/2014
Committee for Human Medicinal Products (CHMP)
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on NIR guideline

“Chemometrics is a chemical discipline that uses mathematics, statistics and formal logic
a) to design or select optimal performance experimental procedures.
b) To provide maximum relevant chemical information by analyzing chemical data.
c) To obtain knowledge about chemical systems”

Design→Learn (Model)→Use

Dow Chemical team: where data is working for us, and we are not working for it.
Method, Model & Procedure ("The Deliverables")

- NIRS model: mathematical relationship between spectrum and the analyte of interest.
- NIRS Method: Describes the key elements, principally within the NIR spectrometers, which enables NIRS measurement of the analyte of interest.
- NIRS procedure: describes how the method and model are used for its intended purpose, within its defined scope.
Calibration sets

Mixtures (Blends)

Unknown (validation set)

Concentration values

Ref Values, Gravimetric, HPLC, UV-Vis

PLS calibration model

PCA Model

Variation Implies Information !!
Analytical methods are not applicable to all materials, they are applicable to a certain formulation or product. First test with PCA determines applicability of method.
Scope

• The NIRS should be developed to reject samples that are outside of its defined scope (e.g. out of range or compositionally incorrect).
Control hardware and software integration

Step 1 - Design

Step 2 – Method for RT analysis

Step 3 – sensors integrated into plant

Step 4 – signal to Control platform
Acceptance criteria for NIR methods

• “The NIRS procedure should be able to reject samples that are outside of its defined scope, such as out of specification product, placebo, samples containing different quantitative composition of proposed excipients, and samples containing different active substance and excipients”.

• Bias should not be statistically different from zero (page 22).
Acceptance criteria for NIR methods

• “It is expected that a good correlation coefficient is obtained (close to 1), with slope, bias and intercept not statistically different from 1, 0, 0 respectively.”

\[
Bias = \sum_{i=1}^{N_p} (\hat{y}_i - y_i)/N_p
\]

Bias – quantifies systematic error

Page 21, European Medicines Agency, Guideline on the use of Near Infrared Spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new submissions and variations. 2014; p 28.
Bias = average of residuals = 0.108
Paired t-test calc. = 0.160
tcrit = 2.064

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M. Popo. S. Romero, R.J. Romañach, Blend Uniformity Analysis Using Stream Sampling and Near Infrared Spectroscopy”, *AAPS PharmSciTech* 2002; 3 (3) article 24 (http://www.aapspharmscitech.org/)
Understanding RMSEP

\[ \text{RMSEP}^2 \approx \text{SEP}^2 + \text{BIAS}^2 \approx (\text{std dev.})^2 + \text{bias}^2 \]

\[
\text{RMSEP} = \sqrt{\sum_{i=1}^{N_p} (\hat{y}_i - y_i)^2 / N_p}
\]

\[
\text{SEP} = \sqrt{\sum_{i=1}^{N_p} \frac{(\hat{y}_i - y_i - \text{BIAS})^2}{(N_p-1)}}
\]

\[
\text{Bias} = \sum_{i=1}^{N_p} \frac{(\hat{y}_i - y_i)}{N_p}
\]

Sources of Variation

Process Validation Guidance

• Understand the Sources of Variation
• Detect the presence and degree of variation
• Understand the impact of variation on the process and ultimately on product attributes.
• Control the variation in a manner commensurate with the risk it represents to the process and product.

Theory of Sampling (TOS): “mass reduction of lot L by selection of a certain subset of units, with the purpose—not always fulfilled—of obtaining a true, reliable sample S (when the conditions of sampling correctness are respected).

Sampling errors, Large part systematic errors.
Definitions

• Calibration set – the set of samples for creating the calibration model.
• Calibration Test Set – “the set of samples, which are drawn from the same population as the calibration set, but were not used to generate the calibration model. In practice, calibration set often consists of two thirds of the available sample population. The calibration set is the remaining third.”
• Validation set – independent set of samples in validating the NIRS model.

What is an “independent set of samples”? 
Calibration sets

Ref Values, Gravimetric, HPLC, UV-Vis

PLS calibration model

Concentration values

Variation Implies Information!!
The EMA guidelines state: “Interpretation of the complex spectra of unprepared samples generated by NIRS measurement usually requires the use of chemometric calibration models. These models are developed using carefully selected and representative samples, which normally require qualification by independent, reference analytical procedures (normally requiring destructive sample preparation to extract or isolate the analyte of interest and calibration and validation using analytical reference standards)”.
Merriam-Webster Definition of Independent

• **1**: not dependent: as **a (1)**: not subject to control by others: self-governing (2): not affiliated with a larger controlling unit <an independent bookstore> **b (1)**: not requiring or relying on something else: not contingent <an independent conclusion> (2): not looking to others for one's opinions or for guidance in conduct (3): not bound by or committed to a political party **c (1)**: not requiring or relying on others (as for care or livelihood) <independent of her parents> (2): being enough to free one from the necessity of working for a living <a person of independent means> **d**: showing a desire for freedom <an independent manner> **e (1)**: not determined by or capable of being deduced or derived from or expressed in terms of members (as axioms or equations) of the set under consideration; especially: having linear independence <an independent set of vectors> (2): having the property that the joint probability (as of events or samples) or the joint probability density function (as of random variables) equals the product of the probabilities or probability density functions of separate occurrence
HPLC Methods are not Independent

Standard Organizations
NIST, ISO

Calibration sets

Always Gravimetric

PLS calibration model

validation set progresssively challenge model
Separate Occurrence \(\approx\) Independent

- Different API and excipients are used (could also be considered as a robustness test).
- Calibration spectra and CTS or validation samples spectra are obtained on different days.
- CTS or validation samples are not prepared at exactly spaced intervals (are not at 70.0, 80.0% of label)-some randomness is included in these preparations.
- The API and excipient proportions in the CTS or validation samples is not exactly the same as in calibration set.
Recommended Approach

Calibration set

Unknown (validation set)

Gravimetric

Concentration values

PLS calibration model

HPLC (separate) Lab

NIR Predicted value
Recommended Approach


Separate Occurrence ≈ Independent

- “Sample independency means that samples are not prepared under the same conditions as the calibration set samples. Validation samples should come from the process that will be monitored and be prepared with excipient and API batches that differ from those used in the calibration set”

Independence and Dependence in Calibration: A Discussion of FDA and EMA Guidelines

Introduction

Two recently published FDA and EMA documents describe expectations for the submission of spectroscopic methods to the regulatory agencies and are important advancements for the implementation of modern non-destructive analytical methods in the pharmaceutical industry. Both documents are focused on the description of near infrared spectroscopic methods. However, the FDA Draft Guidance indicates that the same fundamental concepts of validation may be applied to Raman, X-ray, and other Process Analytical Technology (PAT) analytical techniques. These expectations must become part of the plans or procedures for the development of PAT spectroscopic methods.

The FDA and EMA documents should not be considered a checklist for the validation of methods to be submitted to regulatory agencies. Regulatory submission must include justifications of the strategies followed for the development of calibration models; strategies that define how scientists work. The documents encompass chemometrics; a scientific discipline that is based on careful planning and observation of data to extract the maximum information. The documents describe

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