Project #4
Acceptance Criteria for Low Drug Content Powder Blends in Feed Frames

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Problem Statement

- Validation protocols are required to implement PAT methods in manufacturing. The protocols require acceptance criteria for accuracy, precision, linearity, robustness, etc. How do you justify these acceptance criteria?
- How does FDA evaluate whether accuracy and precision of a PAT method is adequate?
- An approach is needed that takes into consideration all the sources of variation in analytical methods as well as sampling errors.

Objectives

- Demonstrate an approach for setting of acceptance criteria for accuracy and precision with a near infrared (NIR) spectroscopic method in the analysis of flowing powder blends at 3% (w/w) within a feed frame.

- Discern the process variation from the variation due to the analytical and sampling errors

Materials/Methods

- API
  - Acetaminophen
- Excipients
  - Microcrystalline Cellulose (various grades), Lactose (various grades)
- Feed frame from Fette 3090 Tablet Press
- Bruker Matrix FT-NIR spectrometer.

Mateo-Ortiz, D.; Colon, Y.; Romanach, R. J.; Mendez, R., Analysis of powder phenomena inside a Fette 3090 feed frame using in-line NIR spectroscopy. *J. Pharm. Biomed. Anal.* **2014,** *100*, 40-9.

Esbensen, K. H.; Román-Ospino, A. D.; Sanchez, A.; Romañach, R. J., Adequacy and verifiability of pharmaceutical mixtures and dose units by variographic analysis (Theory of Sampling) – A call for a regulatory paradigm shift. *Int. J. Pharm.* **2016,** *499* (1–2), 156-174.

Development of Sampling specifications

Squared sampling error, r^2 (SE), sufficient for the use, r^2 is defined as:

$$r^2(SE) = m^2(SE) + s^2(SE) \leq r^2_{threshold}$$

Where:

m^2(SE) is the squared sampling bias,

s^2 (SE) is the variance of the random sampling error

and

$r^2_{threshold}$ is the maximum tolerable total squared sampling error (variance) defined by the user of analytical results.

Danish-Standards-Foundation, DS 3077(2013). In *Representative Sampling-Horizontal Standard*, Danish Standards Foundation: 2013; pp 1- 42.

Anticipated Impact

- Delivering an approach for setting acceptance criteria for the analysis of powder blends in low drug concentration. Applicable to higher concentrations and other applications with flowing powders.
- Facilitate compliance with section 211.110 of the Good Manufacturing Practices which provides comprehensive requirements for sampling and testing of in-process materials and drug products.
- Facilitate the evaluation of PAT methods for flowing powder by regulatory agencies.

Q & A?