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# DRIFTS-Based Multivariate Calibration and Prediction of Low-Concentration Polymorphic Impurities in Multiple Lots of an Active Pharmaceutical Ingredient, and Outlier Criteria

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## Highlights

- DRIFTS-based multivariate calibrations of the two polymorphic impurities in the ~ 0 to 2% wt/wt range in one API lot produce one very low and one reasonable cross validations error.
- The predictions of both polymorphs via the spectra of numerous independent API lots are biased and with numerous outliers, per Q-residuals.
- Updating the models with the spectra from some of the independent API batches increases calibration errors but reduces the bias in prediction and mostly eliminates outliers.

## Abstract:

Mixtures of two polymorphic impurities with one lot of the desired form of an Active Pharmaceutical Ingredient (API), mostly binary mixtures, with up to 2% wt/wt of an impurity, were used for multivariate modeling via Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectra. The two obtained cross-validated models, significantly differing in accuracy, were used to predict the concentrations of these impurities in independent API lots. The predictions were found to be biased and with outliers, as revealed by the Q residuals criterion but not the other two outlier criteria. Updating the models with the spectra from the mixtures using multiple API lots produced very different calibration results: the model of the impurity with the strong IR response became noticeably worse, while the model of the impurity with less responsive IR signal

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