Calibration model transfer, update and maintenance for on-line application. Comparison of the three existing approaches

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1 Introduction

Spectroscopic methods such as Near Infrared, Ultra-violet, Raman, Fluorescence have widely been used as Process Analytical Technologies in various industries (Pharmaceutical, Food, Oil, Biotechnologies, Polymer, etc.) for rapid and less expensive measurements of quality. The increased benefit of these PAT tools is reflected in its use for real-time measurements of product quality during manufacturing providing online inspection of intermediate and final products.

In order for these methods to be an integral part of the Quality by Design approach the main challenge is their robustness to new acceptable sources of variability on the process (e.g. transfer between process scales, production lines, acceptable variations in process conditions, different physical properties of materials, different spectroscopic instruments, probes, etc.). To tackle different situations where the robustness of spectroscopic calibration models is challenged, a strategy for calibration model transfer, update and maintenance needs to be in place prior to implement a spectroscopic method for real-time quality measurements.

When it is possible to have a standardization set, there are existing algorithms that could be used to either correct the spectra to be predicted (e.g. PDS (Piecewise Direct Orthogonalization) [1]) or to correct the predicted value (e.g. Bias/Slope correction (BS) [2]). When it is impossible to obtain a standardization set, other approaches exist and it consists in using a small experimental design, where the new acceptable sources of variability, disturbing the calibration model robustness, are included. Orthogonal projection is then carried out to make the model insensitive to these new acceptable sources of variability (EPO) (External Parameter Orthogonalization) [3], OSC (Orthogonal Signal Correction) [4], GLS (Generalized Least Squares) [5]).

Finally, the most common case when neither a standardization set nor a small experimental design is available, other existing methods are applicable using few in-process control (IPC) samples to update the model. These methods are: Bias/Slope correction (BS) [2], model redevelopment (MRD) (i.e. exhaustive or global modelling) [6] and Dynamic Orthogonal Projection (DOP) [7-10]. These only 3 existing methods (BS, MRD, DOP) that could be used for improvement of calibration model robustness throughout its lifecycle for on-line application (implementation, transfer, update and maintenance), using only few IPC samples, will be discussed and compared in this paper based on the model performance.

NIR data collected from a pharmaceutical application, i.e. monitoring the critical quality attribute of the drug product during the drying process †, were used for this study. The drying process is very critical because it has a direct impact on the final product. The classical approach to control the drying process is, on a given production line, to dry the drug at a certain temperature to a specified level of solvent and over a defined fixed drying time.

† fluid-bed dryer GEA pharma Aeromatic-Fielder type.
2 Material and methods

2.1 Material

NIR spectroscopy was chosen to monitor the solvent level in real-time in order to determine the drying endpoint. The later provides more consistent endpoint reducing the batch re-work cost, time and risk of quality degradation and therefore, batch rejection. The NIR equipment used on every fluid bed dryer is ABB Bomem FTPA2000 spectrometer connected to a diffuse reflectance probe (Precision Sensing Device).

Figure -1 shows the data collected from two similar production lines (L1 & L2) with different NIR instruments (I1 & I2) and two different drug products (DP1 & DP2) having raw material with different particle size distribution (PSD). Off-line IPC samples were taken following a sampling plan in order to build and validate the NIR models. The overall data collected are the NIR spectral data and the IPC samples for off-line laboratory measurements of the residual solvent content in the drug product.

![Figure 1 - Data flowchart (L1 & 2: production line, DP1 & 2: drug product, I1 & 2: NIR Instruments)](image)

2.2 Methods

A PLS model was built and optimized by leave-one-batch-out cross-validation on data from calibration batches CAL (DP1, L1, I1). This calibration model was applied on the different test sets containing 3 sources of variability, individually or combined: batch difference effect (TEST1) during production over time, over campaigns; Line and NIR Instrument effects and PSD difference effect combined with batch and line effects (TEST2). The prediction results of the calibration model (without correction) were compared with the predictions after correction with the three correction methods (DOP, BS, MRD), using exactly the same 2 IPC samples for corrections. The performance criteria of the prediction models were the RMSEP, bias and R².

3 Results and discussion

Strong biases were observed for the prediction of the test batches using the calibration model (Table 1). The prediction performance was poorer and poorer when dealing with batch, line and product effects respectively. BS correction was successful to correct most of the effects. However, as already known, BS corrected models were unable to perform well when the effect disturbing the spectra disappeared (see batch 58 Table 1). This approach is thus not recommended for long term model maintenance solution. MRD method, that consists of including the IPC samples residual solvent measurement and NIR spectra to the calibration database, did not show satisfactory results to correct strong effects, i.e. PSD effect when only very few IPC samples are available. On the contrary, the DOP correction showed the best results, especially for correcting all the effects together (Figure 2 and Table 1). In this example, only the two first IPC samples of the first batch were needed to give satisfactory prediction, even when the new acceptable source of variation affecting the NIR model disappeared.

![Table 1-Prediction results for the test batches with different line, instrument and PSD (TEST 2).](image)
4 Conclusion

The study showed benefits from using the DOP method over the BS and MRD methods for calibration model transfer and update during its on-line implementation and routine use, using only a very few reference control points to do the model update. It showed a successful transfer between production line and NIR instruments as well as an update against particle size change and maintenance over batch effect. This method could also be used to reduce the cost associated with model robustness improvement during development. However, when deploying this methodology, some attention has to be made on the selection of the samples (IPC) to be measured for correction based on the assessment of the prediction reliability, and the representatively of these control points, i.e. the detection of outliers.

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6 References


