Analytical method specificity is assessed using ICH (International Conference on Harmonisation) Q2 (2005). Although, certain methods are not specific enough for their intended purposes, they may have other advantages. Both titrimetric and UV (Ultra-violet spectroscopy) assays are non-specific, but have superior precision (Ca. 0.1-0.5% RSD (Residual Standard Deviation)) compared with the corresponding specific HPLC (High Performance Liquid Chromatography) assay methods (>0.5% RSD).

A method’s ability to rapidly identify significant changes in the true mean of an API (Active Pharmaceutical Ingredient) is essential for any quality critical test. Hofer et al. modelled a scenario where for the first 50 batches of an API, the true mean was 99.5% and the standard deviation (σ) was 0.5%, thereafter the true mean dropped to 99.0%, with unchanged σ. The modelling showed an inability to identify this significant change by trending the HPLC assay data. The authors proposed the use of a mass balance approach (100% – % total impurities) demonstrating unequivocally that it is relatively straightforward to detect changes using this approach.

The analytical methodology variability is frequently larger than the manufacturing process variability, particularly for API manufacture. Generally, the analytical method σ should be some-sixth of the proposed specification range; i.e. 6σ capability. Ermer et al. assessed the maximum allowable σ for an API assay method. He showed for an API assay method using duplicate determinations, where the lower specification limit is 98.0% and with 0.5% total impurities, that the analytical method σ should be ≤0.17%. Ermer et al. used 44 different APIs, and 16 different stability studies to determine a generic precision value for HPLC assays, i.e. ±1.16%. Similarly, Hofer et al. reported that the mean intermediate precision values were between 0.6-1.1% and Görög et al. indicated variability was about 1%.

Based on this typical analytical variability of ca. 1%, and assuming an API specification ranges of ±2.0% (i.e. 98.0-102.0%), several commentators have expressed significant concerns about the utility of HPLC assay methods to monitor API quality (trending API potency, trending API stability, releasing batches whose true potency is 98.0-102.0% or meaningfully investigating OOS (Out of Specification) results). Skrdla et al. indicated that ‘assay results are simply not stability-indicating’ because of the intrinsic assay variability. The impact of method variability on OOS results is also constrained by the FDA’s 2006 guidance, as individual replicates, as well as the mean value, should lie within the acceptance criteria. Hofer et al. modelled the probability of finding a ‘false OOS’ and demonstrated that this is highly dependent on method variability, as well as the API true mean. They also reflected that there was a 1% chance of OOS results when the σ was 0.6%, with a true mean of 99.4%, but this increased 9-fold when the σ increased to 1%, with an identical true mean. The possibility of seeing ‘false OOS’ increases with the number of tests performed on the same batch, i.e. as in the case of routine stability testing. This issue can be circumvented by registering broader API specifications based on process capability, but this requires regulatory endorsement.

Hofer et al. assessed the potency data from eight API batches using both standard HPLC assay and the mass balance approach. Although the mean assay data were similar, the precision of the former data was about 6-8 fold higher than the corresponding mass balance assay approach. Skrdla et al. modelled the complete removal of the external standard HPLC potency assays from routine use within stability studies and advocated utilising the more precise mass balance HPLC assay approach. Finally, method variability has an adverse impact on the predicted shelf life of the API which can be addressed using an accurate and very precise analytical method.

In conclusion, without some relaxation of the standard API specification limits (normally, 98.0-102.0%) the use of a standard HPLC assay to monitor API quality must be approached with caution due to its inability to monitor quality critical changes.

References