A BAYESIAN PROBABILITY CRITERION TO ASSESS ANALYTICAL RESULTS RELIABILITY

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In pharmaceutical and biomedical industries, quantitative analytical methods such as HPLC play a key role. Indeed, the analytical results obtained from them are used to make crucial decisions such as the release of batches of drugs, the evaluation of safety and efficacy of new drug candidates or the monitoring of patients health. Prior to their routine use, analytical methods are submitted to a stringent validation study [1] where they have to demonstrate that they are fit for their final purpose, i.e. providing accurate results: $\left|x_i - \mu_T\right| < \lambda$

where x_i is the analytical result, μ_T is the theoretical unknown true concentration of analyte in the sample analyzed and λ a regulatory acceptance limit.

Typically this demonstration is made by either providing point estimates of systematic error (bias) and random error (variance) or sometimes by providing interval estimates of these statistical parameters at several well defined concentration levels of the target analyte [2]. They are then compared to maximum acceptable levels. More recently, tolerance intervals approaches have been proposed that are evaluated in a similar way at these key concentration levels [3]. However none of these decision approaches allow knowing the probability to obtain accurate results over the whole concentration range of interest:

$$P_{\mathrm{Re}\,l} = P\left(\left|x_i - \mu_T\right| < \lambda \middle| \theta, data\right) \geq P_{\min}$$

θ is a vector of parameters and P_{min} is a minimum reliability probability.

Frequentist approximations have been proposed to estimate this probability but only at the concentration levels experimentally tested [4,5].

In this work, a linear hierarchical Bayesian approach is proposed. It takes into account the potential random characteristic of the slope and intercept observed from one analytical run to the other, but it also integrates the possible covariance between the parameters. Additionally, heteroscedasticity of the residual variance over the concentration range investigated is taken into account. A situation regularly observed in practice. Finally a reliability profile for the whole concentration range studied is obtained using MCMC sampling. This profile provides the probability (P_{rel}) to obtain accurate results over the full concentration range investigated. This profile is then compared to a minimum reliability probability (P_{min}) that will define the valid concentration range of the analytical method. The usefulness of this approach is illustrated through the validation of a bioanalytical method and also compared with one concentration level at a time frequentist approaches [4,5].

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