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Title:

A Modern Approach to Stability Studies via Bayesian Linear Mixed Models Incorporating Auxiliary Effects (submitted to Journal of Pharmaceutical Sciences)

Primary Data presentation:

Background: Before a pharmaceutical product can be launched, an estimate of its shelf life via stability testing is required by regulatory agencies. The ICH-Q1E guidance has been the worldwide reference to reach this objective, but in recent years several authors have questioned several of its aspects. To that end we propose a complete Bayesian transcript of the ICH-Q1E treating all the apparent shortcomings while addressing the presence of multiple batches by a linear mixed model (LMM) for proper shelf-life prediction by explicitly modelling the batch-to-batch variability.

Materials & Methods: We present two case studies for shelf-life extension. One comprises of 6 batches. Here, we apply both approaches, the ICH-Q1E, but also its Bayesian LMM analogue, and compare their performance and interpretabilities considering the posed questions in a stability study. The second case study focuses on stability data of a product in different dosage forms. After a comprehensive model selection, an appropriate model to interconnect the data sets of the different concentrations is modelled with the ICH methodology and the novel approach followed by a comparison.

Results: A close look at the questions asked in a stability study show that a fixed effect model is a discrete approximation to describe the time dependence of an entire product. In contrast, the random effects in a LMM are exactly the property we need to predict the collective batch behavior of the product given the observed data. Further, the switch to Bayesian statistics does not only come with an easier handling of LMMs, but also with a stronger and simpler interpretability. The first case study points out the approximate equivalency of both approaches and the second case study shows the inherent superiority of LMM in dealing with unbalanced, incomplete and/or reduced data sets at different concentrations (or any other auxiliary/nuisance covariates) while patient safety is retained.