Stability Prediction from Forced Degradation Studies by Using Advanced Kinetics and Statistical Analysis

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Abstract

The stability of vaccines is one of the most crucial factors influencing their worldwide distribution which has a major impact on their quality, potency, and storage conditions. The thermal stability of vaccines is therefore of great interest for the vaccine industry, health institutions and, especially, for the philanthropic organizations. High thermal stability is one of the crucial factors when attempting to increase the distribution of vaccines to people living in countries with poor infrastructure and unreliable transportation and storage facilities because it helps to preserve the vaccines that require refrigeration during and storage.

Accelerated stability studies are designed to determine the rate of vaccine degradation over time as a result of exposure to temperatures higher than those recommended for vaccine storage. However, commonly applied stability predictions based on application of zero- or first-order kinetics are very often too simplified for description of the degradation of biological products, which frequently undergo complex and multistep degradation. It was recently demonstrated [1] that the best description of the reaction course can be done by kinetic computations which allow considering one, two or even more reaction stages by applying unlimited amount of combinations of different kinetic models.

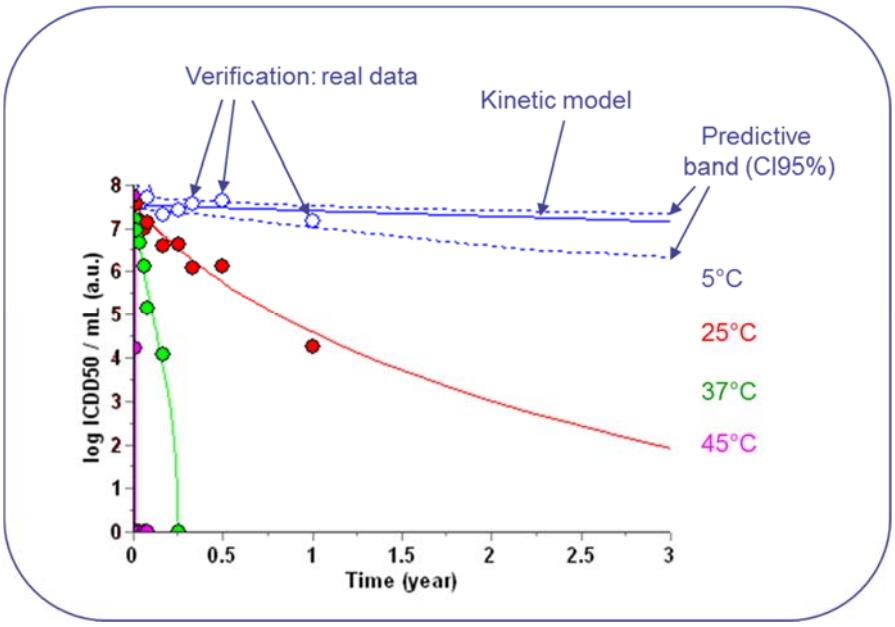
We used for stability modeling the advanced kinetic approach for computation of reaction kinetics and, further, for simulation of the materials stability. The kinetic parameters were calculated using the truncated Sesták-Berggren (SB) approach. This approach is able to describe any kind of kinetic models, from the simplest one (first- or n^{th} order reactions) to the more complex kinetics such as two successive n^{th} order stages with or without an autocatalytic type step. Other kinetics models described such as Avrami nucleation models, power law or Prout–Thompkins or Sourour- Kamal autocatalytic models have been also considered. It is important to mention that the selection of the kinetic models is purely based on statistical analysis and the goodness of fit without requiring that the selected model is assumed as correctly describing the mechanism(s) of degradation of the complex systems under evaluation.

Statistical methods were used to rank the screened models in term of probability to be the more appropriate. We applied the criteria for comparing models based on information theory developed by Akaike and its Bayesian counterpart which allow finding out the most plausible model fitting the experimental points. The Akaike's and Bayesian's criteria determine not only which model is more likely to fit better the considered data but also quantifies how much more likely and identify the most appropriate/simplest one. Those criteria are in line with the well accepted Ockham's razor

principle: “when you have two competing theories that make similar predictions, the simpler one is the better".

When the best kinetic model was chosen, the “bootstrap” analysis was used to determine the prediction band of extrapolated long-term stability behavior of the product under any storage temperature. This statistical approach, which is based on resampling, was obtained with 1000 loops and provided predictions with a percentile confidence interval at 95% (CI95%).

The modeling approach described here was successfully used for vaccine stability prediction, expiry date estimation, and to evaluate the impact of temperature excursions (cold chain breaks). To the best of our knowledge, this is the first study describing a global kinetic analysis of degradation of vaccine components with high prediction accuracy [2].



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[1] B. Roduit, M. Hartmann, P. Folly, A. Sarbach, R. Baltensperger, *Prediction of thermal stability of materials by modified kinetic and model selection approaches based on limited amount of experimental points*, Thermochim. Acta, 579 (2014) 31-39.

[2] D. Clenet, F. Imbert, P. Probeck, N. Rahman, S. F. Ausar, *Advanced Kinetic Analysis as a Tool for Formulation Development and Prediction of Vaccine Stability*, J. Pharm. Sci. 103 (2014) 3055–3064.