NCS Non-Clinical Statistics Conference
Padua, IT / 23 – 25 September 2026

TITLE: Calibrating dissolution surrogate model via conditioning for real time release testing of drug product

SPEAKER: Martin Otava[1]

COAUTHORS: Chellafe Ensoy-Musoro[2], Stan Altan[3]

[1] Discovery and Manufacturing Statistics, Johnson & Johnson, Czechia
[2] Discovery and Manufacturing Statistics, Johnson & Johnson, Belgium
[3] Discovery and Manufacturing Statistics, Johnson & Johnson, NY US

ABSTRACT: Dissolution is a critical quality attribute of the drug product in tablet form. It assesses consistency of the physical properties of the batch as well as possible connections to physiological absorption. Given its critical role in batch release, the standard laboratory analytical method for the measurement of dissolution is a complex and costly process requiring considerable resources and time. In addition, the analytical variability of the method can be substantial. Therefore, replacing the laboratory-based measurement method with a fast real-time predictive model has attracted considerable commercial and scientific attention in recent years
Khaki et al (2023) describes interactions between United States Food and Drug Administration (FDA) and model submissions, while identifying key deficiencies and outlining good practices (such as full profile prediction and proper addressing of uncertainty). Following the recommendations, we will discuss a framework for a multivariate conditional model approach, an extension of approach described in Altan et al (2022). The statistical advantages of conditioning on observed input responses will be emphasized in comparison to using these responses directly on the right side of the model as covariates. We further extend the approach in several ways. First, a full profile prediction will be implemented using a Weibull model fitted to dissolution curves, rather than predicting values at fixed dissolution timepoints (Dumarey et al, 2025). This leads to a four-dimensional multivariate model, where the mean structure could vary per response given the process parameter inputs. Finally, the data structure in practice may be more complicated than in Altan et al (2022), with multiple hierarchical levels. Which of these levels should be included in the conditioning step will be discussed as well (following Graybill, 1976).
Finally, we will discuss the practical implementation of the overall framework using Bayesian modelling via the brms package.

References:

• Kakhi M., Li J. and Dorantes A. (2023) Regulatory Experience with Continuous Manufacturing and Real Time Release Testing for Dissolution in New Drug Applications. Journal of Pharmaceutical Sciences: 112(10):2604-2614. doi: 10.1016/j.xphs.2023.08.004
• Altan, S. et al. (2022) A Bayesian Approach to Multivariate Conditional Regression Surrogate Modeling with Application to Real Time Release Testing, in Case Studies in Bayesian Methods for Biopharmaceutical CMC (Eds. Faya, P. and Pourmohamad, T.), Chapman and Hall/CRC
• Dumarey M., Carducci T.M., Walworth M.J., Smith C.J., García-Muñoz S, Nielsen S., Jacquart S., Tavares da Silva A., Altan S., Otava M., Lan Y. and Zaborenko N. (2025) Dissolution of Oral Solid Dosage Formulations: Surrogate Models and Real-time Release. Dissolution of Oral Solid Dosage Formulations: Surrogate Models and Real-time Release. AAPS J 27, 115. https://doi.org/10.1208/s12248-025-01102-0
• Graybill FA (1976). Theory and Application of the Linear Model. Wadsworth Publishing Company, Belmont, CA, 94002

BRIEF SPEAKER BIO: Martin Otava is currently a Senior Principal Scientist at Discovery and Manufacturing Statistics dpt in Johnson & Johnson. He started at J&J in 2015 after completing his PhD at Hasselt university, Belgium, and spends most of his time supporting chemists and engineers in designing processes for synthesis and manufacture of synthetics products. He focuses on continuous manufacturing, design of experiments and Bayesian hierarchical modelling.