Title: “Drug-Disease Modeling Applied to Drug Development and Regulatory Decision Making in the Type 2 Diabetes Mellitus Arena”

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease that affects millions of people worldwide. The disease is characterized by chronically elevated blood glucose concentrations (hyperglycemia), which result in co-morbidities and multi-organ dysfunction. This is due to a gradual loss of glycemic control as a result of increasing insulin resistance as well as decreasing β-cell function. The objective of T2DM drug interventions is, therefore, to reduce fasting and postprandial blood glucose concentrations to a normal, healthy level without hypoglycemia. Several classes of novel anti-hyperglycemic drugs with various mechanisms of action have been developed over the past decades or are currently under clinical development. The development of these drugs is routinely supported by the application of pharmacokinetics/pharmacodynamic (PK/PD) modeling and simulation approaches that integrate information on the drug’s PK, clinically-relevant biomarker information and disease progression into a single, unifying approach that can be used to inform clinical study design, dose selection, and drug labeling. Respective models can be established at various levels of spatial and temporal complexity ranging from observational and descriptive (pharmacometric; drug-centric) to completely mechanistic (systems pharmacology; network-centric) approaches. There is no one-size fits all model. All models should be fit for purpose, i.e. developed and qualified to provide answers to the question(s) of interest. Tailoring these models to long-term treatment outcome, special patient populations, and accounting for genetic and non-genetic covariates can further enhance their predictive performance for quantitative decision-making and personalized medicine applications in T2DM therapy.