Title: Use of modelling and simulation methods in support of marketing authorisation applications in the pharmaceutical industry

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Strategic consulting and expert support based on the use of modelling and simulation (M&S) methods together with pharmacological / pharmaceutical and pharmacokinetic / pharmacodynamic (PK/PD) knowledge is extremely useful to help pharmaceutical industries in problem solving during all phases of drug development.

The gained value of a model-informed drug development (MIDD) is that it allows to integrate and maximize usability of the data available to anticipate outcomes and probabilities of success, which are then used as a decision-making tool, aimed to support regulatory response documents and to facilitate strategic project decision making (go/no-go). As a consequence, the drug development process is optimized with regard to timelines, resources and investments.

More specifically, application of population PK(PD) M&S methods and subsequent emerging of quantified knowledge via MIDD allows to:

- Integrate all prior proprietary and public domain (literature) knowledge on PK and/or PKPD into a mathematical framework representing the compound and its *in-vivo* properties, thus providing the capacity to simulate instead of clinically testing
- Eliminate the need for additional pilot or pivotal trials or reduce their sample size
- Avoid the performance of efficacy trials in those instances where efficacy can be demonstrated through simulated PK/PD profiles possibly leveraging public domain knowledge
- Define the true need for additional trials but ones that are confirmatory or gap-filling rather than exploratory
- Select the optimal dose for new indications based on prior knowledge (including non-clinical studies)
- Answer critical concerns and requests from agencies
- Quantify / minimize risks inherent to the development and balance them against potential benefits
- Bridge between populations (of different age, ethnic origin or disease state) to answer the question “What will happen if?”
- Support optimization of formulation development, especially referred to complex formulations (e.g., liposomes, inhaled, transdermal, endogenous compounds, locally applied products, etc.) or modified-release formulations, to guarantee adequate efficacy and safety profile based on the knowledge of the specific drug
- Optimize clinical trial design for complicated formulations or products with atypical PK properties via clinical trial simulation (CTS) to anticipate the probability of success with candidate formulations
- Facilitate selection of compounds to enter bioequivalence studies (e.g., through application of *in vitro-in vivo* correlations (IVIVC) for different prototype candidates)
- Perform “direct” IVIVCs with full M&S potential

- Explore underlying physiological mechanisms behind the *in vivo* PK profile having an influence on the formulation behaviour and understand the variability in treatment response
- Build biowaiver based argumentations for different strengths or new requested studies

During the talk, three blinded examples (from Dynakin's own experience with sponsors) where application of M&S methods at different stages of drug development served as a valuable decision-making tool for the pharmaceutical industry will be presented:

1. Simulations to steady state for a formulation with complex PK.
2. Prediction of a bioequivalence outcome via the development of a predictive, semi-physiological *in vitro* to *in vivo* pharmacokinetic model ("IVIV-PK model").
3. Evaluation of suitability of a modified-release formulation based on public domain data.