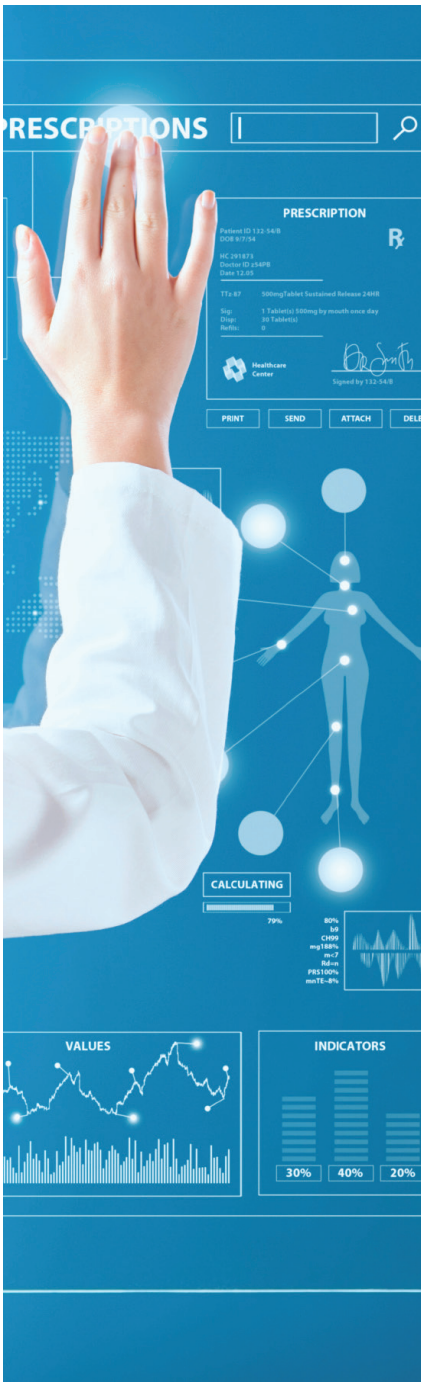
CONSIDER MODELING & SIMULATION

EARLY PHASE CLINICAL TRIALS – MAXIM #3



Improving experimental drug success rate and accelerating clinical development are top priorities for pharmaceutical and biotech companies. Careful decision making is essential to minimize development time, manage costs and improve the probability of commercial success. Modeling and simulation (M&S) can be a very useful strategy to mitigate risks and to make better informed decisions.

With regards to the drug development process, M&S involves modeling compounds, mechanisms and disease level data based on historical observations and existing real life data. Computer simulations are run on these models to generate information that can be used to predict outcomes, thereby improving the quality, efficiency and cost-effectiveness of decision-making, both for internal and regulatory purposes.

M&S studies the effects of a drug in a 'virtual patient population' using mathematical models that incorporate information on physiological systems. Simulations can be used to test assumptions, improve predictability, better characterize risk and identify opportunities to optimize outcomes by observing the effects of different model inputs. For example, an understanding of the full range of potential outcomes can be cultivated by observing the effects of more extreme model inputs than have been observed in real-world patients. In this way, M&S can help drug developers to better plan and design clinical trials by exploring and quantifying risks prior to their start.

Physiologically-based pharmacokinetic (PBPK) modeling and simulation integrates prior knowledge and data generated through the research and development process to inform decisions for the next step of compound development, focusing on understanding and prediction of drug absorption, distribution, metabolism and excretion (ADME) properties of a drug on targeted virtual populations. With PBPK modeling it is possible to investigate drug concentrations at the site of action that may mechanistically drive pharmacodynamic effects. It is also possible to learn about and confirm driven drug development as featured in current regulatory guidelines.
The U.S. FDA, European Medicines Agency (EMA), Japanese Pharmaceuticals and Medical Devices Agency (JPMD), and other global regulatory agencies encourage the use of M&S. They consider it an important drug development tool, which enhances product and process understanding, with the ultimate goal of ensuring consistent performance once the drug is placed on the market.

M&S can be of help in several areas of drug development:

- Can I optimize the starting dose of my first-in-human trial by extrapolating non-clinical data?
- Is it possible to accurately estimate complex drug-drug interaction (DDI) profiles of a compound in silico and explore its potential effects on, for example, cytochrome P450 enzyme (CYP)?
- Could the inhibitor effect at the site of metabolism (gut, liver, or any tissue) be predicted?
- Can I predict drug behavior in pediatric patient populations to support a pediatric investigation plan (PIP), based on my existing adult data?

CASE STUDY 1

M&S TO PREDICT AND STIMULATE THE EFFECT OF CHANGING A DOSE REGIMEN

Established pharma company with epilepsy compound

SGS Exprimo was contacted to quantify the relationship between exposure monotherapy and seizure probability, and to simulate the effect of changing the dose regimen.

A structural time-to-event model for dropouts (not because of a lack of efficacy) and seizures was developed using data from adult patients newly diagnosed with epilepsy and experiencing focal or generalized tonic–clonic seizures, participating in a trial. Dropout and seizure models were used for simulating the effect of changing the initial target dose on seizure freedom.

Outcome: The baseline disease severity was the most important predictor of seizure probability.

Simulations suggest that an adaptation of initial target dose could potentially benefit patients with greater disease severity. This outcome was used to support the further development of the product.

CASE STUDY 2

M&S IN PEDIATRIC DEVELOPMENT

European biotech company with a pediatric development in orphan indication

SGS Exprimo was contacted to perform a phase I trial and proposed a M&S solution to bridge to the phase II study.

SGS worked with a European biotech company with a compound in a pediatric orphan indication. The phase I healthy volunteer study was performed at the SGS Clinical Pharmacology Unit. In preparation of the phase II trial in a pediatric population the M&S modelled the proposed dose for the pediatric population.

Together with the SGS pharmacokinetics team and medical director team the phase II trial was designed and integrated in the clinical development plan. Together with the SGS Regulatory team the pediatric investigational plan (PIP) was developed.

Outcome: The PIP and trial design were successfully discussed with regulators and allowed for a quick start-up of the phase II trial.

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