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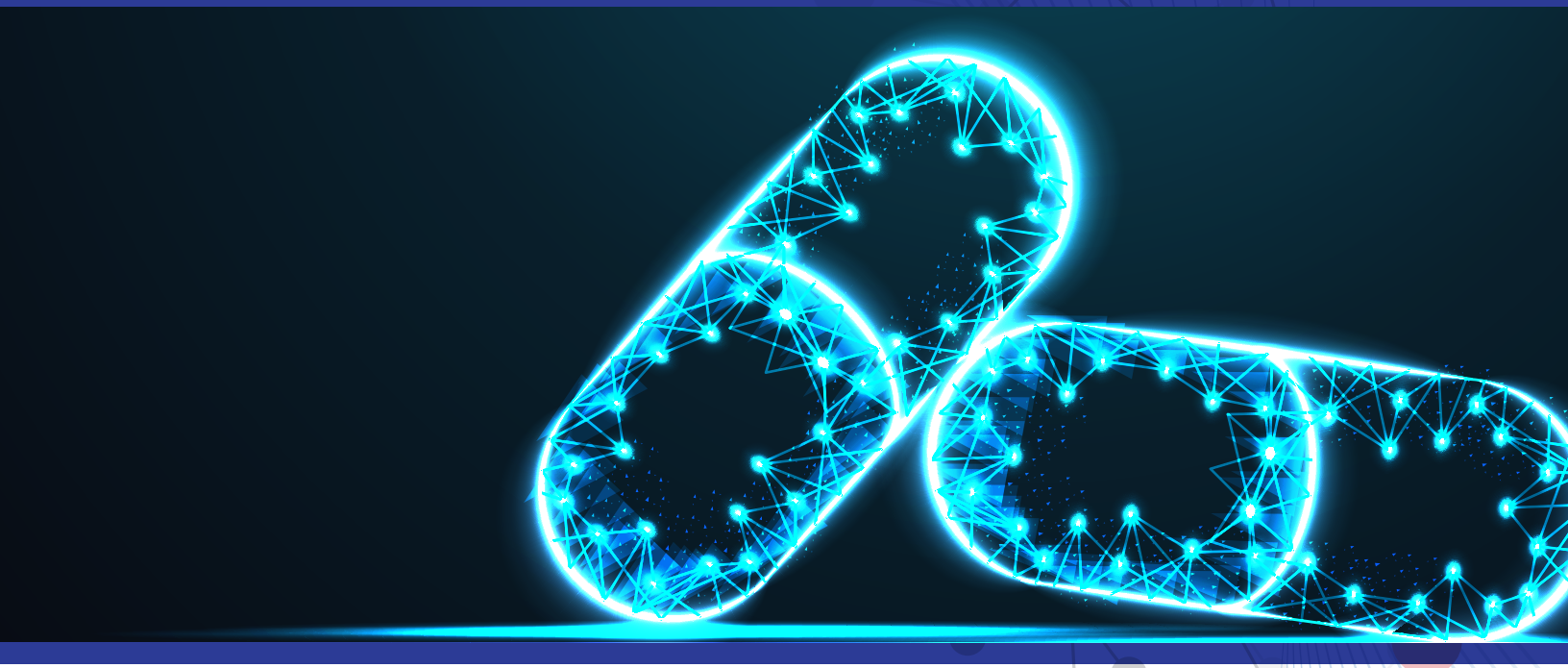
Advancing Biopharmaceutics & Drug Formulation Using *In Silico* Modeling

Model-Informed Formulation Development (MIFD) Increases Speed and Certainty for New and Generic Drugs



By Nikunjkumar Patel

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THE TRIALS AND TRIBULATIONS OF DRUG FORMULATION: MODEL-INFORMED FORMULATION DEVELOPMENT (MIFD)

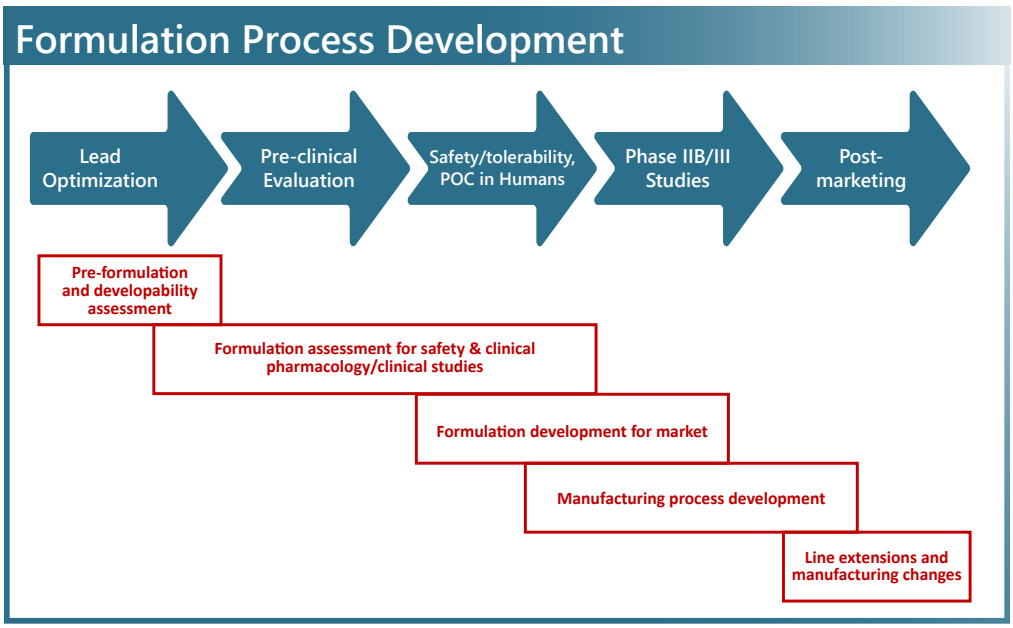
Drug formulation is a multistep process in which the active pharmaceutical ingredient (API) is combined with other excipients to make a drug product that is easy to administer, and safe and effective for patients. It considers factors such as particle size, polymorphism, solubility, and salt forms, by assessing the benefits and limitations of the API, excipients, API-excipient interactions, dosage strength, and manufacturing procedure. Drug formulation involves choosing the best form for a drug product, such as tablet, oral suspension, injection, or other delivery methods.

Biopharmaceutics is the study of the physical and chemical properties of a drug and its dosage form, as related to the onset, duration, and intensity of drug action—a key science area within drug formulation development.

Drug formulation is not a 'one and done' process. It is a critical task across the full drug development paradigm, for different doses, different delivery methods, different manufacturing scenarios, and in post-marketing for both new applications and alongside manufacturing changes (Figure 1). This paper will outline how Model-Informed Formulation Development (MIFD) can be used to expedite and reduce the cost of formulating drugs.

Figure 1:

Formulation development maps across the drug development paradigm.[1] MIFD supports each of these process steps—from early formulation development guidance and modeling the impact of salts, polymorph, excipients, prodrugs, or solid dispersions—to demonstrating virtual bioequivalence, bridging and biowaiver approaches.



WHAT IS MODEL-INFORMED FORMULATION DEVELOPMENT?

Per the US FDA, Model-Informed Drug Development (MIDD) is a powerful approach to support drug development and regulatory review. MIDD applications span the life cycle of the development of new drugs, generics, and biologic products. In new drug development, these approaches are often applied to inform clinical trial design including dose selection/ optimization, aid in the evaluation of critical regulatory review questions such as evidence of effectiveness, and development of policy. It can be used to advise, reduce and/or eliminate clinical studies, thus reducing time-to-market and development costs.

We refer to the use of MIDD approaches in formulation and biopharmaceutics as model-informed formulation development (MIFD). MIFD has demonstrated its value in optimizing drug formulation by aiding scientists in designing a rational and cost-effective approach to formulation development. It can be leveraged to demonstrate virtual bioequivalence (VBE) and obtain biowaivers in an increasing number of cases.

In the biopharmaceutics space, the role of computational modeling to inform formulation development and help strategize future in vivo studies or lifecycle plans in the post approval setting has also been on the rise. As more information and knowledge becomes available post-approval, quantitative mathematical models are becoming indispensable in supporting generic drug development and approval including complex generic drug products and are expected to help reduce overall time and cost.[2]

Formulation development is an iterative process that can benefit from the 'predict, learn, confirm and apply' paradigm. That paradigm can support and strengthen the overall formulation strategy and inform the numerous alternate formulations that will be developed throughout the development cycle and avoid trial-and-error empirical approaches. Formulation selection can profoundly impact drug release, absorption, and metabolism, altering the drug's pharmacokinetic (PK) profile and its pharmacodynamic (PD) response.

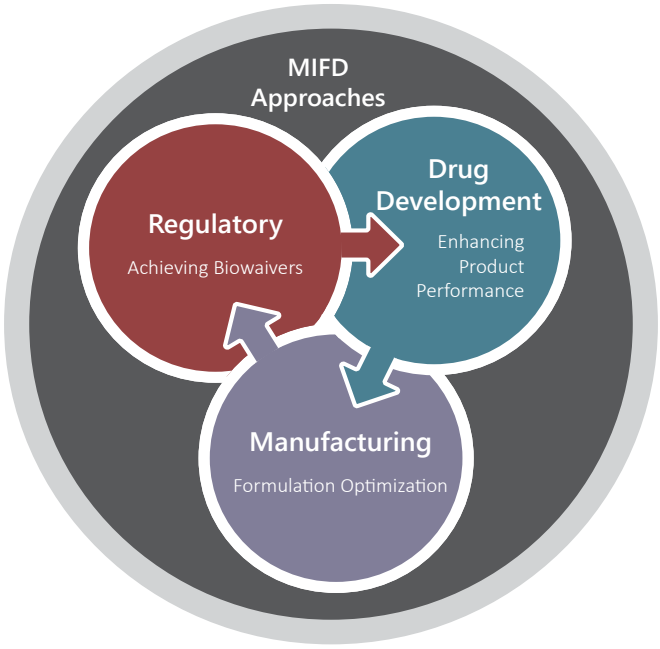


Figure 2:

Successful use of MIFD links the drug development, manufacturing and regulatory science processes.

THE REGULATORS ARE 'OPEN FOR BUSINESS' ON MIDD AND MIFD

Over the past 15 years, the use of quantitative methods and computational models has become part of modern drug development, for both new and generic drugs. MIDD's increased role in drug development can be found in FDA's PDUFA and GDUFA programs and multiple guidance documents. Other global regulatory agencies, including EMA, PMDA, MHRA and others, have followed FDA.

The use of Physiologically-based Pharmacokinetics (PBPK) for MIDD and MIFD has led to the release of draft guidance from regulatory agencies such as US FDA and EMA to guide regulatory use of such biosimulation technologies in drug development and regulatory decision making. PBPK uses models and simulations that combine physiology, population variability, and drug and formulation characteristics to mechanistically describe the PK of a drug product. Throughout a drug's life cycle, PBPK model predictions can be used to support decisions and predict outcomes of clinically untested scenarios. The use of PBPK models to replace human evaluation is widespread in the pharmaceutical industry and accepted by worldwide regulatory agencies.[3]

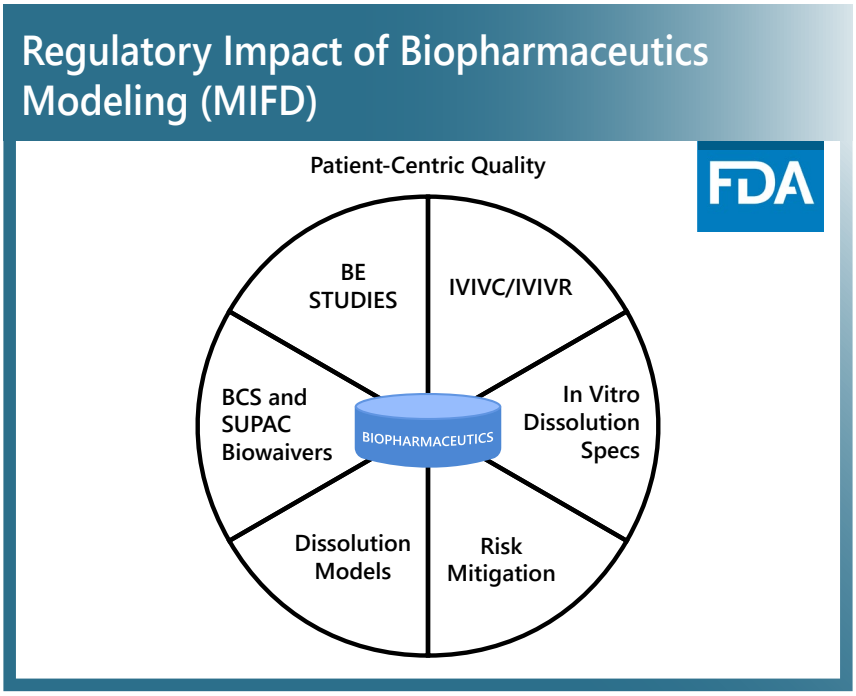
The role and the use of PBPK modeling in biopharmaceutics is expanding during the complex multiphase drug product development, regulatory approval, and life cycle management, by focusing on the use of mechanistic modeling for establishing an *in vitro in vivo* link. Once this link is established then the modeling can facilitate the following, as shown in Figure 3:

i) improve drug product risk assessment
ii) development of patient centric product quality standards
iii) expand regulatory flexibility and facilitate the drug product approval
iv) improve the drug product life cycle management.[4]

PBPK can help in identifying critical drug product quality attributes, specification setting, safe space evaluation and bridging of the drug product formulations.

Figure 3:

Regulatory areas in biopharmaceutics where PBPK modeling plays an important role to support quality aspects of the drug product.[3]



PBPK, THE WORKHORSE OF MIFD

As formulation development is still largely an empirical process — based on trial and error and formulation scientists' experience, we show how using PBPK, beginning in discovery programs can support 'rational' product development, thereby expediting the process of moving potential APIs from discovery to the clinic and subsequent commercialization.

This systematic modeling approach applies to several areas of drug product development such as predicting formulation outcomes, forecasting food-drug interactions, developing *in vitro-in vivo* correlation (IVIVC), predicting virtual bioequivalence, justifying biowaivers, and more. In fact, the mechanistic and predictive ability of PBPK models enables exploring the product design spaces more effectively and can facilitate implementing 'Quality by Design' (QbD) in a more meaningful way.

The mechanistic, physiologically-based Advanced Dissolution, Absorption and Metabolism (ADAM) Model within Certara's Simcyp® population-based Simulator helps formulation scientists predict the variability in human oral drug absorption from physiochemical and *in vitro* drug (product) data. The ADAM model can simulate a variety of formulations: solutions, suspensions, and immediate release (IR) tablets through to single unit (monoliths) and dispersible dosage forms (viz. gastro-retentive, enteric coated tablets and granules, controlled release (CR) monoliths, and CR dispersions) that release the API over time with or without lag time.

Case Study #1

ATTAINING BIOEQUIVALENCE WAIVERS FOR MANUFACTURING SITE CHANGES

Simcyp used to waive BE study for manufacturing site change.

Due to a site closure, the sponsor planned to move production of this BCS Class II drug product to an alternate facility, triggering the request by the FDA for a BE study. The drug has some challenging properties, including a bimodal and variable particle size distribution. The drug's pharmacokinetic (PK) profile is similarly complex, including multiple PK peaks and food effects. As an alternative to running a costly clinical BE study, the FDA indicated they were open to the sponsor using PBPK. Specifically, the agency was aware that the Simcyp Simulator's unique particle population balance (PPB) feature could account for the drug's heterogeneity, and its impact on drug dissolution, a technology which is sufficiently mature to obviate the need for a new clinical study.

The PPB capability was used to account for the particle size differences from the drug being manufactured at the original and new sites. Using the Simulator, they performed *in vitro* to *in vivo* extrapolation, simulated food staggering and verified the model against the original BE clinical data.

The FDA accepted the Simcyp Simulator PBPK modeling results in lieu of requiring a clinical BE study, saving the company an estimated $500,000 and several months.

PBPK Applications (MIFD) using the Simcyp Simulator:

- Early formulation
- Biowaiver strategy
  - Formulation and/or manufacturing site changes
- Pediatric formulation bridging strategy
- Virtual bioequivalence
- Development and optimization of extended release (ER) products for existing immediate release (IR) drugs
- 505(b) 2 application for approved drug products
- Defining safe space
- Enabling clinically relevant dissolution specs
- Discriminating dissolution method development
- Modeling impact of salt, polymorph, excipients, prodrugs, solid dispersions
- Mechanistic model development for diverse administration routes
- IVIVC for IR, controlled release (CR), generics

Case Study #2

DEMONSTRATING VIRTUAL BIOEQUIVALENCE (VBE) FOR PEDIATRICS

Demonstrating virtual BE for pediatrics: oral suspension versus immediate release tablet.

Heterozygous familial hypercholesterolemia is an inherited genetic disorder that causes dangerously high cholesterol levels, which can lead to heart disease, heart attack, or stroke at an early age if left untreated. While adults can be treated with bempedoic acid via an immediate release (IR) tablet, this formulation is not appropriate for pediatric patients, who will require an oral suspension (OS) formulation.

The Simcyp Simulator was used to develop a PBPK model to conduct BE trials in a virtual population of healthy adult subjects to compare the bempedoic acid PK of a child-friendly OS with the existing IR tablet. To support model development, oral dosage forms were differentiated based on dissolution rates; multiple virtual trials (including crossover and parallel), and sensitivity analysis were conducted. OS biopharmaceutical safe space was defined by the extremes of particle size and percent bempedoic acid in solution.

The bempedoic acid PBPK model successfully demonstrated BE between the test OS in development and the reference commercial IR tablet.[5]

Case Study #3

EXPANDING ALLOWABLE MANUFACTURING PARAMETERS

Using Simcyp to predict and inform the impact of changes in dissolution rates to expand the allowable manufacturing parameters.

Elagolix (Orilissa™) is a gonadotropin-releasing hormone (GnRH) receptor antagonist used to manage pain due to endometriosis. It works by decreasing the amount of certain hormones in the body.

A PBPK model for elagolix was developed in the Simcyp Simulator to mechanistically capture all of the known disposition mechanisms of elagolix (i.e., quantify the interplay between metabolism by CYP3A, hepatic uptake by OATP1B1, and efflux by P-gp), and to support drug-drug interaction (DDI) dosing recommendations for the co-administration of elagolix with other drugs such as midazolam (CYP3A substrate) and digoxin (P-gp substrate). The clinically verified PBPK model for elagolix was utilized to evaluate the impact of wider dissolution specifications on elagolix plasma exposures. The simulation results indicated that a slower in vitro dissolution profile, would not have a clinically significant impact on elagolix exposures.

The objectives of this work were to use a model-based approach to assess the impact of dissolution on elagolix exposures and provide evidence to support the expansion of dissolution specifications to ensure bioequivalent elagolix exposures for all the batches released in the market. The newly approved acceptance criteria provided a wider manufacturing space without compromising the clinical benefit to the patient. This allowed the approval of lots with up to 30% slower release compared to the elagolix commercial formulation but were still deemed to be bioequivalent to the reference formulation.[6]

The PBPK model results informed the setting of wider dissolution specifications without requiring *in vivo* studies.

Case Study #4

PBPK GUIDES SELECTION OF REPLACEMENT POLYMER IN FORMULATION

Impacted by supply chain issues – Simcyp leveraged to identify new polymer.

Polymers are widely used in drug formulation to control and optimize the drug release. Used in forms ranging from tablets, capsules and semi-solids to suspensions, gels, transdermal patches and long-acting injectables, individual and blended polymers are used for optimizing drug delivery. Frequently a combination of polymers and excipient combinations are used to obtain the desired drug release profile.

Due to supply challenges, a polymer employed in the sponsor's marketed drug formulation could not be sourced, forcing them to consider alternative excipients. The new polymer and formulation had to demonstrate bioequivalence under both fed and fasted conditions with the original formulation.

The Simcyp Simulator was leveraged to model various polymers and polymer blends to guide both *in vitro* experimentation and optimize the final drug formulation. Evaluation of C_{Max} and AUC, along with fed/fasted simulations were used to triage replacement polymers to support continual manufacturing. The integrated use of *in vitro* experimentation and PBPK modeling successfully enabled the final selection of the polymer and the formulation.

Simcyp along with *in vitro* lab work facilitated the selection of a new polymer/formulation to address a supply chain issue.

Case Study #5

DEVELOPING A NEW, CONTROLLED RELEASE FORMULATION

Developing a new, controlled release formulation using Simcyp.

Due to its short half life, patients receiving a marketed therapy were required to take the drug up to three times daily in order to maintain therapeutic exposures. As this dosing regimen would cause an adherence challenge, the sponsor sought to create a controlled release formulation instead.

Using physiochemical and protein binding data, a PBPK model was built; absorption was predicted using Simcyp's ADAM model with *in vitro* solubility, dissolution, and permeability data. The PBPK model was verified and refined with first-in-human SAD/MAD clinical studies. Simulations were performed under various scenarios – release rates achieving 100% release at increasing time intervals. This resulted in an accurate bottom-up prediction of PK for several extended-release formulation prototypes with PBPK using *in vitro* data. The PBPK model was more predictive than the *in vivo* (dog) data. The sponsor is planning on using that same PBPK model for formulation optimization for phase 2 studies as well as DDI analyses.

The Simcyp PBPK simulations helped guide ER development and are being used for formulation optimization and DDI analyses.

Case Study #6

PREDICTING THE EFFECTS OF CHANGES IN GASTRIC PH ON THE PHARMACOKINETICS

Simulating Impact of Protein Pump Inhibitor (PPI) Drugs to Inform Dosing Using Simcyp.

Protein pump inhibitors (PPIs) are the most commonly used anti-acid drugs. However, drug-drug interactions between PPIs and other agents may lead to decreased drug absorption with possible reduced therapeutic benefit, or even increased toxicity.[7]

Pyrukynd (chemical name mitipivat), approved by US FDA in 2002 [8] is a weak basic compound that has higher solubility in lower pH conditions and has lower solubility in higher pH conditions. The low pH of the fasting state stomach can enhance dissolution. Adding a PPI to counteract patient stomach issues will increase the pH, creating a lower solubility environment. This can potentially impact the bioavailability of the drug.

The ADAM-PBPK model (Simcyp) was applied to assess the impact of simulating an increase in gastric pH on the pharmacokinetics and fraction absorbed of mitapivat. Elevated gastric pH (up to 5) was predicted to have no significant effect on mitapivat pharmacokinetics and fraction absorbed. The predicted decreases in C_{max} and AUC were ≤2%.[8] The totality of evidence suggested that increasing gastric pH is likely not to have a clinically relevant impact on the absorption and pharmacokinetics of mitapivat. The lack of a pH effect may be attributed to the minimal impact of such pH change on overall *in vivo* dissolution as evidenced by the nearly complete absorption of the drug at the therapeutic dose level.

The simulations using Simcyp demonstrated a minimal PPI effect for this new oncology drug, thus avoiding the need for a study and allowing the dosing recommendations to remain unchanged.

Summary

Modeling and simulation, whether for new drugs or generics, clinical stage or biopharmaceutics/formulation, has clearly demonstrated its value in saving time and budget, while strengthening internal decision-making. This paper illustrates the increased adoption of MIDD and MIFD by sponsors and acceptance by regulators. There are many applications to integrate these technologies into drug programs, specifically the use of PBPK to support:

- Predicting the outcome of a BE study comparing test and reference formulations
- Formulation changes in late stage clinical development
- Generic product development
- Dissolution specification setting
- Manufacturing site change
- Waiver of fed BE study
- Minimize the number of “pilot” PK studies
- Provide more confidence in the outcome of a “pivotal” BE study

To learn more, visit: https://www.certara.com/services/virtual-bioequivalence/

About the Author

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A senior director of PBPK consultancy services at Simcyp division of Certara helping clients with advanced PBPK modelling to expedite internal decision-making, support bio-waivers via virtual bioequivalence (vBE) assessment and develop model-informed regulatory strategies for novel products, generic formulations, scale-up and post-approval changes (SUPAC), justification of dissolution specifications, etc. He has more than more 13 years of experience in computer aided drug design and PKPD modelling including 10+ years of experience focusing on PBPK modelling. He joined the Simcyp team in 2011 and led several enhancements of oral and dermal absorption PBPK modelling including development of mechanistic IVIVC module, first versions of virtual BE platform and dissolution and solubility modules of SIVA platform. He has a doctorate degree in the field of Quantitative Systems Toxicology and Safety (QSTS) focused on prediction of QT prolongation and Torsade de pointes (TdP).

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