Unlocking the power of PBPK prediction and ADMET experimentation for a better drug development

In the ever-evolving landscape of pharmaceutical research, the quest for developing safer and more effective drugs is a continuous endeavor. Two crucial pillars in this journey are PBPK (physiologically-based pharmacokinetic) modeling and ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) experimentation. Alone, each of these approaches plays a significant role in drug development, but their true potential is realized when they work hand in hand. PhinC Development (PhinC) and Oncodesign Services (ODS) are joining forces in order to provide valuable data. We've asked our experts what this partnership means to them.

Anne-Pascale Luzy

Anne-Pascale Luzy is the head of Discovery DMPK at Oncodesign Services. With over 25 years of experience in Drug Discovery, she is an expert in DMPK and toxicology. She held several positions in pharmaceutical companies such as Aventis Crop Sciences, Galderma/Nestlé Skinhealth, Syneos Health prior to joining Oncodesign Services in 2020. Anne-Pascale holds a PhD in experimental & clinical pharmacology from the University Paris Sud (France).

Can you explain why is ADMET important in drug discovery?

Anne-Pascale Luzy:

ADMET stands for Absorption, Distribution, Metabolism, Excretion and Toxicity. These are the key factors that determine how a drug evolves in the body. ADMET studies assess the pharmacokinetics, potential drug-drug interactions, toxicity, and metabolic pathways of a drug.

ADMET experimentation is vital for identifying good exposure, reducing potential risks and ensuring that drugs are both safe and effective. It provides valuable insights into how a drug interacts with the human body, guiding decisions on dosage, administration and further development.

When embarking on ADMET studies, a fundamental toolkit includes essential components. The following non-exhaustive list only reflects a typical package:

Absorption
- Permeability studies with Caco-2 cell lines
- Solubility studies and lipophilicity

Distribution
- Plasma protein binding, determination of Fup
- Tissue distribution studies, Blood/Plasma ratio

Metabolism
- Microsomal stability
- Metabolite identification, and CYP inhibition

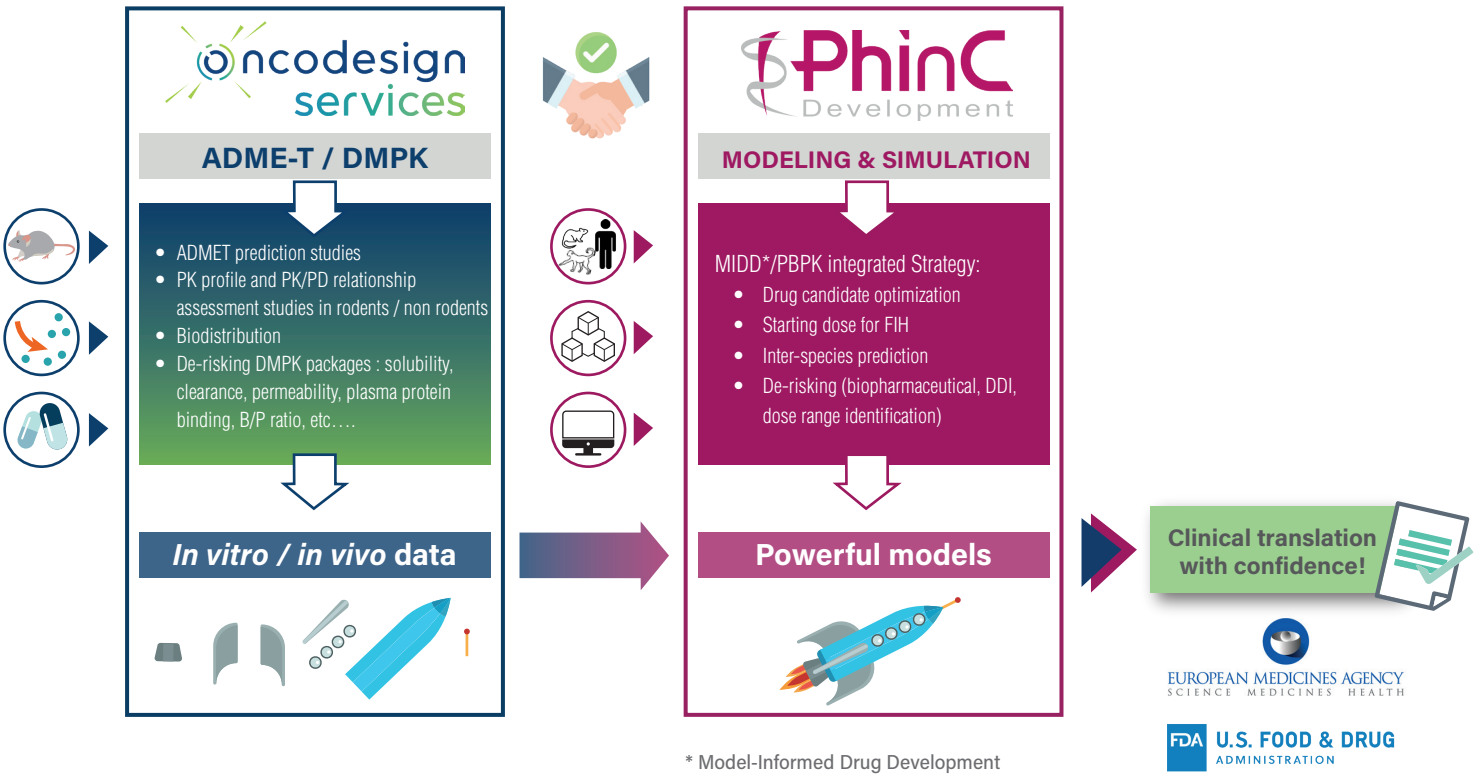
Excretion
- Clearance studies
- Followed by *in vivo* PK studies.

These assays provide quantitative and qualitative data crucial for assessing the pharmacokinetic and safety aspects of potential drug candidates during stages of drug development.

How does PBPK prediction complement experimental data?

Virginie Gualano:

PBPK modeling is a computational method that simulates how drugs move through the body. It factors in variables such as absorption, distribution, metabolism and excretion to predict a drug's behavior. By harnessing knowledge of the body's physiological parameters and mechanisms, PBPK models help researchers understand how a drug interacts with the human system. However, to build the models, it requires reliable, excellent quality data that you will trust. Imagine being able to predict how a drug will behave in different individuals, considering factors like age, gender, and even genetic variations. PBPK modeling makes this a reality, paving the way for personalized medicine and optimized drug dosages.



* Model-Informed Drug Development

How did the collaboration start between the two companies?

Virginie Gualano:

In order to modelize pharmacokinetic and build an accurate PBPK model, a large amount of data is required from both *in vitro* and *in vivo* experimentations. It is really important to be able to trust those data. The proximity between the two companies help to initiate the relationship but it is the quality of the work produced that made it carry on.

We love to compare PBPK modeling to building a rocket and ADMET experimentation is the fuel to propel it to orbit.

What advantages does the PBPK modeling bring to ADMET experimentation?

Anne-Pascale Luzy:

The regulatory requires more and more to use models in order to predict better the pharmacokinetic parameters prior to enter clinic. This will help optimizing experimental design and reducing animal testing. Several parameters can be simulated and therefore human responses predicted, reducing the amount of preclinical and clinical testings which are necessary in the drug development process.

Artificial Intelligence (AI) and Machine Learning (ML) can be used to design and optimize drug candidates by predicting their efficacy, safety and pharmacokinetics. This can help researchers identify the most promising drug candidates and reduce the number of unsuccessful drug trials. Moreover, researchers can make more informed decisions about drug development and improve patient safety.

As some data begins to be produced, PBPK prediction can start, even as early as lead identification. Modeling also helps to anticipate potential problems (like in absorption, drug-drug interactions...) and helps to reduce cost and limits failure in the clinic. If modeling predicts a dose that is too high or with a wrong dosing regimen, it can

Virginie Gualano

Virginie is Vice-president and co-founder of PhinC Development. She is a Pharmacokinetic, PBPK expert, and Consultant in Pharmacometrics. She has developed the PBPK practices within the company since 2012 and she manages the PBPK unit. With more than 25 years of experience, she held many positions in pharmaceutical industry as a PK project leader, Head of the Pharmacokinetic unit and Pharmacometrician. She is a Doctor in Pharmacy and she holds two university degrees in Pharmacokinetic and in Biostatistics.

help to make decision on an investment predicted to fail. It is always best to stop a project early than after years of experiments.

Are there specific requirements coming from the regulatory instance?

Virginie Gualano:

The regulatory instance is demanding to use more often PBPK modeling. At early stage, the law aimed to limit animal experimentations when possible. This is only possible with robust modeling based on reliable data. At later stage during clinical development, PBPK is already recommended in texts from the FDA/EMA in specific contexts such as drug-drug interactions or for identified population such as in liver and kidney failure...

What do you think the future holds?

Virginie Gualano:

The future holds promise. Emerging technologies, such as organ-on-a-chip and artificial intelligence, are poised to further enhance the integration of PBPK and ADMET, making drug development more efficient and personalized than ever.

In the world of pharmaceutical research, the close collaboration of PBPK prediction and ADMET experimentation is akin to unlocking a treasure trove of insights. It allows drug developers to navigate the complex maze of drug development with greater precision, reducing risks, and optimizing outcomes. As the pharmaceutical industry embraces this integrated approach, we can anticipate a brighter future where drugs are safer, more effective, and tailored to the unique needs of each patient.

Anne-Pascale Luzy:

By uniting the computational prowess of PBPK with the empirical wisdom of ADMET, the next breakthrough in drug development may be just around the corner. It's a synergy that promises to reshape the way we approach healthcare and medication, ensuring that every patient receives the treatment they deserve.

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