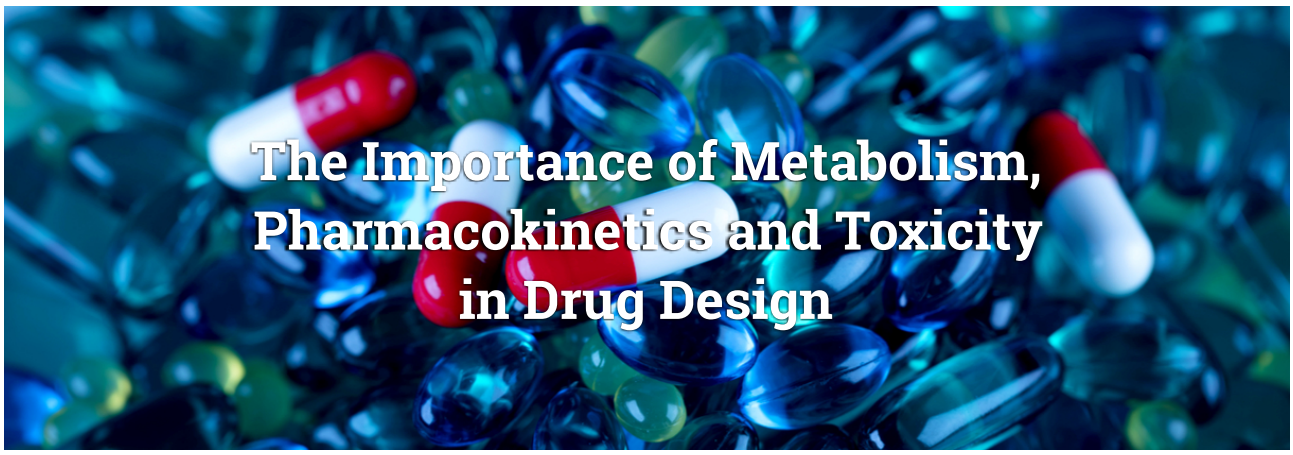

The Importance of Metabolism, Pharmacokinetics and Toxicity in Drug Design

The discovery and subsequent development of more effective and safer new medicines remains a key goal for the biopharmaceutical industry. Growing awareness and knowledge of the chemical space, which is required to engage contemporary drug targets, is steadily increasing the complexity of drug development and challenging the paradigms of the industry.

Therefore, understanding the absorption, distribution, metabolism, excretion and toxicity (ADMET) properties of potential new drug molecules and adapting screening cascades accordingly is essential in order to decrease attrition rates and increase success rates over time.

Within the pharmaceutical industry, the optimisation of ADMET and drug metabolism and pharmacokinetic (DMPK) properties at early stages in drug discovery is paramount. The DMPK properties of a compound determine how much of the drug will reach its target and the amount of time it stays in the target area.

Researchers can optimize ADMET and DMPK properties with the help of high-throughput assays. These allow them to maximize exposure at the desired target site for efficacy and minimize the potential toxicity of a drug.

Why does drug discovery need DMPK?

DMPK screening became an early routine element of the drug discovery process when the pharmaceutical industry realized that the optimization of DMPK parameters – solubility, permeability, metabolism and drug-drug interactions (DDI) – impacts directly the pharmacological efficacy of compounds in development, as well as their safety profiles.

"A key problem historically speaking were the high attrition or failure rates of drugs. They seemed to correspond with suboptimal pharmacokinetics," explains Patrick Barton, Head of DMPK at Evotec in Abingdon and

Associate Professor of Drug Discovery at Nottingham University.

Evotec is a drug discovery and development company that partners with biotech, pharma and academic institutions to study and develop potential therapies in areas such as neuroscience, diabetes, oncology and i nfectious diseases.

"Today, high attrition rates have shifted to toxicology, clinical safety, and lack of efficacy. Central to this attrition is drug exposure, which is also the central concept of DMPK," Barton continues.

Optimizing ADMET and DMPK properties with high-throughput assays allows researchers to maximize exposure at the target site

Advantages of early ADMET integration

Integrating ADMET early in the drug discovery process facilitates the provision of proof-of-concept for efficacy in animal models. This, in turn, generates pharmacokinetic parameters for the later translation into humans, including exposure and clinical dosage. In other words, information is provided, which gives an idea of what happens when a specific drugs is administered to a living organism.

*"The integration of in vitro DMPK screening in drug discovery has resulted in a significant decrease of clinical failure rates of compounds due to the early detection of poor pharmacokinetic properties,"*says Clive Dilworth, Scientific Director at **Cyprotex**, an Evotec company that focuses on ADMET screening and profiling.

"A failure to integrate DMPK early in drug design processes usually leads to failed compounds or significant and extensive delays to development programmes in later stages. This is both time consuming and extremely costly," he says.

Understanding ADMET is key

Having embedded DMPK into drug discovery processes, the pharmaceutical industry is now focusing on rising to the new challenge: Adjusting DMPK processes to new target classes. This includes the understanding of how drug transporters affect the disposition, clearance, toxicity and intracellular concentration of new chemical entities (NCEs) or compounds, and to further deduce structure-activity relationships (SAR).

A part of understanding the therapeutic potential of a new drug is the analysis of

its ADMET properties. Rob Riley, Executive Vice President of DMPK and ADME-Tox at **Evotec** and **Cyprotex**, explains a bit further: *"A close collaboration between DMPK, medicinal chemistry and computational chemistry is pivotal to efficient compound design, synthesis, testing, modelling and optimisation. In essence, these functions form the engine of efficient drug design."*

Today, the role of compound physicochemical properties is well established within the pharmaceutical industry. This means that drug discovery teams often include a design team, which consist of experts from key functions who contribute to design hypotheses. DMPK scientists, for instance, are responsible for identifying key areas in which properties of compounds need to be improved.

Optimizing ADMET in drug design

This is easier said than done. The pharmacokinetic profile of a compound is multi-parametricand interdependent, which means that changing one property can lead to changes in a variety of other properties.

"Imagine, for example, that you introduce excessive hydrogen bonding into a compound to improve its potency," explains Barton. *"This can lead to a decrease in permeability and solubility and introduce an efflux component.*

"That is what the DMPK scientists are there for. Together with the medicinal chemists they can analyze these multiple parameters and assess the benefit or effect of chemical modifications on the profile of the compound."

The success of a drug can also be influenced by the adjustment of ADMET parameters. ADMET parameters drive many of the factors that most companies aim for: a drug should be pharmacologically active, ideally admin istered orally once daily, demonstrate a high efficacy and show no evidence of toxicity. Hereby, the extensive knowledge of the compound's ADMET profile is essential for the development of a safe and effective drug.

"A close collaboration between DMPK, medicinal chemistry and computational chemistry is pivotal to efficient compound design, synthesis, testing, modelling and optimisation" – Rob Riley

"Establishing a toxicity profile is especially important," Dilworth points out. *"Preclinical animal models cannot always predict certain toxicities that might occur in humans. Characterization of a compound's toxicity, in vitro therefore, allows any potential adverse*

events in animal and human studies to be addressed, before these studies are initiated."

Challenges in DMPK integration

Although the integration of DMPK and ADMET processes seems straightforward enough, companies are often faced with a number of challenges. These start within the personnel and structure of the company itself.

More and more research is being done in silico which supports the most effective use of data

"Education and communication play a key role. Alignment across key functions and projects need to be supported by senior leaders," Riley explains. *"Thereafter, teaching or hiring staff with the required skillsets and experience is necessary, together with an investment in automation and analytical equipment."*

Eric Cogo, Head of DMPK at **Evotec** in Toulouse, emphasizes a different sort of challenge: *"There are clear indications that the industry needs to improve the turnaround of in vivo DMPK studies. Only this way, they could establish at early stage a demonstrable in vitro/in vivo correlation in preclinical species that are used in support of translation to humans."*

Diseases and DMPK requirements

No matter what challenges companies and their drug discovery teams face and what disease areas they are working in, the fundamental principles apply to all: achieving the right exposure to exert efficacy at the target and minimizing toxicity at the same time.

"Specific diseases may have their own DMPK requirements, opportunities and risks. Certain ADMET properties can help define a target product profile for the treatment of a specific disease," explains Barton.

"One example are diseases that are treated via inhalation, such as asthma or COPD. They require a very specific DMPK profile, because those drugs often need a sufficient retention in the lung, otherwise they are not effective enough. Also, you want to minimize off-target effects."

Dilworth adds: *"Other examples include the development of prodrugs in oncology, where targeted delivery by tools such as antibodies allows for tumor specific targeting of drugs. Once the tumor is reached, the prodrug becomes enzymatically activated to become cytotoxic."*

Collaboration is key to future success

As with most areas of biotechnology, drug discovery has become significantly more collaborative in recent years. Data, whether *in vitro* or *in vivo*, is being shared via public domains, allowing researchers to access large volumes of data and compare results between labs.

With this increase in collaboration also comes an opportunity to harmonize, which supports the most effective use of data and may, in turn, facilitate further *in silico* innovation.

Collaboration between the different areas of drug discovery is increasing, which allows the sharing of data on public domains and the comparison of results between labs

Throughout the industry, assessments of solubility, permeability, drug metabolism and distribution have become accepted and harmonized over time.

"A specific example of how important standardization within DMPK has become, is the regulatory guidance in the field of in vitro drug-to-drug interactions," explains Dilworth. *"US regulatory agencies have recently published updated, detailed guidance on the methodology of performing and interpreting in vitro drug-drug interaction studies."*

A future outlook on DMPK in drug design processes

Dilworth also notes that i*n vitro* toxicity screening is an area that still lacks harmonization. However, in future, *in vitro* toxicity assays in parallel with ADME and DMPK screening, as well as *in vivo* safety evaluations, will be adopted much earlier and *in vitro* models to support this will continue to evolve.

"These include complex 3D in vitro models and 'organ on a chip' technologies, which can represent the complexity and cellular interplay observed in vivo," says Dilworth. *"Linking in vitro organ compartments, such as the liver and kidney, to an 'organ on a chip' device, enables researchers to investigate the role, for example, of drug metabolism on potential nephrotoxicity."*

This approach will achieve a number of things, including a reduction of timelines and de-risked drug candidates with lower incidence of adverse events.

Increasingly, larger volumes of data will be evaluated much faster and observed in compound design processes. At the same

time, *in silico* techniques will develop further and gain in robustness of predictability.

Interested in learning more about the integration of DMPK into drug design processes? Check out Evotec's website and let them help you! And if you feel like digging a bit deeper into the matter, why not discover Cyprotex's website!

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