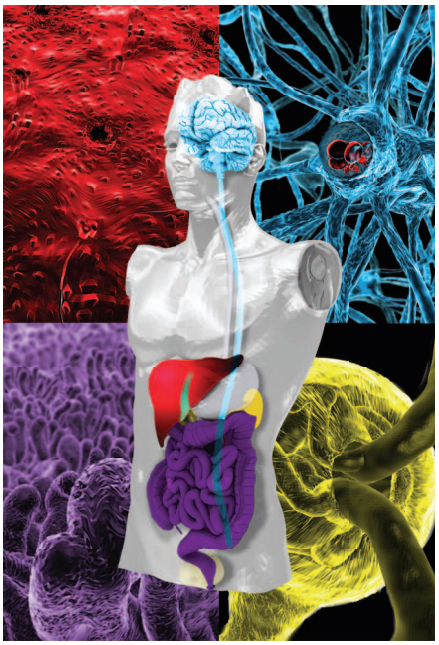
# PHARMACOKINETICS



TNO innovation for life

Predicting oral bioavailability is key in the development of drug candidates and formulations. There is an increasing need for reliable methods to predict human bioavailability and to identify (patho)physiological processes that may adversely affect the bioavailability and consequently the efficacy of a drug.

TNO has extensive experience with *in vivo* measurements of bioavailability, as well as predicting bioavailability using *in vitro* gastrointestinal models, mucosal cell lines, transporter assays, metabolizing systems and *in silico* modeling. In addition, ongoing research is focused on the development and validation of innovative methods to further improve the prediction of bioavailability.
Examples include:

- Predicting human bioavailability and organ concentrations of drugs by using combinations of *in vitro* models and *in silico* (PBPK) modeling.
- Microtracer dosing studies, in combination with accelerated mass spectroscopy to sensitively and accurately detect the minute amounts of test substance.
- Preclinical PET-CT imaging to assess transporter-mediated drug-drug interactions at the blood-brain-barrier.
- tinyTIM system to increase throughput in evaluating bioaccessibility of drugs in TNO's *in vitro* intestinal model

## ADME/DMPK PACKAGES

As part of your dossier TNO can perform the required ADME/DMPK package that typically consist of (non-)rodent mass balance studies, quantitative tissue distribution, whole body autoradiography, biliary excretion, metabolite profiling and identification, protein binding and *in vitro* metabolism studies.

## DRUG TRANSPORTERS

Transporter proteins embedded in plasma membranes actively transport their substrates (drugs, food components or endogenous compounds) into or out of the cell. Thus they play an important role in the absorption, distribution and excretion of drugs.

Drug-transporter interactions can cause unwanted drug-drug or drug-food interactions resulting in either decreased efficacy or enhanced toxicity. TNO provides various models to study the interactions of your compounds with drug transporters, such as:

- Cell-based transporter assays
- Inside-out vesicle assays
- Custom-made cell-lines and transporter assays
- *In vivo* ko or transgenic mouse models

## PBPK MODELING

One of the major challenges in pharmaceutical R&D is to shape each phase of drug development to minimize resources spent on candidates that will eventually fail, while retaining the most valuable compounds. Pharmacokinetic and pharmaco-dynamic modeling and simulation have proven to be valuable tools to integrate available *in silico*, *in vitro* and *in vivo* information to support decision making.

## MICROTRACER STUDIES

Technologies in which very small quantities of substances are tested in humans at a very early stage of drug development, facilitate early compound prioritization based on human data.
In microtracing studies, no more than 100 micrograms of test substance are administered. This is less than one hundredth of the expected therapeutic dose—a quantity that does not cause side-effects.
Analysis of these minute doses requires an Accelerator Mass Spectrometer (AMS) to analyze the radio-isotope labeled compounds. TNO is the first organization on mainland Europe to operate an AMS commercially for biomedical research.

## TNO INTESTINAL MODELS (TIM)

TNO's patented *in vitro* gastrointestinal models TIM-1 and TIM-2 offer rapid insight into the into the release, solubility and availability for absorption of pharmaceuticals within the gastro-intestinal tract. This well-validated and accurate system has a greater *in vivo* predictive value than typical *in vitro* dissolution assays. Additionally, it is a cost-effective alternative for human and animal trials, accelerating the process of product development.

## IMAGING

In collaboration with a network of partners, TNO developed and validated various pre-clinical imaging methods to study efficacy, toxicity and pharmacokinetics of drugs. Examples include:

- PET/CT imaging of drug-drug interaction at the blood-brain-barrier using [18F] gefitinib.
- NMR imaging of liver complications associated with metabolic syndrome.

## CONCLUSION

Overall, TNO provides innovative solutions for virtually any DMPK-related topic that you may run into during your drug development process. Please see our other product sheets for more detailed information on the topics described here. Alternatively, you can always contact us directly to find out which solutions TNO can provide for your specific interests within DMPK research.

**TNO.NL**

TNO HEALTHY LIVING
TNO initiates technological and societal innovation for healthy living and a dynamic society.

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