ACCELERATE YOUR CLINICAL DEVELOPMENT

Microtracer technology is part of TNO's effort to Refine, Reduce and Replace animal testing within the Life Sciences

TNO innovation for life

The development of new medicines is a costly and time consuming process. One way to increase the efficiency of drug development pipelines is by using microtracer dosing. Microtracing is an innovative technology in which very small quantities of substances are tested in humans at a very early stage of development. No more than 100 micrograms, or 30 nmoles for proteins, are administered. This is less than one hundredth of the expected therapeutic dose, a quantity that does not cause side-effects.

When analyzing the effects of minute doses, an extremely sensitive technology is required to trace the substance, such as an Accelerator Mass Spectrometer (AMS). However, in order to be measured by AMS, a compound needs to have a stable radio-isotope label—called a microtracer. AMS allows scientists to analyze microtracers at low (fg/ml) levels. TNO is the first and only organization on mainland Europe to have this machine commercially available for biomedical research. The behavior of new compounds in humans can be studied up to 1000 times more sensitive than by conventional methods such as LC-MS. In the human body, microtracers are mostly absent. Compounds labelled with radio-isotopes can be quickly identified, making them an ideal tool in drug development. TNO distinguishes several different applications for microtracer dosing in drug development, including:

1. Microdosing (Phase 0 research)
2. Microtracing (Information rich phase I research)
   - Absolute Bioavailability
   - Metabolite in Safety Testing (MIST)
3. Biologicals/Biosimilars

1. MICRODOSING (PHASE 0)

By applying microdosing, TNO can determine the fate of new medicines very early in drug development (phase 0). Scientists investigate the absorption, distribution, metabolism and excretion (urine/feces) of a new drug candidate. We can measure the pharmacokinetics of a substance, and all together, this information makes it possible to determine whether or not the medicine is compatible with a patient-friendly dosing regimen.

Since extensive pre-clinical research is scarcely needed to do a microdosing study, fewer lab animals need to be sacrifi ced before the compound can be used in humans.
The main advantage of microdosing is that it supplies extra information, based on research in humans, to arrive at an optimal go-no go decision. Taken the results of the microdosing studies into account, the phase I trials can be designed much more effectively. A typical microdosing study consists of approximately 4–6 volunteers per compound.
Due to the tiny amounts of radiolabelled compounds, microdosing studies are considered to be safe.
TNO owns the extremely sensitive AMS machinery needed for microdosing research. Our pharmacokinetics specialists can analyze the data from the AMS. In addition to that, we have the ability to recruit healthy subjects who take part in microdosing studies.
In short, we have all it takes to conduct microdosing research—a one-stop-shop for microdosing research and a broader view of pharmaceutical research.

2. MICROTRACING (PHASE I)

Absolute Bioavailability

Medicines are commonly administered to humans for the first time in phase I trials, to obtain primary data on pharmacokinetics. We can help extract more information from that compulsory research stage by adding a microtracer intravenously on top of your 'common' phase I study and including the AMS in the subsequent analysis. This way, we can measure how much of the substance is absorbed and thereby determine the absolute bioavailability.

Metabolite in Safety Testing (MIST) Also we would like to increase awareness that during Phase 1 any microtracer study is a potential MIST study that will present the entire human metabolite profile.
TNO 's facility is unique with both HR-MS/MS and AMS. Directly after chromatographic separation the flow is split, whereby one part is on-line coupled to a HR-MS for direct metabolite identification. Simultaneously fractions aree collected for off-line total radioactivity analysis by cAMS (Figure 1).

3. BIOLOGICALS/BIOSIMILARS

Biologicals (and biosimilars) are an upcoming class of drug compounds, unfortunately with a relatively high failure rate during drug development. This is mainly caused by the lack of suitable preclinical models to study PK profiles. Microdosing offers the superior advantage to obtain human data for biologicals, prior to a phase 1 study and after limited preclinical safety testing. The biological can be radio-labeled using carbon-14 or iodine-129.
The first microdosing study with a biological therapeutic protein in humans demonstrated excellent dose-proportionality. In addition a microdose can be used as a safe starting dose of biotherapeutics for FIM studies.
Obviously, not for all biotherapeutics dose-linearity between microdose and therapeutic dose is expected. In these cases microdosing in combination with *in vitro* and PBPK modelling can still be of high value to predict pharmacokinetics at the therapeutic dose.

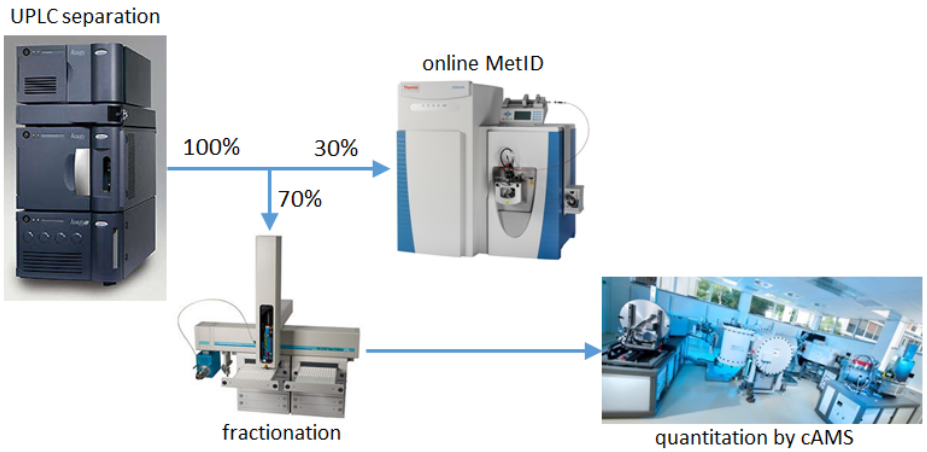

Figure 1. The combined use of HRMS and AMS for simultaneous metabolite quantification and identification

Revolutionized sample preparation
- Automated sample combustion
- On-line coupled to the AMS
- Validated total carbon-14 count in 2µl plasma (LLOQ 0.65 mBq/mL)

Microdosing (Phase 0) and Microtracer studies (Phase 1)
- Pharmacokinetics
- Absolute bioavailability
- MIST
- Mass Balance

TNO as one-stop-shop
- ^{14}C labeling of API
- Other isotopes: ^{26}Al, ^{129}I and ^{41}Ca
- Clinical study design
- Clinical conduct
- Analytical method development and validation
- Sample analysis (LLSC, UPLC and AMS)
- Traditional LC-MS/MS
- Reporting

Advanced applications of microtracers
- Peadiatric microdosing
- Biologicals and Biosimilars

TNO.NL

TNO HEALTHY LIVING
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