

MICROTRACER DOSING IN DRUG 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 timeconsuming process. As a result, companies are always looking for ways to increase the efficiency of their pipeline. One way to do that 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. In microtracing, small quantities, no more than 100 micrograms, 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 needed to trace the substance. An Accelerator Mass Spectrometer (AMS) is a sensitive tool that allows scientists to analyze compounds labelled with radio-isotopes as microtracers. TNO is the first organization on mainland Europe to have this machine available commercially for biomedical research. With the AMS, TNO is able to study the behaviour of new compounds in humans. Conventional methods, such as LC-MS, are generally not sensitive enough to detect these tiny quantities.

In order to be measured by AMS, a compound needs to have a stable radio-isotope label—called a microtracer. Radio-isotopes are atoms, like carbon-14, calcium-41 or iodine-129 that are rare in nature, very stable and long-lived isotopes.

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 three different applications for microtracer dosing in drug development:

1. Phase 0 research (microdosing);
2. Information-rich phase I research (tracerdosing);
3. Calcium-41 for studies on bone metabolism.



1. MICRODOSING

By applying microdosing, TNO can determine the fate of new medicines. Scientists investigate the absorption, distribution, metabolism and excretion of a new drug candidate. This information makes it possible to determine whether or not the medicine is compatible with a patient-friendly dosing regimen. Using microdosing, we can measure the pharmacokinetics of a substance, including the excretion route (via faeces and/or urine). Microdosing is part of phase 0 trials, which come before phase I. Since extensive pre-clinical research is scarcely needed to do a microdosing study, fewer lab animals need to be sacrificed 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.

Additionally, phase I trials can be designed much more effectively when they take the results of microdosing studies into account. 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 very 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 our own clinic. 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. PHASE I RESEARCH

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. Additionally, we will provide you at this early stage with information concerning the metabolites formed.

3. CALCIUM-41

Determining the effect of compounds on bone metabolism has been challenging. TNO is launching a new approach using calcium-41 as a microtracer. Through a single oral dose of calcium-41, the microtracer gets incorporated in bone. After a labeling period (of approximately 3 months), all the calcium-41 is excreted in urine (analysed by AMS) from bone tissue. This excretion of calcium-41 is a measure of bone metabolism. Through a short intervention with a new compound, TNO is able to conclude within two months whether the medicine has effect on bone metabolism. This approach can, for instance, be used to study the effectiveness of compounds on bone metabolism in osteopenia and osteoporosis.

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TNO HEALTHY LIVING

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