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# Metabolite Identification (Met ID): A Critical Step in Drug Discovery and Development

## What is Metabolite Identification?

During the natural biochemical process of degrading and eliminating either inherent or pharmaceutical compounds, bodies form metabolites. To develop safe and effective drugs, it's critical for drug developers to identify and characterize these metabolites. This process is commonly referred to as "Metabolite Identification (Met ID)."

## Why is Met ID important in drug development?

Insights gained during the Met ID process can help drug developers determine not only the rate at which pharmaceutical compounds degrade, but also the duration and intensity of their actions. Understanding of these side effects is an essential step in following Food and Drug Administration (FDA) and ICH guidelines, such as:

- FDA Guidance for Industry: Safety Testing of Drug Metabolites, 2016
- ICH Guideline M3(R2) Q&A, 2011
- FDA Guidance for In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies, 2017

## What does Met ID involve and accomplish?

Met ID requires careful strategic planning, use of modern analytical techniques, such as Liquid Chromatography–Mass Spectrometry (LC-MS), Nuclear Magnetic Resonance (NMR) spectroscopy and in-depth data analysis and interpretation.

These approaches to Met ID are essential steps in understanding which metabolites are likely to be formed *in vivo* and are essential for interpreting pharmacology, pharmacokinetic and toxicology data. This allows clinical drug developers to:

- Determine the exposure-response relationships of metabolites for efficacy and safety
- Determine the pharmacokinetic (PK) characteristics of the drug and its major metabolites
- Address any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding
- Assess preclinical safety testing of metabolites in question when metabolites form uniquely or present at disproportionately higher levels in humans than animal test species
- Design clinical studies to assess major active metabolites in healthy volunteers compared to patients and renal/hepatic impaired subjects

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## At what stages during drug development, should Met ID studies be developed?

Drug developers must perform Met ID throughout the entire drug-development process.

- Early in the drug discovery phase, Met ID studies can be used to identify metabolic soft spots to improve PK properties, or to identify active metabolites if there is a pharmacokinetic/pharmacodynamic modeling (PK-PD) disconnection.
- During the lead optimization stage, Met ID studies are used to select lead compounds with low bioactivation potential and drug–drug interaction (DDI) risk.
- Later in the drugdiscovery phase, drug developers perform Met ID to determine which preclinical safety species should be selected for the best toxicological coverage in humans.
- In preclinical and/or clinical development stages with radiolabeled studies, Met ID must be performed to quantitatively understand the *in vivo* circulating and excretion metabolites.
- Furthermore, in the initial phase of clinical development – the multiple ascending dose (MAD) study – drug developers conduct Met ID to understand circulating human metabolites at steady state and their exposure coverage in safety species.

## What factors are critical to Met ID success?

To ensure successful drug development and speed to market, it is advisable for drug developers to perform comprehensive Met ID as early as possible. This helps identify differences in drug metabolism between animals used in nonclinical safety assessments and humans early on in the drug-development process. The discovery of unique and disproportionate drug metabolites late in drug development can potentially cause development and marketing delays. When isotopic labeling is required to track the passage of a pharmaceutical drug in the body, it's important to choose the correct radiolabel and position. Carbon 14 is the element of choice for radiolabeling over other common radioisotopes, such as tritium. Furthermore, drug developers should consider the radiolabeling position with prior knowledge of the molecule to achieve a metabolically stable labeling position. Poor choice of radiolabel and position could complicate mass balance and metabolite profiling studies.

FDA drug-drug indication (DDI) draft guidance (2017) clarifies area under the curve (AUC) levels of less polar (≥25%) and more polar (≥100%) metabolites in comparison with parent AUC or metabolites with structural alerts for cytochrome (CYP) inhibition studies when a parent drug alone will not inhibit major cytochrome P450 (CYP) enzymes or transporters. To achieve Met ID success, it is imperative to determine those metabolites definitively and synthesize reference standards for inhibition work.

## Why partner with WuXi AppTec for Met ID?

WuXi AppTec's Drug Metabolism and Pharmacokinetics (DMPK) business unit is your single source for a wide range of absorption, distribution, metabolism and excretion (ADME) services across the entire spectrum of drug discovery and development. From animal mass balance studies to quantitative whole-body autoradiography (QWBA) and dosimetry, our DMPK services can be fully integrated to provide a flexible and customized solution for your specific project needs.

When you partner with us, you also benefit from our senior Met ID scientists who have a deep understanding of drug metabolism and organic chemistry fundamentals. The Met ID services you receive from WuXi AppTec can be provided as part of a full ADME package or as a standalone study.

As an established, reliable solution provider, WuXi AppTec has provided comprehensive Met ID services to the world's leading drug developers for more than 30 years. We use state-of-the-art, high-resolution, accurate mass spectrometry (Thermo Scientific™ Q Exactive™ Plus) as the primary LC-MS platform. We also have NMR (500 MHz Bruker DRX) in-house to support definitive metabolite identification.

## For more information about partnering with WuXi AppTec for DMPK and Met ID services:

**Visit**: https://labtesting.wuxiapptec.com/dmpk-services/

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