Rapid metabolism is a major limiting feature of many new drug candidates and can lead to low oral bioavailability, a short in vivo half-life, or the production of potentially active or toxic metabolites. Understanding metabolic liabilities and pathways provides a rationale for structural modifications to reduce associated risks.

The Centre for Drug Candidate Optimisation (CDCO) offers a range of standard or custom designed assays to assess the metabolism of test compounds. The selection of the most appropriate in vitro test system to investigate the metabolic fate of a test compound can be made based on the compound structure, the expected biotransformation pathways and the stage of development.

Metabolic stability studies typically focus on hepatic test systems including subcellular microsomes, S9 or cytosolic fractions, or cryopreserved hepatocytes. With some necessary assumptions, in vitro studies can also be used to predict in vivo clearance and provide inter-species metabolic profiling to guide species selection for initial toxicity testing.

There are also a range of metabolic characterisation studies that include the identification of specific enzymes responsible for biotransformation (reaction phenotyping) and examination of the kinetics of metabolite formation and the potential saturation of metabolic processes. Compound stability can also be assessed in other test systems including blood, plasma or selected intestinal models.

Metabolite identification studies are performed to identify major metabolic products, metabolically labile functional moieties within a structural series and provide a basis for structural modifications to reduce metabolic liabilities. The CDCO utilises the accurate mass capabilities of TOF-MS to identify test compound metabolites and degradation products from in vitro metabolism samples (microsomes, hepatocytes) or in vivo samples (plasma, urine, bile). This assay is run in a preliminary manner to identify putative products or to characterise products with full structural assignment.