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Summary
Discovery drug metabolism and pharmacokinetics (DMPK) studies are critical to efficient drug discovery programs and successful delivery of candidate molecules.

DISCOVERY

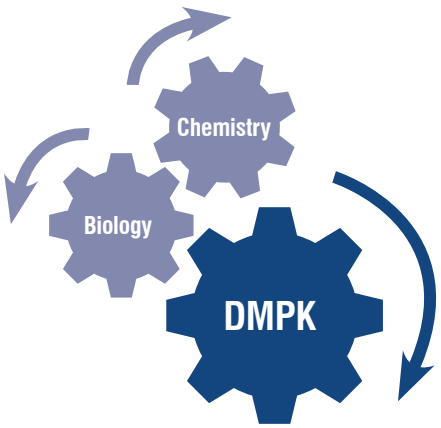
Drug Metabolism and Pharmacokinetics (DMPK) Supporting Discovery Research

Click to learn more

DMPK Services

- *In vitro* ADME
- Physicochemical properties
- Metabolic stability
- Drug-drug interactions
- Distribution
- Safety
- High-throughput and automation
- Pharmacokinetics (PK) support
- Bioanalysis and pharmacokinetic support

The identification and inclusion of appropriate DMPK studies is key to the success of discovery research by helping to de-risk candidate molecules and improve project productivity through more targeted chemical synthesis and progression of the right compounds. Charles River's flexible and collaborative DMPK team offers a variety of partnerships and pricing structures to suit client needs. In addition to fee-for-service assays and expertise, we can embed our DMPK scientists within existing integrated chemistry programs as core team members of multidisciplinary project teams. We offer a wealth of experience in a range of therapeutic areas and biological targets and can help support strategy and implementation of appropriate screening cascades.



Questions for our chemists?
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In Vitro ADME

As compound potency improves during hit-to-lead and lead optimization, *in vitro* ADME assays provide necessary data to establish insight into the key physiochemical properties and structural motifs that will provide the targeted candidate profile. Our *in vitro* ADME scientists have established a suite of assays that routinely support drug discovery programs, continue to work on the development and validation of new assays, and regularly monitor assay performance. Standard protocols help to maximize throughput and reduce lead times, although we can deploy client-specific solutions if necessary.

Standard *in vitro* ADME assays provided to support discovery research				
Physicochemical Properties	**Metabolic Stability**	**Drug-Drug Interactions**	**Distribution**	**Safety**
• Solubility • logP/LogD • pKa • Formulation	• Liver Microsomes • Hepatocytes • Tissue S9 • Plasma/blood • Metabolite ID • CYP450/UGT	• CYP450 inhibition • CYP450 TDI • Reaction phenotyping • CYP450 induction	• Plasma protein and tissue binding • Blood partitioning • Papp: Caco2, MDCK • Transporters: MDR1, BCRP, OATP1B1, OAT1B3, OAT1, OAT3, OCT1, OCT2, BSEP	• Cellular toxicity • hERG

Physicochemical Properties

We routinely employ kinetic solubility to help interpret the performance of compounds within ADME and biology screens while also assessing the effect the structural modifications have upon solubility within chemical series. Experimental logP/logD assessments are also available using miniaturized shake-flask methodology to reinforce *in silico* predictions.

Metabolic Stability

Validated metabolic stability screens can assess a compound's vulnerability to metabolic instability whether through CYP450-mediated or other types of oxidations, conjugations or other bio-transformations. High resolution mass spectrometry is used to identify putative metabolites, elucidate their structures, and characterize the metabolic fate of compounds.

Drug-Drug Interactions

The potential of a compound or chemical series to elicit clinical drug interactions can be assessed during hit-to-lead or lead optimization. This information provides further direction to a chemistry program to minimize the risk of drug-drug interactions occurring *in vivo*. Microsomal assays targeting CYP450 inhibition using specific, industry recognized probe substrates and control inhibitors are routinely employed in our laboratories. Using Capture Compound Mass Spectrometry (CCMS), we can also characterize the potential of compounds to induce P450s in human hepatocytes using both catalytic and mRNA endpoints.

Distribution

The ability of a compound to undergo oral absorption, enter the systemic circulation and distribute to target organs or indeed be restricted to certain compartments are key pieces of information for drug discovery programs. Employing an industry standard set of *in vitro* assays to determine parameters such as plasma protein binding (96-well equilibrium dialysis using RED® device), cell permeation (MDCK, Caco-2) and transfected cell-lines to understand the involvement of uptake and efflux transporters can often be crucial for many projects.

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Safety

Differentiating activity from cellular toxicity can be important for many therapeutic areas. Our HepG2 96-well cytotoxicity screen using CellTitre-Glo® technology for measuring ATP can provide critical information to interpret *in vitro* data and the potential for *in vivo* toxicity. Early assessment of the potential for a compound or chemical series to inhibit the hERG ion channel can be checked using high-throughput automated patch-clamp technology. With many notable drugs removed from the market or in late stage development due to cardiotoxicity, the hERG inhibition assay is routinely applied early in a discovery research program to determine the potential for *in vivo* QT interval prolongation.

High-Throughput ADME Using Robust Technology Platforms

Modern robotic systems, high-throughput mass spectrometry and ELNs expedite sample throughput. We've invested in highly sensitive, robust mass spectrometers and interfaced these with the Apricot Designs Dual Arm (ADDA) technology to enable high-throughput mass spectrometry (HT-MS). Using the 'trap and elute' technology proven at Charles River in support of high-throughput screening (HTS) campaigns, we have successfully translated *in vitro* assays that used the conventional LC-MS approach to this new platform.

In Vivo Pharmacokinetic Support for Discovery Research

The transition of drug discovery projects into pharmacokinetic studies is a major milestone. These studies will provide key information, such as clearance and bioavailability, to answer project questions and facilitate decision making. Drawing from comprehensive and a broad experience base, our pharmacokinetic scientists provide guidance concerning design and choice of appropriate animal models, making recommendations on efficient and informative ways of utilizing the animal resource. Data generated from these studies are assessed using non-compartmental and/or compartmental analysis techniques which can help in the refinement of PK/PD study design through greater understanding of target engagement. The use of cassette studies can provide an opportunity to screen a larger number of compounds while minimizing animal use. Such approaches can quickly build *in vitro-in vivo* correlations (IVIVCs). Ultimately, one of the primary objectives of the discovery DMPK group is the prediction of a human efficacious dose and the selection of appropriate compounds to progress into preclinical development.

Routes of Administration	Species and Tissues	Analysis and Interpretation
• Oral • Intravenous • Intraperitoneal • Subcutaneous • Osmotic mini-pumps • Intramuscular • Inhaled • Intranasal/intratracheal	• Mouse, rat • Hamster, guinea pig, rabbit • Dog, primate, minipig • Plasma/blood/CSF • Tissues (organ or tumor) • Bile and urine (routes of elimination)	• Non-compartmental and compartmental data analysis • Selection of regimen and dose for preclinical PD and efficacy studies • Mechanistic PK/PD (understanding target engagement) • Dose to man prediction

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Bioanalysis and Pharmacokinetic Support

We have considerable expertise in the bioanalysis of biological samples supporting PK and PD studies. Close interaction with the project team helps provide high quality data that addresses specific project issues. Our experience with analyzing a wide variety of animal tissues can provide valuable insight into drug distribution and interaction with pharmacological targets. Highly sensitive and specific LC-MS/MS systems detect and quantify compound in blood, plasma and tissues samples. This data is used to derive the intrinsic pharmacokinetic properties and establish highly informative PK/PD relationships such as theoretical receptor occupancy. Application of this information in a project setting helps to maintain project momentum and provides direction to the program. Ultimately, this data helps the project team transition from one discovery research phase to another or choose a candidate molecule for progression into preclinical development.

Other Charles River Chemistry Offerings

Computer-aided Drug Design (CADD) Services

Charles River's Computer-aided Drug Design (CADD) team unites industry-seasoned scientists with an average of 14 years of biotech/pharma experience with modern software and hardware resources. This combination enables us to support drug discovery projects all the way from hit identification through lead optimization. The group can work in a standalone manner, often for bespoke modeling or virtual screening projects, or act as an integrated project team member, collaborating closely with colleagues in medicinal chemistry, structural biology and allied disciplines.

Integrated and Fee-for-Service Synthetic Chemistry Services

The Charles River Chemistry team is comprised of more than 140 chemists and the team has been involved in the successful delivery of 80 preclinical candidates to date. Over 50% have completed further research to PhD and postdoctoral levels. Our chemists are skilled in the development of multi-stage synthetic routes to previously unknown scaffolds, chemical probes, and novel compounds and have demonstrated this up to kilogram scale. In addition to fee-for service and stand-alone projects, we offer integrated solutions – in-sourced chemistry collaborations where our own chemists are recognized as integral parts of our client's chemistry departments.

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