

Discovery and Imaging Services

We understand that early discovery is a critical stage in your drug development program. The ability to rule out unsuitable drug candidates early in the process is key to the successful development of a new therapeutic. Charles River offers streamlined discovery capabilities to meet the rapid timelines and diverse needs required for the most efficient target validation and drug candidate ranking and selection process.

More than ever, you need a discovery partner you can trust. Working in close collaboration with you, Charles River Discovery and Imaging Services offers customized screening programs to ensure early and late lead candidate optimization. With multiple facilities and expert staff in North America, Europe, and Asia, we help close the gap between the output of combinatorial chemistry and high-throughput screening and the safety testing required prior to initiation of your clinical trials.

Whether you need a single study or intend to outsource your entire discovery program, our capacity and portfolio of services allow us to offer you a comprehensive molecule-to-mouse-to-man program.

To help you make that critical decision to commit a compound into development, here are some of the areas in which Charles River can support your discovery programs:

- *In Vitro* ADMET
- Formulation Development and Analytical Chemistry
- *In Vivo* Pharmacokinetic/ADME Screening
- Bioanalysis
- Pharmacology
- Lead Optimization Toxicology
- Oncology
- Small Animal Imaging
- Phenotyping Services
- Biomarker Analysis



In Vitro ADMET

In vitro ADMET parameters are a set of factors that describe how a drug behaves in the human body and can be a major cause of drug failure. By focusing on *in vitro* ADMET data, you can predict at an early stage which compounds not only possess good binding affinity for a specific target, but also pass the test for good bioavailability and safety. Our wide range of automated *in vitro* assays yields information in the areas of metabolism, toxicity, and physico-chemical characteristics.

- Aqueous solubility
- Cytochrome P450 enzyme inhibition/induction
- Cytochrome P450 reaction phenotyping
- Cell permeability and efflux assays (CaCo-2)
- Cell proliferation and cytotoxicity
- Drug-drug interaction
- Enzyme assays
- hERG inhibition
- Melanin and plasma protein binding
- Metabolic plasma and buffer stability
- Metabolite profiling, assessment, and identification

Formulation Development and Analytical Chemistry

Knowing the physico-chemical characteristics of a drug and having experience with a wide variety of dosing vehicles is vital to successfully formulating a compound for *in vivo* administration.

Charles River offers preformulation screens and analytical chemistry services for a single test article or an analog series. These services can help you better understand your formulation options early in discovery and reduce delays arising from formulation issues later in development. Our experience covers a vast array of formulation types, including oral, parenteral, creams, ointments, and inhalation products such as nebulizer solutions and powder blends.

- pH solubility
- pH partitioning
- Excipient compatibility
- Dosability and suitability
- Container compatibility
- Microscopic behavior
- Bioavailability enhancement
- Analytical chemistry

In Vivo Pharmacokinetic/ADME Screening

Whether you have one compound or a library of compounds requiring drug metabolism assessment, the skilled scientists at Charles River can design, conduct, and interpret the *in vivo* PK/ADME components of your program as part of our streamlined non-GLP screening services.

Quick study initiation, multiple species, and various dose regimens and administration routes, as well as bioanalytical support, provide the necessary tools you need to rapidly identify and optimize potential drug candidates.

- Bioavailability
- Biliary excretion
- Mass balance
- Tissue distribution
- Placental transfer
- Bioequivalence
- Dose ranging
- Linearity
- Proportionality
- Single, multiple, and cassette dosing
- Metabolite profiling

Bioanalysis

The speed of lead candidate selection studies requires an equally rapid analytical tool to efficiently measure drug concentrations in the biological samples collected. Charles River offers non-GLP discovery bioanalytical services either in support of studies conducted in-house or as a stand-alone service with the flexibility and speed to meet the timelines and diverse needs for discovering the best drug candidate.

Our research grade assay approach via LC-MS/MS can quickly analyze samples for compound ranking. Once a lead candidate has been selected in the discovery analytical process, these methods can be transferred to method development for GLP bioanalytical testing including feasibility, validation, and preclinical and clinical sample analysis.

- Research grade assay (RGA)
- Varying grades of accuracy and precision
- LC-MS/MS
- Single compound or analog series analysis
- Dosing solutions, biological fluids, tissue, and excreta

Pharmacology

At Charles River we understand the importance of determining whether your test article is efficacious for its intended use as early as possible to avoid failures further down the development path. Our global pharmacology team conducts early research and proof-of-principle studies in relevant animal models of human diseases to assist your efficacy evaluations.

- Metabolic diseases
- Cardiovascular diseases
- Respiratory diseases
- Inflammatory diseases
- Infectious diseases
- Central nervous system disorders
- Pain models
- Ocular diseases
- Oncology
- Bone and cartilage diseases
- Tissue repair and wound healing

Lead Optimization Toxicology

Even after researchers have identified an active molecule against a disease target, many drugs fail to reach the market because of unacceptable toxicity. Our lead optimization toxicology services can uncover possible safety concerns earlier in the drug development process, enabling you to bring forward drug candidates that are more likely to succeed in preclinical testing.

- Multi-level customized study designs
- Rodent and nonrodent species
- Variety of dose routes
- Analytical and clinical chemistry
- Pathology
- Toxicokinetics
- Preformatted reports

Oncology

Charles River offers over 200 tumor models and a wide array of supporting services for the study of anticancer therapeutics. Traditional evaluation in human tumor xenograft and syngeneic models is supplemented with orthotopic, metastatic, and transgenic tumor models.

Anatomical and functional imaging technologies provide an integrated and quantitative correlation between efficacy and mechanism of action. This enables you to validate intended clinical biomarkers and set expected decision-making thresholds for the modulation of surrogate markers in Phase I and II clinical trials. Our previously validated models are of the utmost scientific integrity, and we can also collaborate with you to develop novel models.

- *In Vitro* IC50 determination
- Maximal tolerated dose (MTD) determination
- Tumor growth delay and challenge survival studies
- Combination chemotherapeutic studies
- Combination radiotherapy/chemotherapy studies
- Orthotopic and metastatic models
- Models of angiogenesis
- Pharmacodynamic studies
- Small animal imaging services

Small Animal Imaging

Noninvasive imaging capabilities allow our customers to detect changes at the anatomical and molecular level in a variety of small animal models of disease without sacrificing the animal. This reduces the number of animals needed for a study while providing drug effect assessment over time.

Charles River can also validate the use of clinical imaging modalities, ensuring that treatment with your compound does not alter the interpretation of the imaging signal.

- Positron emission tomography (PET)
- Magnetic resonance imaging (MRI)
- Computed tomography (CT)
- *In vivo* bioluminescence and fluorescence imaging
- High-resolution ultrasound
- Dual-energy X-ray absorptiometry (DEXA)

Phenotyping Services

We know that genetic manipulation in mice can present you with unique phenotypes. Charles River's phenotyping screens offer a comprehensive, multi-step characterization of the anatomical, physiological, and behavioral changes in your newly created genetically engineered models.

- PhenoFirst®
- Metabolic diseases
- Cardiovascular diseases
- Respiratory diseases
- Central nervous system disorders
- Inflammatory diseases
- Small animal imaging
- Reproductive diseases

Biomarker Analysis

Finding more and better biomarkers for all diseases has been a high priority for decades as an indicator of biological processes and as a measurement of pharmacological response. At Charles River we assist in the development and analysis of both tissue and plasma biomarkers across multiple disciplines.

- **Tissue Biomarkers:** To further characterize your models, quantitative PCR-based expression testing, immunohistopathology, and *in situ* hybridization can determine effects on key cellular and molecular processes. Quantitative analysis of biomarker expression can help define mechanism of action for targeted therapeutics and assess their efficacy.
- **Plasma Biomarkers:** Plasma biomarkers can help you identify disease conditions, as well as monitor progression and response to therapy. Biomarker patterns are critical to applications such as drug safety and efficacy, disease diagnosis, and disease modeling. Our multi-analyte profiles provide an evaluation of protein expression patterns indicative of a response to disease, drugs, and the environment.

Once your drug has passed the discovery milestone, Charles River provides a seamless transition to preclinical and clinical development, creating a more efficient program that can save you valuable time and accelerate your drug development, exactly.