



SAFETY ASSESSMENT

Investigational New Drug Development Programs

Experience with innovative modalities:

- Small molecules
- Proteins/peptides
- Nucleic acid-based therapeutics
- Cell therapy
- Gene therapy
- Engineered bacteria
- Antibody/antibody-like
- Novel excipients
- Other innovative and complex therapies

Evolving market pressures are changing the focus of the drug development industry, further accelerating early phases in order to create late-stage pipeline growth. Given these increasing pressures, understanding how and when to plan a preclinical investigational new drug (IND)-enabling program is an integral part of meeting specific milestones necessary for timely and efficient IND submission.

Charles River has several decades of IND research experience, a unique range of services and best-in-class expertise to help clients successfully initiate and complete an IND-enabling program on time and within budget. Of course, the same experience can also be applied to the design of suitable studies or programs for submission to any global regulatory authorities.

As a true end-to-end CRO, our IND programs are enriched by collaboration with our discovery scientists who can help guide and inform the lead candidate selection process. Our historical knowledge of vehicle suitability and formulation expertise allows us to identify the most suitable formulation for our clients' preclinical programs. In addition, clients who choose Charles River as their IND program partner can benefit from the Charles River Scientific Advisory Services. This comprehensive service brings together a team of industry-proven professionals to help clients navigate the ever-changing landscape of drug development. Our collaborative approach and deep scientific and regulatory understanding of each molecule helps us shape the best strategy for bringing a novel therapy to market and design custom studies and programs that reduce risk and accelerate timelines.

Program Features:

- Standardized and efficient timelines
- Analytical support
- Repeat-dose toxicology
- Customized studies
- Formulation analysis
- Safety pharmacology
- Lead candidate selection
- Bioanalysis
- Toxicology
- Formulation, drug metabolism and pharmacokinetics
- Immunogenicity testing
- Tissue cross-reactivity
- Preliminary toxicology
- Data & SEND

EVERY STEP OF THE WAY

 [Click here for our IND Gantt Chart Builder](#)

This interactive tool is meant to provide you with an estimated timeline to help you better plan your IND program.

Standardized and Efficient Study Timelines

In response to the evolving needs and expectations of our clients for accelerated IND timelines, Charles River has adopted new standardized reporting timelines. These include time allotted for analytical and bioanalytical method development and validation, repeat-dose toxicology in-life and recovery phases, standard safety pharmacology battery and genetic toxicology tests. Our unique approach is based on standardized on best practices for reporting, monitoring and automation, optimized pathology evaluation timelines. We leverage internal scheduling for laboratory support (e.g., analytical, bioanalysis and toxicokinetic evaluations) and efficient scheduling of both draft and final reporting, including SEND, at protocol finalization.

Customized Studies

We work with clients to customize a specific IND-enabling study program based upon the type of drug, its intended route of administration and its clinical indication. We can also guide the steps leading up to the program's implementation, including lead candidate selection and drug metabolism and pharmacokinetics. As the success of an IND program relies as much upon the planning as the execution, every program is overseen and carried out by scientists dedicated to both discovery and development, allowing lead candidate selection to flow seamlessly into the development phase.

Lead Candidate Selection

While compound failure during the preclinical stage is less costly than subsequent failure in clinical trials, preclinical compound failure could potentially be reduced or even prevented by earlier investment in better lead candidate selection. Increased investment in lead candidate selection not only provides good evidence of efficacy in an animal model of human disease, but also helps to reduce the time spent in IND/NDA testing by elucidating possible safety and metabolic concerns earlier in the drug development process. Charles River has a proven track record of successful lead candidate screening, using non-GLP bioavailability, pharmacokinetics and toxicity analysis. In addition to *in vivo* toxicology studies, we can assess the cardiotoxic and genotoxic potential of candidate molecules. This work can involve technology transfer, method development and validation, and it is essential to plan this aspect well in advance of any IND-enabling preclinical work.

Formulation, Drug Metabolism and Pharmacokinetics

Development of a clinical test article formulation is a key milestone and can often be one of the most common reasons for the unexpected delay of a preclinical program. We help clients make the best decision regarding formulation options and avoid unnecessary delays with advice on how properties such as bioavailability, tissue distribution, mass balance, metabolism (metabolite profile and identification) and pharmacokinetics may differ for different formulations of the same drug. Our formulation chemists then optimize the selected formulation for improved results and minimal toxicity of formulation components. Our comprehensive drug metabolism services are designed to satisfy the requirements of international regulatory authorities and to provide safety data to assess the validity of laboratory species as appropriate toxicological models for humans. Additionally, our skilled ADME scientists, together with our pharmacokineticists, surgeons and bioanalytical chemists, can design and interpret both *in vitro* and *in vivo* components of drug metabolism studies based on program goals.

Analytical Support

Laboratory scientists at Charles River use fully validated, networked data management systems at all laboratory locations for test article/item and sample management. We continue to make significant investments in highly trained chemists, facilities and instrumentation to increase our capabilities and capacity to produce rapid and reliable quality data. Full method development optimization, validation and high-throughput sample analyses are all performed in accordance with GLP regulations. In addition, we can tailor assay qualification to requirements in support of early drug discovery studies.



[Click here to get started on your IND Program.](#)

Formulation Analysis

Our staff adhere to strict guidelines, including tightly controlled test article receipt, storage, distribution, use and disposal, at all of our global facilities. We use a variety of chromatographic/spectroscopic techniques to analyze formulations for concentration of test article, with methods uniquely suited for small and large molecules. We use various detector types according to the nature of the test compound, including specialized techniques (e.g., mass spectrometry) when necessary, to ensure that sensitivity and specificity requirements are met.

Bioanalysis

Our bioanalysis experts have extensive experience in supporting drug development programs from early discovery pharmacokinetic screening through GLP toxicology studies to clinical trials. This includes the *de novo* development of bioanalytical methods and the transfer and refinement of bioanalytical methods from our clients' laboratories to our own. Our facilities feature the latest instrumentation and equipment, allowing us to measure drug and metabolite concentrations in biological matrices using a wide range of techniques and technology platforms. These facilities ensure our capacity to support rapid lead-in times and meet critical deadlines.

Immunogenicity Testing

The assessment of immunogenicity must always be considered in preclinical and clinical testing of biologics. With ten years of experience in preclinical and clinical immunogenicity testing of biotherapeutics and novel compounds, our Immunogenicity group has developed and validated a large number of assays for many different types of compounds. We can fully integrate these results into the interpretation of pharmacokinetic and toxicokinetic data. Methods are developed, optimized and validated following the current FDA and EMEA draft guidelines and relevant white papers.

Preliminary Toxicology

In vitro toxicology screening approaches are key tools to decrease the attrition of novel drug candidates as they progress through the discovery and development process. Recent advancements in developing physiologically relevant *in vitro* model systems are showing promise when it comes to improving the translation of assay results to predict adverse effects in humans. A comprehensive portfolio of *in vitro* toxicology assays is available across several of our facilities between North America and Europe, encompassing a wide range of services along the *in vitro* toxicity assay continuum

Our study directors work with clients to design preliminary range-finding studies to guide dose level selection for pivotal toxicology studies. Optimized GLP toxicology study designs limit the need to repeat such studies and support our global efforts to adhere to the principals of the 3Rs: replacement, reduction and refinement. As part of our standard preclinical packages, we can combine single-dose toxicity and repeat-dose range-finding into one preliminary effective rodent study (although these are still available separately). This combined approach also provides the information on acute toxicity and maximum tolerated dose needed to satisfy regulatory expectations.

Repeat-Dose Toxicology

Well-designed GLP toxicology studies are paramount to a successful IND program. Charles River's study directors work with clients to design an optimal GLP toxicology study by including the appropriate endpoints to meet the needs of an IND-enabling preclinical program. In addition, we also offer a wide selection of validated preclinical and clinical biomarker assays across several therapeutic areas. We conduct both standard and novel study designs, and can help clients determine next steps if and when unexpected findings or toxicity issues arise during the course of a program.



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Genetic Toxicology

Our Genetic Toxicology team works to conduct studies assessing the potential for genetic mutations or chromosomal damage. We can run the appropriate assays to meet the unique requirements of your specific chemicals or drugs. Determination genotoxicity is essential to completing the safety assessment for new products (e.g., pharmaceutical ingredients and impurities, unique human metabolites, industrial chemicals, agrochemicals, cosmetics, etc.).

We work closely with other Safety Assessment groups to improve study results and integrity with supplementary services, such as formulation and analytical chemistry, pathology, and bioanalysis. We can also support other studies by evaluating genetic toxicology biomarkers and determining mechanism of action (MOA) identification via *in situ* hybridization, flow cytometry, and determining apoptosis, if applicable.

Safety Pharmacology

Charles River is an industry leader in the design and execution of safety pharmacology studies, with vast experience in stand-alone and integrated repeat-dose designs. Our safety pharmacologists are fluent in the latest technology and assessments, including the use of jacketed animals for telemetry for the collection of continuous electrocardiographic and hemodynamic data in large animals. Our standard safety pharmacology studies incorporate the core battery of testing required for small molecule drugs, including the CNS/Irwin screen, evaluation of respiratory function, cardiovascular assessment and the *in vitro* hERG assay (to identify potential risk of QT interval prolongation). Any or all of these safety parameters may be incorporated into toxicology studies as a cost-effective means of addressing regulatory expectations while actively fostering the 3Rs.

Tissue Cross-Reactivity

We hold a full range of tissues from various animal species. As outlined in FDA guidelines, we store an array of human tissues from multiple donors sourced from ethically approved tissue banks with full patient consent. Our commitment to new and improved pathology techniques has led to the generation of highly specific mechanistic drug action/tissue response data critical to worldwide regulatory filings.

For immunohistochemistry-based tissue cross-reactivity (TCR) studies, we provide efficiency of scale in full compliance with Good Laboratory Practice (GLP) regulations and interpretation of findings, and can represent you in presenting to the applicable regulatory agencies

Data & SEND

SEND is an implementation of the CDISC Study Data Tabulation Model (SDTM) that provides a framework for the standardized, electronic representation of individual animal study data. SEND is intended to increase the effectiveness and efficiency of data review for regulatory submissions. Biotechnology and Pharmaceutical partners are responsible for providing the FDA with respective SEND datasets in accordance with the guidelines. Charles River SEND experts have experience working with all report types, even if reports come from other vendors. It is important to understand if your vendor is SEND compliant and can provide the necessary datasets for submission.

