



SAFETY ASSESSMENT

Respiratory Services

Charles River has a long history of experience in the field of respiratory disease research. Our expert scientists provide a wide range of capabilities to support our clients' development programs from discovery to safety. Our capacity for inhalation toxicology studies is among the largest in the world, and we offer seamless, one-stop service through our in-house analytical support.

Drug Discovery

- Assay development and screening
- Synthetic and medicinal chemistry
- *In vivo* pharmacology studies
- *In vitro* and *in vivo* PK screening
- Biomarker services
- Pharmaceutical sciences

Safety Assessment

- *In vitro* toxicity testing
- *In vivo* toxicology studies

Laboratory Support

- Blending
- Immunology
- Bioanalysis
- Clinical pathology
- Histopathology

EVERY STEP OF THE WAY

Drug Discovery

Assay development and screening

Our scientists have extensive experience in the development and execution of novel assays in a wide variety of target classes, including a broad range of ion channels. Alternatively, when possible, we can transfer in a client's own validated assay. In addition, we have developed a host of disease-relevant assays in human primary cells, which includes assays for inflammatory and respiratory conditions.

Synthetic and medicinal chemistry

Charles River can assist in all aspects of drug discovery chemistry, including medicinal and synthetic chemistry, route development and optimization, purification and scale-up activities. Our scientists bring a wealth of experience from their prior roles in leading pharmaceutical and biotechnology companies. Consequently, they are well-equipped to address the challenges of drug discovery projects and deliver high-quality outcomes to our clients. There is extensive knowledge in the field of respiratory drug discovery, both oral and inhaled. The teams have a superb track record of delivering successful candidate drugs, and a detailed understanding of the design of inhaled compounds. We combine the latest synthetic chemistry methodologies and technologies with innovative synthetic route designs to ensure high productivity and maximum efficiency. We also utilize CADD with a history of success in computational screening.

In vivo pharmacology studies

Our validated rodent models provide rapid, cost-effective methods for evaluating the potential efficacy of novel anti-inflammatory and bronchodilator agents targeting chronic obstructive pulmonary disease (COPD), lung fibrosis and asthma. We also develop specific bespoke models to meet a partner's needs, and build early markers of safety into such efficacy studies. The teams also have extensive experience with respect to de-risking inhaled compounds and projects, with the ability to assess compounds using both *in vitro* and *in vivo* models.

In vitro and *in vivo* PK screening

Charles River can aid in the design and testing of compounds targeting the lung via both the inhaled and systemic routes. At the *in vitro* level, specialized screens and assays relating to inhaled delivery are used. Our integrated approach to PK studies means our scientists and study directors act as the single point of contact and are engaged from formulation to data delivery.

Biomarker services

The scientists at Charles River can support clients' drug discovery pipelines by providing biomarker analysis in a non-GxP environment. This includes translation of assays from core screening at the *in vitro* and *in vivo* level to the clinical end users. Whether a study is performed at the client's facility or designed and implemented at ours, our focus on strategic assay validation/qualification enables us to accurately test study samples and provide reliable biological translation to drug discovery programs.

Pharmaceutical sciences

We are able to profile potential inhaled compounds to ensure compatibility with delivery devices, excipients, and also with other potential combination partner compounds.

Safety Assessment

In vitro toxicity testing

MucilAir™ is a mucus-secreting, ciliated epithelial model of the human airway produced by Epithelix Sàrl, Switzerland. It is derived from human airway cells that have been collected from healthy donors and cultured at the air interface on permeable membranes. Its morphology and functions mirror the tracheobronchial epithelium, making it an ideal model to identify potential airway toxicants in candidate molecules. We are also able to de-risk projects investigating, for example, particulate cytotoxicity and neutrophil-mediated bacterial killing.

In vivo toxicology studies

Charles River has been assessing the toxicology and toxicokinetics of compounds intended to be given via the inhalation route for nearly 50 years. A significant portion of the work performed in recent years has focused on inhalable formulations aimed at cystic fibrosis, chronic obstructive pulmonary disease (COPD), asthma, bronchitis and other indications, such as diabetes.

Our team of scientists can conduct inhalation toxicity studies for inhaled products in both rodents and nonrodents. Test formulations can be either dry powder, solution/suspensions or delivered through metered dose inhalers. All of these formulations require conversion into a respirable aerosol targeted to the different areas of the respiratory tract. Our specialists have experience working with sponsors to ensure that their compound is properly aerosolized, regardless of the formulation.

Study designs

In the development of an inhaled drug, exposure may occur only once, in the case of acute single-dose toxicity or toxicokinetic studies, or repeatedly for up to two years, when carcinogenicity is the endpoint. Other study designs include a comprehensive portfolio of developmental and reproductive toxicology (DART) studies, as well as neonatal and juvenile toxicology in various species, and safety pharmacology.

Laboratory Support

Blending

Powder formulation can be prepared on site for use on GLP toxicology studies. Micronized test article can be blended with an appropriate excipient, using a validated, custom-designed, high-efficiency blending system. The uniformity of the resultant blend and its achieved concentration is determined. Results are then processed, verified, audited by our Quality Assurance unit, and a certificate of use prepared, allowing the blend to be released for use on the study.

Immunology

With over 25 years' experience, the Immunology Group offers a range of services, including assessment of immunotoxicity, immunomodulation, immune biomarkers, immunogenicity, and molecular biology assays. Depending on the pharmacology and toxicology of the compound to be tested, it is possible that inhalation studies may have one or more of these assessments and assays included.

The Immunology Group provides guidance and assays as per ICHS8 to support immunotoxicology evaluation of compounds. In addition, the Immunology Group has conducted numerous assays to assess immunomodulation, such as measurement of immune biomarkers including cytokines, chemokines, complement factors and immunoglobulins. The Immunology Group also supports other immunogenicity testing needs, including screening, confirmatory assays, titration and neutralizing antibody assays.

Bioanalysis

At Charles River, we provide routine and specialized bioanalytical services in support of discovery, preclinical and clinical programs. Our bioanalysis groups perform high-throughput non-Good Laboratory Practice (GLP) research-grade assays to assist in lead candidate selection and develop and validate quantitative bioanalytical assays from first principles or by method transfer from a client's laboratory. We also validate assays in full compliance with GLP and other internationally recognized regulatory guidelines. These methods are then applied to determine the concentrations of specific compounds and/or metabolites in a range of biological matrices. Compounds routinely analyzed range from small new chemical entities (NCEs) to large macromolecules. To assist in bioanalysis, our Chemical Synthesis Group can produce nonlabeled or stable-labeled compounds for use as internal standards. We also accept sample deliveries for analysis as a stand-alone service.

Pathology

Our Pathology Division is one of the largest and most experienced in the industry and is constantly developing new techniques that aid in the determination of drug toxicity.

Clinical pathology

Services provided include clinical chemistry, hematology, coagulation assays and urinalysis performed by experienced technical, scientific and biomedical staff. For inhalation studies, bronchoalveolar lavage analysis can be performed with cell count and other evaluations.

Histopathology

The Histology Group prepares over 1,000,000 tissues per year and is at the leading edge of new developments. The resultant slides from inhalation studies prepared by the Histology Group are evaluated by in-house pathologists who participate in peer reviews and pathology working groups, and several of whom specialize in inhalation toxicology. Not only can digital microphotography be included in the contributing pathology report, but we are also able to share digitalized images of glass slides (for illustrative purposes) directly with the sponsor without them having to leave their office, through the use of the Aperio system.