charles river

SAFETY ASSESSMENT

Pathology Services

Supporting Drug Development from Discovery to Safety Assessment

A comprehensive assessment of pathologic changes is integral for determining safety, efficacy, and mechanism of action of novel therapeutic agents. Anatomic and clinical pathology endpoints are critical for maintaining experimental animal colonies and characterizing disease models used in the drug discovery and development process. Our senior veterinary pathologists have actively participated in formal quality assessment and peer review programs since 1982. With over 100 pathologists, Charles River employs the largest assembly of pathologists in the contract research industry, offering multidisciplinary expertise for all types of drugs, biologics, chemicals, and devices. We perform a wide array of routine and specialized pathology services either in support of *in vivo* studies performed at our sites, or as a standalone service. Our anatomic and clinical pathologists are recognized experts in toxicologic pathology, from investigative to regulatory studies for pharma, agrochemical and animal health, carcinogenesis research and testing, and diagnostic pathology.

In addition to our unique pathology support, we provide flexible product-specific and therapeutic area resources in the nonclinical testing arena. Clients benefit from our unique ability to integrate services such as consulting, program design, and regulatory guidance into their research, efficacy, and safety programs. We apply technical and scientific expertise to every project, from routine procedures to highly specialized analyses, assays, biomarker development, and scientific consultation. Our activities and evaluations are conducted in compliance with international regulatory standards and designed to meet the evolving requirements for developing products worldwide.

- Discovery Pathology
- Toxicologic Pathology
- Molecular Pathology
- Developmental & Reproductive Pathology
- Clinical Pathology

- Specialty Endpoints
  - Electron microscopy
  - Immunohistochemistry/ *in situ* hybridization
  - Histomorphometry/image analysis
  - Stereology
  - Tissue microarray
  - Tissue cross-reactivity

- Therapeutic Area Expertise
  - Musculoskeletal pathology
  - Neuropathology
  - Inhalation pathology
  - Ocular pathology
- Medical Device Pathology

EVERY STEP OF THE WAY

Discovery Pathology

Charles River experts from across the company work together to provide clients with a comprehensive approach to animal model evaluation for oncology, cardiovascular, respiratory, CNS, ophthalmology, inflammation and metabolic disease, and many other specialized therapeutic areas. Adding anatomic and clinical pathology endpoints in discovery studies enhances the understanding, characterization, and translational ability of animal models. This allows for comparison of developmental candidates and lead optimization, and may provide early efficacy information. Anatomic pathology endpoints in discovery studies vary widely from basic histopathology to sophisticated staining and histomorphometry. Clinical pathology endpoints span from basic hematology, coagulation, clinical biochemistry, urinalysis, and bone marrow evaluation to more specialized assays, including services that meet development needs for specific biomarkers used to identify and interpret pharmacodynamic, efficacy, or safety endpoints.

Our team includes trained experts in pathophysiological mechanisms of disease and in all areas of anatomic and clinical pathology. This allows us to recognize and identify significant changes in study data, to provide interpretation that will take into consideration species and study design, and integrate with in-life and toxicokinetic data, linking changes to pathophysiological processes and organ function, as well as with test article pharmacological activity. We've established an extensive array of assays to aid in the early identification of toxicity and efficacy of test articles. Where appropriate, these can be transferred into the clinical phase of development for human use.

Toxicologic Pathology

Charles River operates full-service laboratories with facilities and program/project offices at numerous locations around the globe. All facilities are functionally integrated and offer interactive services to fulfill our clients' needs. Every laboratory is equipped to provide complete GLP-compliant necropsy, histology, and histopathology, and many offer a wide variety of specialty pathology-based services to support our clients' research programs.

Molecular Pathology

Our team combines a strong history in molecular biology and histopathology to relate gene expression to tissue histomorphology in both normal tissues and therapeutic models of disease, providing you with valuable functional genomics information. This results in the best possible interpretation and troubleshooting of molecular-based tools, such as chromogenic *in situ* hybridization (CISH) and real-time quantitative polymerase chain reaction (qPCR), applied to toxicological pathology issues.

Developmental & Reproductive Pathology

Offering comprehensive histopathology analysis of reproductive tissues, our staff is skilled in the detection of adverse effects of test articles and agents on reproduction and fertility. Our unparalleled historical control database across numerous species aids in the interpretation and relevance of results. Specific services include male and female reproductive analysis and mobile (on-site) sperm analysis compliant with GLP regulations.

Clinical Pathology

With nine state-of-the-art clinical pathology labs, we can support all stages of human and veterinary drug development. We offer a complete range of clinical pathology services to support an extensive array of safety assays and investigative biomarkers. These assays have been established to aid in the early identification of toxicity and efficacy of test articles and, where appropriate, can be transferred into the clinical phase of development for human use.

Clinical pathologists certified by the American College of Veterinary Pathologists and/or the European College of Veterinary Clinical Pathology can assist with protocol development, assay development/method validation, interpretation of clinical pathology data, and translation of data for clinical applications.

Specialty Endpoints

Charles River leads the industry in providing specialized pathology and related technologies designed to address the specific efficacy and safety needs of novel therapeutic agents. Pathology-based technologies are used to address mechanistic, cell response characterization, and issue-driven needs of a comprehensive array of therapeutic modalities and chemical classes.

Electron microscopy

Recognized for our experience in this field, Charles River offers full-service GLP ultrastructural microscopy evaluations with both transmission (TEM) and scanning (SEM) electron microscopic capabilities. Ultrastructural morphology procedures enable the visualization of unique details of the structure and the quantification of cellular organelles. This imaging technique gives investigators precise data on mitochondria, peroxisomes, smooth and rough endoplasmic reticulum, Golgi cytoskeletal components, cytoplasmic granules, and inclusion bodies, which assist in determining a compound's mode of action and understanding the pathogenesis of toxicologically-related lesions. SEM enables the investigator to examine the surface topography and morphology of cells, tissues, or medical devices by scanning a beam of electrons across a sample. This imaging technique may be employed in studies in which exterior damage or integrity is of concern.

Immunohistochemistry/*in situ* hybridization

Immunohistochemistry and *in situ* hybridization are valuable tools for localizing cellular expression of specific proteins or RNA transcripts within the context of the tissue. Our staff uses the latest staining instruments to optimize and stain many unique and novel targets.

Histomorphometry/image analysis

Histomorphometry is a specialized technique that uses the latest technology in microscopy and image analysis software to describe and evaluate changes in tissue morphology. This technique is applied to tissues and biomaterials of all types to measure tissue or device area, perimeter, linear and curvilinear distances; to quantify cellular proliferation; and to determine object or staining density. Histomorphometry allows us to further evaluate and quantify histopathologic changes in tissues in support of government and commercial pathology service efforts, and for molecular and cellular pathology.

Stereology

Charles River is the global leader in contract stereology services for the biopharmaceutical community, performing state-of-the-art stereological analysis on a variety of tissues from a wide number of species for both discovery and safety assessment studies. Stereology is a highly specialized, unbiased technique that supplies accurate 3-dimensional quantitative data, including number, volume, surface area, and length. This provides a sensitive, accurate quantitative assessment of changes in histologic tissue sections.

Tissue microarray

Our team can create custom microarrays of tissues from a variety of laboratory animal species or from cell pellets. These microarrays can be used for optimization of immunohistochemical or *in situ* hybridization markers for molecular or discovery pathology studies. This technique can also be combined with state-of-the-art image analysis tools to quantify biomarker expression across tissue types or cell pellets with varying levels of antigenic stimulation.

Tissue cross-reactivity

Charles River supports monoclonal antibody research with our extensive expertise in the initial stages of safety assessment for therapeutic large molecules targeted for use in humans. We've worked with numerous large molecules and nearly every type of therapeutic antibody, including unconjugated antibodies, antibodies conjugated to a variety of substances, and Fab fragments.

Therapeutic Area Expertise

Charles River employs experts who are uniquely capable of supporting a wide range of systems (e.g., ocular, otologic, and musculoskeletal diseases) and specialty endpoints for unique studies (e.g., inhalation and phototoxicology), and our expertise continues to grow to match the diverse needs of our clients.

Musculoskeletal pathology

We provide comprehensive bone, cartilage, and hard tissue pathology-based services to support the evaluation of metabolic bone diseases, arthritis, and orthopedic devices. Our experienced pathologists and scientists, together with a team of highly trained technicians, provide study design and project execution services for therapeutics devised for the treatment and prevention of osteoporosis, arthritis, and bone and cartilage healing.

Neuropathology

Our dedicated neuropathologists work in tandem with highly trained technical staff to assist with study design, development strategies, and regulatory submissions for a wide variety of compounds, viruses, genes, and stem cell introductions involving the nervous system.

Inhalation pathology

With more than 30 years or experience and the successful completion of innumerable specialized studies, Charles River provides the largest and most experienced inhalation toxicity team in the contract research industry. Our team of pathologists is skilled in interpreting the histopathological findings of inhalation studies, including even the most subtle and discrete toxic changes in the respiratory tract.

Ocular pathology

Highly specialized and more rigorous than standard toxicology procedures, histopathologic assessment of the eyes is critical for therapies with ocular indications. Our team is skilled in the comprehensive assessment of safety and efficacy of compounds that use the ocular route of administration or involve the development of intraocular devices. These studies are available in both GLP and non-GLP conditions, and as part of standard or specialty toxicology programs.

Medical Device Pathology

Our team supports developers and manufacturers of medical devices from the proof-of-concept stage to pivotal safety and efficacy evaluations. Our services include a broad range of GLP-compliant specialty histology techniques with high-throughput plastic capability and advanced imaging methods. As needed, we customize histology approaches on an individual basis to maximize the yield of information from medical device specimens. We routinely integrate relevant imaging methods (e.g., micro-CT, SEM, and others) with pathology data to provide multifaceted safety assessment. Comprehensive pathology reports are prepared with consideration to providing actionable data for relevant phases of device development, from preliminary development to efficient regulatory review.