Safety Pharmacology

ICH S7A and S7B guidelines for the conduct of safety pharmacology evaluations recommend a core battery of studies on three vital systems – the central nervous system, cardiovascular system and respiratory system – to assess the acute and potentially life-threatening risks of novel pharmaceuticals for human use.

Combining our established core battery with a comprehensive selection of supplementary tests and safety pharmacology models, Charles River can customize safety pharmacology studies to suit both the compound and entire program, providing meaningful data to drive decision making and satisfy current regulatory requirements.

Proven Experience

Because every compound is unique, it takes specialized knowledge of regulatory guidance documents to develop the most appropriate safety pharmacology program. With more than 25 years of experience interacting with pharmacology and toxicology reviewers, our team has completed more than 1,500 safety pharmacology studies across the range of NCEs and biologics since the finalization of ICH S7A and S7B guidelines in 2005. Expert guidance is guaranteed through Scientific Advisory Services led by a former FDA reviewer and world-renowned cardiovascular authority, and a staff that includes 25% of the world’s Diplomates in Safety Pharmacology (DSPs).

Cost-Effective, Timely Solutions

For safety pharmacology studies, timing is critical. Charles River streamlines studies without sacrificing quality or responsiveness. Our network of sites allows us to offer study lead-in times as short as three weeks, with study-ready colonies of instrumented animals supporting quick starts. Communication with our dedicated project managers and our convenient online mycharlesriver portal connect clients with their studies, providing ready access to study status updates and data. Using global protocols, reports and statistical templates, we deliver audited draft reports within six to eight weeks with an on-time reporting history of 98%.
Traditional testing is performed using jacketed telemetry and/or an unrestrained approach in a variety of species, including rodents, guinea pigs, minipigs, and large animals. We continually invest in the most scientifically robust, state-of-the-art equipment to support cost- and animal efficient study designs. We have eleven facilities with dedicated telemetry suites, surgical capabilities and custom-built cardiovascular laboratories with remote data monitoring. Our sites employ the DSI™ Ponemah Physiology Platform (P3P) for respiratory and cardiovascular data analysis and include ECG pattern recognition software to increase the sensitivity of ECG analyses. We have also validated the non-invasive DSI JET™ (jacketed external telemetry) for ECG collection in large animals and have validated the minimally invasive blood pressure add-on.

**In Vitro Assays**

With expertise with whole-cell, inside-out, outside-out and cell-attached patch clamp electrophysiological configurations, Charles River offers a variety of cardiovascular and central nervous system *in vitro electrophysiology services*. A comprehensive survey of non-GLP assays, including cardiac and neuronal ion channels and cardiomyocyte and brain tissue assays, provide insight into potential cardiac and seizure risk and aid in effective decision-making in early preclinical development.

Our cardiac assays include the hERG serum shift assay, ion channel trafficking assay, action potential duration (ADP) assays, integrated human cardiomyocyte assays (impedance and field potential), cultured cells (e.g. HEK-293) and isolated cardiomyocytes and Cardiac Channel Panel™ assessment of hERG (Ikr) hCav1.2 (L-type ICa ++ ) and hNav1.5 (peak and late INa), and the comprehensive *in vitro* proarrhythmic assay (CiPA) battery. CiPA aims to improve the accuracy of predicting cardiac risk with an assessment of drug effects on multiple human cardiac currents using appropriate voltage protocols, *in silico* reconstruction of the human cardiac action potential, and *in vitro* effects in human iPSC-derived cardiomyocytes.

Offering a large portfolio of ion channel testing, we can assess risk for neurodegeneration and stroke, pain and inflammation, psychiatric disorders, and seizure/convulsion. Additional neuronal assays include *in vitro* electrophysiology assessments that use electrical or chemical stimulation of acute brain slices and cultured and/or dissociated neurons through various extracellular or intracellular electrophysiological configurations.

GLP offerings, including hERG and action potential duration (ADP) assays, are recommended for candidate selection and IND submissions. Our integrated *in vitro* and *in vivo* scientists can interpret results and design *in vivo* assays to advance programs further.

**Industry-Leading Services**

In 2010, the Safety Pharmacology Society (SPS) acknowledged the need to establish a Best Practices guideline for cardiovascular safety studies. Charles River is engaged with our vendors in developing technological advances in safety pharmacology data acquisition and analysis and is proactively implementing those aspects of the Best Practices dialogue for which there was a broad consensus. We will continually monitor and contribute to the evolution of the SPS CV Best Practices guidelines, implementing consensus recommendations in our safety pharmacology studies as they are developed.

**Supplemental Studies**

- **Cardiovascular**
  - cardiac output/arterial flow
  - contractility indices vascular/ peripheral resistance
  - blood biomarkers
- **Respiratory**
  - lung resistance
  - lung compliance
  - pulmonary artery pressure
  - blood gases
  - blood pH
- **Central Nervous System**
  - behavior pharmacology
  - learning and memory
  - quantitative motor performance
  - CNS electrophysiology (EEG)
  - higher order neurofunctional endpoints
- **Renal/Urinary**
  - renal function
  - clinical chemistry
  - glomerular filtration rate
- **Gastrointestinal**
  - *in vivo* gastric motility and function
- **In Vitro Electrophysiology**
  - CiPA battery
  - stimulation of brain tissue/ neurons

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