SRI Biosciences™

A DIVISION OF SRI INTERNATIONAL

Idea to IND®

Drug Metabolism, Pharmacokinetics, and Toxicology

Learn more

SRI Biosciences is ideally positioned as your single-source partner to seamlessly integrate target identification, early-stage and identification, and nonclinical development.

Outsourcing to SRI maximizes your investment dollars while minimizing risk. We offer comprehensive contract services for small molecule drugs and biologics—a one-stop solution to take your product candidates all the way through the regulatory filings to initiate first-in-human clinical trials.

Through our comprehensive drug metabolism, pharmacokinetics, and toxicology services, we help you achieve your goals—from Idea to IND® and beyond.

Drug Discovery | ***Drug Metabolism, Pharmacokinetics, & Toxicology*** | *Pharmaceutical Sciences* | *Clinical Analysis Laboratory* | *Clinical Trials*

Discovery ADMET and *In Vitro* Metabolism

SRI is a leader in the development and application of *in vitro* models for ADMET evaluations (ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity). Obtaining data on potential toxicity early in the development process can help you make informed decisions to move promising leads forward and exclude liabilities. Our staff has extensive experience in elucidating tissue-specific mechanisms of toxicity for various species and organs. We pioneered the application of human tissue preparations to predicting interspecies differences in drug metabolism, potential drug interactions, and human drug metabolizing enzymes.

Predictive ADMET

- Membrane permeability: PAMPA, Caco-2, MDCK cells
- Metabolic stability: liver or small intestine microsomes
- Plasma stability
- Cytochrome P450 (CYP) inhibition
- Plasma protein binding
- p-Glycoprotein substrate assays
- *In vivo* pharmacokinetic screens
- High-throughput LC-MS/MS quantitation
- First *in vivo* dose to mice

In vitro *Metabolism and Toxicity*

- Metabolite profiling and identification
- Reaction phenotyping: CYP, UGT, SULT
- Drug-drug interactions
- Peroxisome proliferation
- Co-incubation screens
- Therapeutic index estimations
- Cytotoxicity and hepatotoxicity screening
- Mini-Ames mutagenicity screen
- Mini I (hERG) cardiotox liability screen*

**Offered through agreement with ChanTest Corporation*

*** *SRI pioneered predictive* in vitro *metabolism*

Drug Metabolism and Pharmacokinetics

SRI offers comprehensive drug metabolism and pharmacokinetic (DMPK) services to meet your needs. We give you access to a complete range of capabilities, beginning with dose administration followed by full-service bioanalytical support and pharmacokinetic data analysis and interpretation. We offer PK studies that fully comply with U.S. FDA GLP regulations.

Bioanalytical Quantitative Methods

- Bioanalytical method development and validation
  - » Small molecules: LC/MS/MS, GC-MS, HPLC with UV, fluorescence, radiochemical detection
  - » Proteins: ELISA, antibody titer
- Quantitative PCR
  - » DNA/RNA test article, e.g., plasmid, virus
  - » Biodistribution, persistence, integration
  - » mRNA expression levels
  - » Subcellular localization
  - » Chromosomal integration

Pharmacokinetic and Pharmacodynamic Analyses

- Single-dose pharmacokinetics
- Bioavailability
- Multiple-dose pharmacokinetics
- Drug accumulation
- Metabolite identification
- WinNonlin™ compartmental and noncompartmental analysis
- PK/PD interpretation
- Bioequivalence
- Allometric estimations
- Formulation screening

Comprehensive ADME

- Absorption and clearance
- Tissue distribution
- DNA/RNA biodistribution, persistence, integration
- Interspecies comparative metabolism
- Metabolite profile
- Excretion and mass balance
- Radiolabeled drug synthesis

*** *SRI is an AAALAC-accredited facility.*

Toxicology and Safety

SRI offers you mammalian toxicology testing services, in all major species, that follow either routine or customized study designs. Our expertise spans a wide range of pharmaceutical and therapeutic agents, including anticancer drugs, anti-infectives, vaccines, antisense therapeutics, nucleosides, peptides, antibodies, and proteins. We also offer testing of genetically engineered products and medical devices, such as combination 510(k) products, using protocols designed to meet your needs.

Standard Mammalian Toxicology

- Acute, subchronic, and chronic toxicity
- Dose escalation and range-finding
- Maximum tolerated dose (MTD)
- Definitive dose administration
- Lifetime and carcinogenic potential

Specialized Safety Assessments

- Irritation and sensitization
- Local lymph node assay
- Immunotoxicology
- Biological product testing
- Vaccine safety
- *In vitro* mitochondrial toxicity
- 510(k) medical device safety evaluation
- Safety evaluation of cell-based therapeutics
- Medical imaging products
- Neonatal and juvenile animal studies
- Combination products and delivery systems
- Learning and memory evaluations
- Radiation studies

Pediatric Product Development

- Neonatal and juvenile animal studies
- Initiation of dosing at age-appropriate developmental stage
- Routine evaluation endpoints
- Sensorimotor central nervous system evaluations
- Pharmaco-and toxicokinetic evaluations

Evaluation Endpoints

- Cage-side observations
- Body weight measurements
- Food and water consumption
- Ophthalmic examinations
- Clinical pathology
- Necropsy and organ weight measurements
- General and specialized microscopic pathology
- Dose verification
- Pharmacodynamics
- Toxicokinetic analysis
- DNA/RNA biodistribution, persistence, integration
- Toxicogenomics assessment
- Immunogenecity
- Specialized biomarkers
- Cardiovascular evaluation
- Neurobehavioral evaluation
- Micronucleus evaluation
- Toxicology interpretation
  - » Overall interpretation of findings
  - » Maximum tolerated dose (MTD) estimation
  - » No observable adverse effect level (NOAEL) estimation
- Quality Assurance (QA) review and QA statement

**** Can generate SEND datasets with SUBMIT®*

Safety Pharmacology

SRI's services meet worldwide standards and regulatory requirements for an IND application. The ICH S7 guidelines on Safety Pharmacology outline recommendations for evaluating the potential for adverse pharmacodynamic and pathophysiological effects on vital functions. The ICH S7A Core and Supplemental Batteries describe safety assessments of the central nervous system, cardiovascular system, respiratory system, and effects on organ system function. The ICH S7B guideline recommends a strategy to assess the potential for cardiac safety liability using *in vivo* and *in vitro* approaches.

ICH S7A Core Battery

- Central nervous system
- Cardiovascular system
- Respiratory system

ICH S7A Supplemental Battery

- Learning and memory
- Behavioral pharmacology
- Ligand-specific and receptor binding and neurochemistry
- Electroencephalography
- Drug dependency potential
- Sleep/circadian rhythm
- Cardiac output, ventricular contractility, vascular resistance
- Pulmonary arterial pressure, blood gases, and pH
- Cardiac biomarkers: B-type natriuretic peptide, troponin I, myoglobin
- Urinary chemistry profile
- Gastric motility and function
- Immune functional profiling—ICHS8
- Organ-specific character
- Urinary chemistry profile
- Gastric motility and function
- Immune functional profiling—ICHS8
- Organ-specific characterization and functional profiling ization and functional profiling

ICH S7B Cardiac Safety and QT Prolongation

- hERG (human ether-a-go-go -related-gene) assay*
- APD Purkinje fiber*

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Administration Routes

- *Oral gavage & capsule*
- *Subcutaneous injection & implantation*
- *Intravenous bolus & infusion*
- *Intranasal*
- *Intramuscular*
- *Ocular & intraocular*
- *Dermal & cutaneous*
- *Intrahepatic*
- *Electroporation*
- *Pressure-mediated delivery: epidermal, subcutaneous, intramuscular*
- *Vaginal*
- *Rectal*
- *Diet & drinking water*
- *Specialized routes*
- *Specialized delivery devices*

**** SRI offers full formulation and analytical chemistry support for your studies.*

Genetic Toxicology

SRI is a pioneer in genetic toxicology: we developed and validated many of the currently used assays, and members of our staff were instrumental in writing the genotoxicity test guidelines that are used by industry today. SRI's experimental results were the primary input for major portions of the U.S Environmental Protection Agency (EPA) and the National Toxicology Program (NTP) genetic toxicology databases.

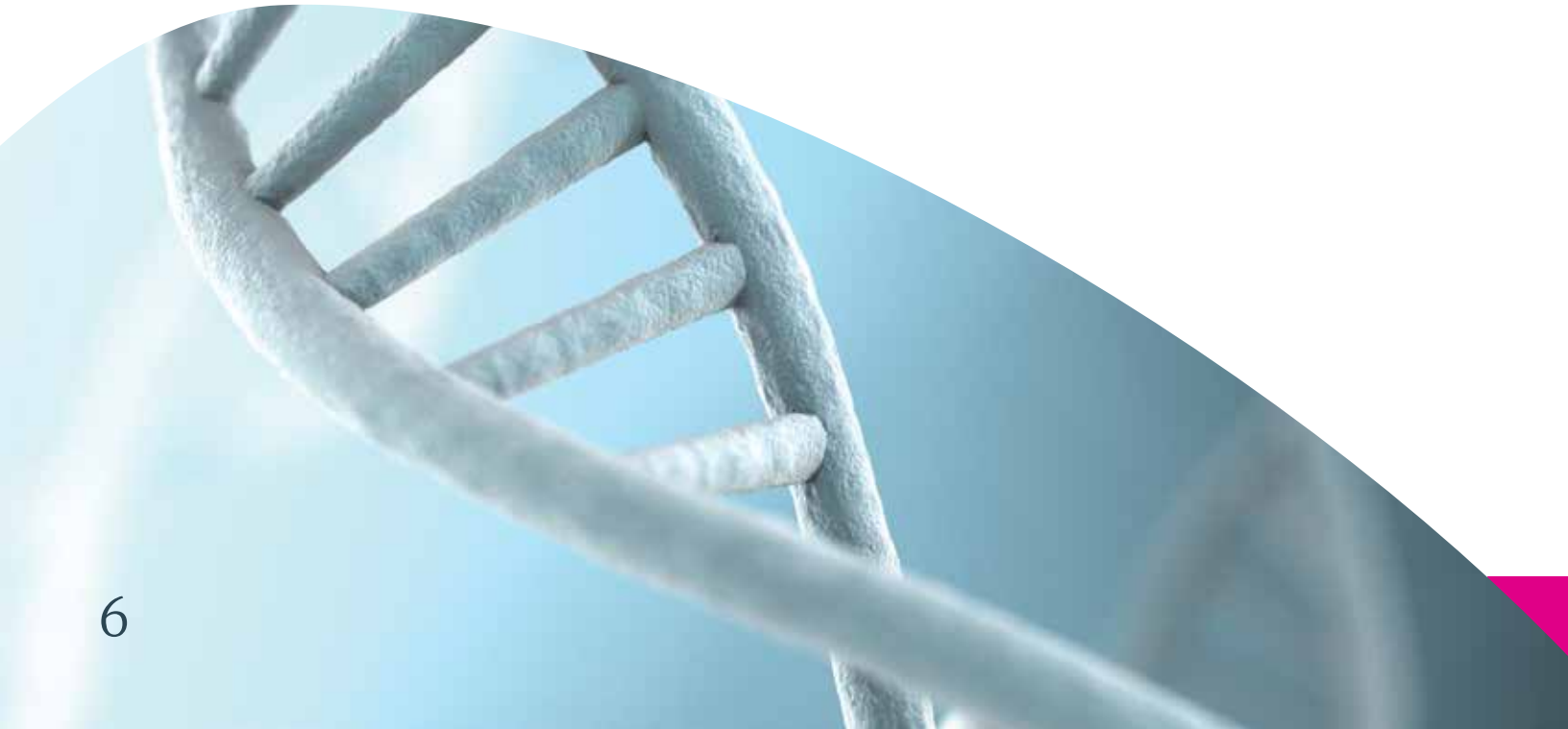
In addition to routine genetic toxicology test services, we offer you the benefits of extensive experience in solving unique genetic toxicology problems related to pharmaceuticals, biotechnology products, chemicals such as dyes and inks, agrochemicals, and medical devices.

ICH Core Battery

- Ames test microbial mutagenesis
- Mouse lymphoma gene mutation
- *In vitro* and *in vivo* chromosome aberration
- *In vivo* micronucleus
- Big Blue® transgenic rodent mutagenesis assays
- *In vitro* and *in vivo* sister-chromatid exchange assays
- Unscheduled DNA synthesis

Other Genetic Endpoints

- Quantitative PCR and RT-PCR
- Biodistribution, persistence, integration
- Mutation analysis
- FISH cytogenetic analysis
- Microarray analysis
- Target gene expression
- Customized, molecular endpoints



Developmental and Reproductive Toxicology

SRI's Developmental and Reproductive Toxicology (DART) program is an integral part of our pharmaceutical safety evaluation services. We offer a full spectrum of regulatory-compliant DART studies to complement any preclinical development package.

Standard ICH S5(R2) Studies

- Fertility and early embryonic development to implantation —Sec. 4.1.1, Segment I
- Embryo-fetal prenatal development —Sec. 4.1.3, Segment II
- Perinatal and postnatal development, including maternal function —Sec. 4.1.2, Segment III
  - » Dose range-finding studies
  - » Multigenerational dosing studies
- Toxicity to male fertility—ICH S5 (R2) part 2

Fertility, Anti-fertility, and Contraception Studies

In vitro *screens*

- 3ß-Hydroxysteroid dehydrogenase activity
- D5-3-Ketosteroid isomerase activity
- Progestagenic and anti-progestagenic activity
- Uterotrophic and anti-uterotrophic activity
- Androgen, estrogen, progesterone receptor binding
- Super-ovulating model

In vivo *studies*

- Spermatostatic contact
- Sperm motility and cytokine induction
- Clauberg-McPhail endometrial proliferation
- Androgenic assay
- Antigonadotropin assay
- Oocyte antimeiosis assay
- Sperm motility and morphology assay

Evaluation Endpoints

- Standard toxicology study routes and endpoints
- Fetal evaluations
- Spermatogenesis evaluations
- Neurobehavioral evaluations
- Sensorimotor evaluation in F1/F2 neonates and juveniles
- Pharmacokinetics, pharmacodynamics, toxicokinetics
- Immunogenicity/antibody levels
- Immunotoxicity
- Cytokine levels
- Drug levels in plasma, tissues, fetus, pups, milk
- DNA/RNA biodistribution, persistence, integration

**** All services are designed to meet Good Laboratory Practices (GLP).*

SRI International®

SRI Biosciences, a division of SRI International, integrates basic biomedical research with drug and diagnostics discovery and preclinical and clinical development. SRI International, a research center headquartered in Menlo Park, California, creates world-changing solutions to make people safer, healthier, and more productive.

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