SRI

Drug Metabolism, Pharmacokinetics, & Toxicology

SRI is ideally positioned as your single-source partner to seamlessly integrate all stages of early development.

We are here to help you move through the drug development pipeline from target identification through nonclinical development and into early-stage clinical trials. We offer comprehensive contract services for small molecule drugs and biologics to maximize your investment dollars while minimizing risk. Our comprehensive drug metabolism, pharmacokinetics, and toxicology services will help you achieve your product development goals.

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 elucidating tissue-specific mechanisms of toxicity for various species and organs. We pioneered the application of human tissue preparations for predicting interspecies differences in drug metabolism, potential drug interactions, and human drug metabolizing enzymes.

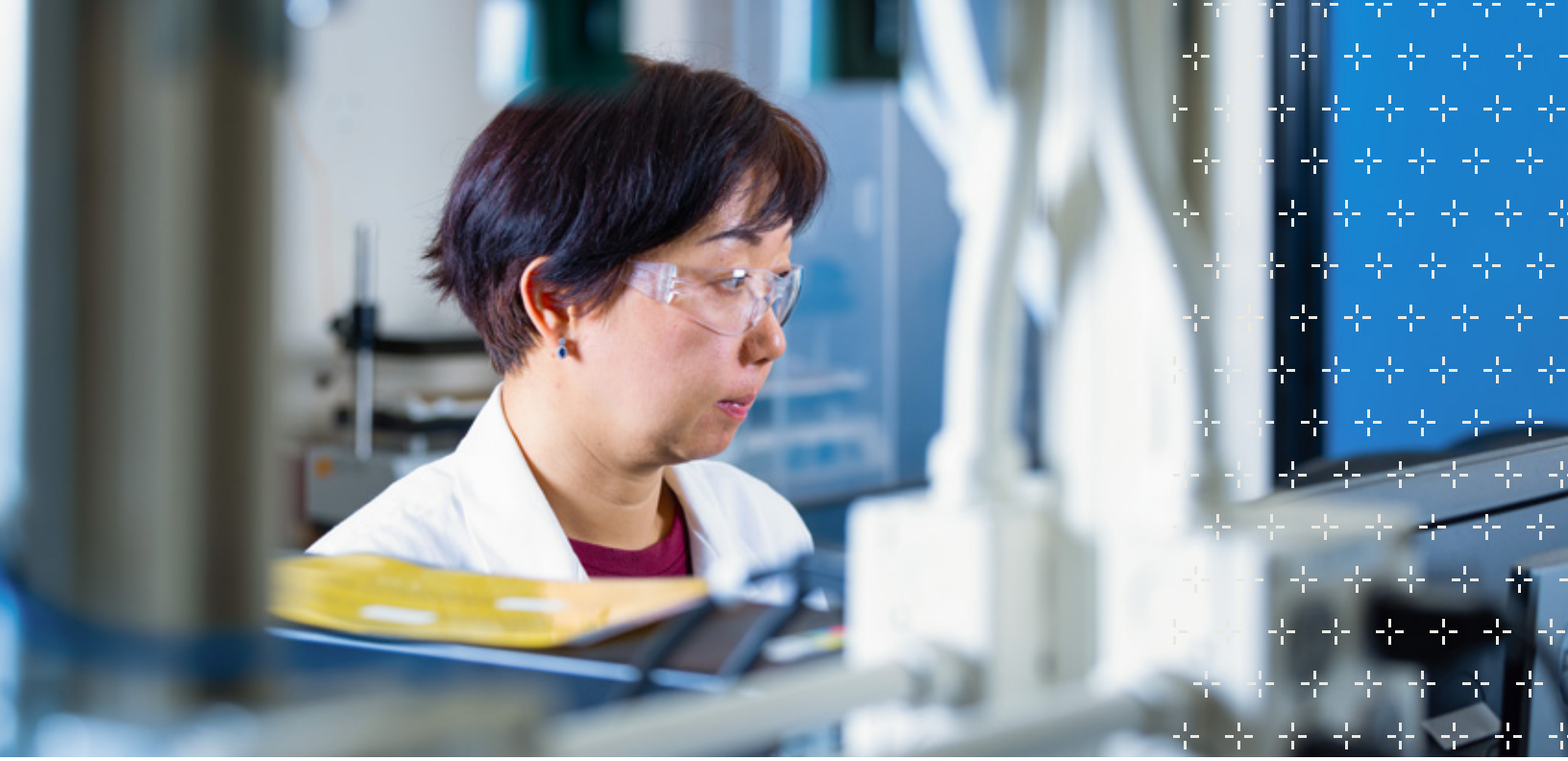
Predictive ADMET

- 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 rodents

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

Our expertise spans a wide range of pharmaceutical and therapeutic agents, including anticancer drugs, anti–infectives, vaccines, antisense therapeutics, nucleosides, peptides, antibodies, nanoparticles, and proteins.



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 meet all U.S. and European IND submission requirements.

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

Pharmacokinetic and Pharmacodynamic Analyses

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

Comprehensive ADME

- Absorption and clearance
- Tissue distribution
- Metabolite profile
- Excretion and mass balance

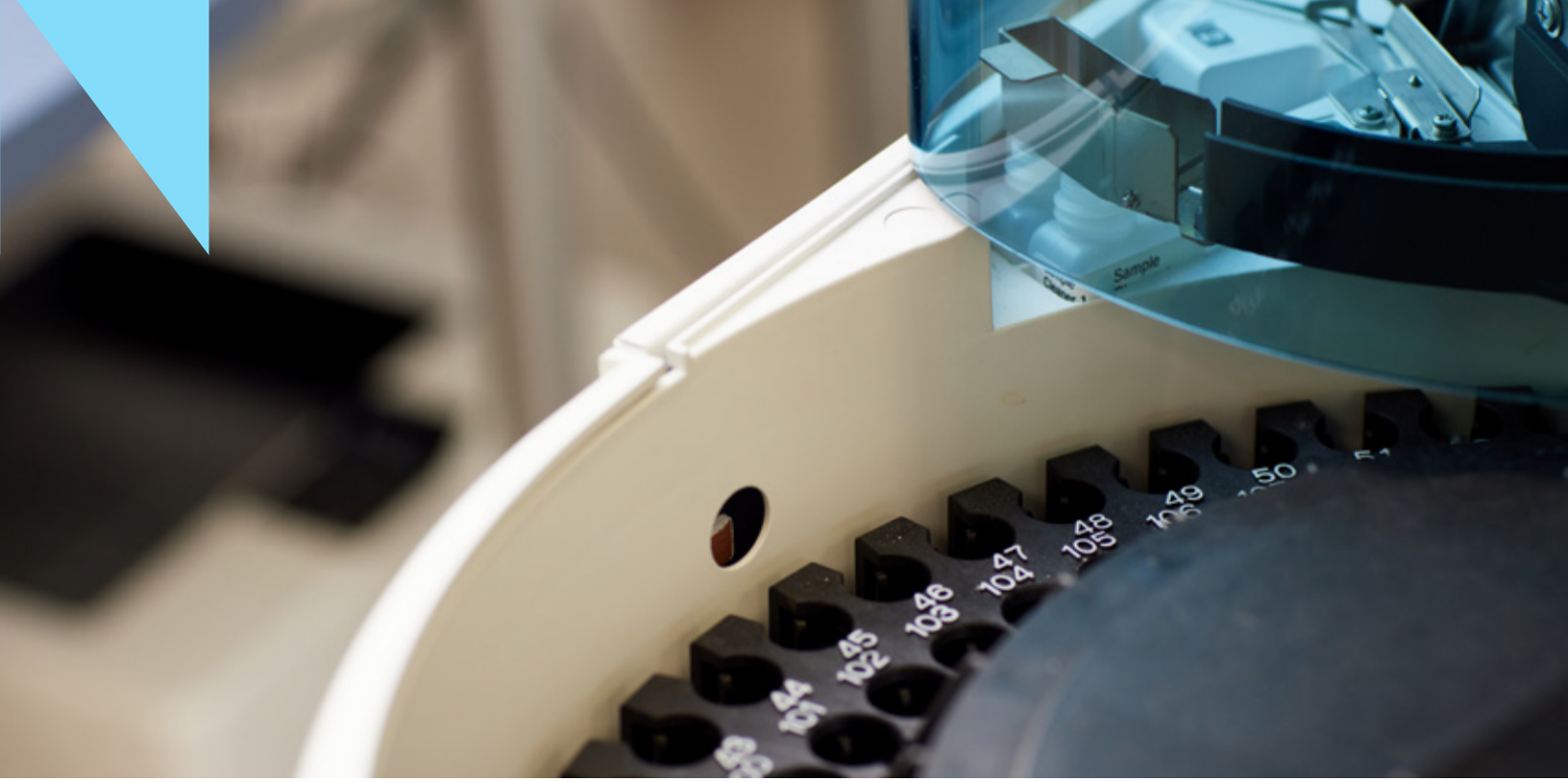
Toxicology and Safety

SRI offers 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, CNS therapeutics, medical countermeasures, vaccines, antisense therapeutics, nucleosides, peptides, antibodies, nanoparticles, and proteins. We also offer testing of genetically engineered products and medical devices, such as combination 510(k) products.

Standard mammalian toxicology

- Acute, subchronic, and chronic toxicity
- Dose escalation and range-finding
- Maximum tolerated dose (MTD)
- Pharmacokinetics and toxicokinetics
- Lifetime and carcinogenic potential
- Reproductive and developmental toxicology (DART)
- All major laboratory species
- All major routes of administration (except inhalation)

Through our comprehensive drug metabolism, pharmacokinetics, and toxicology services, we will help you achieve your product development goals.



SRI has been accredited by AAALAC since 1974, is licensed by the USDA, holds an OLAW assurance, as well as Select Agent Clearance, radioisotope use licenses and DEA Schedule I-V Controlled Substances licenses. Most assays can be performed under Good Laboratory Practice (GLP) regulations.

Specialized safety assessments

- Irritation and sensitization
- Safety evaluations of biological and cell-based therapeutics
- Vaccine safety
- 510(k) medical device safety evaluation
- Medical imaging products
- Neonatal and juvenile animal studies
- Combination products and delivery systems
- Radiation studies
- Sensorimotor central nervous system evaluations

Evaluation endpoints

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

Specialized services

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.

- Central nervous system
- Cardiovascular system
- Respiratory system
- ICH S7A Supplemental Battery (please inquire)

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. We offer a standard set of mutagenesis and clastogenesis assays including the Ames test, micronucleus and pigA mutations. Please inquire.

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.

Standard ICH S5(R3) Studies

- Fertility and early embryonic development to implantation (FEED)
- Embryo-fetal prenatal development (EFD)
- Pre and postnatal development, including maternal function (PPND)
  - Dose range-finding studies
  - Multigenerational dosing studies
- Toxicity to male fertility – ICH S5 (R3) part 2
- Fertility, Anti-fertility, and Contraception Studies – in vitro screens and in vivo studies

SRI Biosciences, a division of SRI International, integrates basic biomedical research with drug and diagnostics discovery and preclinical and clinical development.

SRI is an independent nonprofit research instituteheadquartered in Menlo Park, Calif., with a rich history of supporting government and industry. We create and deliver world-changing solutions for a safer, healthier, and more sustainable future. For more than 75 years, we have collaborated across technical and scientific disciplines to discover and develop groundbreaking products and technologies and bring innovations and ideas to the marketplace.

Learn more at www.sri.com.

SRI Biosciences
Toll-Free: 866.451.5998
Tel: 650.859.3000
E: biosciences@sri.com

San Francisco Bay Area
SRI Headquarters
333 Ravenswood Avenue
Menlo Park, CA
94025-3493
Tel: 650.859.2000

Shenandoah Valley, VA
140 Research Drive
Harrisonburg, VA 22802
Tel: 540.428.6600

Life Sciences Corridor, MI
SRI Biosciences
Clinical Trial Unit
46701 Commerce
Center Drive
Plymouth, MI 48170
Toll-Free: 866.451.5998