Pharmacology Discovery Services

A Eurofins Discovery Partner Lab

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Pharmacokinetics Services for Drug Discovery

A Guide to *In Vivo* PK Profiling for Optimal Drug Development

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Pharmacokinetic Studies at Pharmacology Discovery Services

Pharmacology Discovery Services (PDS), a partner lab of Eurofins Discovery, provides specialized services for your novel molecular entities. PDS offers an array of tailored solutions to facilitate the progress of your novel molecular entities through the drug discovery pipeline.

PDS = Pharmacology Discovery Services = PK, Disease Models, Safety

Understanding pharmacokinetic (PK) character is crucial for drug development. These studies delve into the absorption, distribution, metabolism, and excretion (ADME) of drugs within biological systems. Proficiently conducted PK studies illuminate the drug's behavior, guiding dose selection, and optimizing therapeutic strategies while minimizing toxicity. It's the bedrock upon which effective and safe therapeutics are built.

Our experts collaborate closely with you to discern the unique physicochemical characteristics of your test materials. This collaborative approach enables the design of bespoke dosing and sample collection strategies, suited to diverse administration routes and sample types, from blood to brain tissue. Our proficiency extends across various administration techniques, ensuring meticulous and insightful study designs.

By working with PDS, you gain access to a wealth of knowledge and experience, crucial for navigating the intricacies of PK studies. Our commitment to quality and detail provides a robust foundation for your preclinical toxicity and efficacy assessments. Reach out to PDS to discover how our expertise can enhance your drug discovery journey, offering tailored solutions to complex PK challenges.

Your Best *In Vivo* Partner to Establish Pre-Clinical Proof-of-Concept

We provide therapeutically focused disease efficacy models that incorporate biomarkers and outcome measures to enable greater prediction of success in the clinic.

Overview of PK Services at PDS

In Vivo PK services

- Bioavailability
- Organ and tissue distribution (non-radioactive)
- Blood brain barrier (BBB)
- Nephrotoxicity
- Non-compartmental and compartmental PK
- PK in humanized animals
- Toxicokinetics
- Customized studies

Accessory *In Vitro* ADME Services

- Solubility test
- Plasma protein binding (dog, human, mouse, and rat matrices)
- Plasma stability (dog, human, mouse, and rat matrices)

Administration Routes and Collection

- Dosing by oral (PO), intravenous (IV), intraperitoneal (IP), subcutaneous (SC), etc.
- Serial and parallel sampling
- Microsampling
- Tissue, urine, feces, BALF collection

Species

- Mouse
- Rat
- Guinea pig
- Hamster

Surgical Models

- Vascular access ports
- Portal vein cannulation
- Bile duct cannulation

Our portfolio is expanding rapidly. To get a head start on accurate PK studies, speak to our expert: ClientServices@pharmacologydiscoveryservices.com, for the most effective dosing and sampling strategies prior to efficacy testing evaluation of your molecules.

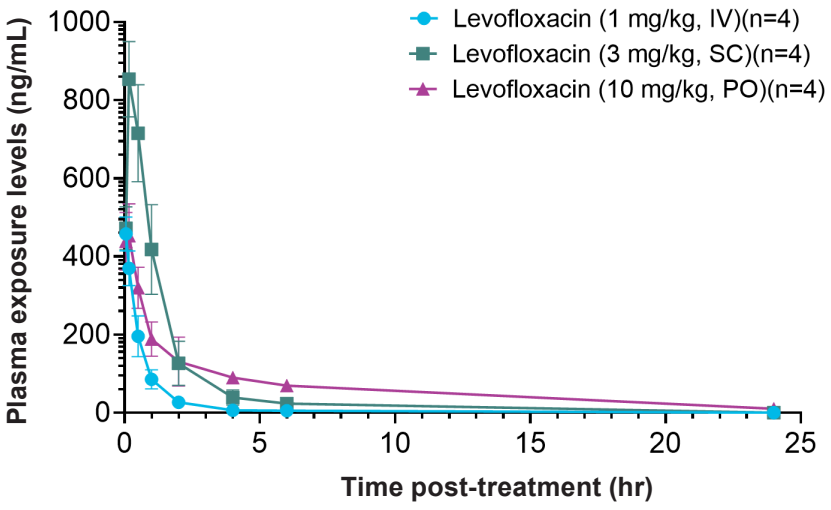
Serial Microsampling

Harnessing the essence of precision and economy in PK studies, our Serial Microsampling service takes into account the critical individual variations across test animals. Primarily implemented in rats and, with specific considerations, in mice, this approach ensures minimal disruption to the circulatory blood volume, recommending no more than 20% withdrawal within a 24-hour period. With a comparative overview of three blood sampling paradigms -- serial, semi-serial, and terminal, as outlined in Table 1 -- this model optimizes cost and utility.

Serial Microsampling offers the most economical option, necessitating only three mice per group and providing sufficient plasma for singlet bioanalysis. The semi-serial paradigm requires six mice, yielding slightly larger plasma volumes suitable for singlet bioanalysis, albeit at a moderately increased in-life cost. The terminal bleeding method, producing one data point per mouse and requiring a total of 24 mice per study, allows for duplicate or even triplicate analysis but comes with the highest in-life cost due to the single-use nature of the sampling.

Type of Blood Sampling	Minimal Plasma Volume per Collection	Collection Time Points (total sample #)	Bioanalysis Replicates	# of Mice
Serial bleeds	20 µL	8 (24)	Singlet	3 (8 time points/mouse)
Semi-serial bleeds	50 µL	8 (24)	Singlet	6 (4 time points/mouse)
Terminal bleed	150 µL	8 (24)	Duplicate or Triplet	24 (1 time point/mouse)

Table 1. Standard mouse PK sampling schemes comparison.



	t1/2 (h)	AUCInf (h*ng/mL)	AUC/D (h*kg*ng/mL/mg)	F(%)
1 mg/kg, IV	0.88	344	344	-
3 mg/kg, SC	2.35	1368	456	133
10 mg/kg, PO	4.56	2038	204	59

Figure 1. Levofloxacin was administered to 4 mice per group. The exposure levels (ng/mL) of levofloxacin in mouse plasma samples after levofloxacin (1 mg/kg, IV; 3 mg/kg, SC; and 10 mg/kg, PO) administration were analyzed through the LC-MS/MS. The mean ± SD values vs. time were plotted in line chart (semi-log).

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Available PK Studies

Study	Type	Species	Sampling Option	TAT	Item #
PK-Plasma	In-life	Mouse	Semi-serial sampling	15 Days	515550
		Rat	Serial sampling		515500
	In-life and Bioanalysis	Mouse	Semi-serial sampling		515555
		Mouse	Serial sampling		515560
		Rat	Serial sampling		515510
PK-BBB	In-life	Mouse	Terminal collection		515570
		Rat	Terminal collection		515520
	In-life and Bioanalysis	Mouse	Terminal collection		515580
		Rat	Terminal collection		515530

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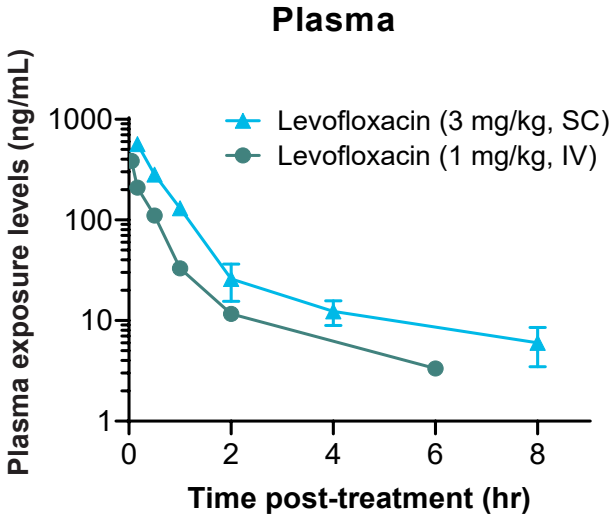
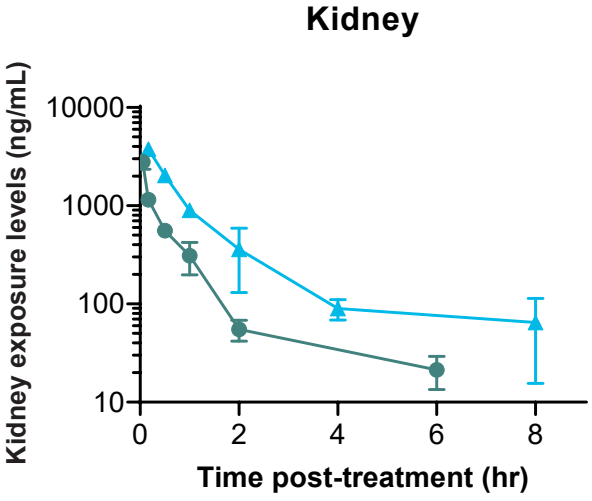
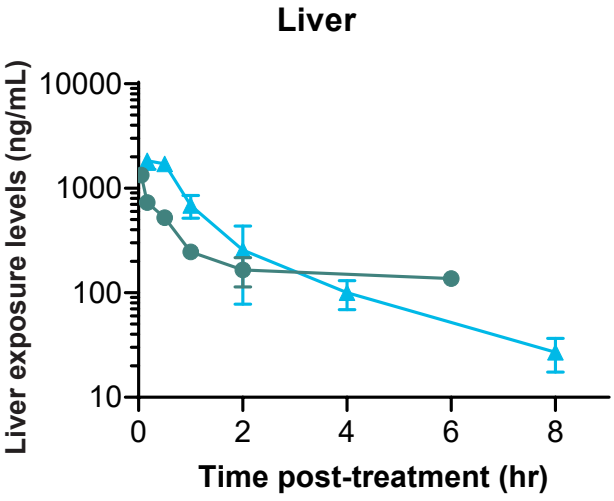
Organ Distribution

Delving into the intricate process of drug delivery and distribution, our Organ Distribution service examines the route and accumulation pattern of drugs in various tissues post-administration. In addition to the influence of both physical properties like ionization degree and lipophilicity, and physiological factors like protein binding and systemic blood flow, this model measures the distribution volume – a fundamental PK parameter crucial for half-life and dosing regimen determination.

We offer *in vivo* distribution PK testing utilizing ICR mice. The administration of test articles is tailored according to the Sponsor's preference, involving IV, IP, PO, or SC modes. Post-dosing, the plasma and organ samples are harvested, processed, and analyzed using the Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS). Plots of plasma and organ concentration versus time are constructed, and the non-compartmental analysis (NCA) of plasma data is performed using WinNonlin to ascertain key pharmacokinetic parameters. Plasma: organ ratios are also accurately calculated to offer comprehensive insights into the drug distribution process.







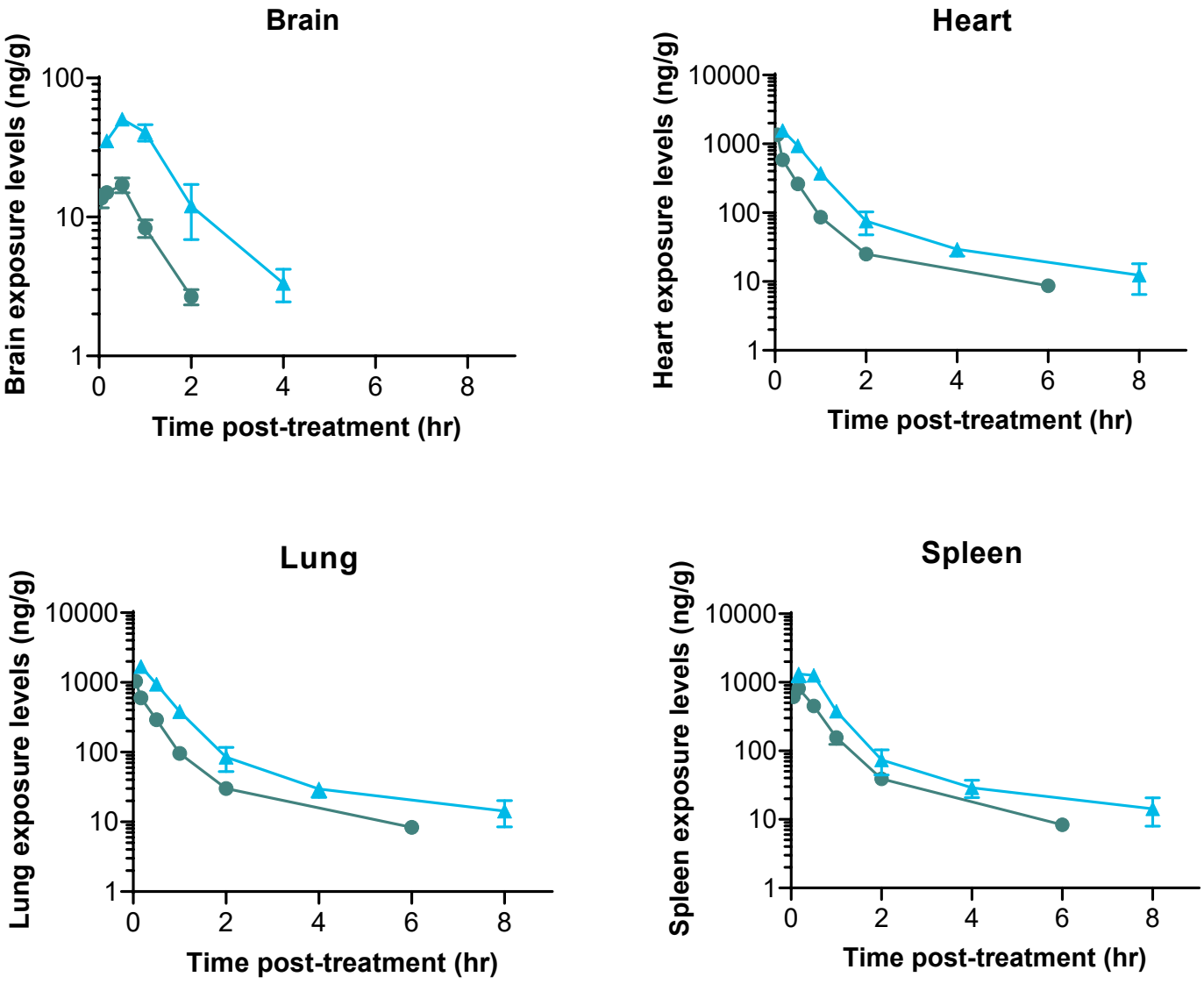


Figure 2. Concentration-time profile of levofloxacin, administered via SC or IV, in multiple organs.

Available PK – Organ Distribution Studies

Study	Type	Species	TAT	Item #
Organ Distribution	In-life and Bioanalysis	Mouse	30 Days	515585

PK Analysis in Humanized Mice

Elevating the predictability of drug response and facilitating the study of human-specific pathways, our Humanized Mouse Model, specifically the PXB-mice, offers a superior tool in preclinical studies. This model involves the transplantation of human hepatocytes into an immunodeficient mouse, essentially equipping the mouse with a largely human-populated liver. This unique configuration empowers the mouse to metabolize drugs akin to a human liver, thereby allowing scientists to closely examine drug metabolism and pharmacokinetics in a model that parallels the human scenario.

Here we provide an example of our PK analysis utilizing PXB-mice compared to CB17-SCID mice. The animals were IV or PO administered with amlodipine and naltrexone. The plasma samples are analyzed using LC-MS/MS, and key PK parameters are determined through NCA using WinNonlin. Bioavailability is also calculated to understand the proportion of the orally administered drug that is accessible in the body. The differential bioavailability profile observed across the strains aligns with established oral bioavailability values in human and mouse PK studies, making PXB-mice a reliable model for human PK predictions.

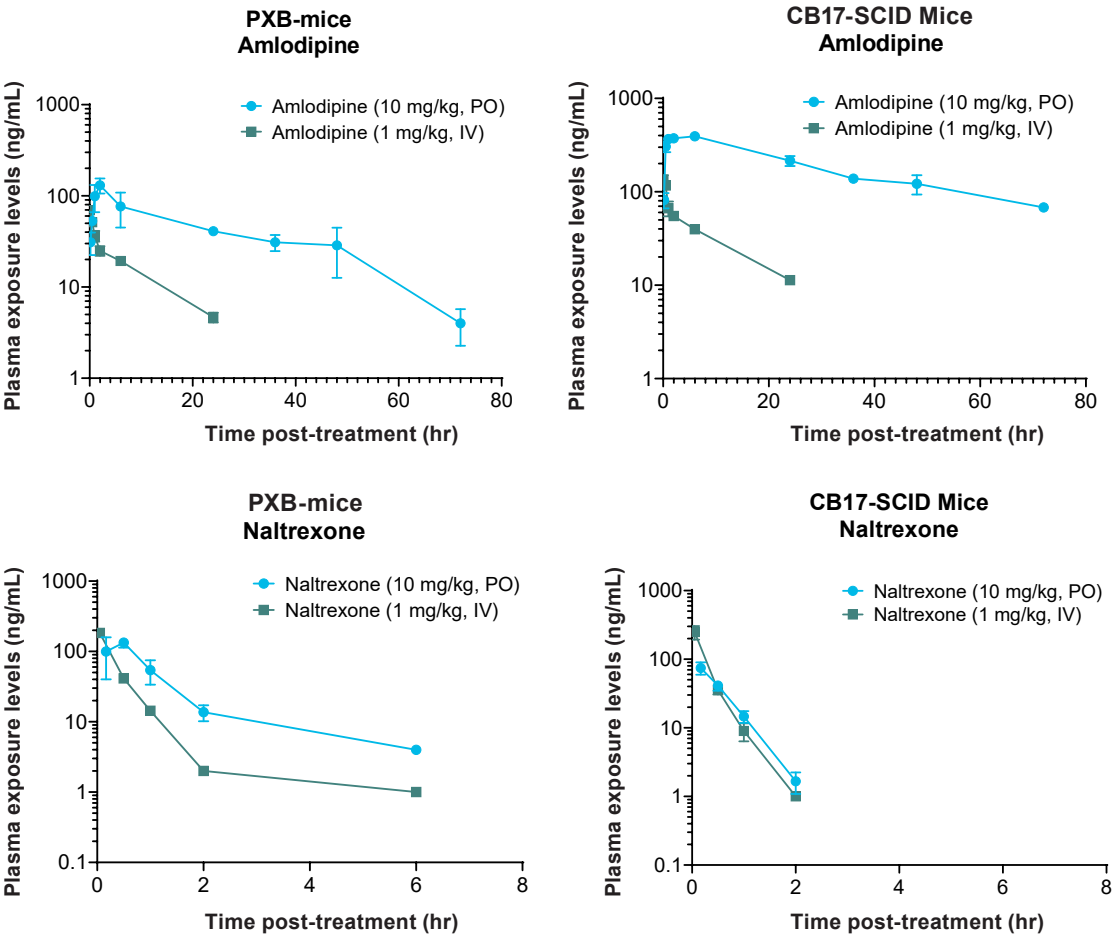


Figure 3. Concentration-time profile of amlodipine and naltrexone, administered via IV at 1 mg/kg or PO at 10 mg/kg, in PXB-mice or CB17-SCID mice.

	PXB-mice	CB17-SCID Mice
Amlodipine	Moderate F (%) as expected	High F (%) as expected
Naltrexone	Relatively higher F (%) as expected	Relatively lower F (%) as expected

Table 2. Summary of the PK analysis of amlodipine and naltrexone in PXB-mice or CB17-SCID mice.

Accessory *In Vitro* ADME Service: Plasma Stability and Plasma Protein Binding

In the intricate process of drug discovery, ADME (Absorption, Distribution, Metabolism, and Excretion) studies stand as pillars, offering critical insights into a drug's interaction with the human body. These insights are pivotal in determining a drug's efficacy and safety. Key components of these studies are plasma stability and plasma protein binding assays, both of which are now available at PDS for various plasma matrices, including those of rats, mice, humans, and dogs.

Plasma Stability Assays

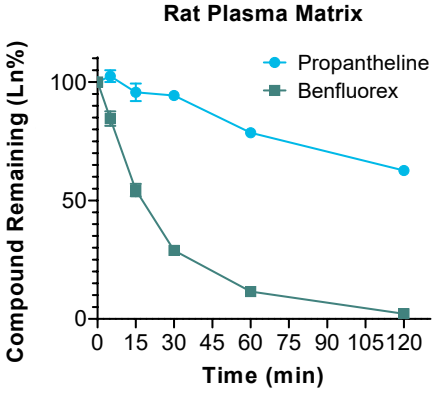
At PDS, we offer streamlined plasma stability tests to assess the lifespan of drugs in the bloodstream. Our method involves dissolving the drug in DMSO and adding it to plasma in a 96-well plate. After incubating at 37°C for various time intervals, the mixture is analyzed with LC-MS/MS to quantify the remaining drug. Results show the percentage of compound stability over time.

Plasma Protein Binding Assays

Our plasma protein binding assays determine how drugs interact with plasma proteins, influencing their distribution and elimination. The plasma is spiked with the test drug, and dialysis is conducted against PBS via rapid equilibrium dialysis (RED). After incubation, both samples undergo LC-MS/MS analysis. The results, presented as a percentage, reflect the binding efficiency of the drug to plasma proteins.

A

Plasma Stability Test in Rat Matrix



B

Plasma Protein Binding Assay in Rat Matrix

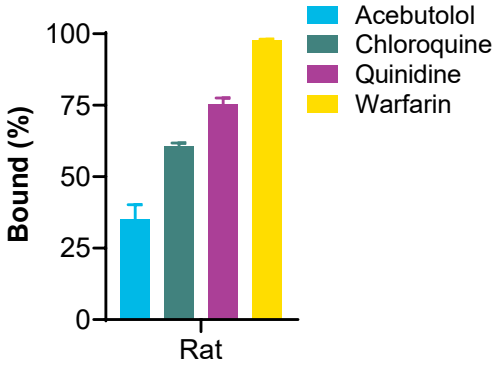


Figure 3. Various accessory services related to *in vitro* ADME. A. Plasma stability of benfluorex and propantheline in rat matrix. B. Plasma protein binding assay of acebutolol, chloroquine, quinidine, and warfarin in rat plasma protein matrix.

Available *In Vitro* ADME Assays

Study	Type	Species	TAT	Item #
Stability Test	Plasma	Dog	20 Days	516040
		Human		516030
		Mouse		516020
		Rat		516010
Protein Binding		Dog		516080
		Human		516070
		Mouse		516060
		Rat		516050

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Animal Facility and Accreditations

- AAALAC accredited vivarium
- Office of laboratory (OLAW) assurance
- In Compliance with EU Directive 2010/63/EU
- ISO 9001 certification
- Biosafety level 2 facility

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AN ACCREDITED ANIMAL CARE & USE PROGRAM SINCE 1971

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1669 m² Vivarium Plus 186 m² Bioanalytical Lab

- 50 years CRO business experience, formerly Panlabs Inc.
- 45 FTEs ; >10 year average tenure
- Biosafety Level 2 Facility
- 3,000+ rodent holding and 20 procedure rooms

Expert Provider of Non-GLP Safety, PK, and Efficacy Studies in Rodents with 350+ Validated Models

INFECTIOUS DISEASE
145+ validated models, CDC/WHO priority pathogens, *In vitro* antimicrobial assays and rodent infection models

NEUROSCIENCE
50+ validated models, CNS, pain, neurodegeneration, addiction, behavioral endpoints

GASTRO-INTESTINAL
20+ models, UC/Crohn's models, gut barrier function, FITC transport, DSS, TNBS, AKI, 5/6 SNx

350+
validated models across all major therapeutic areas

INFLAMMATION/IMMUNOLOGY
60+ validated models, comprehensive portfolio auto-immune, dermal inflammation, lung inflam-ation, liver injury and fibrosis, NASH, sepsis, miles assay, gout

METABOLIC/ENDROCRINE
20+ validated models, diabetes and obesity acute and chronic intake monitoring, taste aversion, IP/IV/oral glucose tolerance test

ONCOLOGY
60+ validated models, human cell-line derived xenografts (CDX) models, immortalized mouse cancer cell lines, custom *in vivo* development

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A Partner Lab of Eurofins Discovery

Providing Deep Technical Expertise from Discovery to Preclinical

Eurofins Discovery, a partner lab of PDS, has been supporting Drug Discovery research for over 40 years and offers thousands of assays to advance your test agents from Target Validation to Pre-Clinical Development. Offerings include medicinal and synthetic chemistry, *in vitro* pharmacology, safety pharmacology, ADME-Toxicology, cell-based phenotypic assays, *in vivo* safety & efficacy, and custom proteins and assay development. The DiscoveryOne™ integrated drug discovery service is also available for clients to access all services, and it includes dedicated project management to drive the delivery of your preclinical candidates. With the combined expertise of our team, we deliver high-quality, actionable insights to solve drug discovery challenges

Chemistry

Access synthetic and medicinal chemists; expertise in computational chemistry; flexible business models from full-time equivalent (FTE) based to FlexLab Custom Chemistry projects or insourcing of chemists.

ADME & Toxicology

Over 500 *In vitro* ADME & Toxicology assays providing comprehensive solutions for assessing drug metabolism and safety profile; delivering cost-effective, high-quality, and reproducible data with rapid turnaround times; flexible, tailored solutions to accommodate the specific testing needs of clients.

Safety & Efficacy

Industry-leading *In Vitro* Safety Pharmacology Panels include robust and proven binding and functional assays for thousands of targets; precise and efficient safety evaluation; predict and mitigate potential risks associated with off-target-related adverse drug reactions (ADRs) and enable the identification of unsafe compounds early in the development process.

DiscoveryOne

Benefit from seamless project management, design, and execution capabilities; manage hit identification, triage, and validation programs under one roof.

For more information on *in vivo* PK, please visit:
→ pharmacologydiscoveryservices.com/pk-safety/pk