Discovery Research

Pharmacokinetic Capabilities for Differentiated Products

Discovery Research
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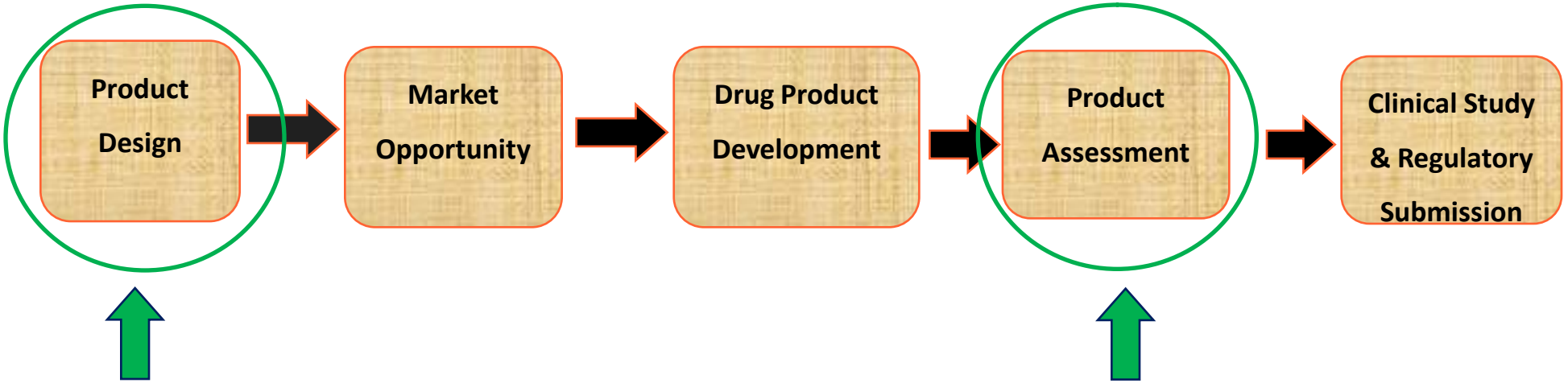
Overview

Potential Differentiated Products: Suven Preclinical Support

- Change in dosage form or dosage regimen
- Conversion to lower or higher strength
- Route of administration
- Change in formulation
- New indication for previously approved drug
- Modified active ingredient (i.e. salt, ester etc.,)
- New molecular entity (NME) – Eg. prodrug, active metabolite
- Substitution of an active ingredient in a combination (FDC)
- Conversion from prescription drug to Over-The-Counter (OTC) indication

Strategies for Developing Differentiated Products

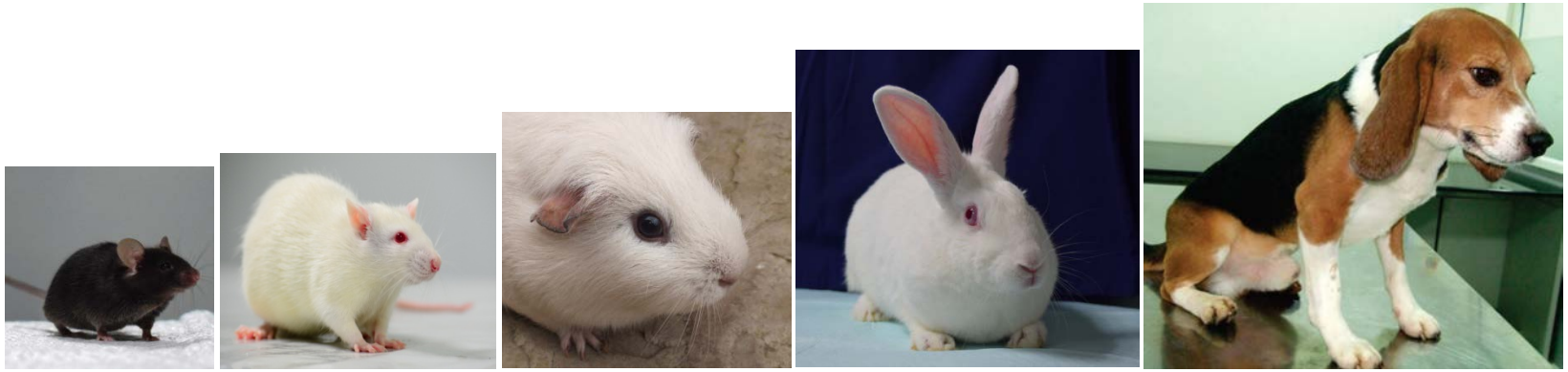


"Bridging studies are required to show that changes to the innovator drug product lead to the desired impact on safety, efficacy and tolerance of the proposed drug product"

In Vivo PK Capabilities

- ***In Vivo* Studies**
  - Bioavailability
  - Bioequivalence
  - Food effect studies
  - PK in target site (CNS or peripheral)
  - Single and multiple-dose pharmacokinetics
  - Tissue distribution (cold and ^{14}C labelled)
  - Biliary vs. urinary excretion (cold and ^{14}C labelled)
  - PK/PD studies in animal models
- **Biological Matrices**
  - Blood, plasma, serum
  - Bile, urine, feces
  - Synovial fluid, cerebrospinal fluid
  - Aqueous humor, Vitreous humor, Ocular tissues
  - Microdialysis samples (brain, dermal, blood, ocular)
  - Tissues (skin, muscle etc)
- **Route of Administration**
  - IV bolus (single and cassette)
  - IV infusion
  - Oral
  - Sucutaneous
  - Intra-nasal
  - Sublingual
  - Topical/ Intradermal
  - Ocular
  - Specialized CNS drug delivery/ Sampling

Animal Species for Pharmacokinetics



Mouse Rat Guinea pig Rabbit Dog

Small animals

Large animals

- ❖ Oral
  - Solutions, Suspensions, Films
- ❖ Parenteral (Intravenous, subcutaneous infusions)
  - Bolus, Continuous and Intermittent Infusion
- ❖ Intranasal (Powders and Liquids)
- ❖ Ocular and Dermal Formulations

Oral PK Studies

Products

- Solution or Suspension
- Capsules filled with solutions or suspensions
- Tablets, ODT, Films and FDC products
- Capsules (Soft or Hard gelatin)
- Sublingual, Buccal

Study Designs

- Single and multiple dose PK
- Food effect
- Cross-over study design (two-way to four-way)
- PK exposures – Test Product vs. RLD

Oral PK Studies (oral dosage forms): Case Study 1

Pharmacokinetics of Ondansetron in rabbits at 4 mg dose.			
Dosage Forms	**T_{max} (hr)**	**C_{max} (ng/mL)**	**AUC_{last} (ng*hr/mL)**
Oral Spray (Vomi-spray)	0.75 (0.5 - 0.75)	17.10 ± 5.34	25.43 ± 9.73
Sublingual Tablet (Zofer MD 4, ODT)	0.75 (0.75 - 2.0)	8.20 ± 2.66	19.12 ± 7.23
Sublingual Film (Vomi-fast)	0.75 (0.75 - 1.0)	7.89 ± 3.34	19.17 ± 7.56
Oral Solution (Zofer 4)	0.75 (0.75 - 1.0)	2.52 ± 0.74	7.05 ± 1.82
Oral Tablet (Zofer 4)	3.0 (2.0 - 3.0)	1.54 ± 1.0	3.18 ± 1.24

Product: **Ondansetron**

Oral dosage forms: Oral spray, Sublingual tablet, Sublingual film, ODT and Oral solution.

Groups: Five groups

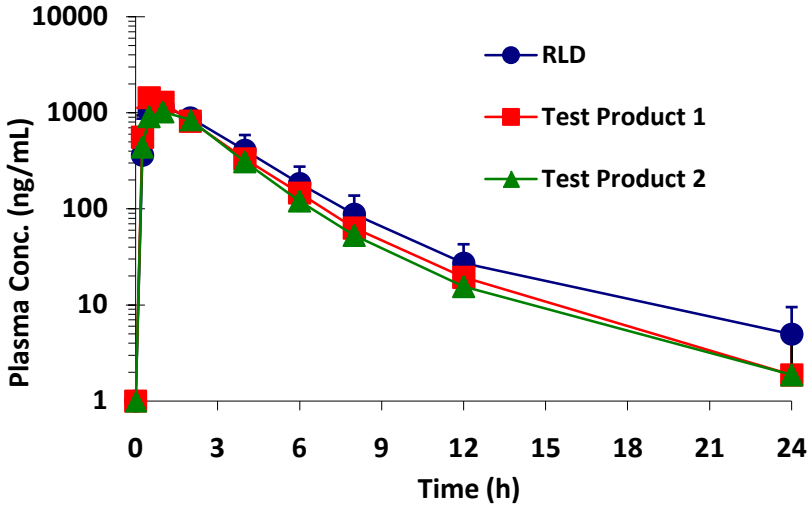
Design: Parallel study, N = 5 animals/ dosage form

Gender / Species: Male Newzealand white Rabbit

Ondansetron exposures were high in Oral Spray

Sublingual film administration in Rabbits

Oral PK Studies: Case Study 2



Test Product 2 did not meet BE criteria

Product: **Proprietary Solid oral dosage form**

Groups: RLD, Test Product 1 (T1) and Test Product 2 (T2)

Design: Three-way Cross-over study, N = 6/group

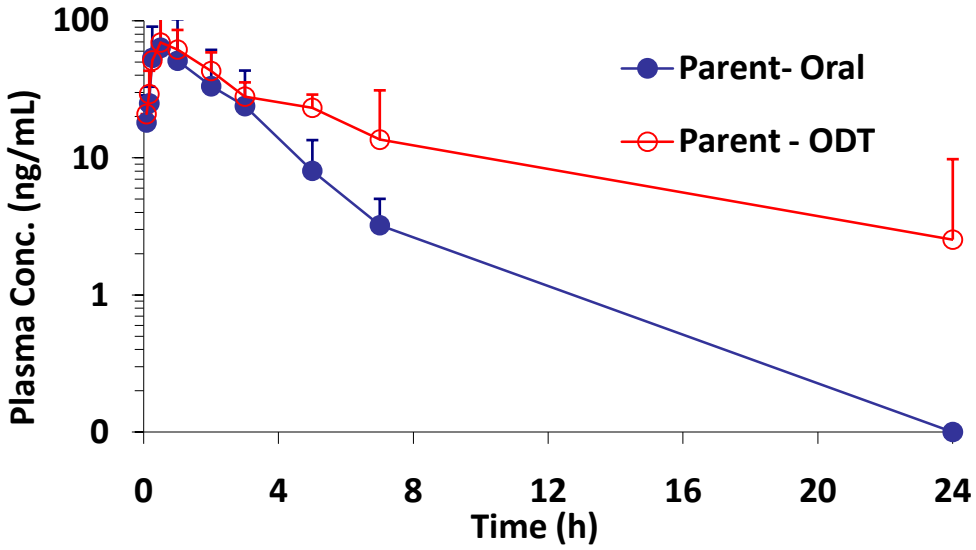
Species: Non-rodent

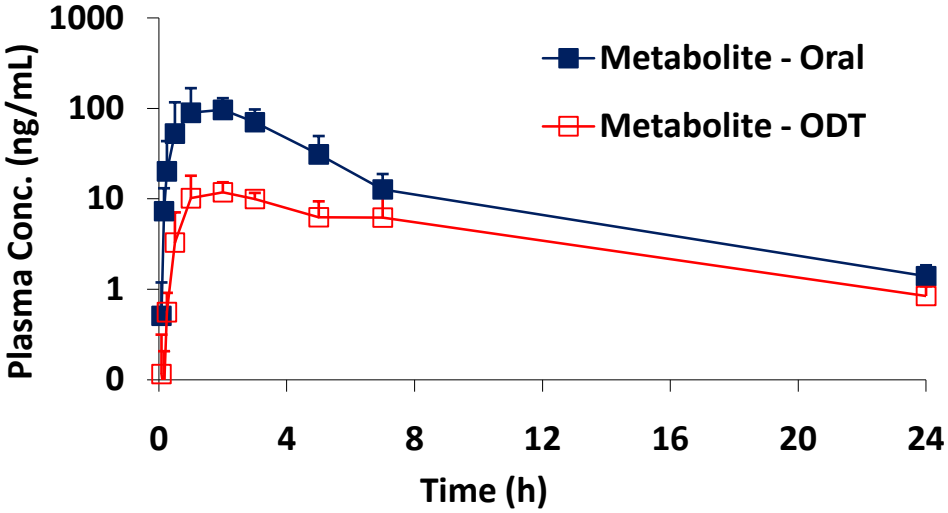
Route: Oral

Time points: 24 hour post dose

Group	Parameter	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)
RLD	Geometric LSM	1263	4395	4395
T1	Geometric LSM	1475	4206	4368
	% Ratio (T/R)	117	96	99.38
	Lower CI (90%)	103	91	83
	Upper CI (90%)	120	112	120
T2	Geometric LSM	1326	3608	3674
	% Ratio (T/R)	105	82	84
	Lower CI (90%)	91	73	72
	Upper CI (90%)	121	99	98

Oral PK Studies: Case Study 3 (ODT vs. Oral)





ODT vs. oral exposures of parent and metabolite

Metabolite exposures are significantly reduced in ODT

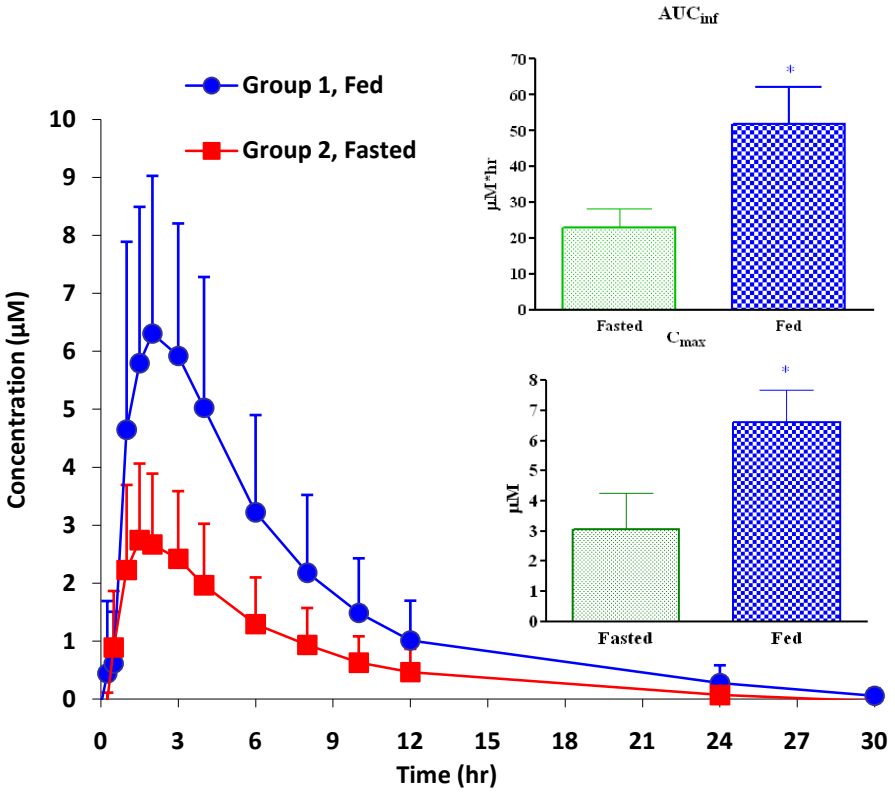
Product: Proprietary ODT

Design: Two-way Cross over study, N = 3/group

Species: Non-rodent

Route: ODT, Oral

Oral PK Studies: Case Study 4 (ODT vs. Oral)



➢ Unpaired t-test $p<0.05$ for fed group when compare to fasted group.

Product: **Proprietary oral dosage form**

Groups: Fasted (G11) and Fed (T2)

Design: Cross-over study, N = 6/group

Species: Non-rodent

Route: Oral

Time points: 30 hour post dose

Food had increased the exposures significantly

Injectable PK Studies

Infusion Study Types

Intravenous, subcutaneous infusion studies

- Continuous infusion
- Intermittent infusion
- Slow bolus infusion
- Indwelling catheters
- Percutaneous catheters
- Tail vein infusion

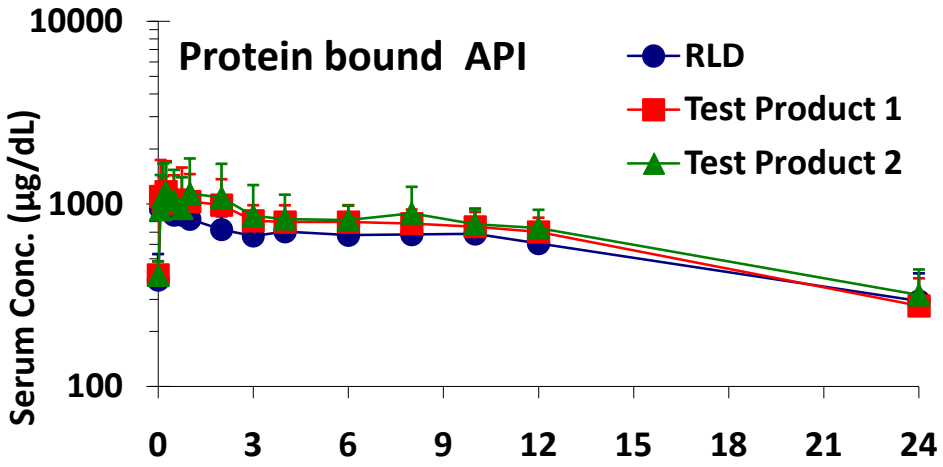
Specialized Techniques

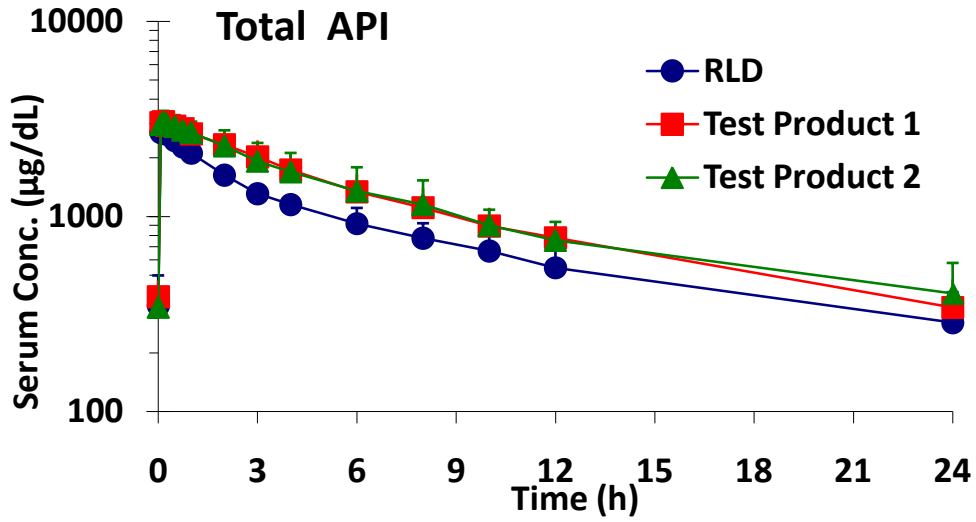
- Intrathecal
- Intraintestinal
- Intraarterial
- Intracerebroventicular

Infrastructure

- Micro infusion pumps
- Special delivery techniques

Injectable PK Studies: Case Study 5 (IV Infusion for ANDA)





Product: Colloidal injection formulations

Groups: RLD, Test Product 1 and Test Product 2

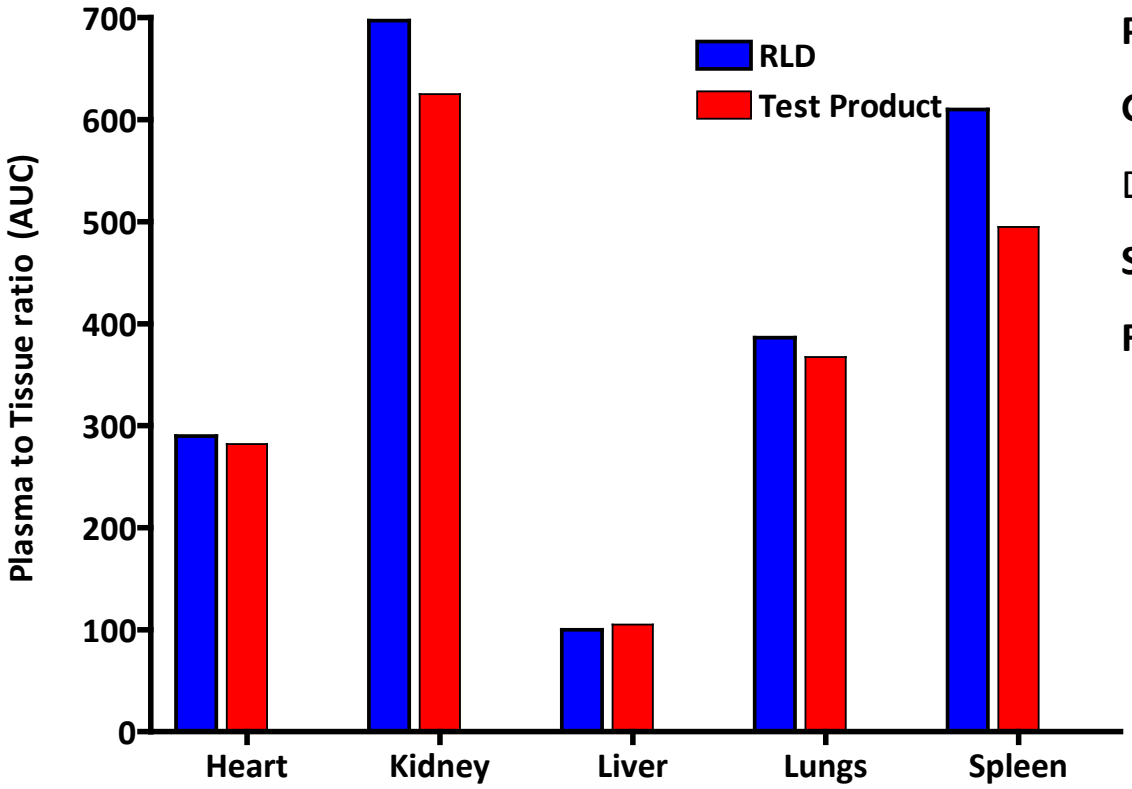
Design: Three-way Cross-over study, N = 12/group

Species: Non-rodent

Route: Short infusion (5 min)

Both test products are not meeting BE criteria

Injectable PK Studies: Case Study 6 (Tissue Distribution)



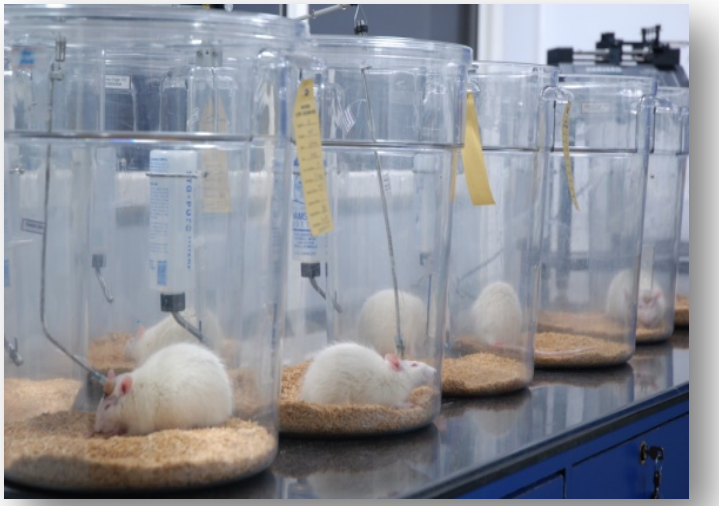
Product: Proprietary Injections

Groups: RLD, Test Product

Design: Discrete up to 48 hours, N = 5/time point

Species: Rats

Route: Infusion (60 min)

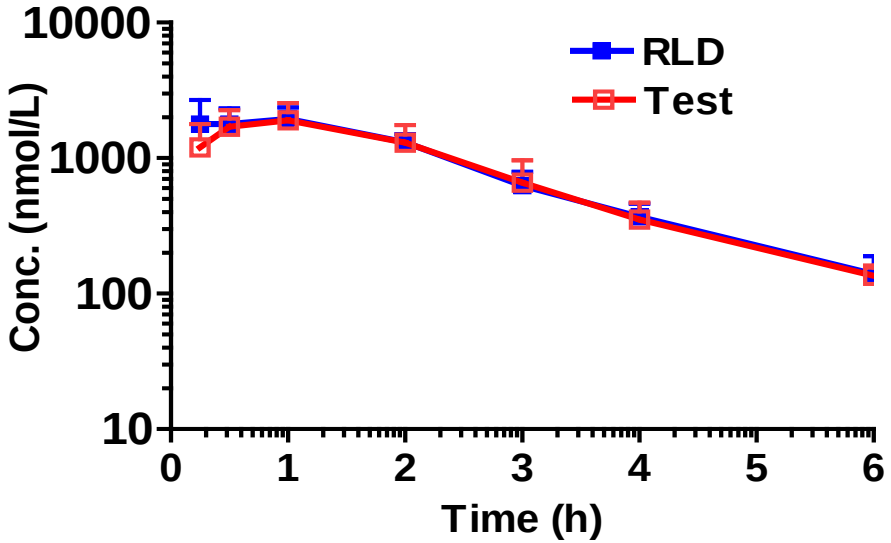


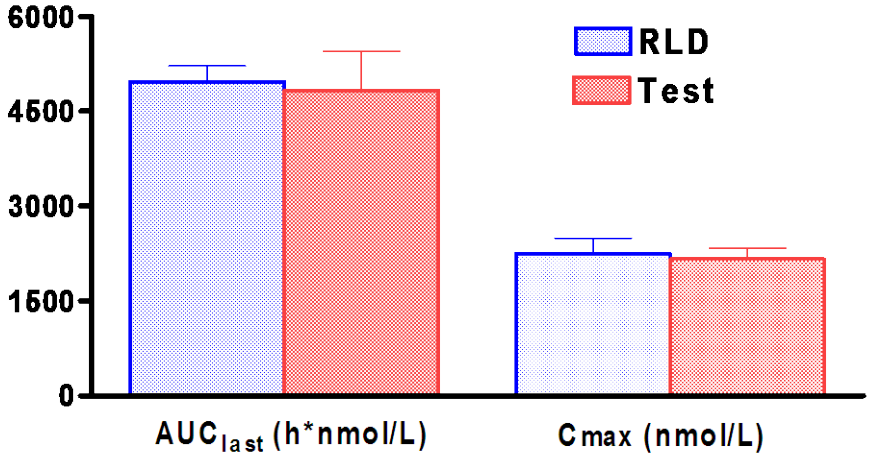
Comparative tissue versus plasma ratio exposures were observed (Test product vs. RLD)

Ocular Studies

	Study Type	Species	Duration	Endpoints (RLD Vs Test)
PK	Direct sampling (aqueous humor)	Rabbits	6-8 samples, up to 24 hours	C_{max}, AUC, CI
	Microdialysis (aqueous and vitreous humor)	Rabbits	Up to 8 hours	C_{max}, AUC, CI
	Tissue distribution (ocular tissues)	Rabbits	Up to 24 hours	C_{max}, AUC, CI
Efficacy	IOP measurement	Rabbits (Ocular normotensive/ Hypertensive)	Up to 8 hours	Changes in IOP
	Allergic conjuctivitis model	Guinea pigs	-	Biomarkers
Safety	Ophthalmoscopy by veterinarians	Rabbits/ Guinea pigs	-	Clinical scoring
	Microscopic examination	Rabbits/ Guinea pigs	-	Clinical scoring

Ocular PK Studies: Case Study 7 (Aqueous Humor- Direct Sampling)





Animals : Male New Zealand Rabbits; n = 6 /group

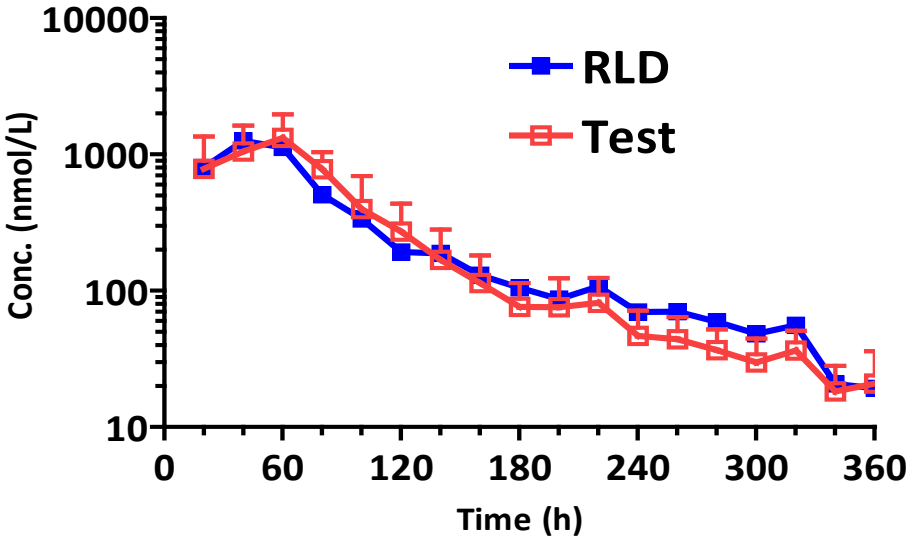
Test Agents : RLD, Gatifloxacin 0.3 % w/v
Test Product; Gatifloxacin 0.3 % w/v

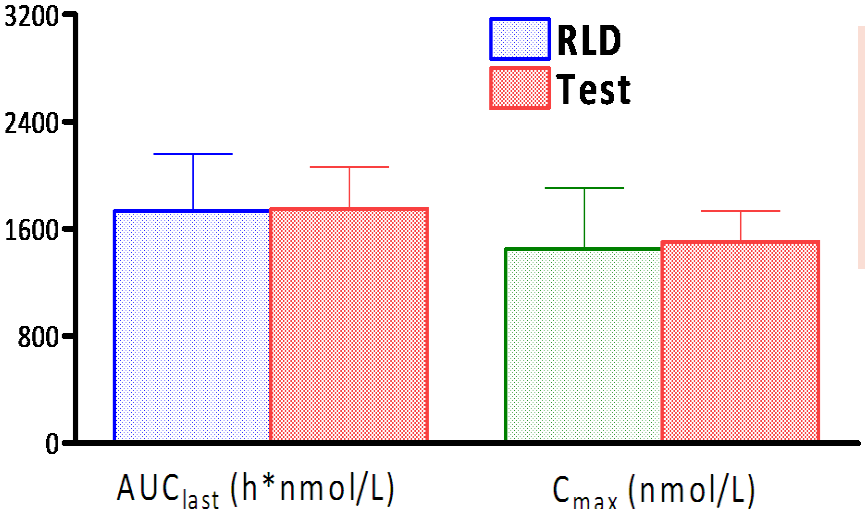
Administration : 50 µL local instillation

Method : Repeated sampling of aqueous humor under lignocaine (4 %) local anesthesia

Comparative PK profiles in aqueous humor concentrations were observed (RLD vs. Test Product)

Ocular PK Studies: Case Study 8 (Ocular Microdialysis)





Animals : Male New Zealand Rabbits; n = 6/group

Test Agents : RLD; Zymar, Gatifloxacin 0.3 % w/v
Test; Gatiblu, Gatifloxacin 0.3 % w/v

Administration : 50 µL local instillation

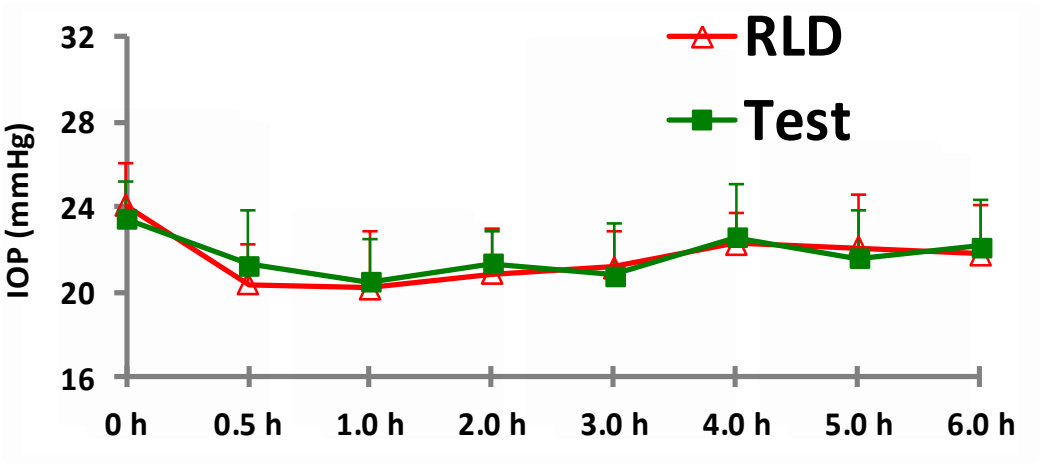
Method : Aqueous humor- 5 mm linear probe

Perfusion Fluid : Ringer Solution

Flow Rate : 2 µL/min

Unbound PK profiles in aqueous humor concentrations were observed (RLD vs. Test Product)

Ocular Efficacy Studies: Case Study 9 (IOP Measurement)



Time (h)	IOP Decrease (mmHg)			
	RLD		Test Product	
	Mean	SD	Mean	SD
0.5	-4.4	1.7	-3.3	2.1
1	-4.3	1.8	-4.0	1.3
2	-4.1	1.7	-2.7	0.7
3	-3.5	1.6	-3.5	1.9
4	-3.0	1.7	-3.0	0.6
6	-3.4	1.3	-3.1	1.1

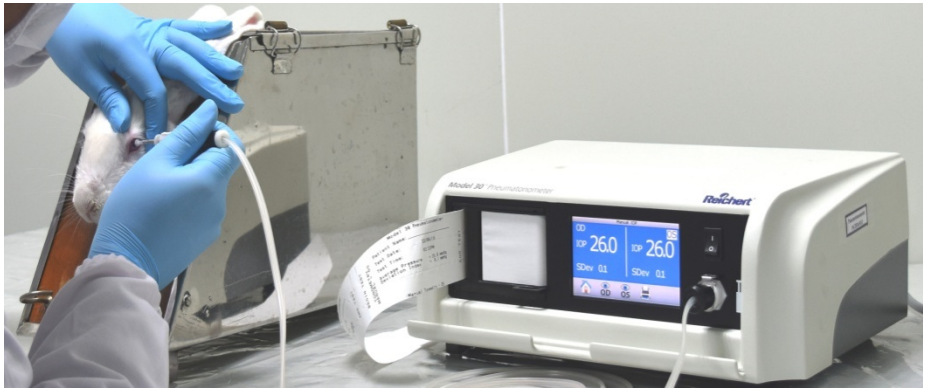
Animals : New Zealand Rabbits; n=6/ group

Test Agents : RLD; Timolol 0.5 % w/v
Test Product; Timolol 0.5 % w/v

Administration : 50 µL local instillation (acute)

Anesthesia : Lignocaine 4 %

Similar decrease in IOP (RLD vs. Test Product)



Dermal PK Studies

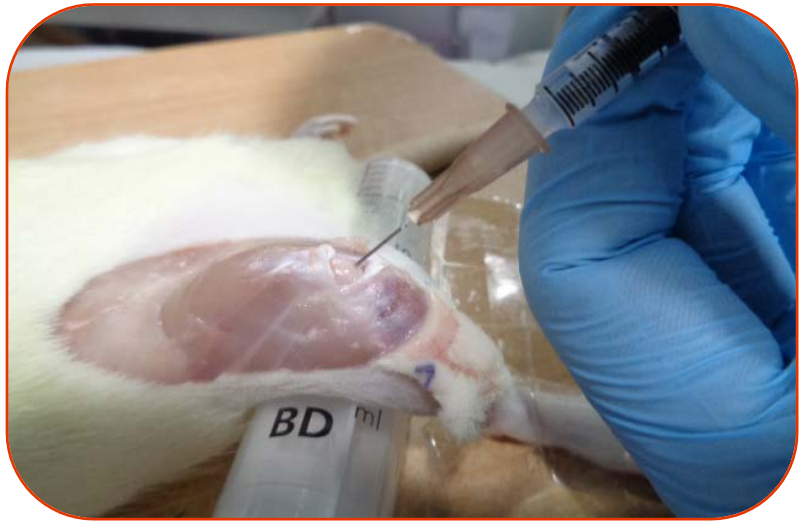
Products

- Topical
- Intradermal
- Dermal Microdialysis
- Solutions or Suspensions
- Semisolids Products

Study Designs

- Single and multiple application PK
- PK exposures
  - ✓ Skin layers (dermis, epidermis)
  - ✓ Synovial fluid
  - ✓ Blood

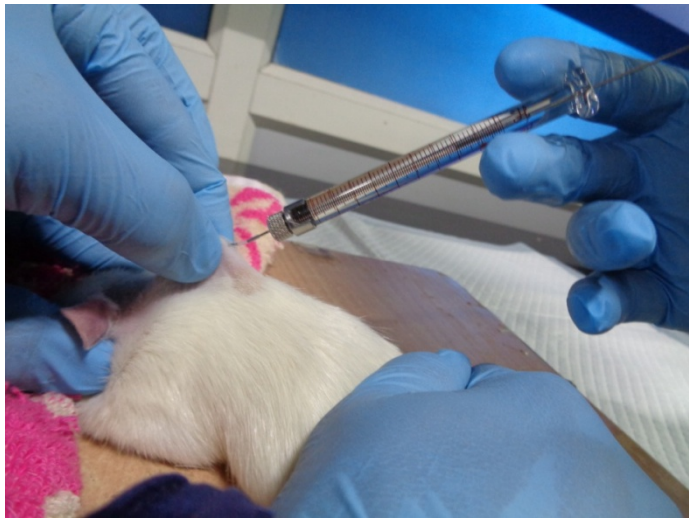
Dermal PK Studies: Case Study 10 (Oral vs. Topical – Synovial PK in Rats)

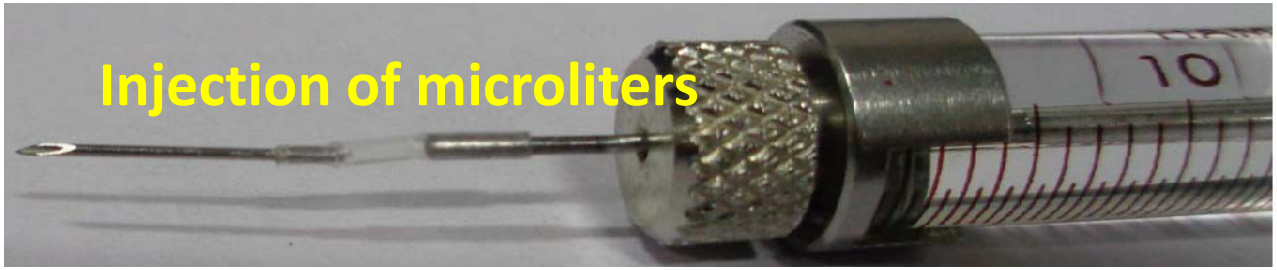


Route	Site	Synovial Fluid (ng/mL) Right Leg	Synovial Fluid (ng/mL) Left Leg	Plasma (ng/mL)
Topical	Knee	16.7 ± 6.8	4.8 ± 3.8	163 ± 68
	Dorsal	3.2 ± 0.8	2.9 ± 0.8	148 ± 96
Oral	Gavage	13.6 ± 2.0	12.9 ± 1.2	1301 ± 80

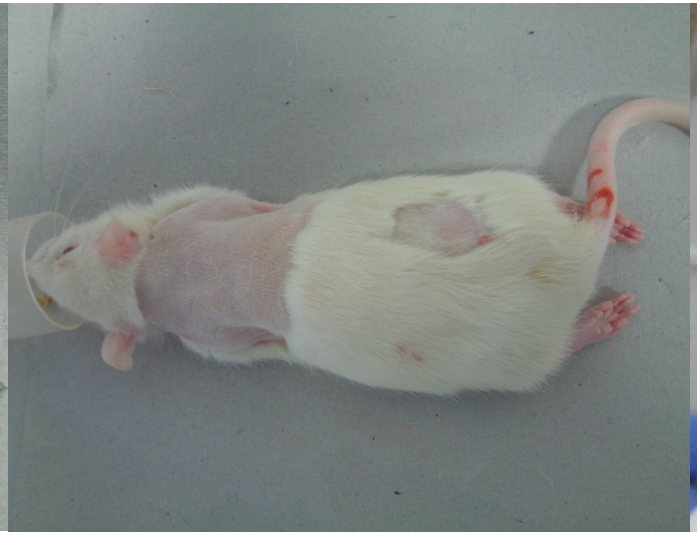
Target site has high concentrations in Topical vs. Oral

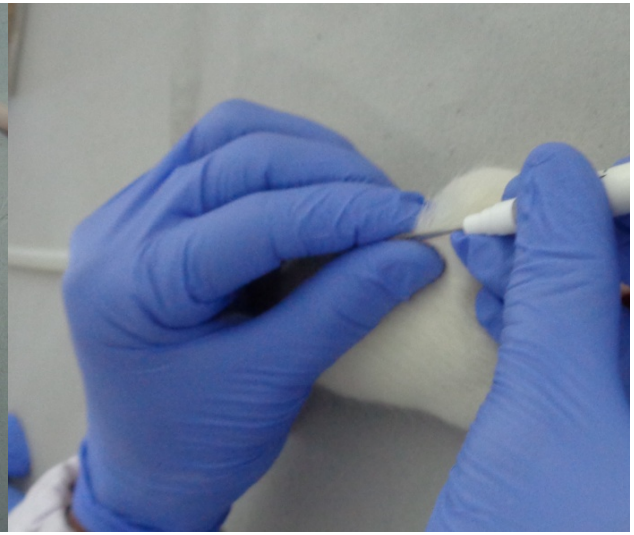
Dermal PK Studies: Low Volume Injections/ Implant Delivery





Rodents are suitable for quick and comparative assessment of depot release





Dermal PK Studies: Case Study 11 (Microdialysis)

Animal Preparation

Rat, Guinea Pigs, Rabbits

Implantation of Probe in Dermis
(10 mm)

Dermal Microdialysis

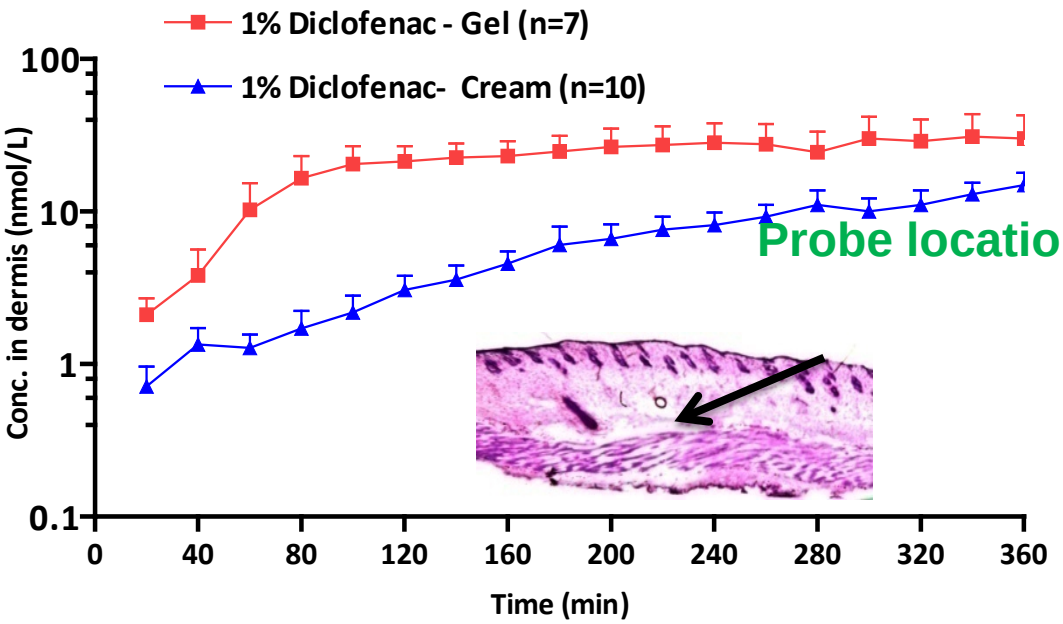
Stabilization

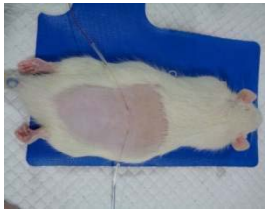
Sample Collection

Treatment
50 mg, infinite occlusion

Dialysate Collection

Bio-analysis





Probe location in dermis

Dermal microdialysis enables understanding of different release patterns

Data expressed as mean ± SEM

Intranasal PK Studies

Products

- Solutions
- Powder
- Nasal spray device

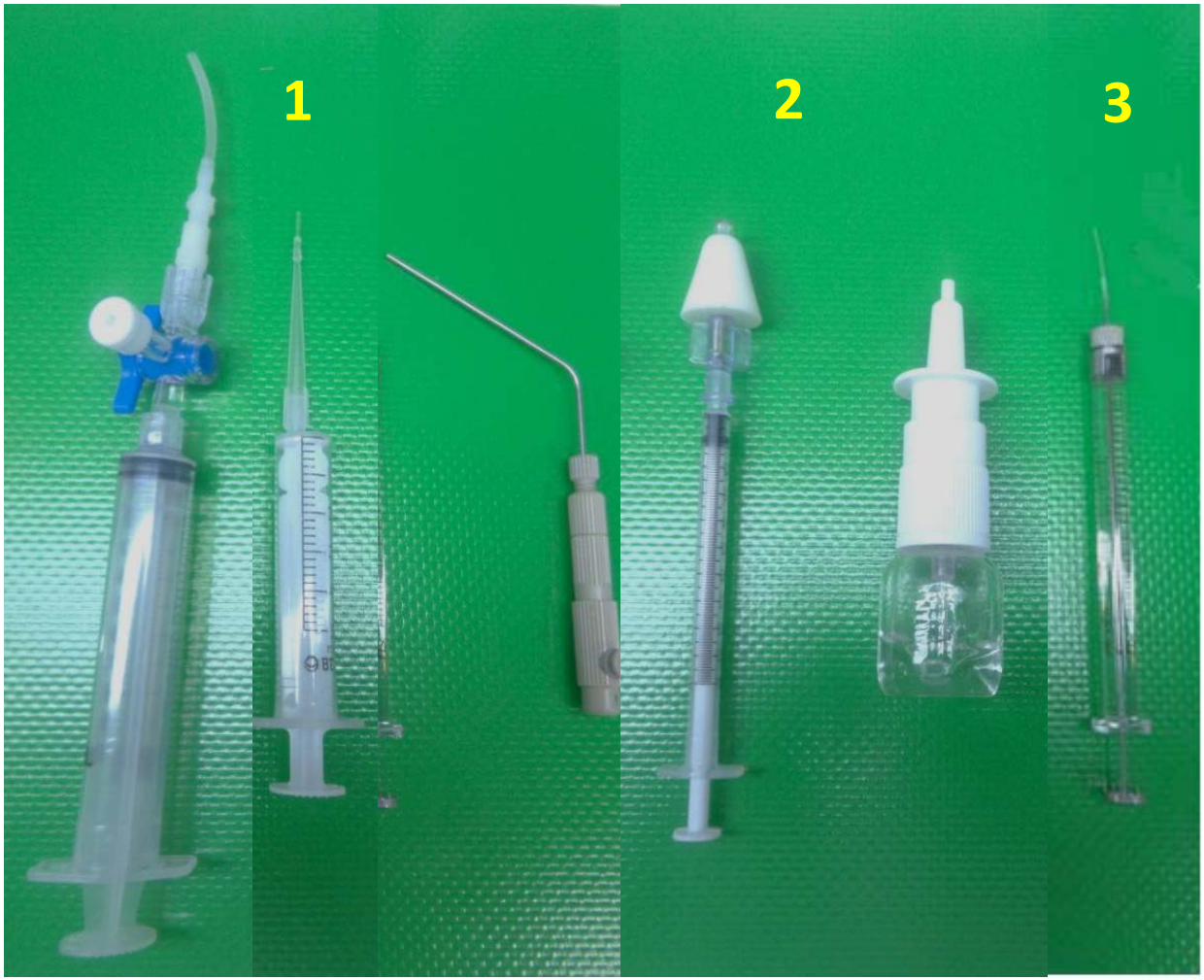
Study Designs

- Single and multiple dose PK
- Cross-over study design
- PK exposures – Test Product vs. RLD

Advantages of Intranasal Delivery

- Delivery of drug directly to the brain
- Non-invasive, rapid absorption and amenable for biologics

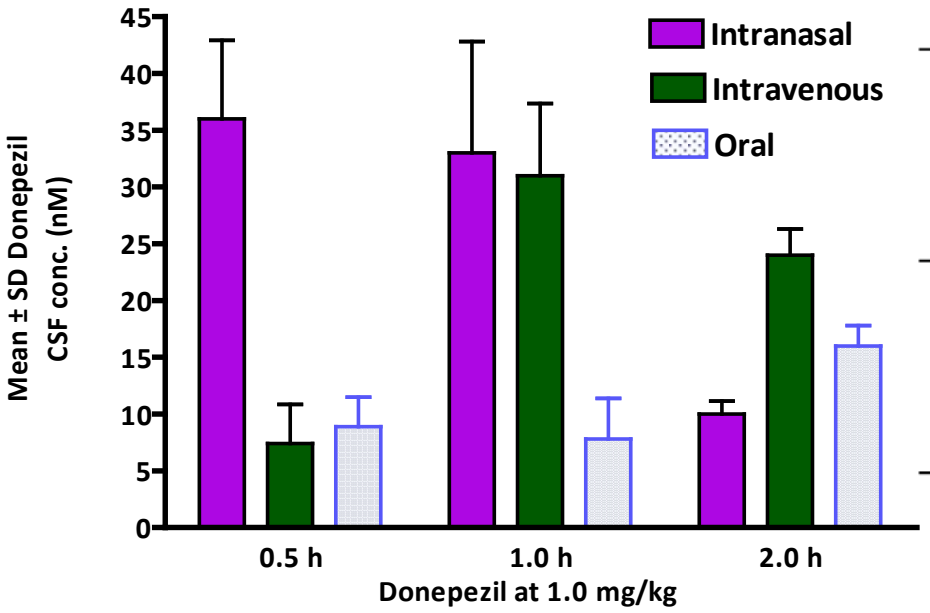
Intranasal PK Studies: Devices for Preclinical Species



1. Devices for powder
2. Device for spray
3. Device for liquid

Designed devices suitable for intranasal administration of Powders, solutions and sprays in preclinical species

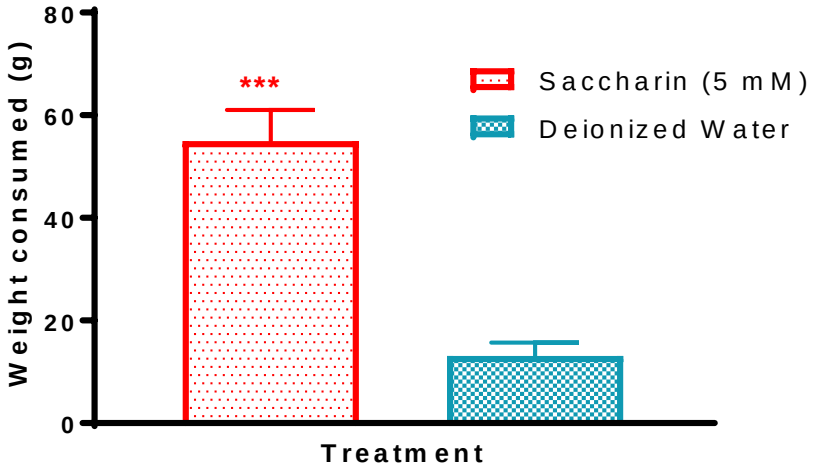
Intranasal PK Studies : Case Study 12 (Nose to Brain)



Route	Time (h)	CSF (nM)	Brain (nM)	Plasma (nM)	Cb/Cp
IN	0.5	36 ± 12	1024 ± 163	213 ± 15	4.80 ± 0.55
	1	33 ± 17	722 ± 137	139 ± 35	5.28 ± 0.70
	2	10 ± 2	354 ± 64	57 ± 15	6.29 ± 0.65
IV	0.5	7.4 ± 6.6	1127 ± 262	178 ± 24	6.27 ± 0.64
	1	31 ± 11	740 ± 45	133 ± 24	5.65 ± 0.82
	2	24 ± 4.5	494 ± 18	90 ± 15	5.60 ± 0.85
PO	0.5	8.9 ± 4.5	136 ± 92	43 ± 22	3.03 ± 0.61
	1	7.8 ± 6.2	340 ± 12	48 ± 11	7.26 ± 1.69
	2	16 ± 3.1	225 ± 55	46 ± 21	5.43 ± 2.32

Brain and CSF concentrations of Donepezil were comparable to intravenous administration in rats

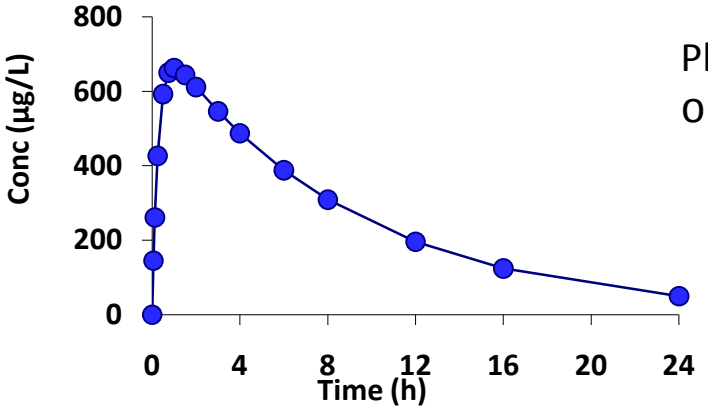
Palatability Test, Taste Preference Test in rats : Case Study 13



Animals : Male Wistar rats

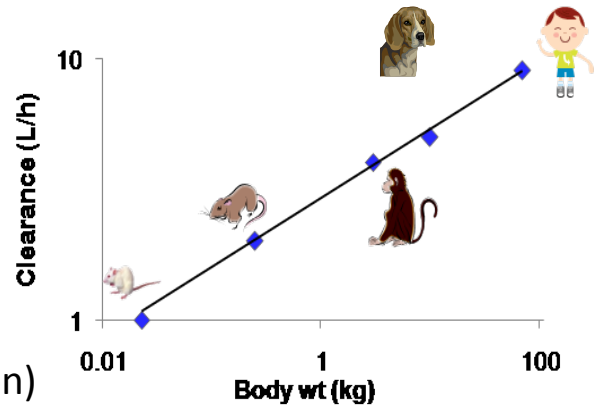
Palatability test is most accepted to evaluate taste preference and can be used to differentiate pediatric formulations

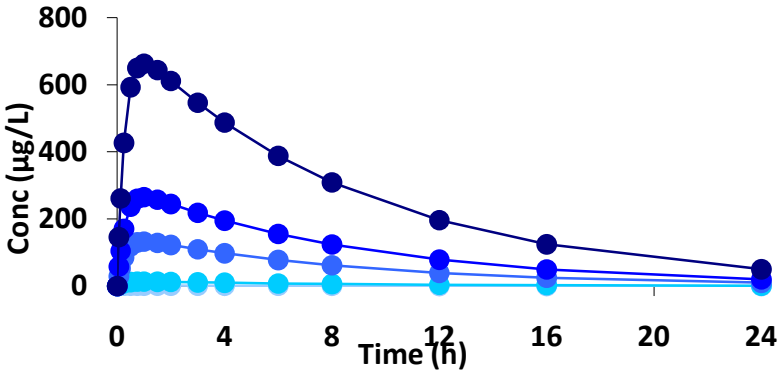
Pharmacokinetic Modeling and Simulation



Pharmacokinetic modeling of animal PK

- o Mice to Monkey
  - o 1 comp / 2 comp models
  - o Determine CL & Vd
  - o Allometric scaling
  - o Predict human CL & Vd
  - o Species difference in metabolism
  - o IVIVE (In-vitro In-vivo extrapolation)
  - o Microsomes
  - o Hepatocytes
  - o Consider gut metabolism and permeability in human bioavailability prediction
  - o Simulate human PK combining CL, Vd, and Bioavailability
  - o Fix PK and Simulate PD

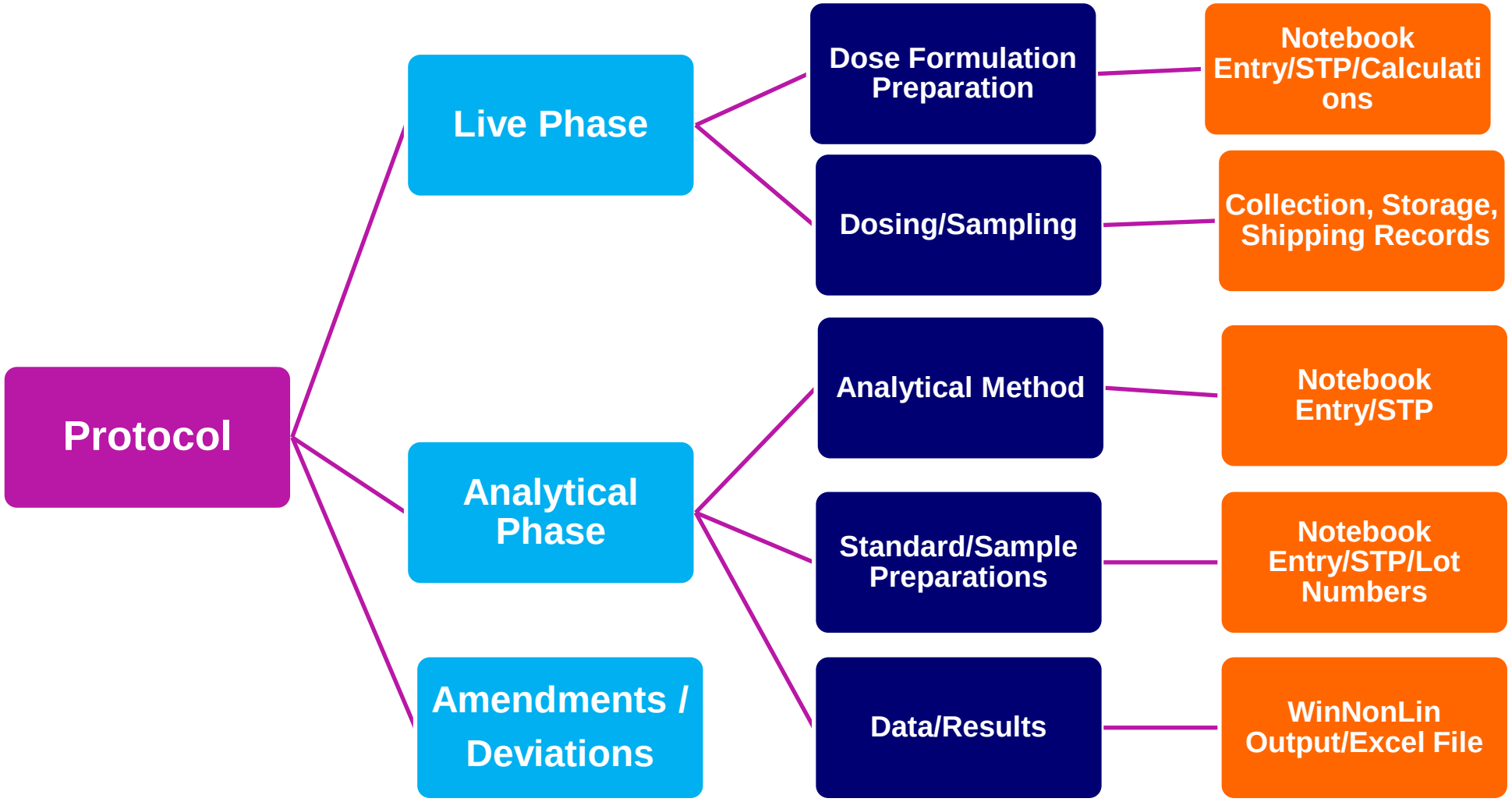




Quality Assurance

- Independent Quality Assurance team
- Quality System Procedures (QSP's) for Quality System Management and Standard Operating Procedures (SOP's) for Operation, Calibration, Maintenance of Equipment's
- Accredited by ISO/IEC 17025:2005 Quality System since 2005
- Document and Data Control, Conducting Internal Audits, Study Specific Audits
- Dedicated Archive facility for the retention of the records
- Facility audited and approved by many global pharmaceutical companies and majority of Indian Pharma Companies
- Integrity of studies is maintained by following critical components of GLP compliance like SOP, test and control article handling, data handling, training documents, archives etc.

Flow Scheme



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