JUBILANT BIOSYS

DMPK, Preformulation and Toxicology Expertise

Jubilant Life Sciences – An Integrated Global Life Sciences Company

JUBILANT PHARMA | JUBILANT LIFESCIENCES | JUBILANT BIOSYS

- A publicly listed integrated global pharmaceutical & life sciences company
- Jubilant Life Sciences revenue for FY'19 $ 1,310 Mn

Life Science Ingredients

Specialty Intermediates
- Advance Intermediates
- Fine Ingredients
- Crop Science Ingredients

Nutritional Products
- Vitamins
- Animal Nutrition

Life Science Chemicals
- Life Science Chemicals
- Ethanol & Specialty Gases

Pharmaceuticals

Generics
- API's
- Dosage Formulations
- Indian Branded Pharmaceuticals

Specialty Pharmaceuticals
- CMO-Sterile Injectable
- Radiopharmaceuticals
- Allergy Therapy Products

Drug Discovery and Development Solutions

- Drug Discovery Services
- Development: GMP and Non-GMP NCE supply
- Integrated Discovery Collaborations
- Proprietary Innovation Assets for out-licensing
- Machine Learning

Jubilant Biosys: an Innovation Driven CRO…

Company	Founded in 2000; part of Jubilant Life Sciences
Employees	750+ employees. Most PhDs have >10 years of US/EU experience
Customers	Global top 10, mid-size and virtual pharmaceutical and biotech companies
Track Record	Delivered over 75 integrated projects

Bangalore, India

Integrated discovery capabilities from target to clinical candidate and Digital Drug Discovery Services

Noida, India

Pre-clinical Chemistry capabilities including GMP and Scale-up

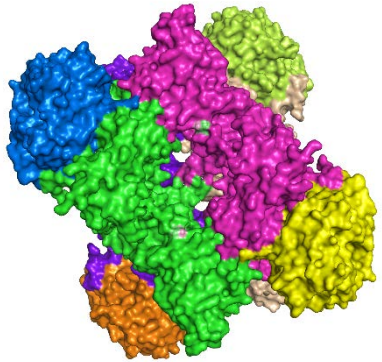
Integration of Discovery Process Designed for Speed

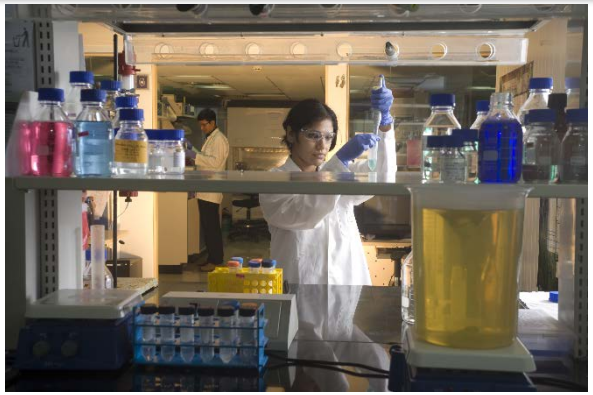
- Structural Biology (Protein Science, Crystallography)
- Medicinal and Computational Chemistry
- Screening & Profiling
- Early ADMET & PK
- *In vitro* / *In vivo* Pharmacology

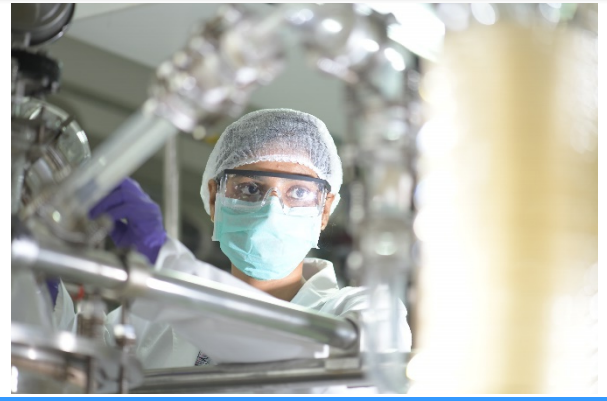
- Medicinal Chemistry
- DMPK
- SBDD (Co-crystallization, Computational Modelling)
- Target Engagement & Disease Models
- Safety Profile
- Pre-formulation

- Process Development
- Scale-up & GMP API Supply
- Genotox
- Non-GLP & GLP Tox
- D2M Predictions (WinNonlin)

Target to Lead Generation → **Lead Optimization** → **Candidate Selection (IND)**



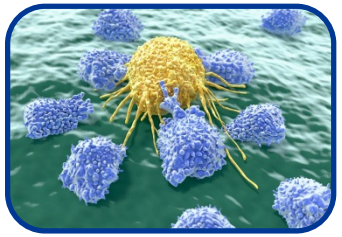


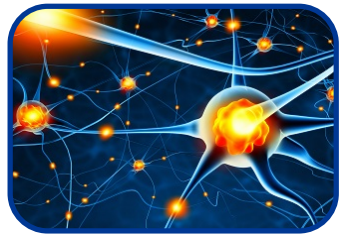
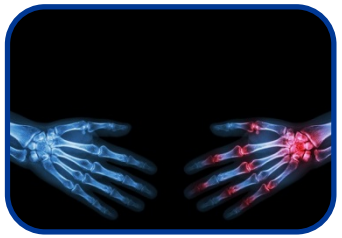


Gained experience through a broad portfolio of programs which drive successful outcomes

Disease Biology Expertise

Oncology	Metabolic Disorder	CNS	Pain & Inflammation (P&I)



Kinase

20 + Programs

GPCR

15 + Programs

Enzyme

15 + Programs

Non Enzymatic

15 + Programs

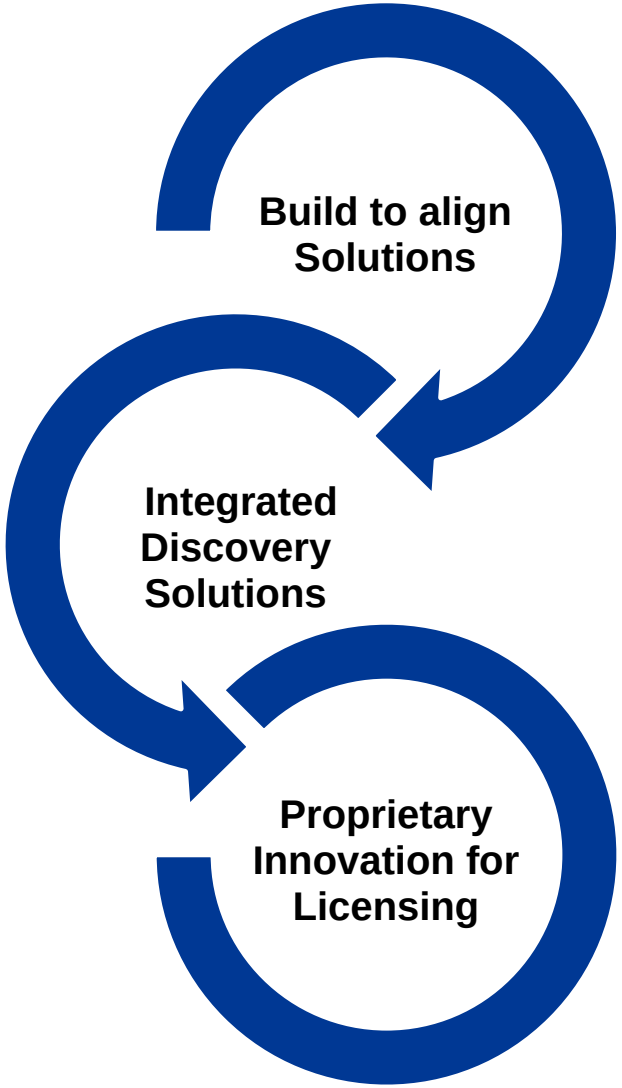
TV → Target to Hit → Hit to Lead → Lead Op → Candidate ID → Ph I / II

Why Jubilant Biosys?

"We share your passion of Drug Discovery & Development"

- ✓ **A highly experienced scientific team; delivered >75 integrated discovery programs**
- ✓ **New technologies applied to accelerate drug discovery and improve decision-making quality**
- ✓ **A boutique CRO with a talented team of >550 scientists giving your program priority**
- ✓ **Investing in the future of drug discovery and development through expansion**
- ✓ **Leadership with global pedigree in US, EU and Japan**

JDDS Flexible Business Models
Sustainable Innovation & Outcomes to Our Partners



Discovery, Preclinical & Clinical Solutions (FTE / FFS)

Medicinal Chemistry, Structural Biology, Molecular Modeling, Discovery Biology, Pharmacology, Bioinformatics, Bio analysis, Toxicology (GLP / non GLP), Scale-up, cGMP, Synthetic chemistry

Jubilant Shared risk for Integrated Drug Discovery Programs

Focused across Therapeutic areas– Oncology, CNS , MD and P&I

Target to Preclinical Candidate, Candidate to POC

Jubilant Innovation for Licensing / Partnerships

Proprietary drug discovery programs funded by Jubilant to create small molecule assets (up to IND) to be partnered or licensed to our clients

DMPK Services – Reliable, High Quality Data with Quick Turnaround Time

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Absorption

Permeability

- Caco-2 (A→B and B→A)
- PAMPA; MDCK-MDR-1

Solubility

- Aqueous (various pH)
- SGF and SIF

Pharmacokinetics

- Mice, Rats, Rabbits, Guinea pigs, Hamsters
- Dogs (outsourced)
- Cassette dosing
- Microsampling in mice
- Dose escalation studies
- DBS (dried blood spot)

Distribution

Protein binding

- Equilibrium dialysis (ED) method to determine fu in plasma, tumor & brain
- Ultra filtration

Tissue distribution

- In Rats (using cold compound)

Cross functional activities

- PK-PD
- Toxicokinetics
- D2M prediction
- Preclinical formulation

Metabolism

Metabolic stability

- Liver microsomes
- S-9 fractions and Hepatocytes

CYP

- CYP inhibition
- CYP induction

Metabolite ID

- *In vitro* using liver microsomes, hepatocytes
- *In vivo* from plasma, bile, urine and feces
- Glutathione trapping
- Blood/plasma partitioning
- Time dependent inhibition
- Plasma and Chemical stability

Excretion

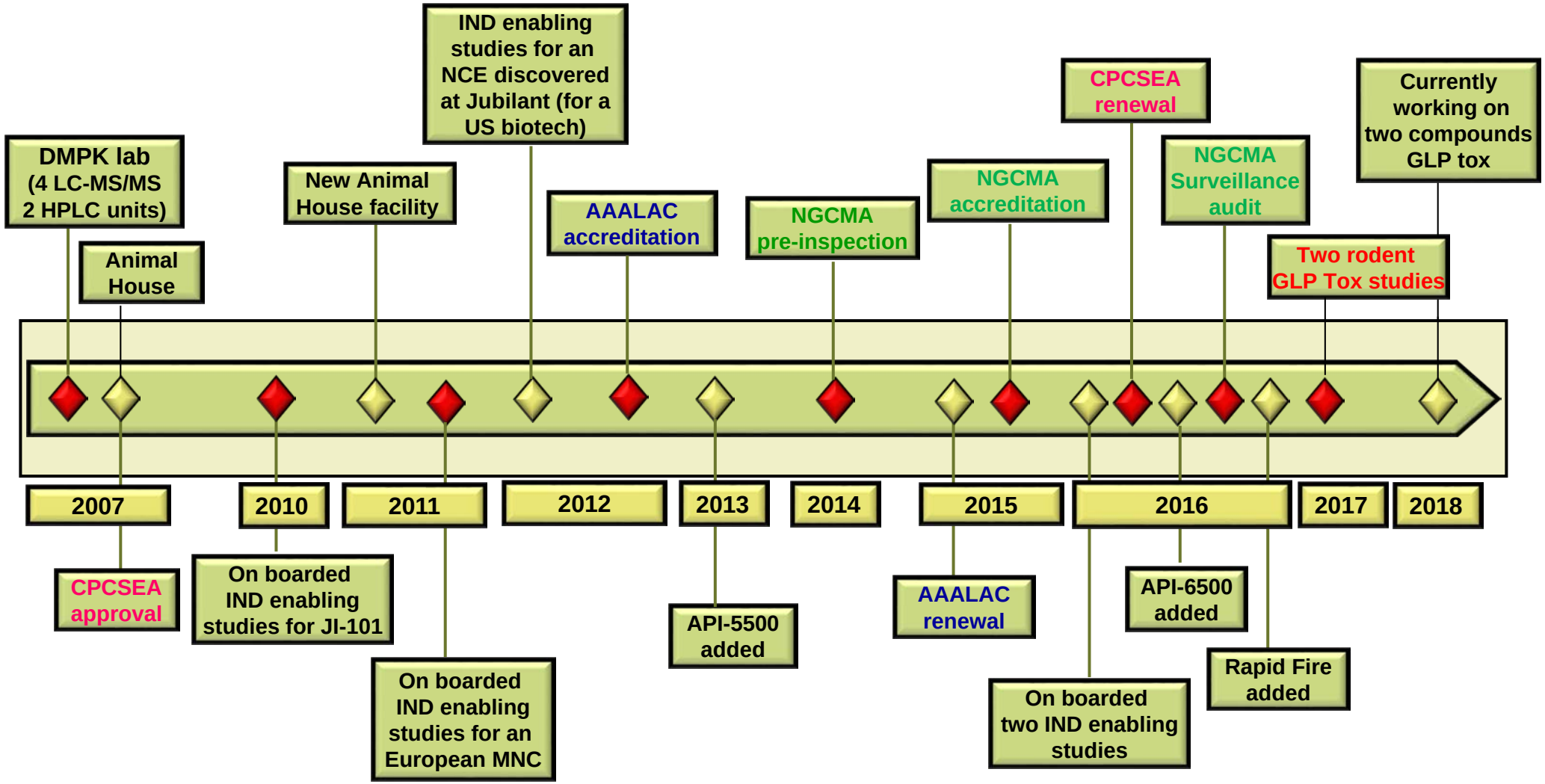
Mass balance (metabolic cages)

Biliary and Urinary excretion

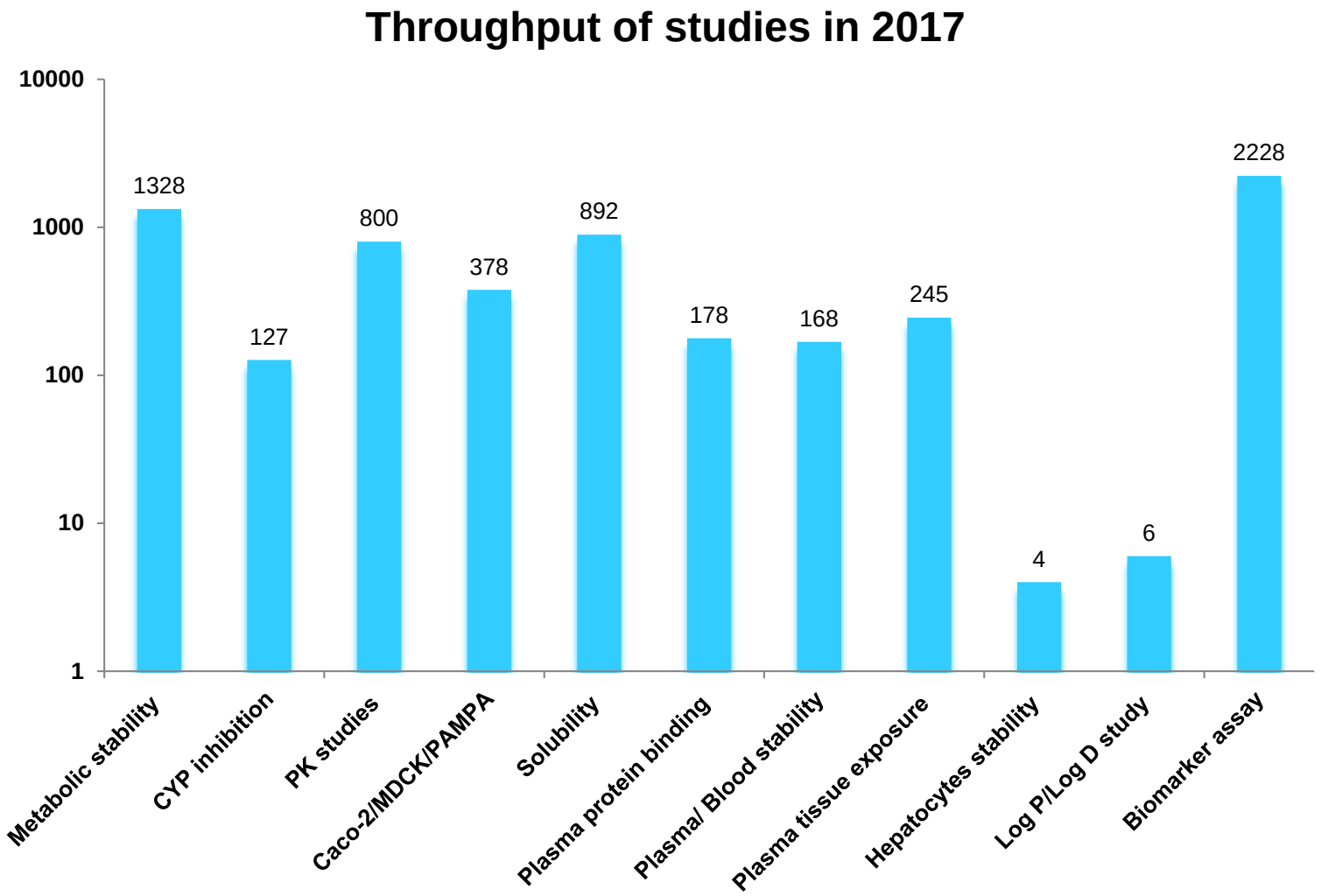
Turnaround time

- 5-6 Days most of the *in vitro* studies
- 6-7 Days for IV and oral PK study

Road map - DMPK and Tox



Demonstrated Expertise in Reliable Time Bound Deliverables - Throughput of Studies in 2017



Instrumentation and Software

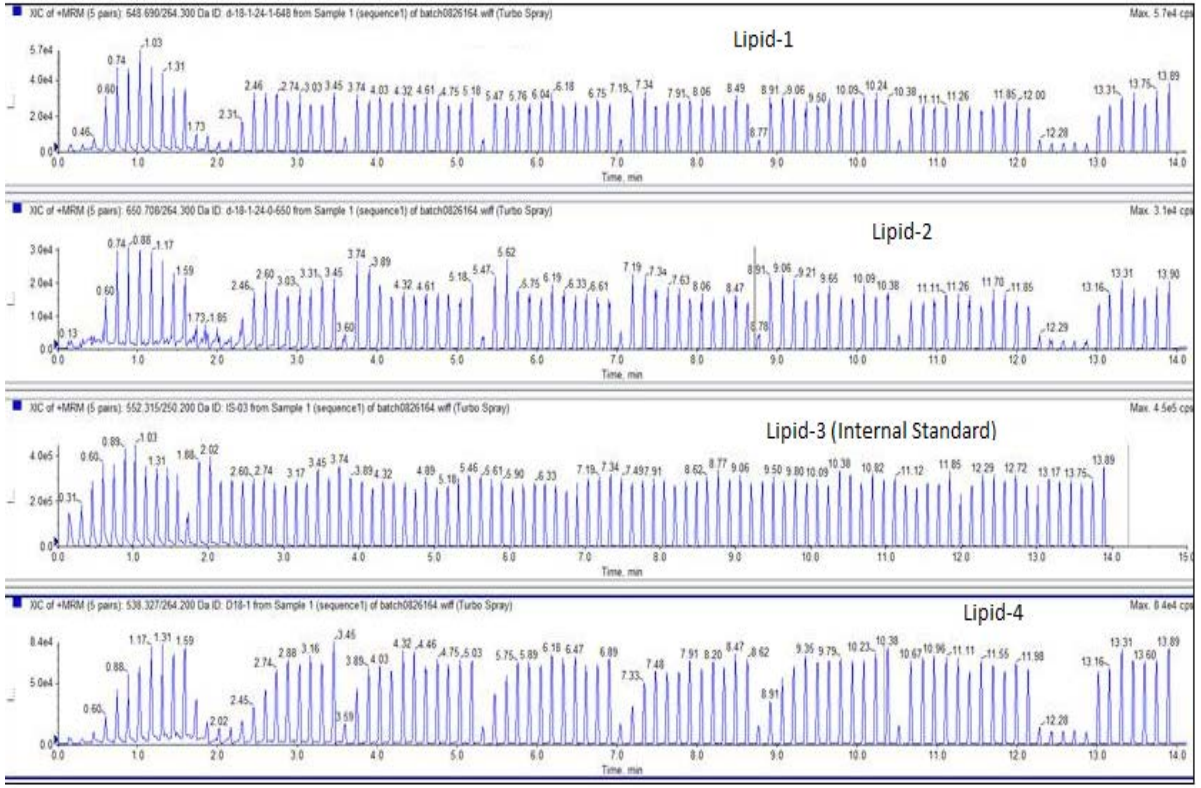
- Six LC-MS/MS instruments (API-6500, API-5500, API-4000: 2; Thermo Ultra and API-4000 Q-Trap with UPLC)
- Two HPLC units
- Nitrogen evaporators
- Refrigerated centrifuges
- Deep freezers (-80°C and -20°C)
- Freeze-drier
- Tissue homogenizer
- Franz Diffusion cell
- Shaking water bath (Julabo)
- CO_2 incubator
- Genevac evaporator (to remove DMSO)
- Microbalances with printer
- Positive pressure SPE
- Vacuum manifolds with pump
- Ultrasonicator
- Milli-Q water system
- UPS and Standby Generator

- Franz diffusion cells – Skin permeation
- RapidFire – For library screening

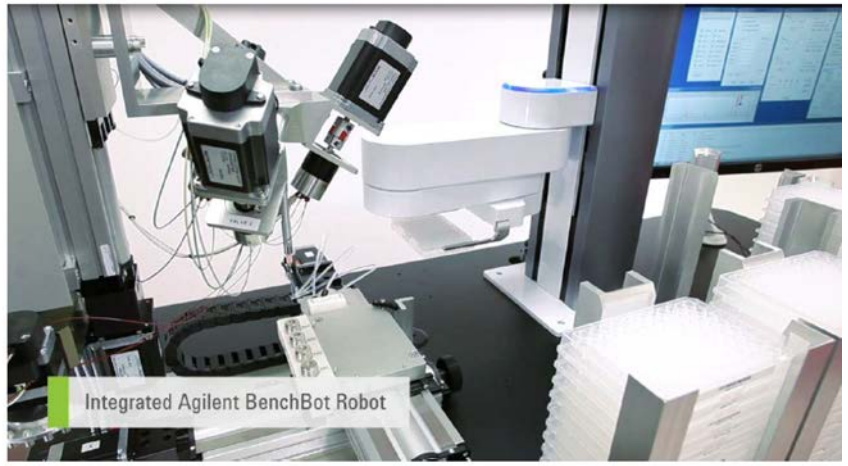
- WinNonlin
- Graphpad Prism
- Galileo LIMS
- LightSight software for MetID
- Automaton (method development)

RapidFire Screening System

RapidFire – 96 well throughput screening with a run time of 15 minutes (4 analytes)



RapidFire 365 – new plate handling



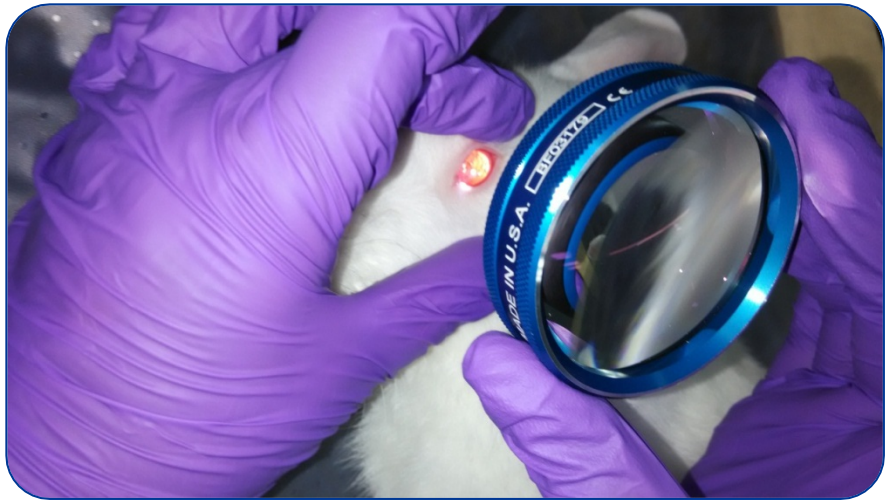
- **First in India to install state-of-the-art RapidFire high-throughput screening system**
- **Ensures reliable, high quality data with quick turn around time**

In vivo Pharmacokinetics

	Rodent	Dog	Monkey
Species	Mice (C57BL/6, BALB/c, Nude, SCID, SAM) and Rat (Sprague Dawley, Wistar)	Beagle dog (tie-up with PalamurBio, Mahaboobnagar, Hyderabad and Vimta Labs, Hyderabad)	Cynomolgus (Southern Research Inst, USA; Covance, China)
Animal Source	Vivo Bio Tech, Hyderabad; Reliance, Mumbai; RCC; Harlan and Charles River	Breeding and colony maintained at Palamur Bio by Isoquimen, Spain.	Details will be provided on request
Routes of administration	Oral, Intravenous, Subcutaneous, Intraperitoneal, Perfusion etc. Capability to cannulate bile duct, portal vein, urinary bladder etc.		
Blood sampling	Retro-orbital /Tail vein / Jugular Vein (100 µL)	Jugular Vein and Radial Vein (0.5 to 1 mL)	
Regimen	Single or Repeated (4/7/14/28-day) dosing		
Time points	0.08 or 0.17 (IV only), 0.25, 0.5, 1, 2, 4, 8, 10 (PO only) and 24 h		
Matrix for analysis	Plasma in case of PK studies (in rodents, dog and monkey). In case of rodents we can analyze NCE concentration in all tissues including brain		
Turnaround time	5-6 days (PO + IV)	7 days (per route)	Will be provided on request
Current capacity	20 compounds/week	Will be provided on request	

Ocular Studies in Rats and Rabbits

- Animal species
  - Rats (Sprague Dawley and Wistar)
  - Rabbits (New Zealand white)
- Route(s) of administration
  - Intravitreal, intracameral and topical
- Dose volume
  - 25-50 µL/eye (rabbits) and 5 µL/eye (rats)
- Duration of study
  - One day to two weeks
- Tissues collected
  - Aqueous humor, vitreous humor, retina + choroid, iris ciliary body, sclera, cornea and rest of the eye along with plasma
- Bioanalysis
  - On Sciex (API-4000/API-5500/API-6500)



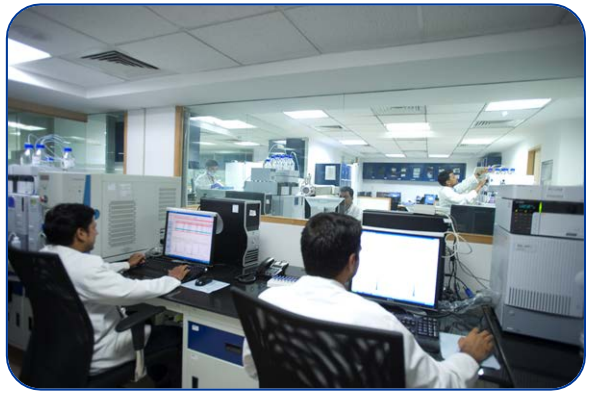
Turnaround Time for Various DMPK Studies

S.No	Study title	Turn around time
1	Solubility in PBS, SGF, FaSSIF, FeSSIF	5-6 days
2	Metabolic stability in microsomes	5-6 days
3	CYP liability	5-6 days
4	Protein binding	5-6 days
5	Caco-2/MDCK-MDR-1/PAMPA assay	6-7 days
6	Stability in plasma/Chemical stability	5-6 days
7	Reactive metabolite study	5-6 days
8	*In vivo* PK in rodents	6-7 days
9	Tissue distribution	10 days
10	Biliary excretion	10 days
11	Bioanalytical method validation	15 days
12	Met-ID	15 days
13	CYP profiling	5-6 days
14	Time dependent inhibition	5-6 days

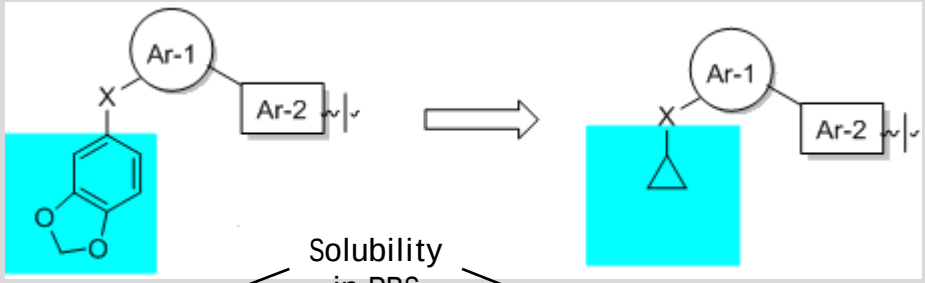
Turnaround time can differ with respect to number of compounds

Expertise in Bioanalysis

- Strong bioanalytical team with capabilities to enable fit-for-purpose and/or full validated HPLC and LC-MS/MS methods
- Wide range of in vitro and in vivo assays
- Expertise in handling various matrices (plasma, blood, bile, urine, feces and various tissues)
- Array of sampling processing techniques like precipitation, liquid-liquid extraction, solid-phase extraction and derivatization process
- Enabled highly sensitive methods (pg/mL as LLOQ) for several client programs
- Developed fit-for-purpose bioanalytical methods for various biomarkers (to support efficacy / target engagement studies)
- Chiral separations
- Cassette analysis
- Prodrug analysis



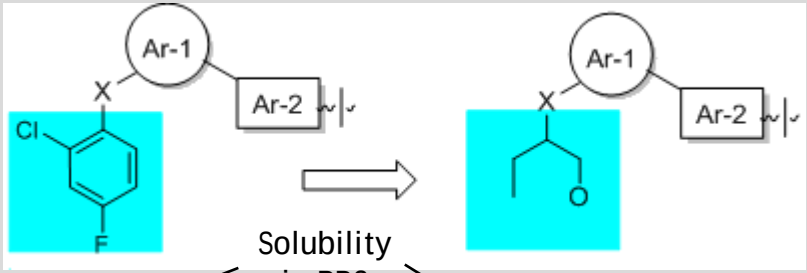
Increasing Solubility, Addressing Metabolic Stability and Permeability



Solubility in PBS

< 1 µM

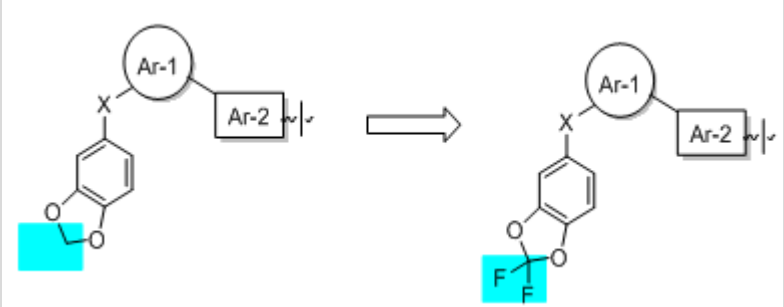
121 µM



Solubility in PBS

7 µM

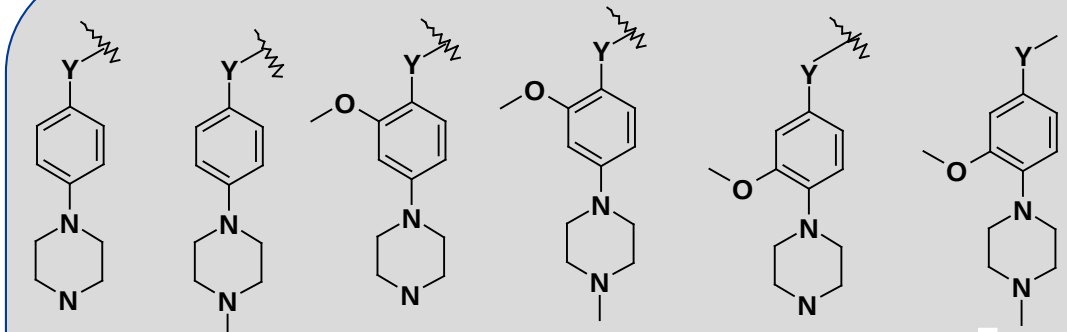
368 µM



NCE-A

NCE-B

	NCE-A	NCE-B
% Remained in MLM	<5	90
% Remained in RLM	<5	41
Solubility	7.0	7.0



Caco-2 data	NCE-1	NCE-2	NCE-3	NCE-4	NCE-5	NCE-6
B to A / A to B	62.1/4.6	61.1/76.2	64.0/3.2	37.8/46.8	44.6/0.7	55.4/32.6
Efflux ratio	13.5	0.8	20.2	0.81	61.9	1.7

Toxicology Services

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General Toxicology (GLP/Non-GLP)

- Maximum Tolerable Dose (MTD) study
- Single dose toxicity study
- Dose range finding study
- Repeated dose toxicity study (4, 7, 14 and 28 day)
- Toxicokinetic studies

Genetic Toxicology (GLP/Non-GLP)

- Ames study / Mini-Ames study
- Micronucleus test (In vivo & In vitro)
- Chromosomal aberration test (In vivo & In vitro)

Histology Services

- Animal Necropsy and Tissue Grossing
- H & E Staining
- Special Staining
- Microscopic evaluation

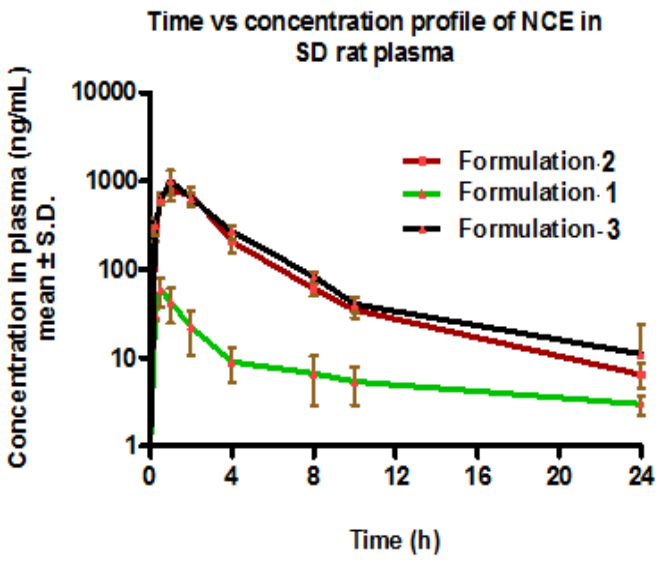
Clinical Pathology Services

- Hematology
- Clinical Chemistry
- Urinalysis
- Coagulation
- Cytopathology
- Bone Marrow Evaluation

GLP certified by National GLP-compliance Monitoring Authority (NGCMA) to conduct Toxicity studies, Genotoxicity studies and Analytical & Clinical Chemistry testing in rodents, guinea pigs and rabbits in compliance with OECD, ICH, FDA and Schedule Y.

Addressing Poor Oral Bioavailability by Pre-Formulation Approach

- **Issue**
  - Poor oral bioavailability despite having good permeability and metabolic stability
- **Action taken**
  - Compound solubility was tested at various biologically relevant pH and found that at neutral pH compound is having poor solubility (~10 µM) and it improves upon lowering the pH.
  - With the help of pre-formulation group we found out a suitable solution formulation, which helped in improving the dissolution and translated into improving the oral bioavailability.



Formulation-1 : 0.1 % Tween-80, 0.5% Methyl cellulose (suspension formulation)
Formulation-2 : 10% DMSO,15% Cremophor, 75% Milli-Q water (solution formulation)
Formulation-3 : 5% NMP, 40% PEG-200, 15% Tween-80, 40% of 20% HP-β-CD solution (solution formulation)

Formulation	$t_{1/2}$ (h)	Cmax (ng/mL)	Tmax (h)	AUC0-t (ng·h/mL)	AUC0-∞ (ng·h/mL)	% F
Formulation-1	5.78	59.1	0.50	179	211	6
Formulation-2	5.19	795	1.25	3088	3137	84
Formulation-3	3.64	1003	1.25	3347	3408	91

Office and Research Sites:

Jubilant Biosys Limited
#96, Industrial Suburb 2nd Stage,
Yeshwantpur Bangalore - 560 022
Karnataka India.
Tel. : +91 80 66628400

Jubilant Chemsys Limited
B-34, C Block, Sector 58,
Noida, Uttar Pradesh 201301
Tel: +91 120 409 3300

For More Information:

www.jubilantbiosys.com

bd@jubilantbiosys.com

Thank You for your Time

OUR PROMISE
Caring, Sharing, Growing

We will, with utmost care for the environment and society, continue to enhance value for our customers by providing innovative products and economically efficient solutions; and for our stakeholders through growth, cost effectiveness and wise investment of resources

Our Values

INSPIRE CONFIDENCE

ALWAYS STRETCH

NURTURE INNOVATION

EXCELLENT QUALITY