Pre-Clinical Division Capabilities

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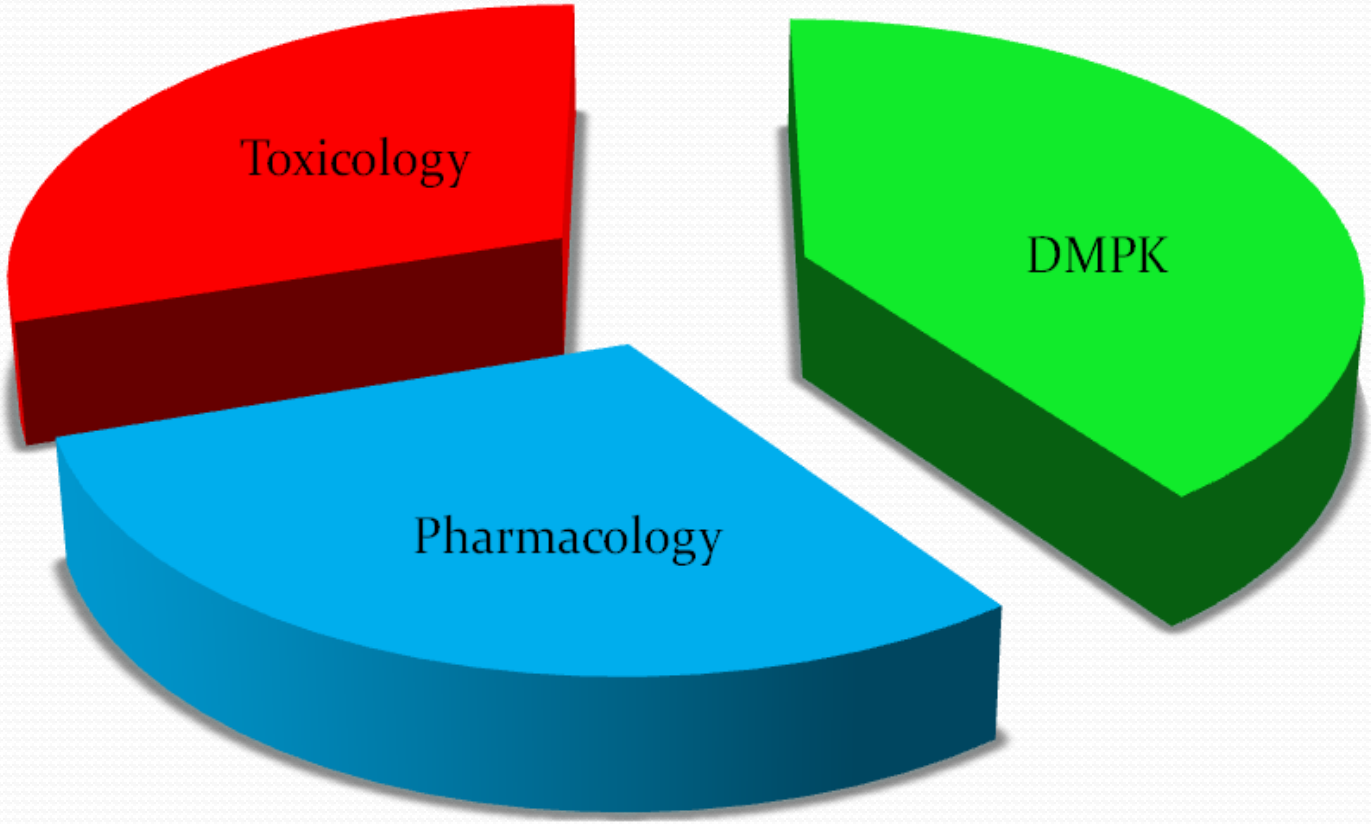
February 2010

Pre-Clinical Focus



A strategic business unit with state-of-the-art Infrastructure to facilitate multi therapeutic screening, DMPK & safety assessment services

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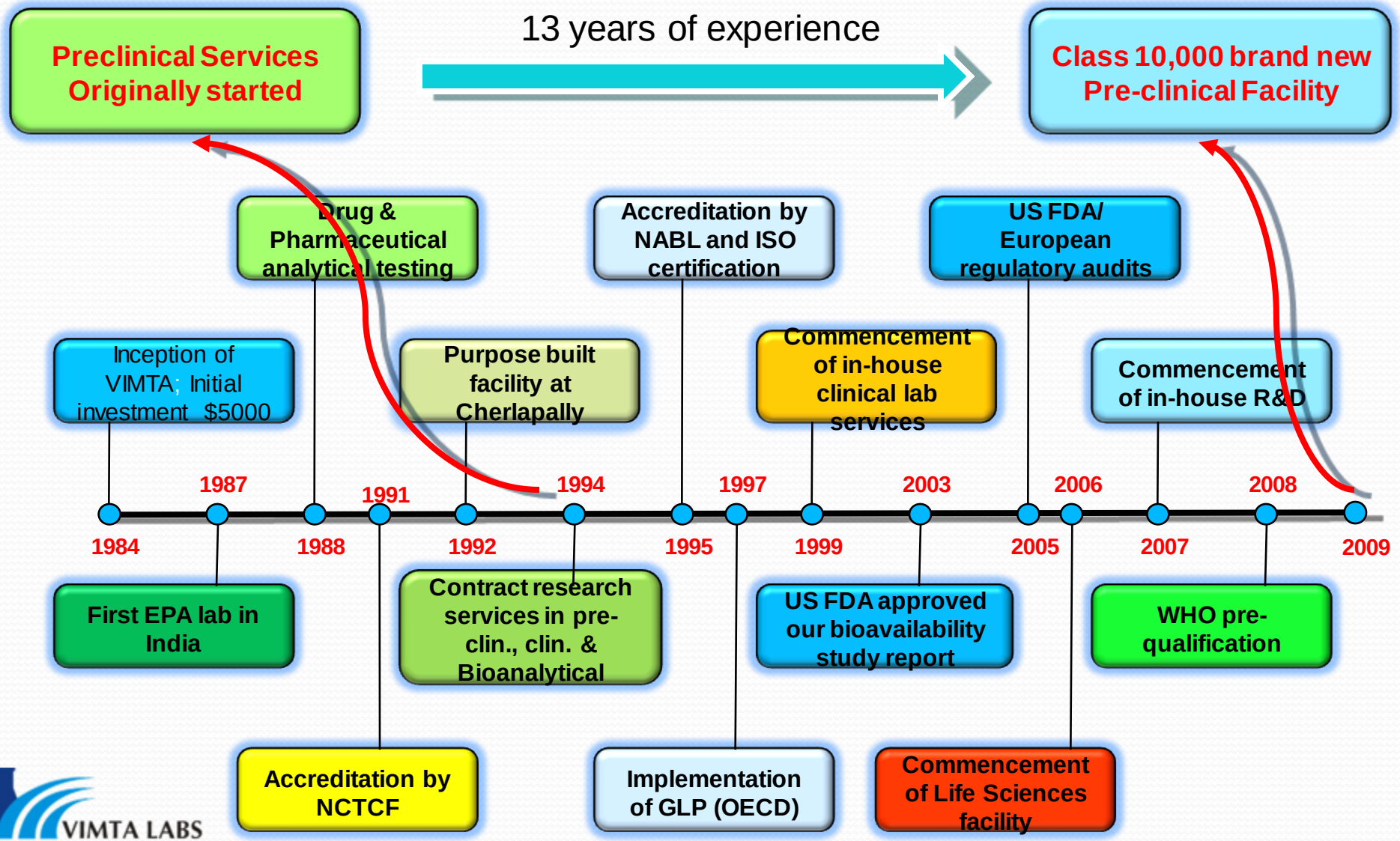
Preclinical Services - History



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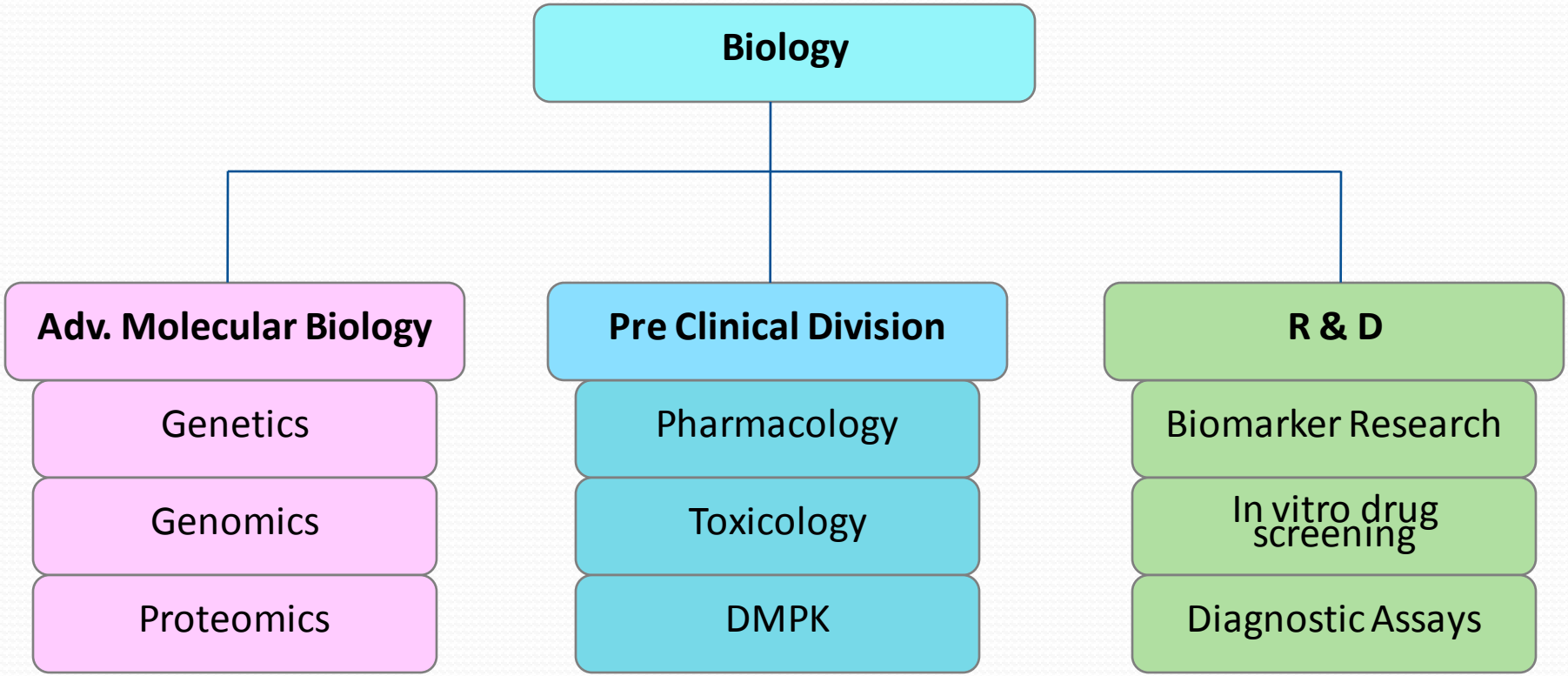
Biology Core Areas



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Business Model

- Integrated drug discovery screening support to facilitate lead identification / optimization
- Partnering on long term pre-clinical projects - Fee for service / FTE / risk sharing
- Non-GLP fast track DMPK & safety assessment for go no-go decision making
- Full fledged GLP IND-enabling DMPK, Safety pharmacology & Toxicology studies to facilitate regulatory submission

Vimta Advantage / Value Addition

- 13 Years of experience in preclinical toxicology
- Integrated preclinical support services for Pharma & Biotech companies to facilitate innovative & efficient drug discovery and development through strong quality commitments
- State of the art infrastructure
- Core competency in early and late multi therapeutic *in vitro* & *in vivo* pharmacology, DMPK, safety pharmacology & toxicity screening capabilities
- No in-house drug discovery program negating conflict of interest.
- Extending complete drug discovery solution for lead optimization & identification. Enhancing go no-go decision making for identifying drug candidates for “First in Man Studies”

Human Resources

Scientific staff	- 23
• Doctorates (Ph.D.)	- 05
• Veterinarians (BVSc/MVSc)	- 07
• Masters (MS, Pharm)	- 11
Technical staff	- 08
Lab Attendants	- 11
Total	**- 42**

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FACILITY

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Infrastructure

- A total built up area of 33,000 Sq.ft.
- Only Animal Facility in India recognised as **Green Building Facility with Gold Rating** by Indian Green Building Council (IGBC)
- 27 animal holding rooms (200 Sq.ft. each) with ante rooms and 5 procedure rooms & Separate quarantine rooms
- Separate quarantine rooms
- 48 kennels (12 Sq.ft. each)
- Segregated area for radiolabel test substances
- Facility constructed in modules of 5, 10 and 12 experimental rooms to provide dedicated space & services to customers as required
- Robust Building Management System to control environmental parameters round-the-clock through individual room sensors

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State-of-the-art Laboratory Design

- Delineated clean and return corridors with dedicated service elevators
- Animal rooms provided with individual motor controlled dampers to prevent cross contamination
- Positive pressure animal rooms with individual access controls and dynamic pass boxes
- Efficient bio-security practices

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Instrumentation

- Large animal telemetry
- Single channel patch clamp
- Whole body plethysmograph
- Autotrack
- Multiplate reader
- Diffusion cell aparatus
- Plantar test
- Digital plethysmometer
- Electron Von Frey Meter
- Randall Sellito apparatus

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Test Models

- Rodents – Rats, Mice, Guinea Pigs and Hamsters
- Beagle Dogs
- Rabbits

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Accreditations

- Registered with the Committee for the Purpose of Control & Supervision of Experiments on Animals, Govt. of India
- Animal experimental activities are governed by Institutional Animal Ethics Committee
- Formerly certified under GLP by Standard Australia Quality Assurance Services (SAQUAS)
- To seek AAALAC accreditation in Q2, 2010
- To seek Indian GLP Certification in Q4, 2010
- To seek OECD GLP Certification in Q1, 2011

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Key Personnel and Experience

- **Dr. Ranjan Chakrabarti, Sr. Vice President - Life Sciences:** 15 Years of Industrial research experience in drug discovery at Dr.Reddy's Laboratories and CRO AT GVK Biosciences Ltd; 14 years of academic experience in USA & India; 7 IND filings from Phase 1 to Phase 3; 40 U.S. patents and 50 publications.
- **Dr. Nitin Shetty, Vice President - Pre-Clinical Division:** 18 years of Industrial research experience at Ranbaxy and Wockhardt. 5 years of Academic experience in India; 20 publications and presentations
- **Dr. Sreedhara Chaganty**, **Manager-Bianalytical:** 18 years of experience in drug discovery and development in USA. Developed and validated bioanalytical methods (LC/MS/MS) for more than 150 compounds in biological matrices to support animal and human pharmacokinetics, and toxicokinetics studies, in early non-GLP and GLP. 6 Publications
- **Dr. Nandu Gattu, Vice President –In Vitro Biology:** Ph.D. (Pharmacology); 14 years of Industrial research experience in drug discovery at Schering-Plough , USA and GlaxoSmithKline, USA; 5 years of academic experience in USA; 17 patents and 16 publications

Key Personnel and Experience

- **Anil Ghate, In Charge-Animal Pharmacology:** 30 Years of experience in Drug Discovery at Pharma Majors like Hoechst , Nicholas Piramal & Dr.Reddy's. 18 patents in US & Europe and 6 publications
- **K. S. Rao, In Charge-Animal Facility:** 19 years of experience in Dr. Reddy's OECD accredited GLP Tox facility in Drug Discovery and Development
- **Dr. D.M.R. Rao, Manager-Toxicology:** 22 years of experience in both non-GLP and GLP toxicology at Vimta Labs.
- **Dr. Jomy Jose, Veternary pathologist:** 8 years experience at an AAALAC accreditated and GLP Certified CRO Advinus
- **Dr. C.R. Santosh, Veternary Pahrmacologist:** 4 years of experience in GLP Toxicology

Capabilities
Drug Metabolism & Pharmacokinetics

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In Vitro DMPK

Absorption studies

- Cell permeability assays ($Caco_2$ and MDCK cells)
- P- Glycoprotein efflux/ inhibition studies
- Parallel Artificial Membrane Permeability Assay (PAMPA)
- Skin permeability assay (Franz Diffusion cells)

Drug – Drug Interaction studies

- Cytochrome P450 Inhibition / induction studies
- IC_{50} / Ki
- Time dependent inhibition
- Metabolic CYP pathway identification

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In Vitro DMPK Contd…

Metabolic stability and identification studies

- Liver Microsomes – mouse, rat, dog, monkey and Human
- Hepatocytes – Rat and Human
- Clearance and half life determination

Physico-chemical Studies

- Solubility studies for NCE
- Determination of LogP and LogD

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In Vitro DMPK Contd…

Plasma / Whole blood studies

- Plasma Protein Binding – mouse ,rat, dog and human
- Plasma / Whole blood stability – mouse, rat, dog and human

Leveraging lead optimisation, identification & selection

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In Vivo DMPK

Fast Track non-GLP & GLP PK/TK Profiling

- Single or multiple dose (s) – in Mice, Rat and/or Dog
- Oral &/or IV (or intended) route
- 2-6 animals/dose; 5-12 time points / client specific designs
- PK study in canulated animals as per client's requirement
- Tissue distribution studies
- In -vivo blood – brain barrier penetration studies.
- Submission of encrypted results through secured electronic media
- Data generation & compilation

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In Vivo DMPK Contd…

End-points

- Oral BA (provided data on PO & IV is available)
- Elimination half life/cleavage, Clearance, Distribution vol.
- Metabolite identification
- Follow up with GLP support with tissue kinetics

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Bio-Analytical Services

- Internal bio-analytical support for in vitro & in vivo DMPK
- Proprietary method development
- Method validation
- Method transfer
- Sample analysis using HPLC / Mass Specs
- Efficient group to deliver high quality analytical data

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Bioanalytical Infrastructure

- Provided bio-analytical services to national and international customers
- Over 14 years of experience in bio-analytical analysis with more than 60 bio-analysts in the group
- 27 Mass specs covering technologies such as single quadrapole, triple quadrapole, ion trap, LC-MS/MS, MALDI/TOF/TOF, GC-MS/TOF, HRGCMS, ICP-MS
- Multiple HPLCs with PDA and fluorescence detectors
- Different matrices tested include human whole blood/plasma/serum and urine; rat plasma; dog plasma; & monkey plasma

Capabilities
Pharmacology Screens

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Animal Pharmacology Capabilities

- Pain and Inflammation
- Metabolic disorders

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Pharmacology – Pain and Inflammation

- FCA induced hyperalgesia in rats by Randall Selitto
- TNBS induced colitis in rats or mice
- Carrageenan induced paw edema in rats (Edema, Mechanical and thermal Hyperalgesia)
- LPS induced systemic inflamation model
- CIA & AIA Models (Will be ready by April'10)
- Acetic acid induced writhing in mice
- Mouse Hot Plate model
- Ovalbumin Induced COPD in G. pig (Will be ready by April'10)
- PSNL and CCI model in rats (Thermal & Mechanical Hyperalgesia; Tactile Allodynia, Incapacitance)
- Paclitaxol and STZ Induced Pain model (Will be ready by April'10)
- License to import DbA1/J mice, Lewis Rat and Brown Norway rat

Pharmacology – Metabolic Disorder Screens

In-vivo

- HFD induced obesity in rats or mice
- STZ-HFD induced Metabolic Syndrome model
- License to import Db/db, ob/ob

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Capabilities
Preclinical Safety Assessment (Toxicology)

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Safety Pharmacology

(Exploratory & Regulatory)

Cardio-vascular

- hERG cardio-vascular toxicity (Potassium and Calcium ion channels) – May'10
- Radio-telemetry in conscious dogs – June'10

Respiratory

- Rodent whole body plethysmography in rats and guinea pigs

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Preclinical Safety Assessment Services

(Exploratory & Regulatory)

Non-GLP toxicity screens (early identification of ADEs)

- MTD studies in rodents with TK
- 7-14 day DRF studies in rats
- In vitro genotoxicity studies in CHO, HL cell cultures – May'10
- Target organ toxicity studies – Hepatotox, Bone marrow suppression
- Cytotoxicity studies (using target specific or battery of cell lines)

Preclinical Safety Assessment Services- Contd.

(Exploratory & Regulatory)

Regulatory toxicity studies – Rodent & Dogs

(IND-enabling GLP Compliant)

- General
  - Single Dose , short and long term toxicity studies with toxicokinetics in mice, rats, rabbits

- Genetic toxicology
  - *In vitro* (Ames test, miconucleus test and Chromosomal (May'10) in mammalian cell lines)
  - *In vivo* (chromosomal test and micronucleus test in rats and mice) – June'10

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Preclinical Safety Assessment Services- Contd..

(Exploratory & Regulatory)

Regulatory toxicity studies (Post-IND)

- Reproductive toxicology studies (Segment-I) in rats
- Dermal irritation & Hypersensitive studies in guinea pigs/rabbits
- Local tolerance studies in rats/guinea pigs/rabbits

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Preclinical Track record

- Initial focus is on agrochemicals. Conducted many acute, repeated dose sub chronic studies, dermal irritation sensitization tests, inhalation toxicity studies, genetic tox studies and eco toxicology studies using daphnia, fish, honey bee for different agrochemicals and industrial chemicals.

- An Indian company got marketing license on Neem based pesticide from US EPA based on the data generated by Vimta.

- From 1999 focus shifted to pharmaceutical and biotech industries. Conducted toxicity studies on more than 100 bulk drug molecules as per Schedule Y of Drugs and Cosmetics Act, Government of India for marketing license.

Preclinical Track record

- Carried out efficacy and safety evaluation of New drug formulations in rodents for a US-based pharma company.
- Conducted safety studies involving both *in vitro* and *in vivo* toxicity studies on hypertensive drugs
- An Indian company got marketing license for condom samples by US FDA based on the bio-compatibility data as per ISO 10993.
- Studied effect of vas irrigation in male albino rabbits on local toxicity along with pharmacokinetics under WHO funded project

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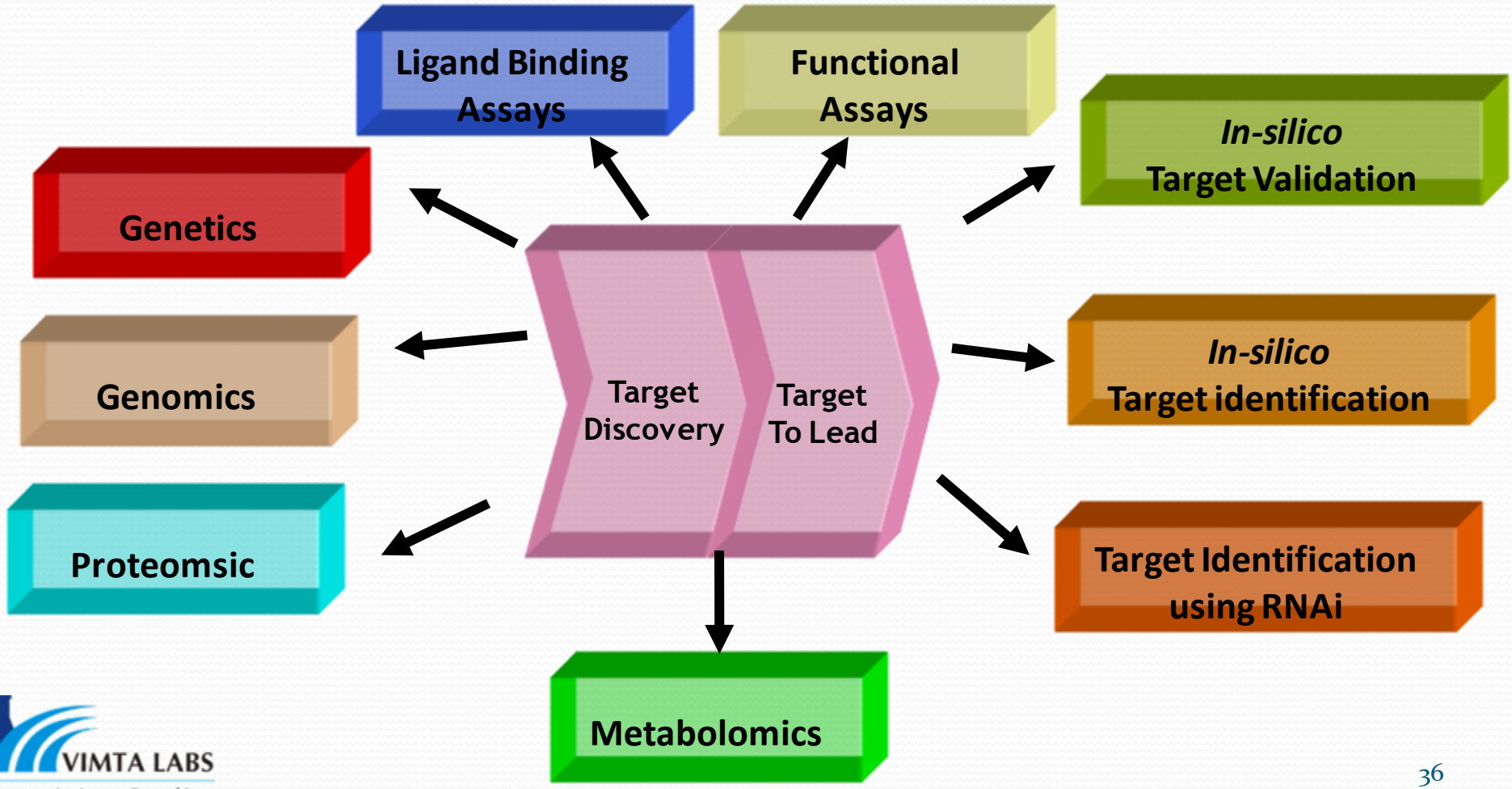
Ongoing Studies

- Efficacy studies with Recombinant biosimilars
- Efficacy studies in metabolic disorders area for International clients
- Short and Long term toxicology studies in rodents for MNCs
- Screening of NCEs in pain models for International clients
- DMPK studies for MNCs
- Genotoxicity study for national clients

Early Phase of Drug Discovery Services at VIMTA



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Thank you

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