Role of the Veterinarian In Pharma
Prologue

- Drug discovery at Pharma
- Preclinical evolution
- PK and PD
- Safety Pharmacology
- Toxicology
- Parameters to be evaluated
- Laboratory Animal Management
Drug Discovery

Drug Discovery Process

Preclinical Studies
- Research team formed and objectives set
- Novel chemicals synthesized
- Chemicals tested for efficacy and safety in test tubes and animals. Results used to choose drug candidate
- Formulation, stability scale up synthesis, chronic safety in animals
- Company files Investigational New Drug (IND) application with FDA

Clinical Studies
- Drug is approved for marketing
- FDA Reviews NDA
- Company files New Drug Application (NDA)
- Phase III: large clinical trials in many patients
- Phase II: Student in patients (efficacy)
- Phase I: Studies in healthy humans (Tolerance)
Costing

Traditional Pharmaceutical R&D
Costly* and Time Consuming**

Lead Discovery
Research
6 Years

Drug Development
8.9 Years

Target ID
Synthesis/
Screening
Target Validation
Lead Optimization

Preclinical
Ph1
Ph2
Ph3
Filed

$230m
+$71m
+56m
+169m
+169m
+44m

$739m*

*Lehman Brothers, 1997; ** Tufts CSDD
Pre-clinical Studies in Laboratory Animals

Pre-clinical Studies

New Drug (NCE)

Safe drug
Pharmacokinetic/Toxicokinetic

- Pharmacokinetics Studies
- What does the body do to the drug?
- Absorption
- Distribution
- Metabolism
- Excretion
Pharmacodynamics studies

What does the drug do to the body?

Drug actions at receptor sites and the physiological/chemical/behavioral effects produced by these actions

- Studies of drug mechanisms of action at the molecular level
- Provides basis for rational therapeutic uses and the design of new, superior therapeutic agents
Pharmacology studies

-- Proof-of-concept studies for intended indications
-- investigate mechanism of action: primary pharmacology
-- MABEL: minimum anticipated biological effect level
-- Secondary pharmacologic effects

Safety Pharmacology studies

undesirable effects on vital functions
-- Cardiovascular
-- Neurological
-- Respiratory
-- GI & renal
**Toxicology:**
A science of studying adverse/toxic effects of chemical agents on biological system

**Pre-clinical Toxicology (Safety Evaluation):**
To evaluate safety of a “Candidate-Drug”, in *in vivo* or *in-vitro* test systems to ascertain its safety for human consumption

**Paracelsus: (1493-1541)** has said that “All things are poisons. It is the dose, that differentiates between poison and remedy”

And the Toxicologist shows that difference!
New Drug to Investigational New Drug Application (IND)

(New Chemical)

Efficacy Studies in Animal Models to Find a Lead Molecule

Toxicology/Safety Evaluation with TK on Lead Molecule

Single dose LD50 in Rats & Mice

Genetic toxicology- (Ames, CA & Micronucleus)

14-30-day Daily Repeat-Dose Toxicity Study in Rats on Candidate-Drug

14-30-Day Daily Repeat-Dose Toxicity Study in Dogs on Candidate-Drug

‘Investigational New Drug’ Application (IND) to get permission of ‘FIM’
IND to New Drug Application (NDA) for Marketing Permission

Clinical Trials

Phase: I Safety and PK (~100 healthy volunteers)

Phase: II Efficacy, Safety and PK (~500 patients)

Phase: III Confirm efficacy and Long term safety (~5000 patients)

3-Months Daily Repeat-Dose Study in M & F Rats and Dogs with TK

6-Months/1-year Daily Repeat Dose Study In M & F Rats & Dogs with TK

Reproduction Toxicology: Seg I, II, III with TK and 2-year Carci-studies in M & F rats & mice with TK

‘NDA’ for Marketing Permission
Parameters to be Evaluated

- Selection of Breeding pair, Breeding, Pre and post natal care, Health monitoring of Laboratory Animal
- Proper handling and sample collection technique in laboratory animals
- Dose formulation and administration by different routes
- Daily careful symptom-records
- Blood withdrawal for clinical chemistry evaluations
- Electrocardiography (ECG)
- Ophthalmoscopy
- Necropsy techniques and gross pathology
- Correct diagnosis and interpretation of histopathological lesions of several hundred organs
- Final judgment of go/no go decision for FIM studies
Questions / Discussion
Role of Veterinarian: A multidisciplinary science

- Veterinarian
- Toxicologist
- Pharmacologist
- Histopathologist
- LAR management
- Clinical Pathologist
- LAR Healthmonitoring
Laboratory Animal Breeding Facility:

It acts as a supplier of animals for preclinical studies*. Hence, it should have a quality certification (e.g. AAALAC**) to ensure high quality animal supply. The facility should be as per NIH guidelines in following areas:

- Construction, environment, housing, temp & RH, separation of species, sanitation, cages, feed, water, veterinary care, personnel qualifications, training, health and safety, animal procurements, transportation, quarantine, etc.

*Animals are raw material of biologists, its quality must be assured
**Association for Assessment & Accreditation of Lab Animal Care
DIVISION OF LABORATORY ANIMAL SCIENCES
Pharmacologist

- Animal and Dose Selection,
- Efficacy studies,
- PK and PD studies,
- Model Development
- Safety evaluation by Telemetry studies for CNS, CVS, Respiratory studies

- Cardiovascular system: pigs, dogs, primates
- Skin: pigs, primates
- Eye: rabbits, dogs
Toxicologist

- Dose Selection
- MTD, DRF, Repeated Toxicity studies from Day 1-2 year I Rat, Mice, Rabbit, Dog
- Genotox (MNT, CA studies)
- Reproductive tox studies (segment 1, 2, 3)
- IND-NDA filing Briefing Package and CTD
- Final judgment of go/no go decision for FIM studies
Hematology and coagulation
Clinical chemistry
Urinalysis and urine chemistry
Evolution of Clinical hematology and chemistry data of different Pharmacology and Toxicology studies
By interpretation of Clinical pathology help in dose selection and study report preparation.
To assist in NOAEL, NOEL, LOAEL establishment.
Histo-Pathologist

This is a very specialized job and requires an experienced and qualified Veterinary pathologist, who can evaluate microscopic histopathological lesions.

**Pathologist decides the fate of drug by:**

Identifying microscopic pathological lesions in organ/s. Relationship of the lesions with treatment of NCE. Making a final decision if organ toxicity observed was acceptable or not to take the drug to man.
1. Institutional Animal Ethics Committee (IAEC) has recommended and the Committee for the Purpose of Control and Supervision of Experiment on Animals (CPCSEA) has approved the Project proposal.

2. AAALAC: Association for Assessment and Accreditation of Laboratory Animal Care is committed to enhancing animal welfare


4. 21 CFR Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies (April 1, 2004).

5. OECD Principles on Good Laboratory Practice, Number 1 (revised in 1997), OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring.


8. ‘The preclinical development studies performed with TGN1412 did not predict a safe dose for use in humans, even though current regulatory requirements were met’

9. Jan. 2007 - Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) announced that a guideline would be created ‘Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products’ was final July 19, 2007 Application to both biologics and NCEs.
Thank You
for Your Attention
Frequency (Hz) and magnitude/intensity (decibels of sounds cause changes in air pressure)

Human detects sound frequencies from 20 Hz to 20 kHz. Animals detects sounds inaudible to man as shown bellow.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Frequency Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>0.04 Hz - 46 kHz</td>
</tr>
<tr>
<td>Rhesus Monkey</td>
<td>0.13 Hz - 45 kHz</td>
</tr>
<tr>
<td>Rat</td>
<td>0.25 Hz - 76 kHz</td>
</tr>
<tr>
<td>Mouse</td>
<td>0.80 Hz - 100 kHz</td>
</tr>
</tbody>
</table>

Adverse effects of sound reported, in lab animals, are: Food and water intake, weight loss, blood pressure, reproduction, teratogenicity, ECG, behavioral parameters, glucose metabolism and immune function.

Noise, excessive movement and any other alterations in the environment increase cannibalism in most rodents.