Prof Mandeep Kaur

- Consultation times:
- Monday: 11:30- 12:00
- Wednesday: 12:00- 13:00

Mandeep.kaur@wits.ac.za

Office: GateHouse- 508

Practical reports to be submitted in the box at ground floor of MCB in GateHouse on the due date or handed-over to your TA before leaving the lab, as announced.

Basic principles of drug discovery and development [electronic resource] / Benjamin E. Blass.

Author **Blass, Benjamin, author.**
Title **Basic principles of drug discovery and development [electronic resource] / Benjamin E. Blass.**
Shelf # RM 301.25 BLA
Imprint **London, UK : Elsevier/AP, [2015]**
©2015

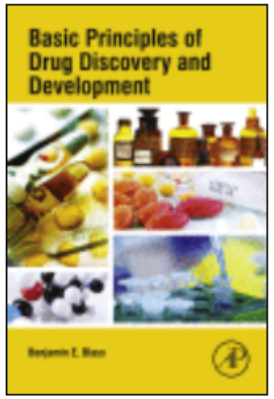
Connect to
this title online. Multiple user license.

Copies

LOCATION	SHELF NO	STATUS
ONLINE (Bib)	**RM 301.25 BLA**	ONLINE

1 copy being processed for Biophy Library.

Description 1 online resource
Note Online resource; title from PDF title page (EBSCO, viewed April 29, 2015).
Subject **Drug development.**
Drugs -- Design.
ISBN 9780124115255
012411525X



Basic Principles of Drug Discovery and Development

Author(s):
Benjamin Blass
ISBN: 978-0-12-411508-8

Add to Favorites

Table of Contents

Download PDFs | Export

Lecture and practical Schedule	Date
Lecture -1-2, Drug Discovery process, Methods and Principles	12th September
Lecture- 3-4, Methods and Principles, How do drugs work	13th
Methods and Principles and Introduction to practical 1	14th
Practical -1	17th
Lecture 5-6, How do drugs work	19th
Lecture 7-8, How do drugs work	20th
Lecture 9	21st
Public holiday	24th
Lecture 10-11, Cell culturing, Screening Assays	26th
Lecture 12-13, Medicinal Chemistry	27th
Lecture 14, Intro to practical-2	28th
Practical -2	01st October
Lecture 14-16, Animal Models	03rd
Lecture 17-18, Apoptosis	04th
Lecture 19, Intro to practical 3	05th
Practical -3	08th
Revision	10th
Test	11th
Lecture 22- Drug Approvals and IP	12th
Lecture 23- Drug toxicity, Pharmacogenetics and use of translational biomarkers	15th
ADME	17th
ADME	18th
ADME	19th
Revision	22nd

Drug Discovery Learning Outcomes

Background of drug discovery and development

- Understand the broader concept of drug discovery and development.
- Explain different stages of drug development.
- Summarize methods and principles involved in the drug discovery process.
- Discuss the processes involved in target selection and hit identification.
- Compare properties of drug molecules to identify the clinical candidate.
- Explain different phases of clinical trials.
- Demonstrate knowledge of drug approval process.
- Use in silico example to demonstrate different phases of drug development.

Drug Discovery Learning Outcomes

Mechanisms of action of drugs

- Define the term ‘druggable target’.
- Summarize known key drug targets (enzymes, GPCR, Ion channels, transporters) of drugs in the cell.
- Explain enzymatic mechanisms involved in drug action including substrate binding, enzyme catalysis etc.
- Show with diagrams how enzyme inhibitors work.
- Compare competitive and non-competitive inhibitors.
- Explain receptors and their functions.
- Explain structure of GPCRs and signalling pathways involved in their action.
- Summarize cAMP and IP_3 signaling pathways.
- Explain biology behind drug-receptor interactions
- Explain and compare agonists, antagonists with examples.
- Explain structure, function and gating mechanisms of Ion channels.
- List ways to modulate activity of ion channels.
- Define membrane transporter proteins.
- Differentiate between membrane transporter proteins and ion channels.
- Describe mechanisms involved in transporter inhibition by drugs.
- Explain therapeutic index.

Drug Discovery Learning Outcomes

Drug molecule screening methods including cell culturing

- Define bioassays and assay development.
- Differentiate between primary assays and secondary assays during drug screening process.
- Understand and differentiate between in vitro and in vivo screenings methods.
- Demonstrate understanding of biochemical and cell-based assays.
- Identify causes of assay variation.
- Explain high throughput screening methods.
- Underline importance of miniaturization and automation in drug screening.
- Comprehend mammalian cell culturing methods, instruments, and safety guidelines for performing cell-based assays in laboratory.
- Demonstrate knowledge of statistical parameters used during high throughput screening methods.
- Perform cell-based assays such as cell growth inhibition using trypan blue and cell death using apoptosis assay.
- Perform throughput assay in 96-well plate after treating cells with different concentrations of the test compounds.
- Perform statistical analysis to calculate percentage if viable cells after drug treatments, generate graphs based on data obtained.

Drug Discovery Learning Outcomes

Fate of a drug and Pharmacokinetics

- Outline the fate of drug in the body from intake till excretion.
- Differentiate between pharmacokinetics and pharmacodynamics.
- Explain ADME (Absorption, Distribution, metabolism and Excretion) processes.
- Explain with examples the physiological effects of ADME.
- List different enzyme involved in drug metabolism such as CYP450.
- Define terms related to drug such as clearance, volume of distribution, half-life and bioavailability.

Drug Discovery Learning Outcomes

Concepts involved in drug toxicity, Pharmacogenetics and use of translational biomarkers

- Define maximum tolerable dose of a compound.
- List types of toxicities (cardiac, liver, nervous system etc.) with examples.
- Explain why different individuals respond differently when given same drug.
- Define pharmacogenetics with example.
- Define the term ‘Biomarker’.
- Demonstrate knowledge of use of biomarkers to advance drug development process.

Drug approval

- Demonstrate understanding of the drug approval process
- Understand intellectual property issues around drug development.

From The Lab To Your Medicine Cabinet:

A Pharmaceutical Drug's Journey

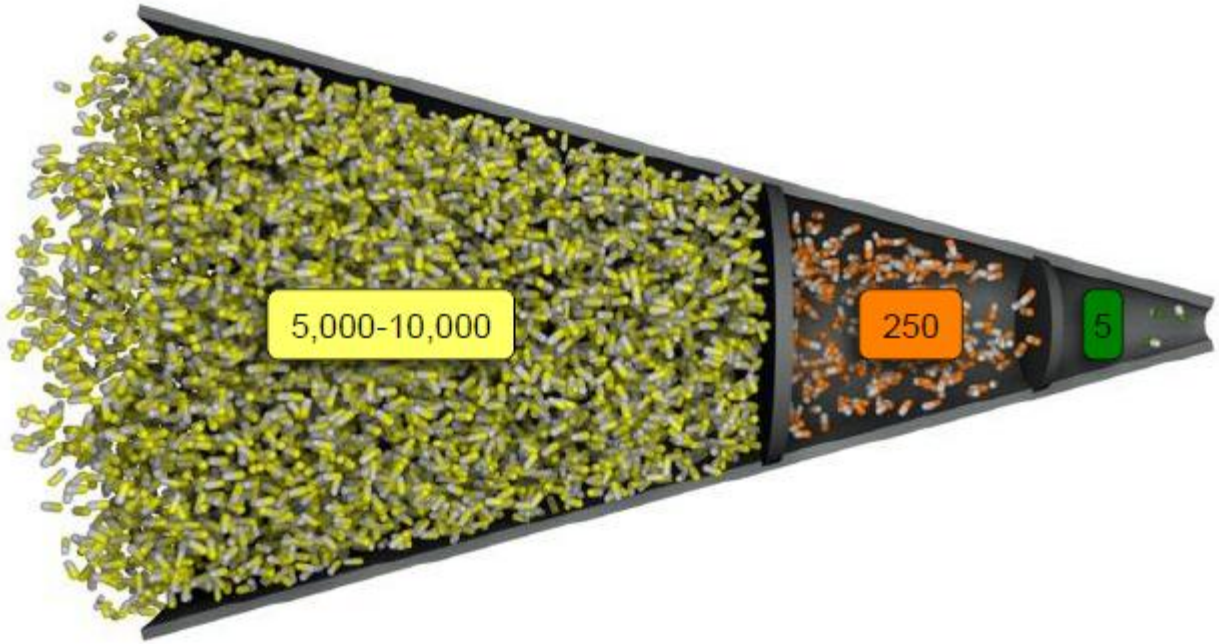
Courtesy

Dr. Steven Hansel
Sr. Director; Pfizer

Drug Repurposing

	Novel Drug	Drug Repositioning	Drug Repurposing
Cost	>$1 Billion	$300 Million	$ 250K
Time to Get to Market	13-15 Years	6.5 years	3 Years
Success Rate	1 in 10,000	4 in 10	3 in 10

The Drug Development Process



- The development process is difficult, time consuming, and expensive
- Project teams = key functional unit
  - Looking for individuals desiring team success

Discovery	Pre-Clinical	Clinical	Post-Marketing
2-4 years	1-2 years	4-6 years	1-4 years

The Food and Drug Administration

Regulates Pharmaceutical Market

Ensuring Human Safety & Efficacy

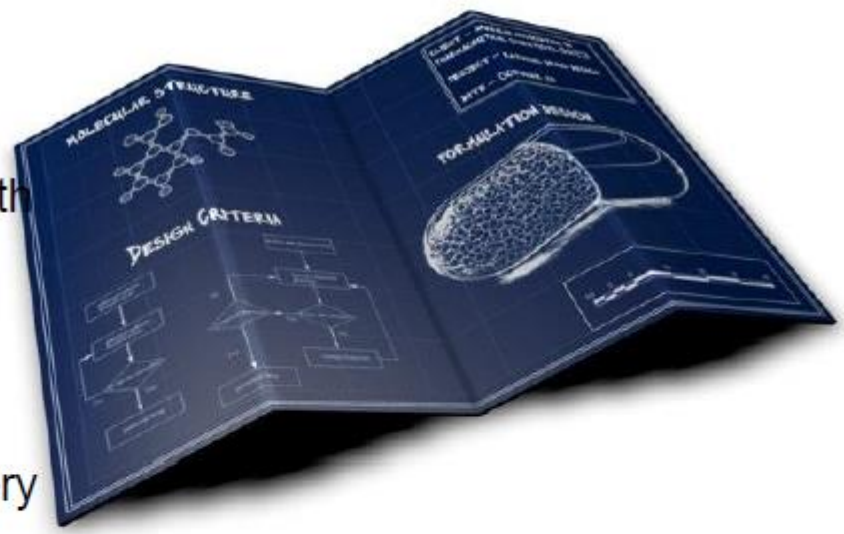
Federal Food, Drug, and Cosmetic Act

Where do we start?

- Identify disease (metabolic diseases, inflammation, neuroscience) or indication (diabetes, rheumatoid arthritis, Alzheimer's) class
  - New Target Idea !

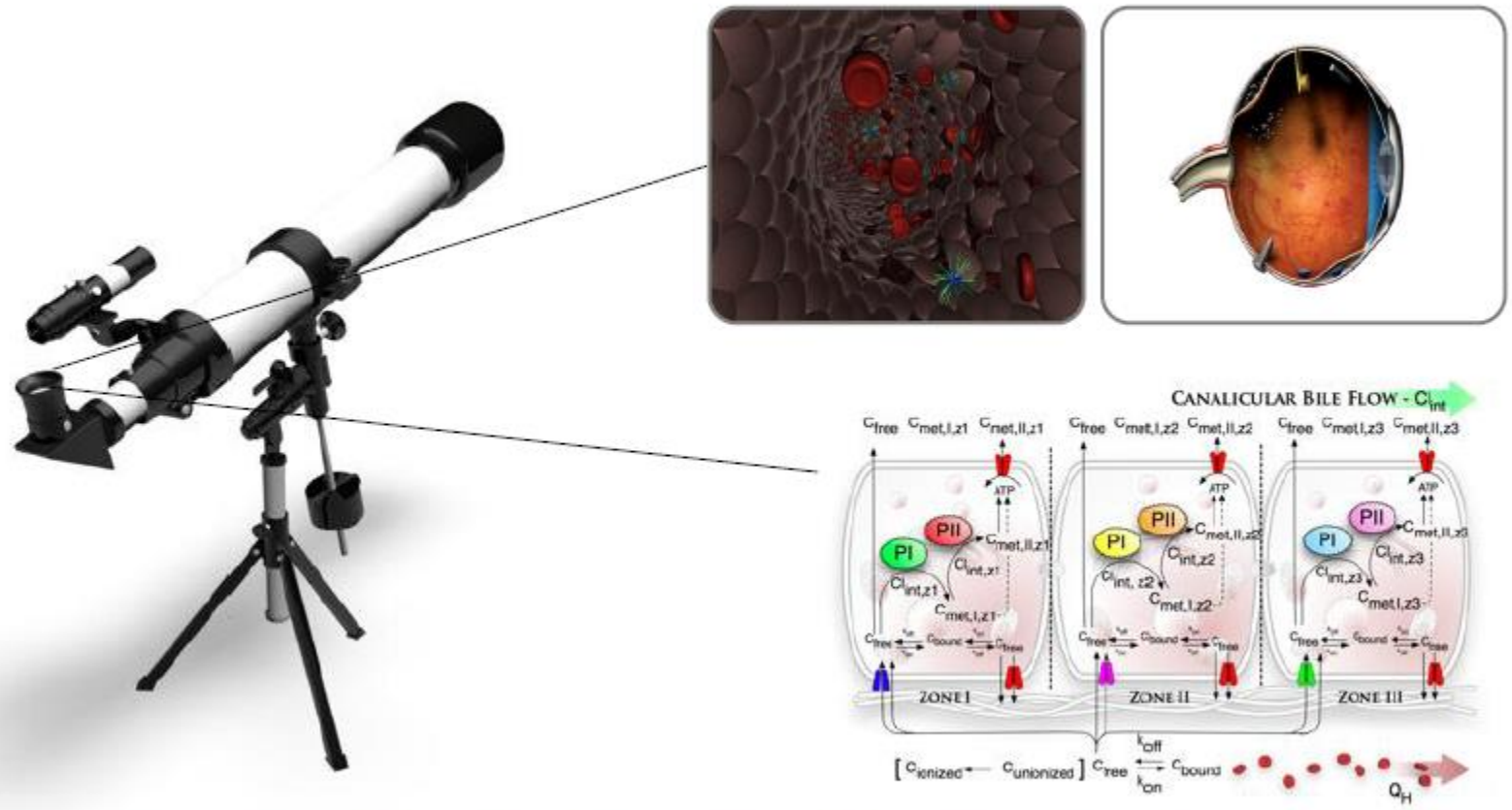
Formation of discovery project team

- Biology experts share knowledge of target and develop tools to further study
- Chemistry engages to identify lead chemical matter to interact with desired target (receptor, enzyme, etc.)
- ADME experts understand what body does to the drug
- Toxicology experts evaluate the safety
- Pharmaceutical Sciences - Expertise in formulation & drug delivery



Target Identification

- As disease biology is more fully understood, new potential drug intervention points are identified (receptors, enzymes, ion-channels, circulating agonists, etc.)”



Target Validation

Clinical Proof of Concept (POC) =
Right Target + Right Drug

- Evaluate target and confirm its role in the disease state
- Avoid research paths that lead to dead ends

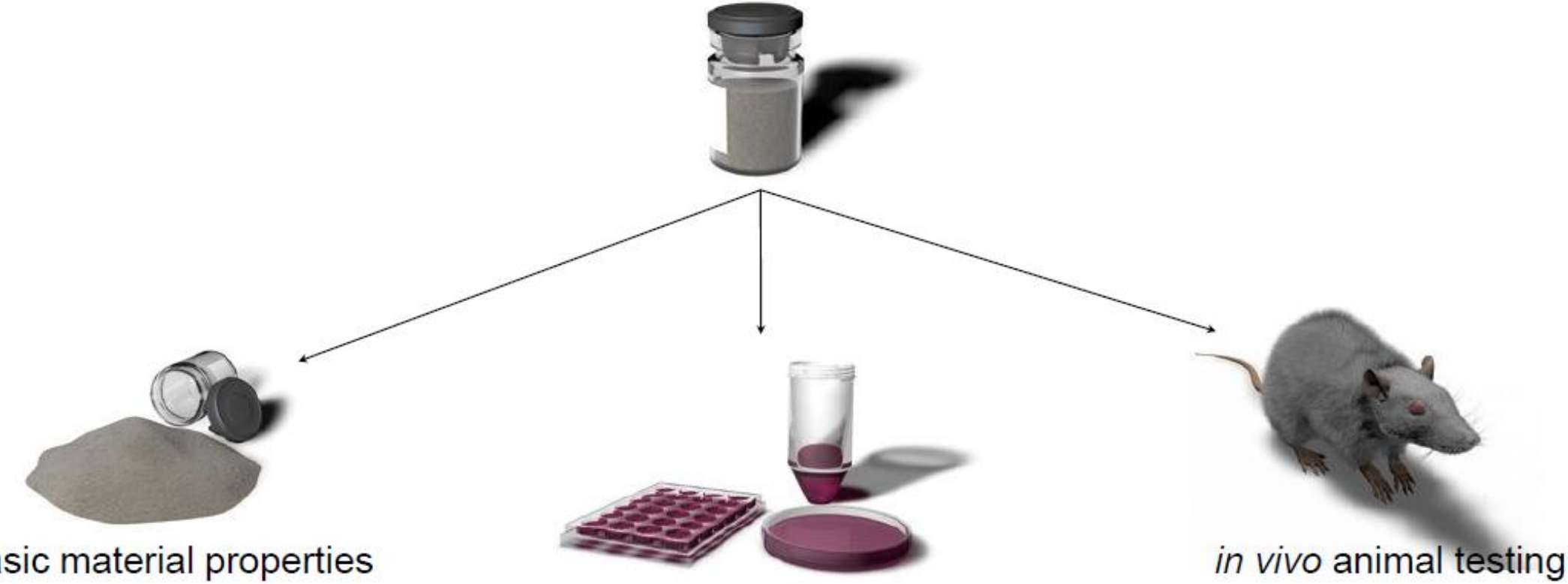
Creation of New Drug Molecule

- Where do chemical starting points (leads) come from?
  - High Throughput screening
  - Competitor information
  - Literature
  - Academia
  - Computer-Assisted Drug Design (CADD)

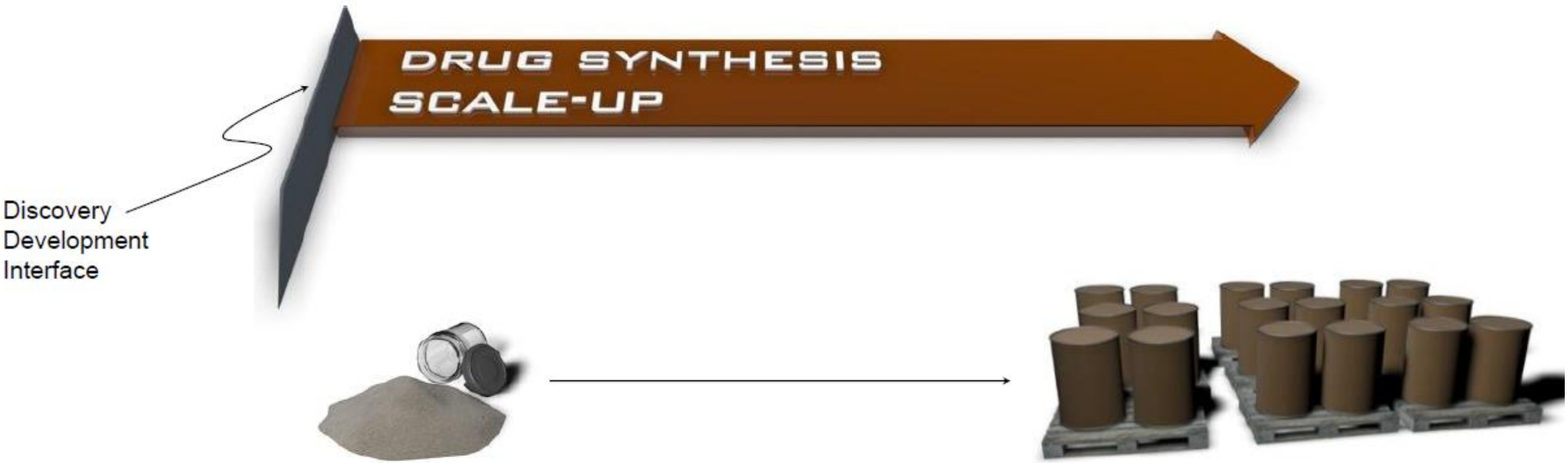
Lead Optimization

- Chemically-related series that survive initial screening are then optimized to IMPROVE their safety and efficacy
- Structure-Activity Relationship (SAR) with chemical structure of a current drug

Candidate Selection Stage of Drug Discovery

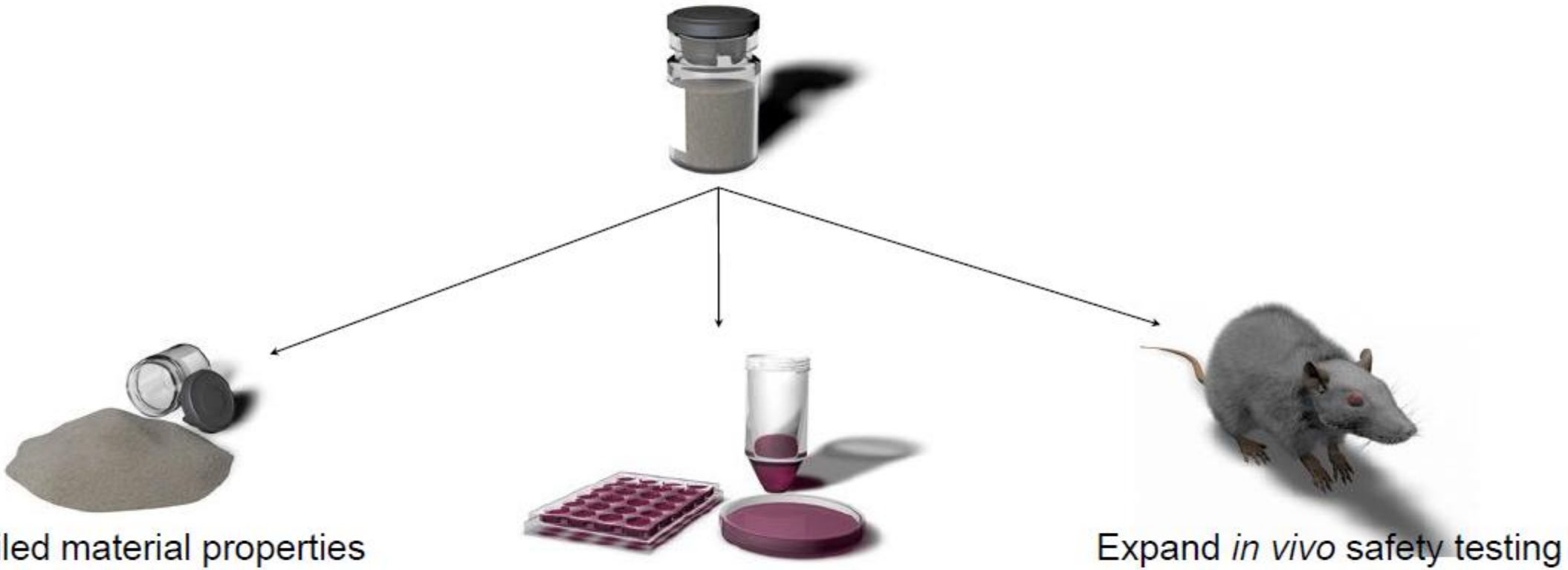


Drug Substance Scale-Up



- Chemical engineers and industrial chemists make enough drug to use up through early clinical studies

The Preclinical Stage



Detailed material properties

Detailed *in vitro* safety testing

Expand *in vivo* safety testing

Pre-Clinical Testing

- Evaluate 1–3 best compounds
- Higher TI ratio = safer medication

$$\text{Therapeutic Index (TI)} = \frac{\text{Drug concentration associated with safety finding}}{\text{Drug concentration associated with predicted human efficacy}}$$

IND Application

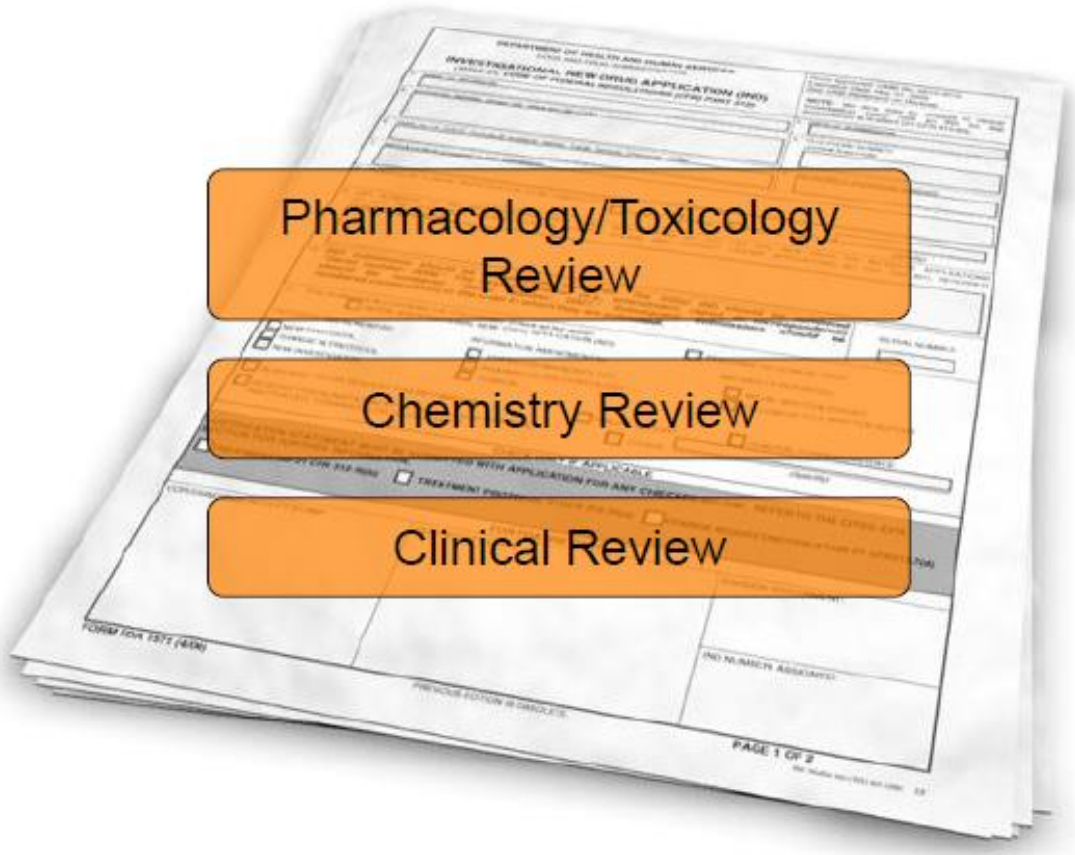
- FDA must approve prior to First-in-Human (FIH) clinical trial
- Contains:
  - Acute toxicity of drug substance in at least 2 species of animal
  - Short-term toxicity studies
  - Pharmacological profile of drug substance

IND Application

Sufficient data on safety & efficacy

Implication on human pharmacology

Protocols describing clinical studies in detail



Results from pre-clinical testing

Manufacture & analysis of chemical composition

Describe the qualification of personnel

Phases of Clinical Trials

- First-in-human (FIH) dosing to healthy volunteers
- Administration of single escalating doses of drug to a small number of subjects
- Short-term multiple doses (2 weeks)
- 10-15 volunteers
- Assess safety & PK

- First dosing to patients
- Fewer dosages studied than in Phase I
- First evaluation of efficacy
- Safety profile & PK monitored.
- 20-100 subjects studied
- Assess Proof-of-Concept

- Test effectiveness of drug for particular indication(s) in patients
- Common effects documented in larger population
- > 1,000 subjects
- Finalize prescribing label

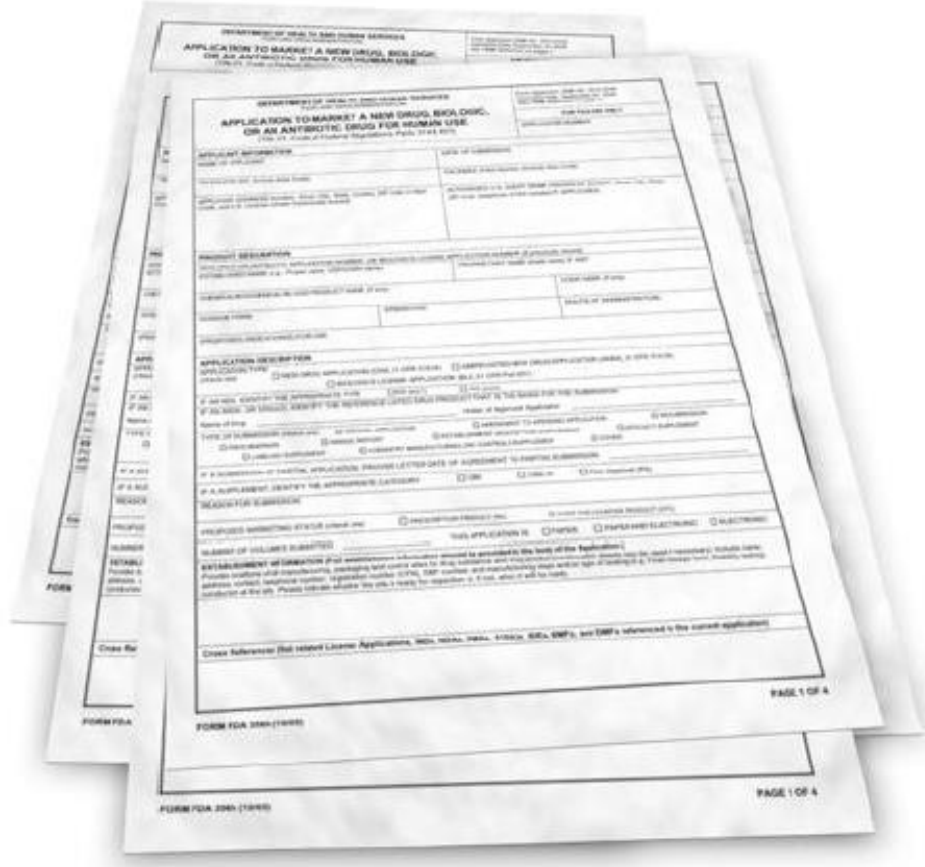
- Post-marketing approval studies
- Additional information about effectiveness and safety
- 300-3000 volunteers

New Drug Application

Proposed labeling details for the product

Results on safety & efficacy of the drug

Results from clinical trials



Details on long-term studies and post-marketing surveillance

Method of manufacture of drug and quality control analysis

FDA Review of NDA

- Pharmacology/Toxicology Review
- Chemistry Review
- Clinical Review
- Statistician
- Biopharmaceutical Review
- Microbiological Review

- The FDA approval process may take 6-18 months.
  - FDA establishes the final label of new drug.
- Sponsor must file separately in every global region or country.

Where do YOU fit in?

- Chemists
  - Medicinal, Synthetic, Analytical, Computational
- Biochemists
- Biologists
- Pharmacologists
- Pharmaceutical Scientists
  - Formulation, Physical Pharmacy, Pharmacokinetics
- M.D.s, Pharmacists, Nurses
- Mathematicians
- Automation experts
- Toxicologists
- Report Writers
- Human Resources
- Business
- Managers
- Animal Experts
- Regulatory Experts
- Marketing
- Sales