NEW DRUG DEVELOPMENT

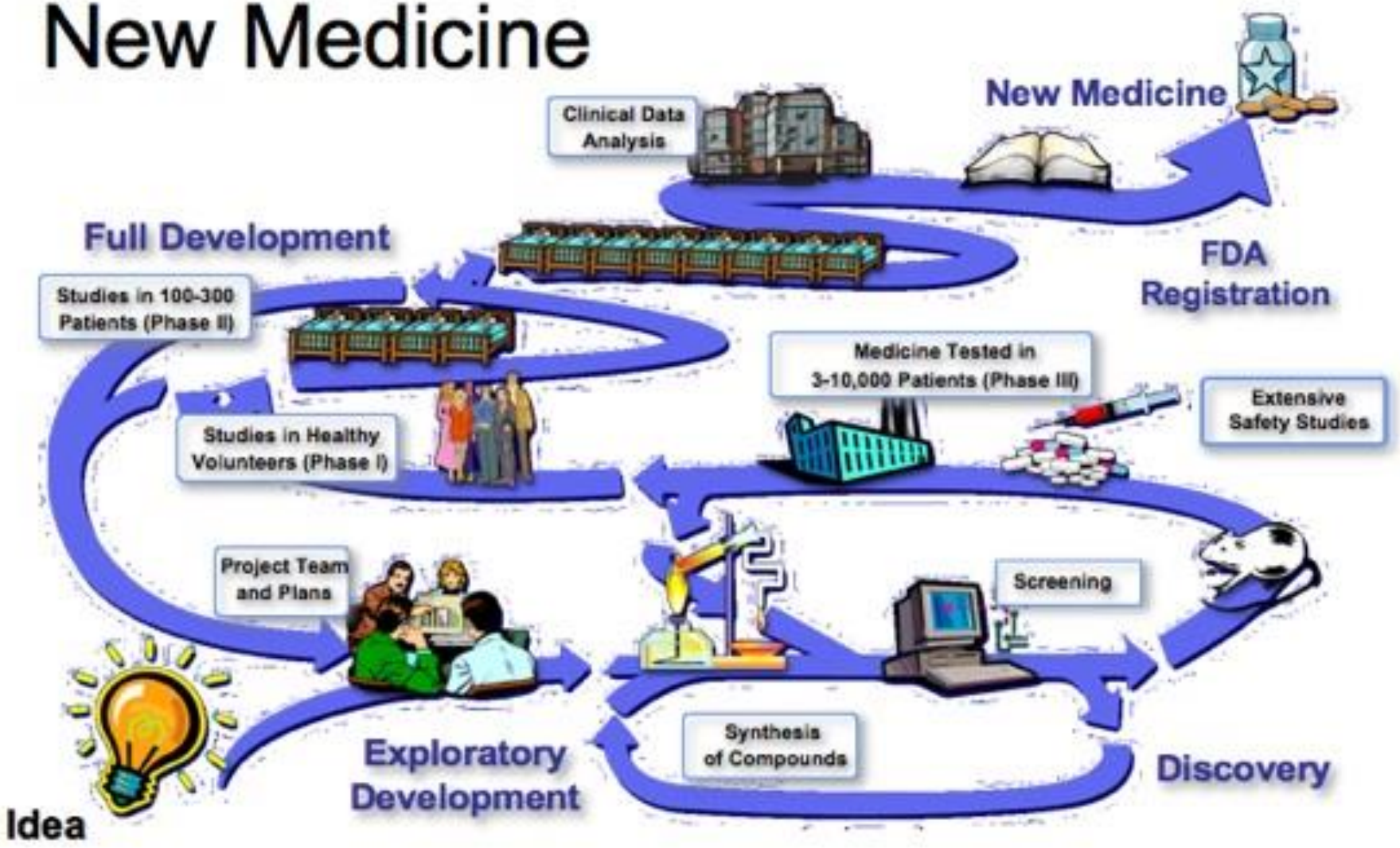
LEARNING OBJECTIVES

- Describe the processes involved in drug discovery and development.
- Define lead compound and drug screening
- Describe pre-clinical and clinical studies
- Define placebo, placebo response and nocebo response
- Define no-effect dose and minimum lethal dose
- Describe phases of clinical trials
- Define post-marketing surveillance.

LEARNING OBJECTIVES

- Define single-blind, double-blind, crossover and ADME studies
- Describe the role of Food and Drug Administration (FDA) in the drug development process
- Differentiate between IND (Investigational New Drug) and NDA (New Drug Application).

The Long Road to a New Medicine



NEW DRUG DEVELOPMENT

DRUGS

- A drug is broadly defined as any chemical agent that affects the living processes
- Some drugs are formed inside the living organisms such as hormones (insulin), neurotransmitters (noradrenaline) etc..
- Drugs which are introduced into the body from the outside are known as

NOCEBO VERSUS PLACEBO

NOCEBO

- A **situation in which a patient develops side effects or symptoms that can occur with a drug or other therapy** just because the patient believes they may occur.
- **Example :** the severe adverse effects experienced by patients taking a placebo during a clinical trial

PLACEBO

- Latin == 'I will please'
- The placebo effect is **when a person's physical or mental health appears to improve after taking a placebo or 'dummy' treatment**.
- A treatment that appears real, but is designed to have no therapeutic benefit.

NOCEBO VERSUS PLACEBO

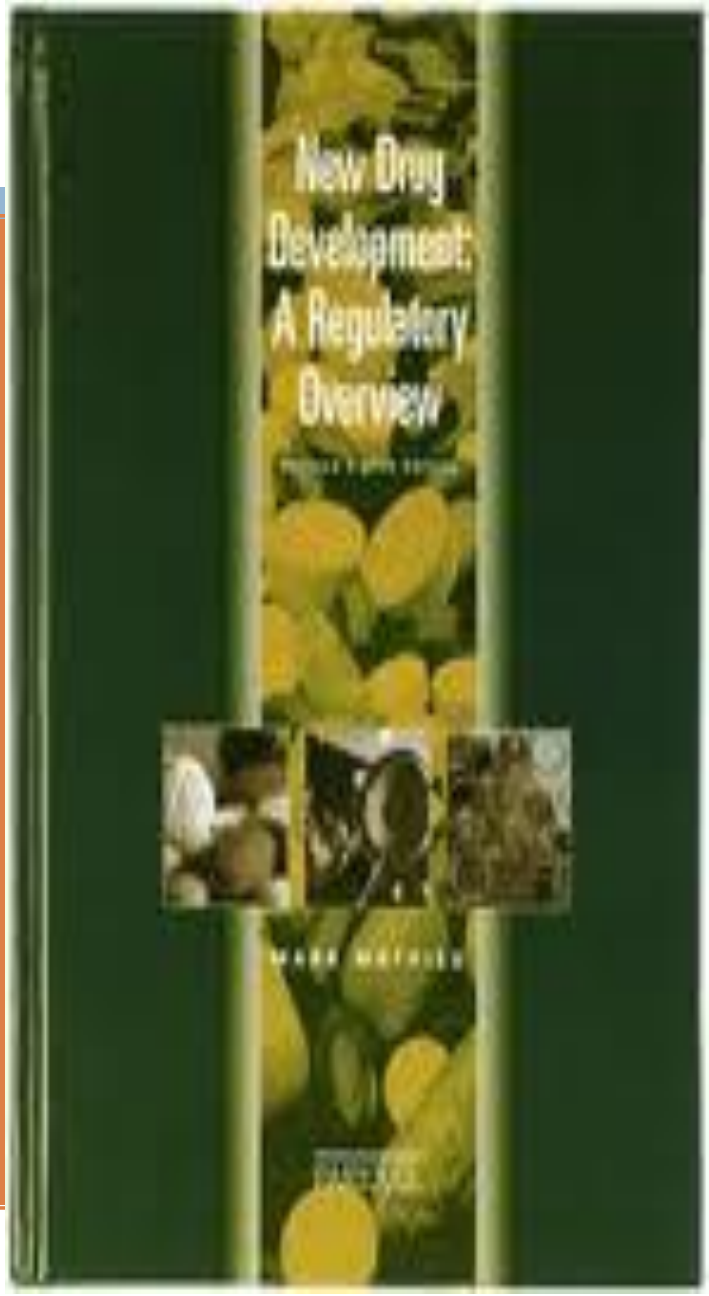
- Placebo is defined as **an inert substance** that provokes perceived benefits

WHEREAS

- the term nocebo is used when an inert substance causes perceived harm

NEW DRUG DEVELOPMENT

- Major step toward better health of community
- Expenses are involved and it is a highly complex, competitive, costly and commercially risky process
- Developed from natural and synthetic route
- Revolution in the medical practice
- Discuss process by which new drugs are discovered, developed and



STAGES IN NEW DRUG DEVELOPMENT (ESTIMATE TIME)

- **SYNTHESIS / isolation of the compound:**

  (1-2 years)

- **PRECLINICAL STUDIES: screening, evaluation, pharmacokinetic and short-term toxicity testing in animals:**

  (2-4 years)

- **Scrutiny and grant of permission for clinical trials:**

  (3-6 months)

- **Pharmaceutical formulation, standardization of chemical / biological / Immuno-assay of the compound:**

  (0.5-1 year)

- **CLINICAL STUDIES: phase I, phase II, phase III trials; long-term animal toxicity testing:**

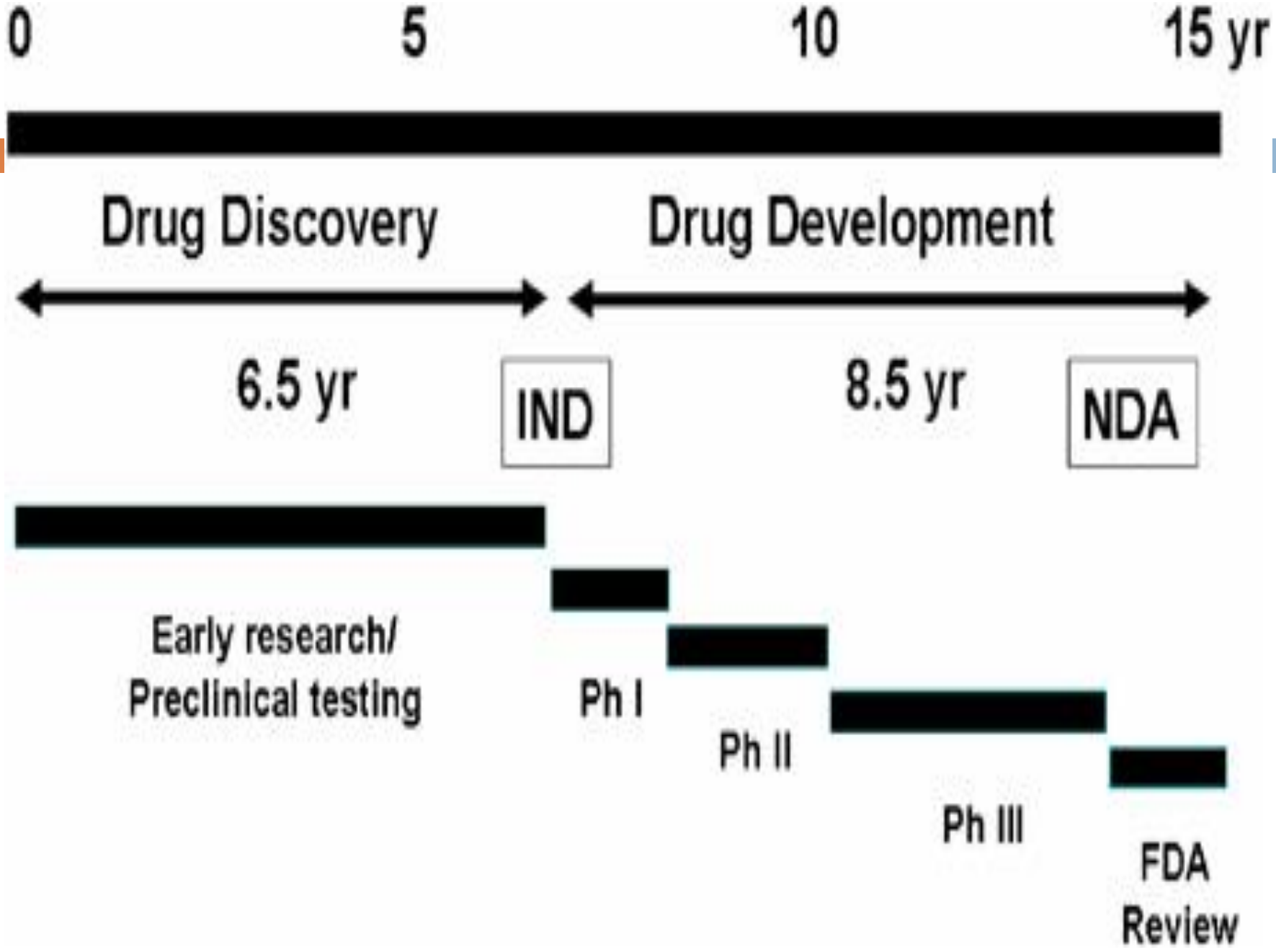
  (3-10 years)

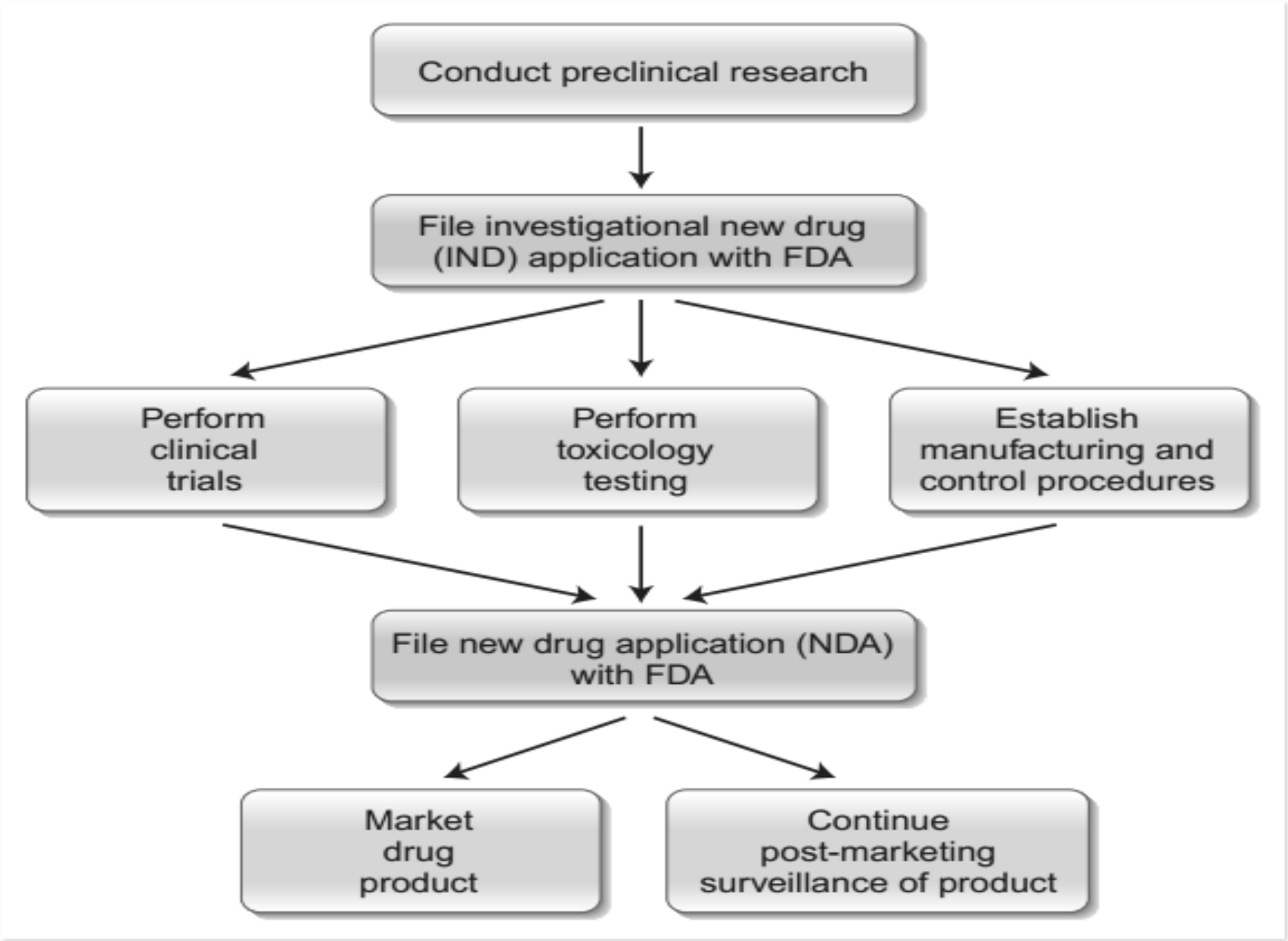
- **Review and grant of marketing permission:**

  (0.5-2 years)

- **Post marketing surveillance:**

  (PHASE IV STUDIES)


0
5
10
15 yr
Drug Discovery
Drug Development
6.5 yr
IND
8.5 yr
NDA
Early research/
Preclinical testing
Ph I
Ph II
Ph III
FDA
Review


Conduct preclinical research
File investigational new drug (IND) application with FDA
Perform clinical trials
Perform toxicology testing
Establish manufacturing and control procedures
File new drug application (NDA) with FDA
Market drug product
Continue post-marketing surveillance of product

Drug Discovery Process

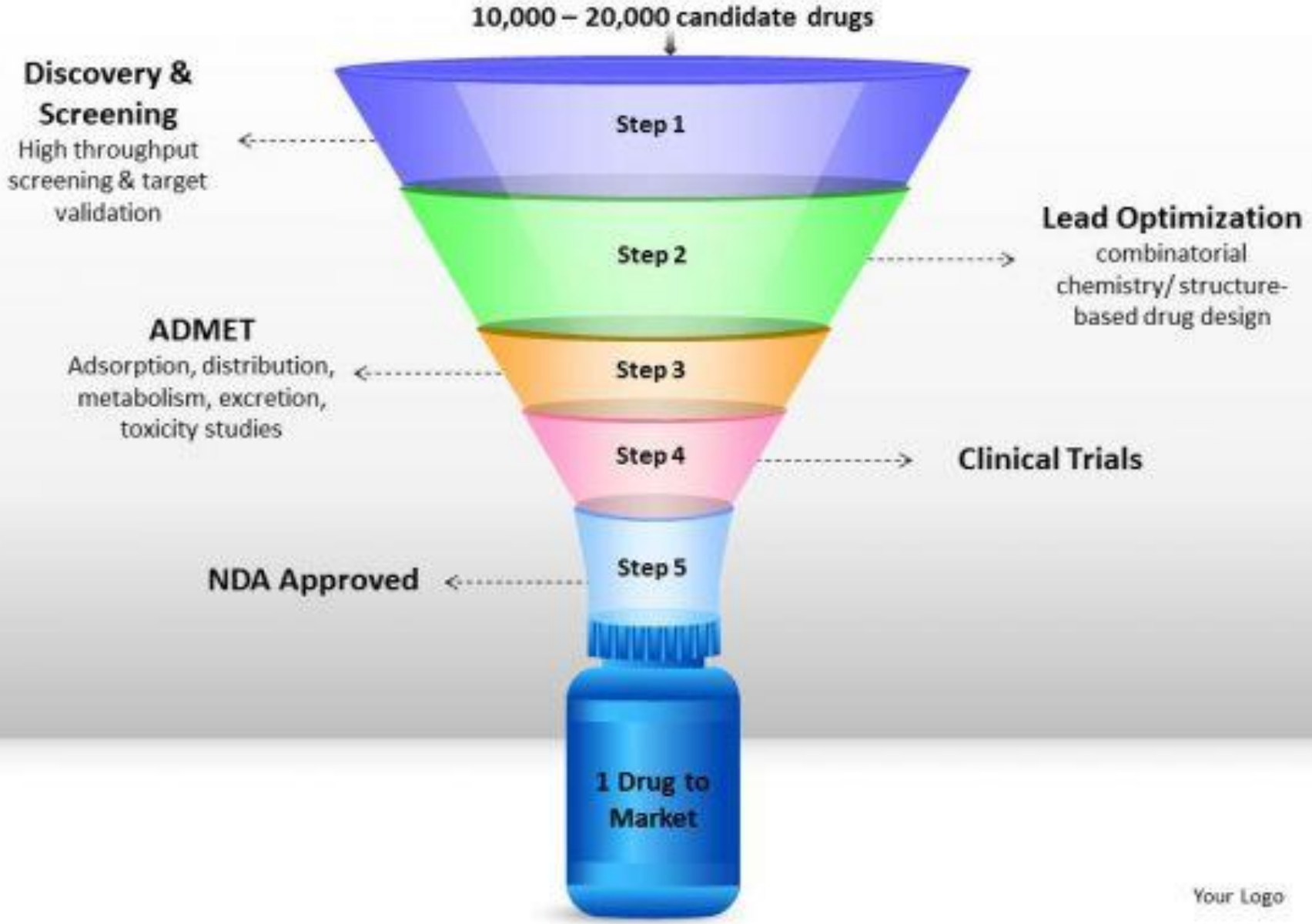
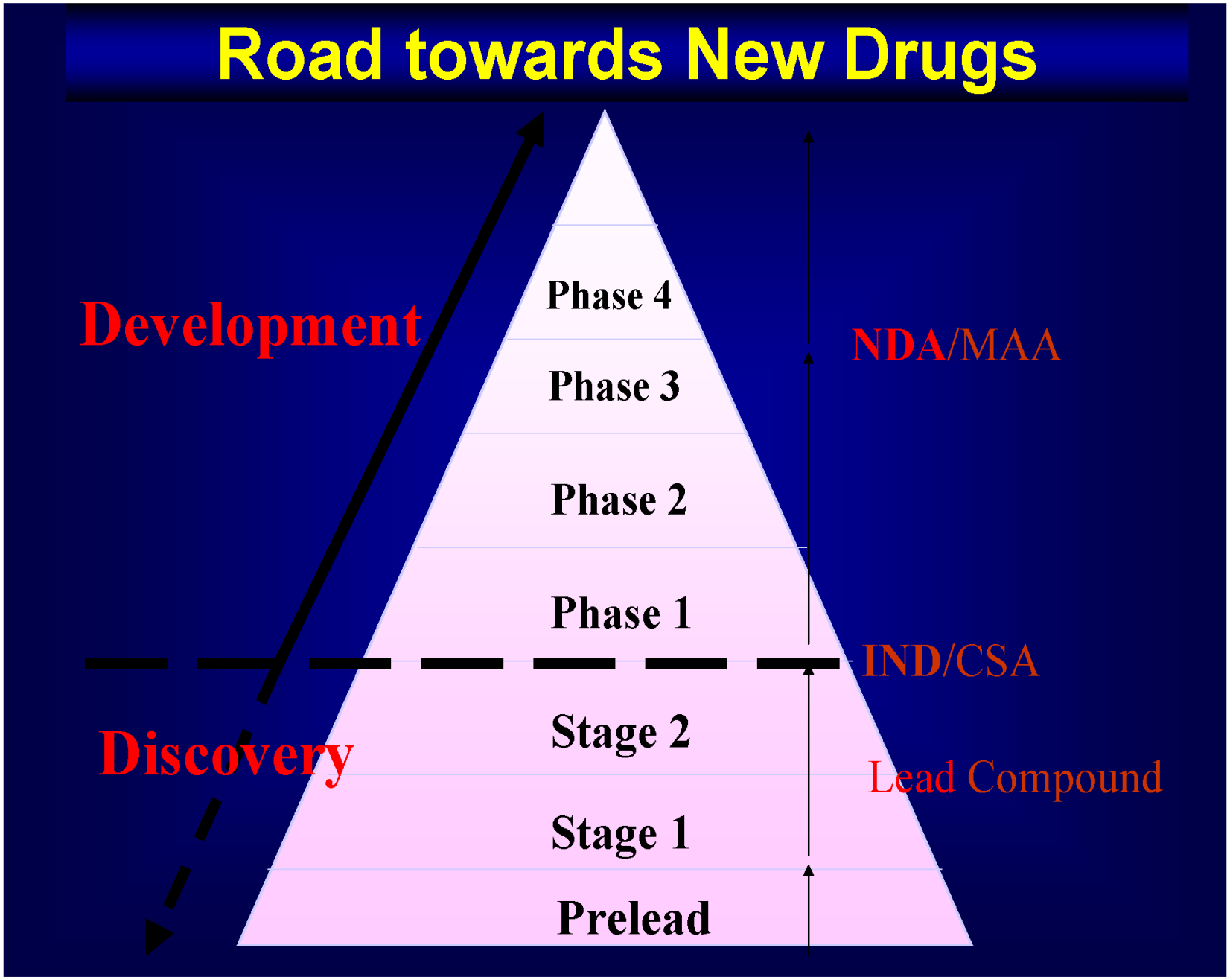
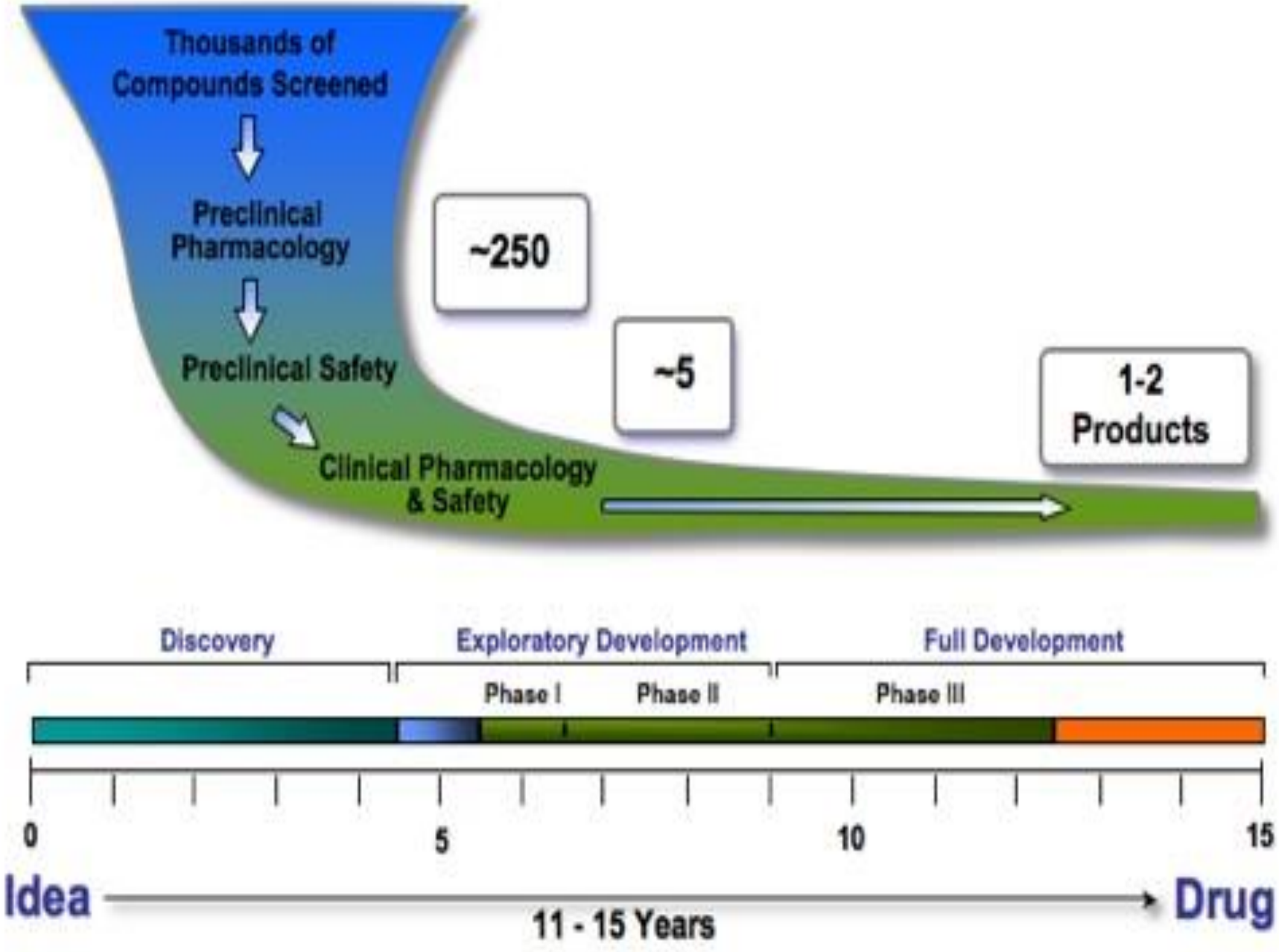


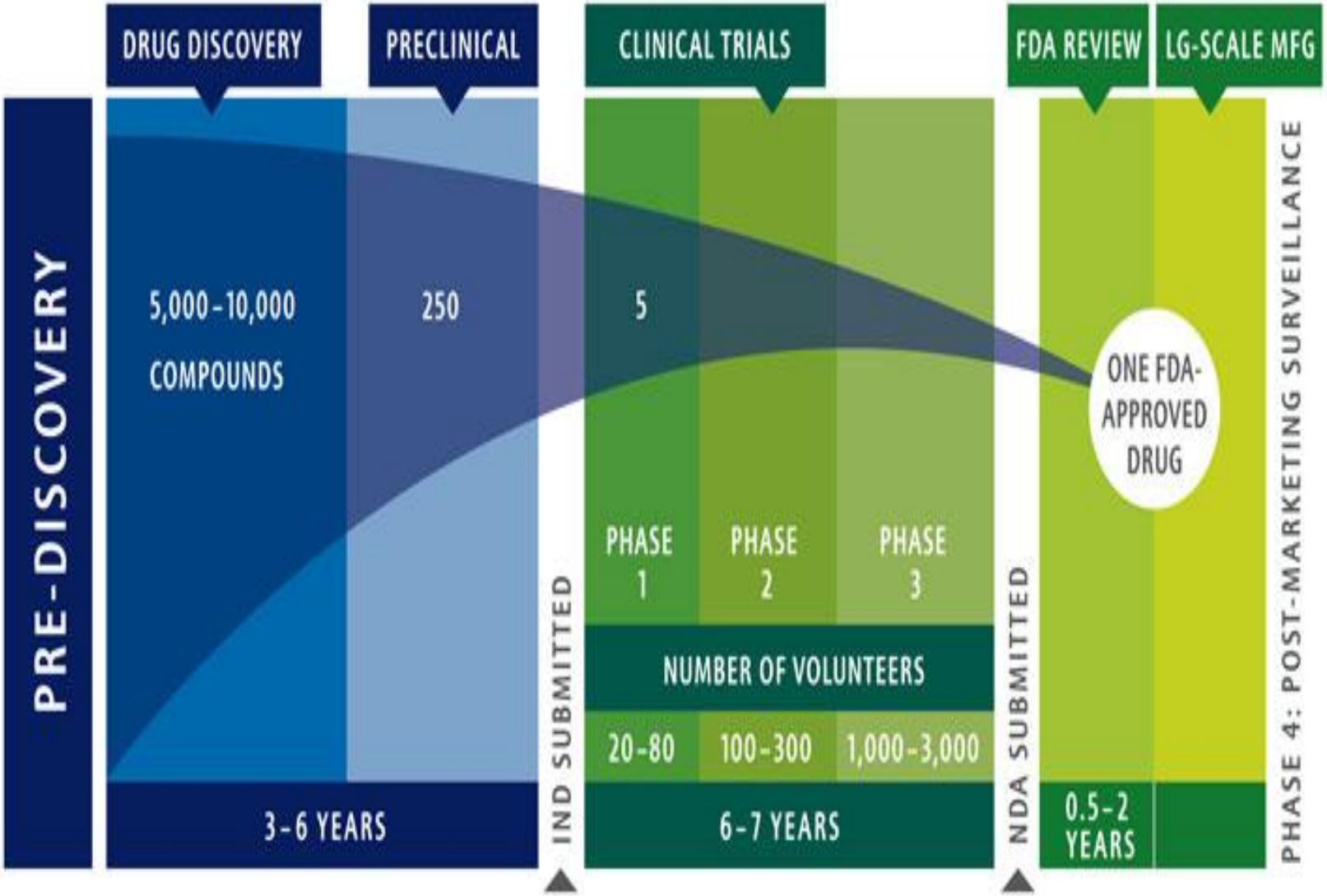
Figure 5. *Data from multinational pharmaceutical companies in the period 2005-2010, including data from FDA-approved NMEs versus R&D spending (in million US Dollars) for nine big companies (AstraZeneca, Bristol--MeyersSquibb, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Roche, and Aventis. Adaptation of ref. 49*

Road towards New Drugs




Thousands of Compounds Screened
Preclinical Pharmacology
Preclinical Safety
Clinical Pharmacology & Safety
~250
~5
1-2 Products
Discovery
Exploratory Development
Full Development
Phase I
Phase II
Phase III
0
5
10
15
Idea
Drug
11 - 15 Years

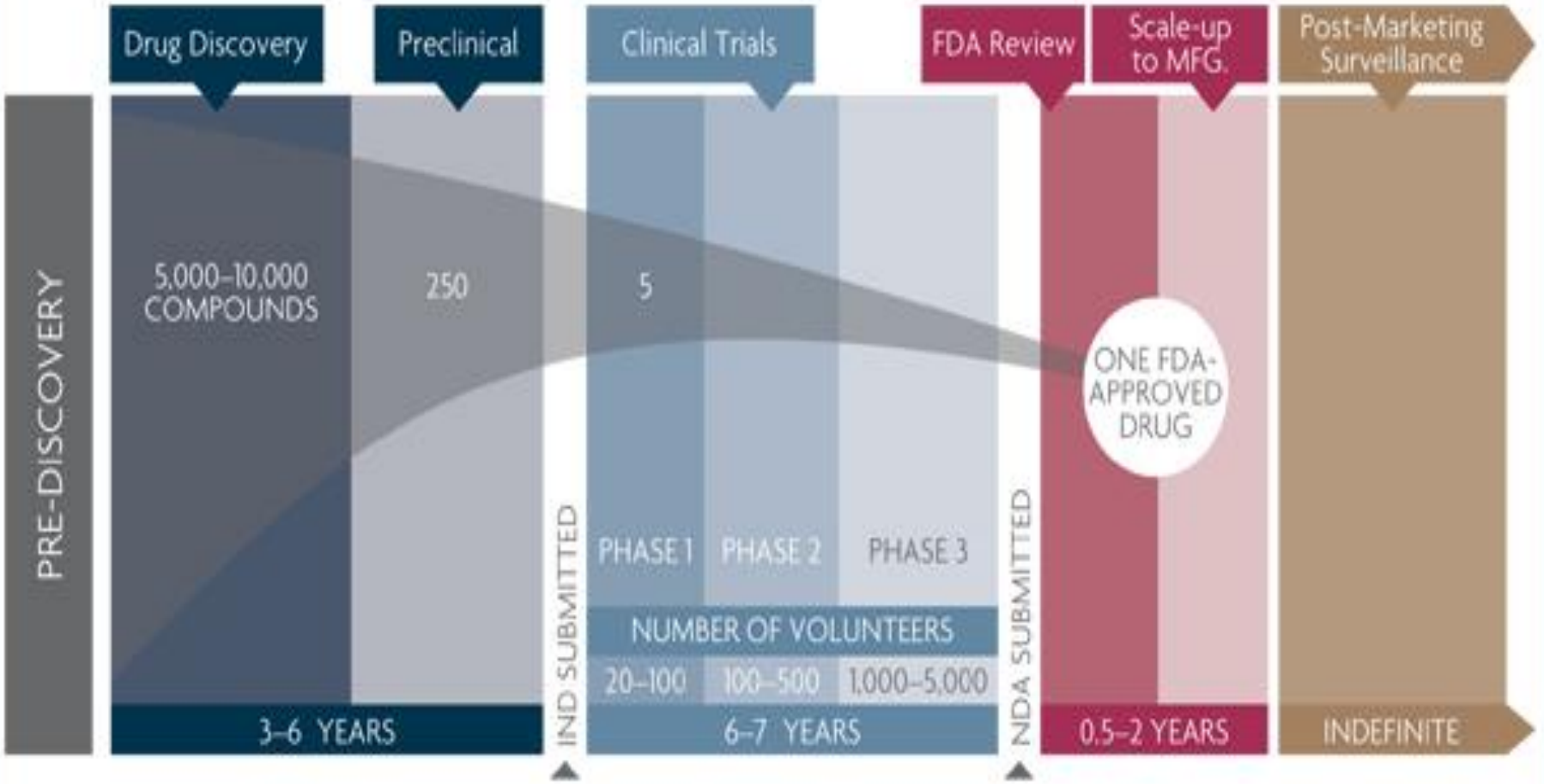
Drug Discovery and Development: A LONG, RISKY ROAD



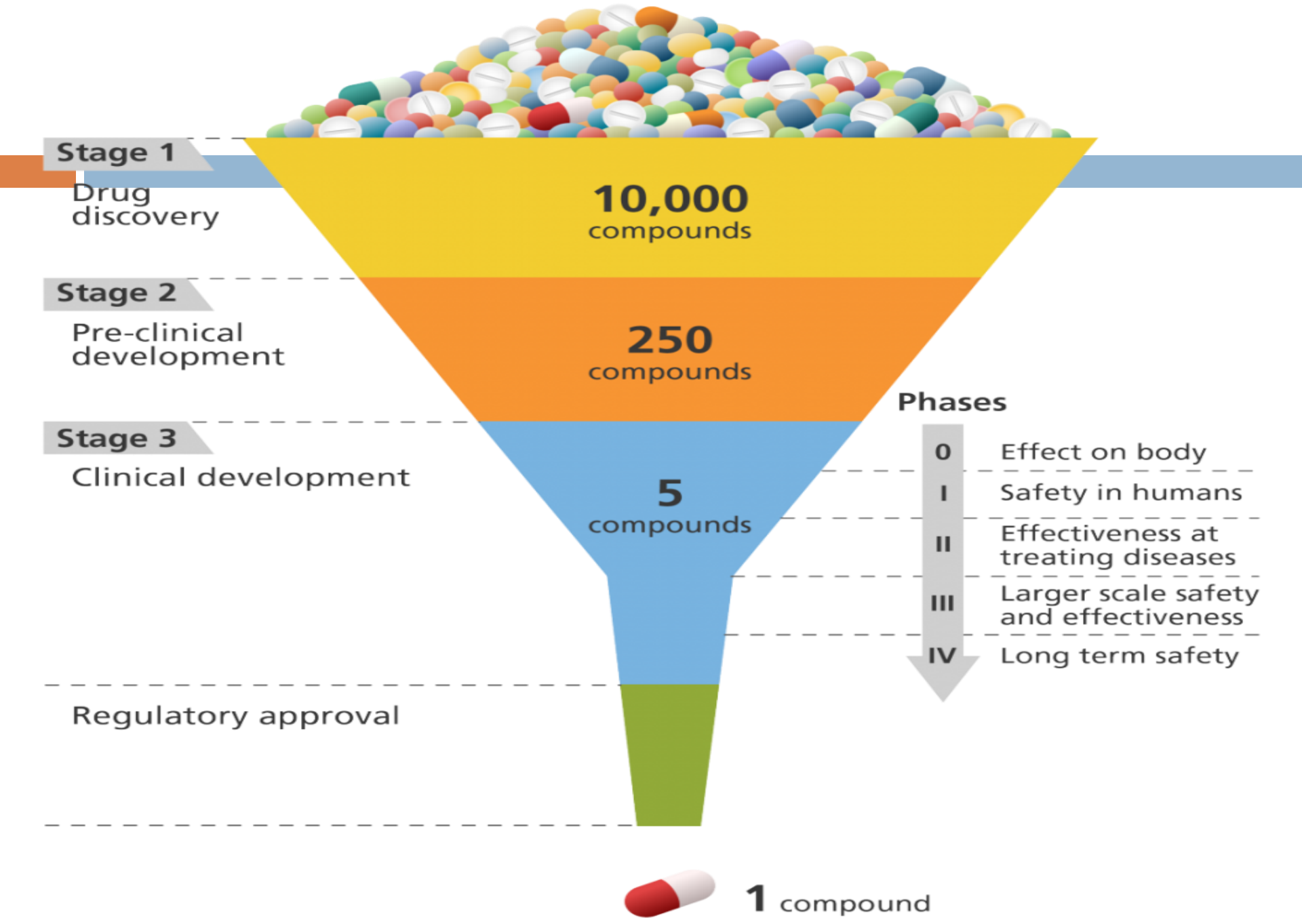
Source: Pharmaceutical Research and Manufacturers of America

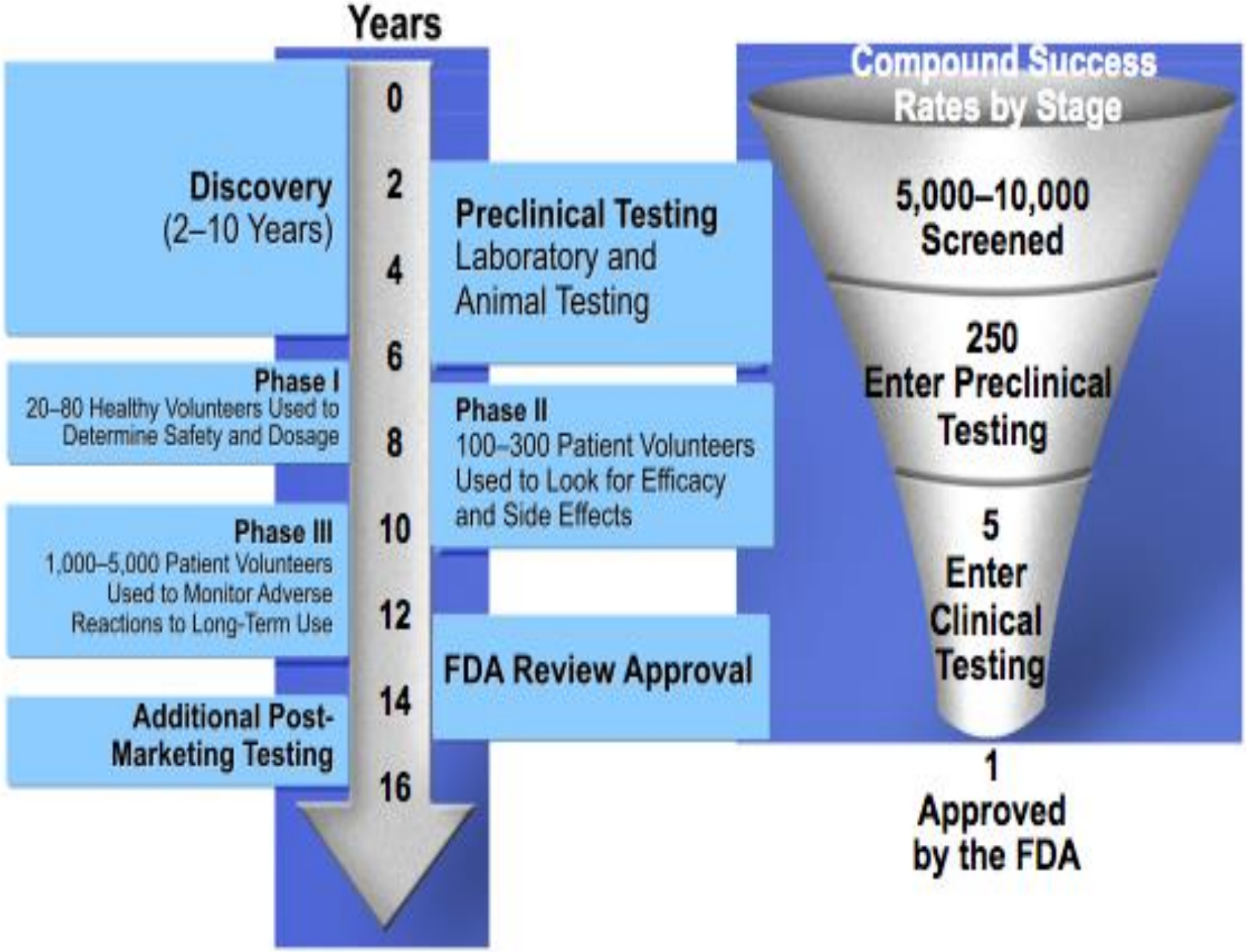
The Research and Development Process

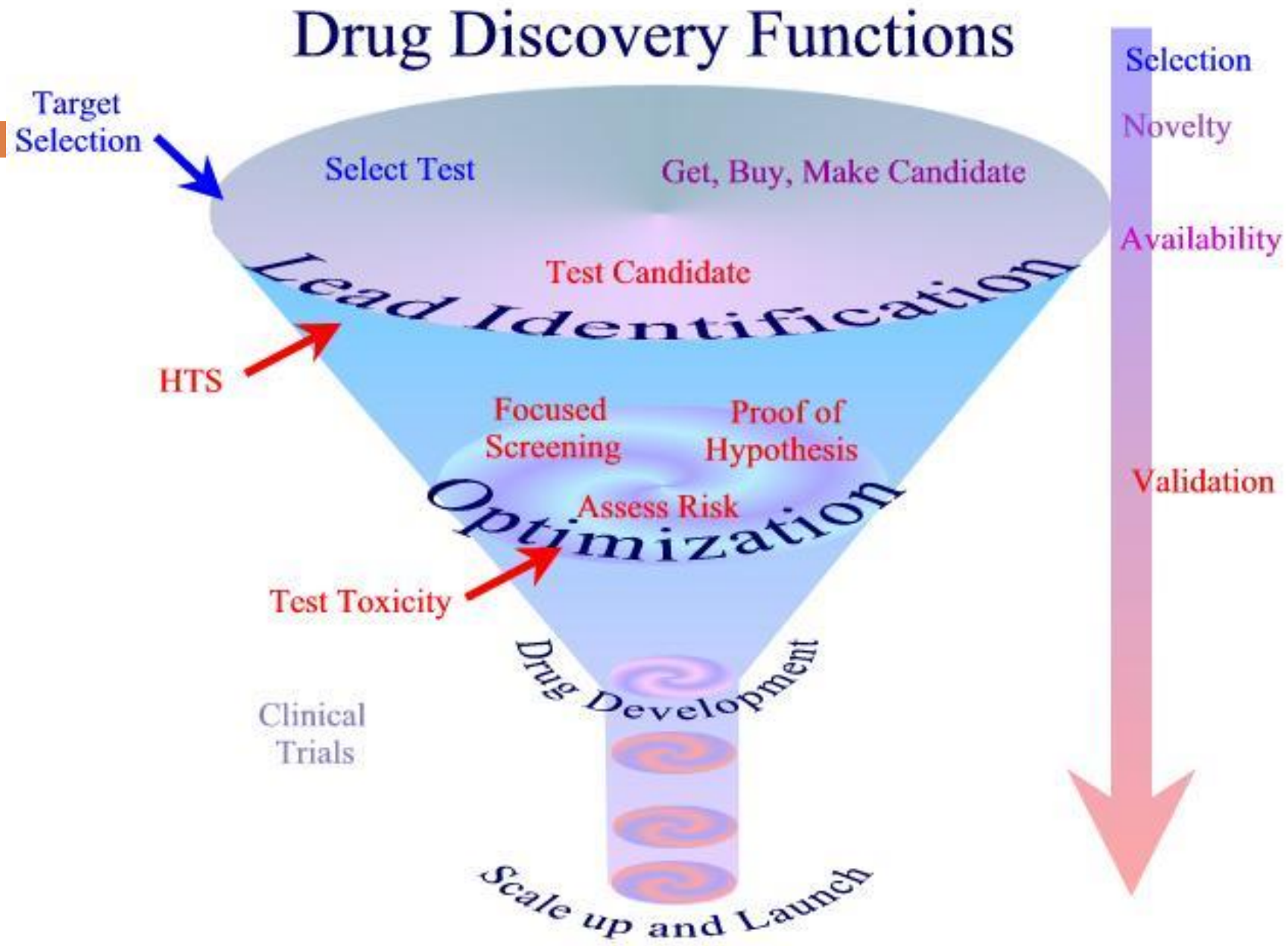
Developing a new medicine takes an average of 10–15 years.



Source: PhRMA[1]


Stage 1
Drug discovery
10,000 compounds
Stage 2
Pre-clinical development
250 compounds
Stage 3
Clinical development
5 compounds
Regulatory approval
Phases
0 Effect on body
I Safety in humans
II Effectiveness at treating diseases
III Larger scale safety and effectiveness
IV Long term safety
1 compound

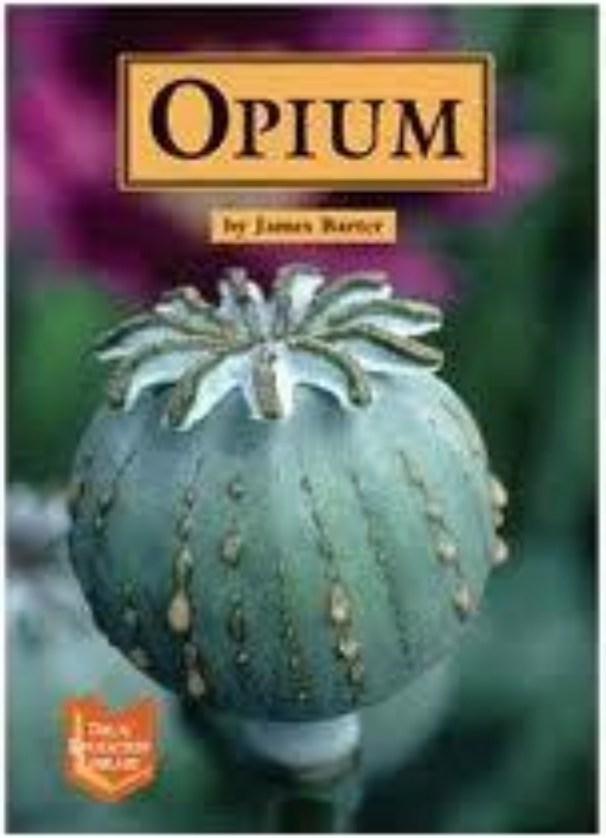

Years
0
2
4
6
8
10
12
14
16
Discovery
(2–10 Years)
Preclinical Testing
Laboratory and
Animal Testing
Phase I
20–80 Healthy Volunteers Used to
Determine Safety and Dosage
Phase II
100–300 Patient Volunteers
Used to Look for Efficacy
and Side Effects
Phase III
1,000–5,000 Patient Volunteers
Used to Monitor Adverse
Reactions to Long-Term Use
FDA Review Approval
Additional Post-
Marketing Testing
Compound Success
Rates by Stage
5,000–10,000
Screened
250
Enter Preclinical
Testing
5
Enter
Clinical
Testing
1
Approved
by the FDA


Drug Discovery Functions
Target Selection
Select Test
Get, Buy, Make Candidate
Test Candidate
Lead Identification
HTS
Focused Screening
Proof of Hypothesis
Assess Risk
Optimization
Test Toxicity
Drug Development
Clinical Trials
Scale up and Launch
Selection
Novelty
Availability
Validation

Approaches to drug discovery

- Natural sources.
- Chemical synthesis.
- Relation Approach.
- Molecular Modeling.
- Biotechnology


Cinchona
Bark


OPIUM
by James Barter

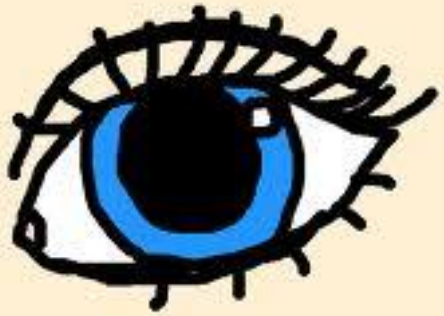
NATURAL SOURCES

PLANTS

- Opium (morphine)
- Ephedra (ephedrine)
- Cinchona (quinine)
- Curare (tubocurarine)
- Belladonna (atropine)

ANIMALS

- Adrenaline
- Thyroxin
- Insulin
- Liver extract
- Antisera

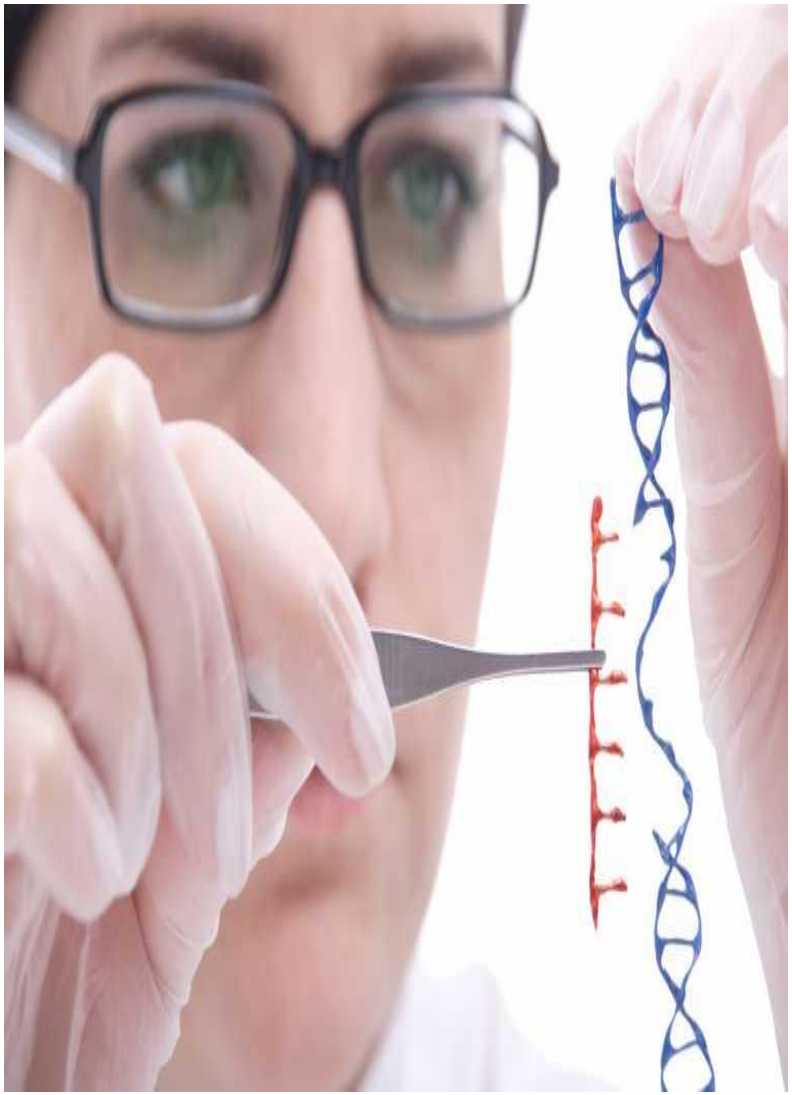


"Belladonna" is derived
from Italian
 MEANS == "beautiful woman"
Dilated pupils make them
appear beautiful.

CHEMICAL SYNTHESIS

- Barbiturates
- Chlorpromazine
- Selective β_2 agonists
- β blockers

(adrenergic drugs have been produced by modifying the side chain of histamine.)



RELATION APPROACH

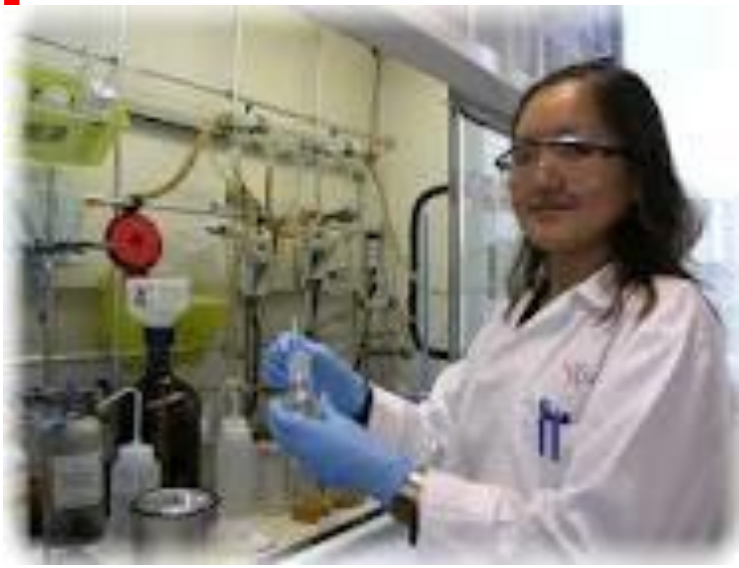
- Omeprazole = H+K+ATPase enzyme
- Abciximab = Glycoprotein IIa/IIIb receptor.
- Levodopa = deficiency of dopamine
- Cancer chemotherapy
  - The purine
  - Pyrimidine
  - Folate antimetabolites

MOLECULAR MODELING

- Protein chemistry and computer
- Designing of targeted compounds
- Example:

Designing of selective COX-2 inhibitors was prompted by the comparative configuration of COX-1 and COX-2 enzyme molecules.

BIOTECHNOLOGY



Recombinant DNA technology

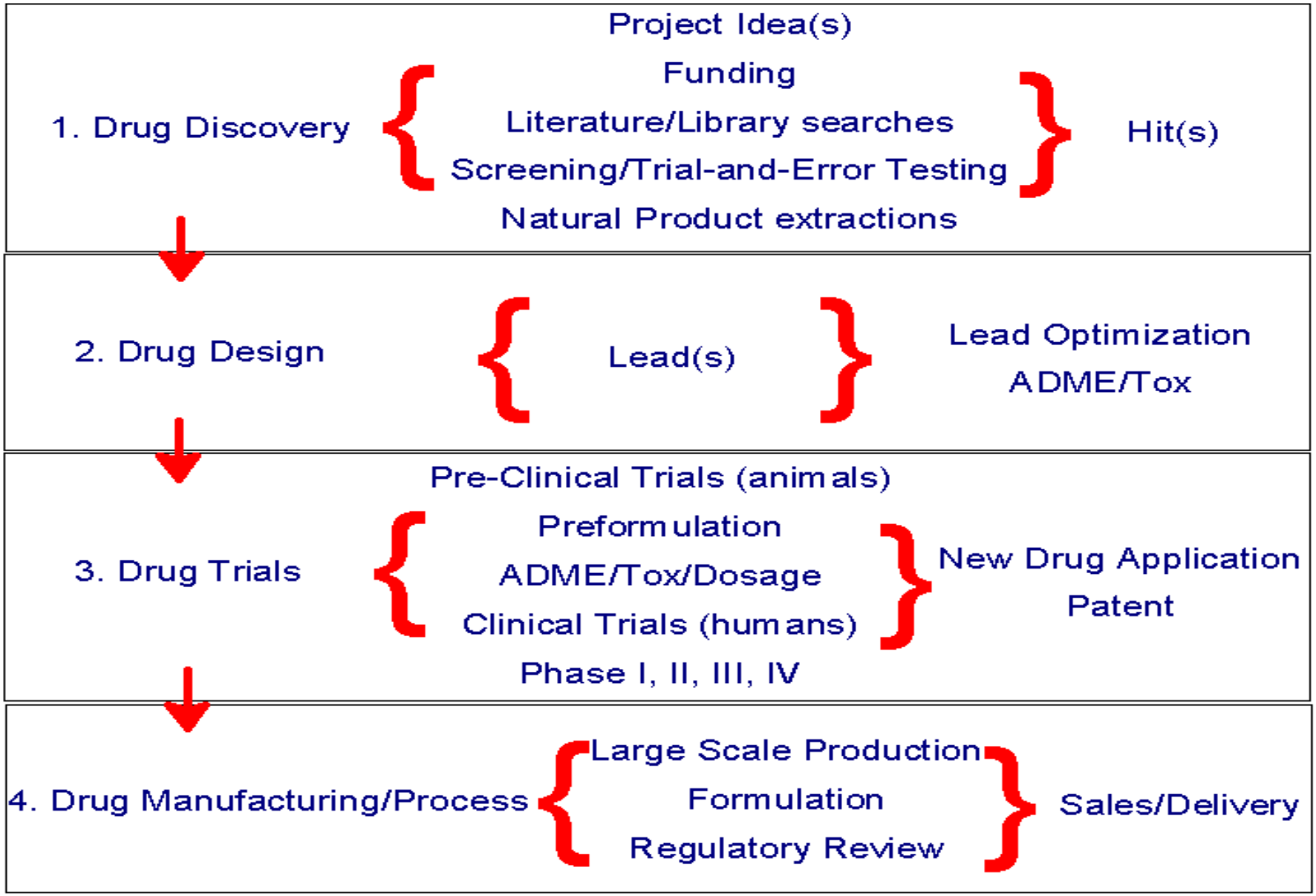
- Human growth hormone
- Human insulin
- Interferon
- Monoclonal and chimeric antibodies
- Antibiotics
- Regulatory peptides
- Growth factors
- Cytokines

DRUG DISCOVERY

SIX PRINCIPLES

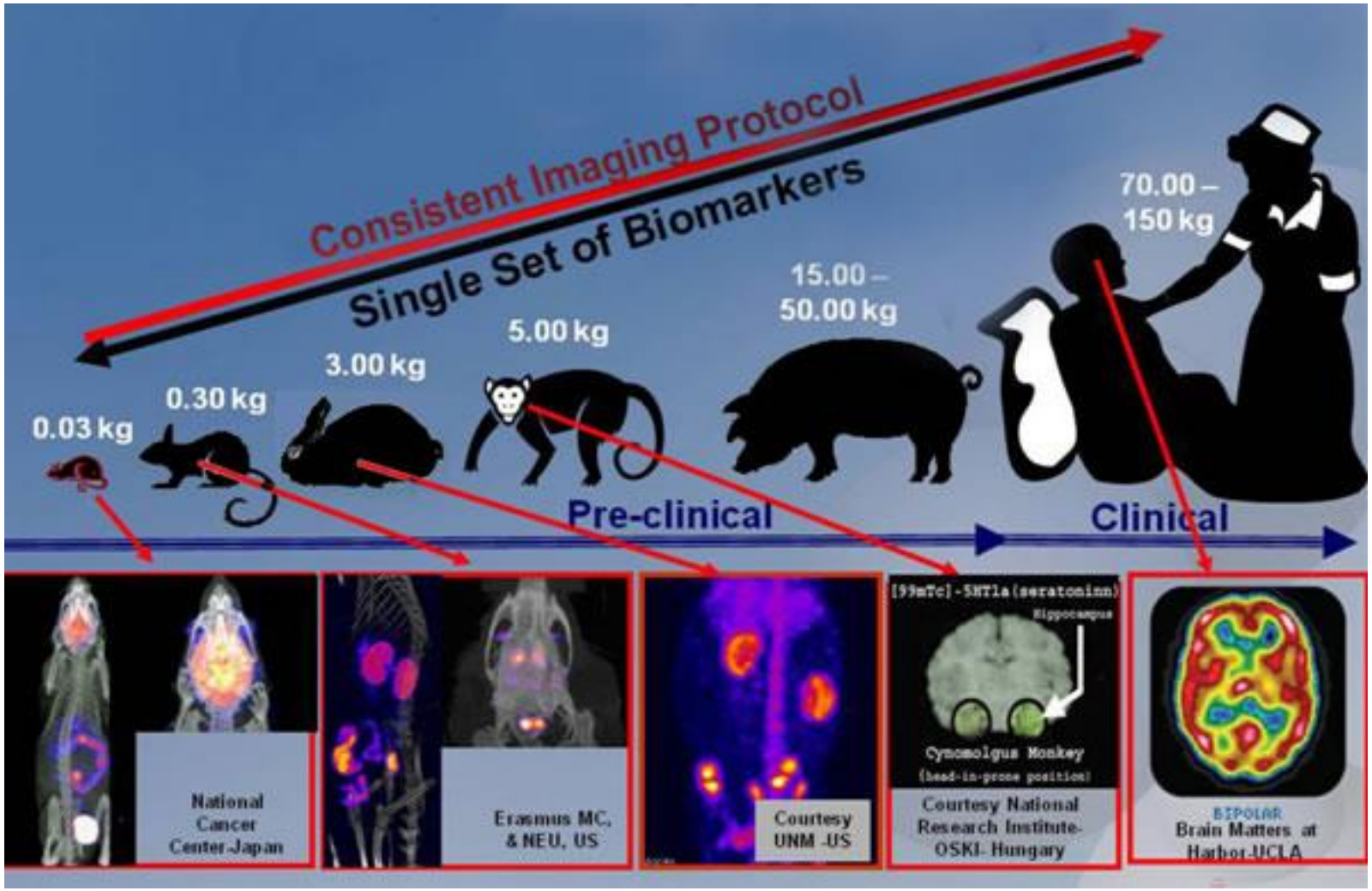
- Identification of new drug
- Rational drug design
- Chemical configuration
- Elucidation of biological activities
- Biotechnology
- Mapping the therapeutic role and combinations

The Various Stages in New Drug Development




Drug Discovery
0-2 years
Target Selection
Biological Target
Target Chemistry
2-3 years
Discovery & Screening
Extraction, purification of natural glycomolecules
In vitro screening of 200-500 samples
1-2 years
Lead Selection
In vitro efficacy screening
Identify 10-20 best candidates
1-2 years
Lead Optimisation
In vitro mode of action screening
In vivo efficacy studies
Identify 2-3 best candidates

PRE-CLINICAL STUDIES



PRECLINICAL SAFETY

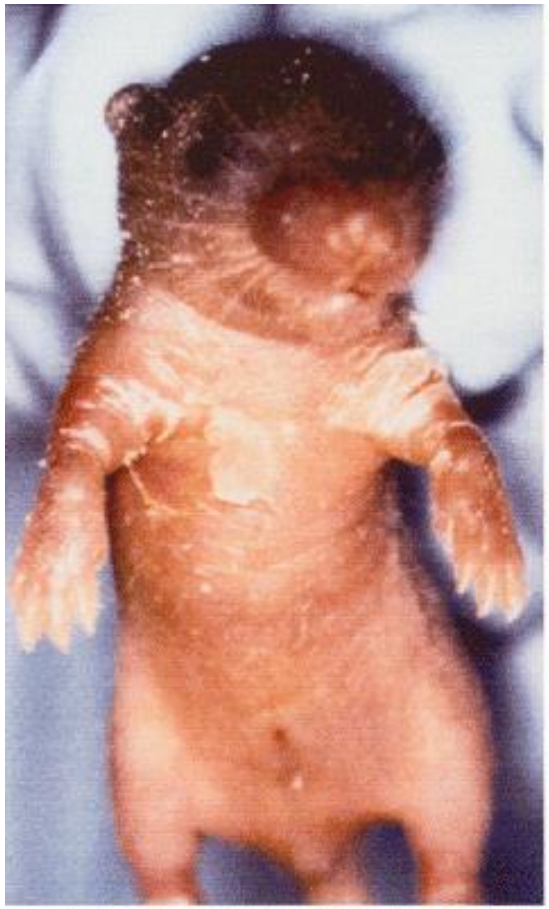
ANIMAL STUDIES

- Acute toxicity
- Sub acute or sub chronic toxicity
- Chronic toxicity
- Teratogenicity
- Carcinogenicity
- Mutagenicity
- Investigative toxicology

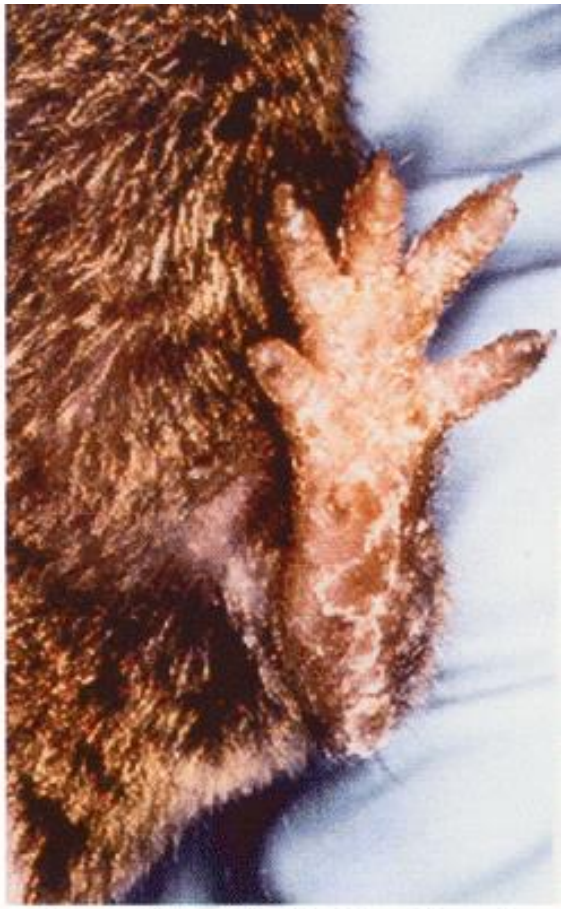
PRECLINICAL STUDIES

Lab and animal testing to determine if the drug is safe enough for human testing

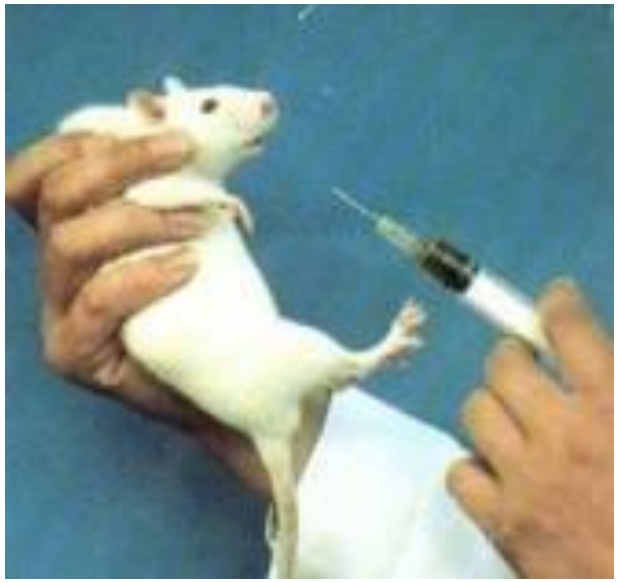
- After synthesizing / identifying a prospective compound , it is tested on animals to expose the whole pharmacological profile.
- Generally performed on a rodent (mouse, rat, guinea pig, hamster, rabbit)
- Then on a larger animal (cat, dog, monkey).
- As the evaluation progresses unfavorable compounds get rejected at each step



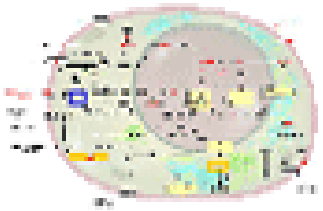
4 d after start of treatment with activator



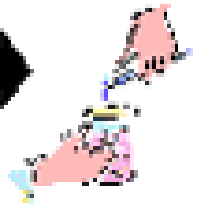
3 mo after start of treatment with activator



How does pre-clinical work help ?



Cellular
Target
Eg.- kinase
Or chemokine
receptor



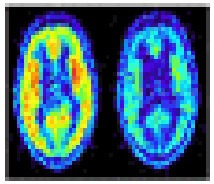
In vitro
inhibition
of target

In vivo
inhibition
of target

TRANSLATIONAL SCIENCE

Demonstration
of target inhibition
in vivo which
can be applied
in the clinic as
a 'biomarker'

Imaging



Serological
marker

Ex-vivo
Stimulated
PBMCs

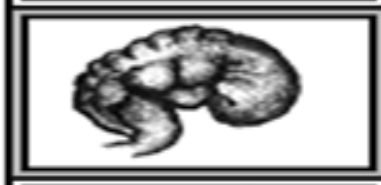
TYPES OF **TESTS** performed to find out safety of drug

Acute, Subchronic and Chronic Toxicity Tests

Determine the effect of a chemical on health and mortality during various lengths of exposure

Reproductive Toxicity Tests

Assess the effect of a chemical on fertility and fecundity



Develomental Toxicity Tests

Evaluate the capacity of a chemical to cause abnormalities in an embryo, fetus or newborn

Ocular- and Skin-Irritation Tests

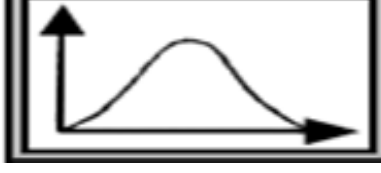
Measure the ability of a chemical to inflame or irritate the skin or eyes

Hypersensitivity Tests

Assess the tendency of a chemical to elicit rashes and other allergic responses

Phototoxicity Tests

Determine the extent to which a chemical is activated by sunlight, thereby enhancing its toxicity



Toxicokinetic Studies

Explore the absorption, distribution, metabolism, storage and excretion of a chemical

ANIMAL STUDIES: NATURE

ACUTE TOXICITY

- Two species; one rodent and a no rodent
- Two different routes of administration
- Determines the "*no effect*" and "*lethal*" *dose*
- Tests maximum tolerated dose

ANIMAL STUDIES

SUB ACUTE OR SUB CHRONIC TOXICITY

- Two weeks to three months of testing
- Three doses
- Two species; one rodent and a no rodent
- Determines biochemical profile
- Characterize the physiological effects

ANIMAL STUDIES

CHRONIC TOXICITY

- More than six months of testing
- Two species; one rodent and a no rodent
- Required for drugs used in humans for long term/life long
- Usually concurrent with “CLINICAL TRIALS”
- Determines biochemical profile
- Characterize the physiological effects

ANIMAL STUDIES

TERATOGENICITY

- Two species; one rodent and one rabbit
- Focus and research on
  - Mating behavior
  - reproduction
  - parturition
  - progeny
  - birth defects
  - post natal development

ANIMAL STUDIES

CARCINOGENICITY

- Study span over Two years
- Involving Two species
- For drugs intended for use over long time
- Gives information about gross and histopathology

ANIMAL STUDIES

MUTAGENICITY

- Ames test: genetic stability and mutation in bacteria
- Mammalian cells in culture
- Dominant lethal test
- Clastogenicity in mice

ANIMAL STUDIES

INVESTIGATIVE TOXICOLOGY

- Sequence and mechanism of toxic action
- *No Effect Dose* and *Minimum Lethal Dose*
- New methods of assessing toxicity
- Computer assisted modeling
- Discovers
  - Genes
  - Proteins
  - pathways

ANIMAL STUDIES

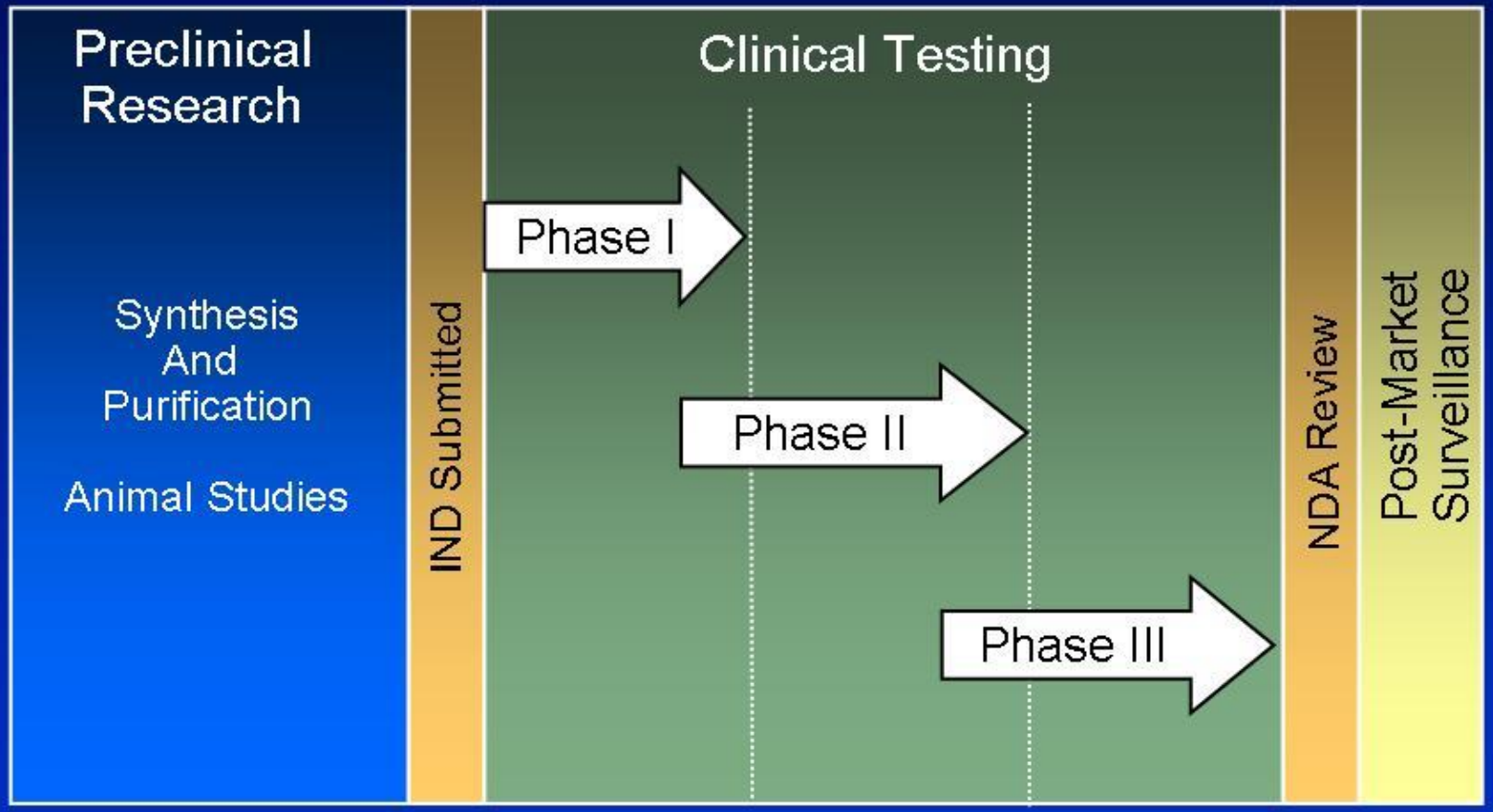
LIMITATIONS

- Time consuming and expensive
- Ethical : large number of animals
- Cell and tissue culture = limited predictive value
- Extrapolation to humans = not always precise
- Rare adverse effects are not detected

TYPE OF BLIND STUDIES.

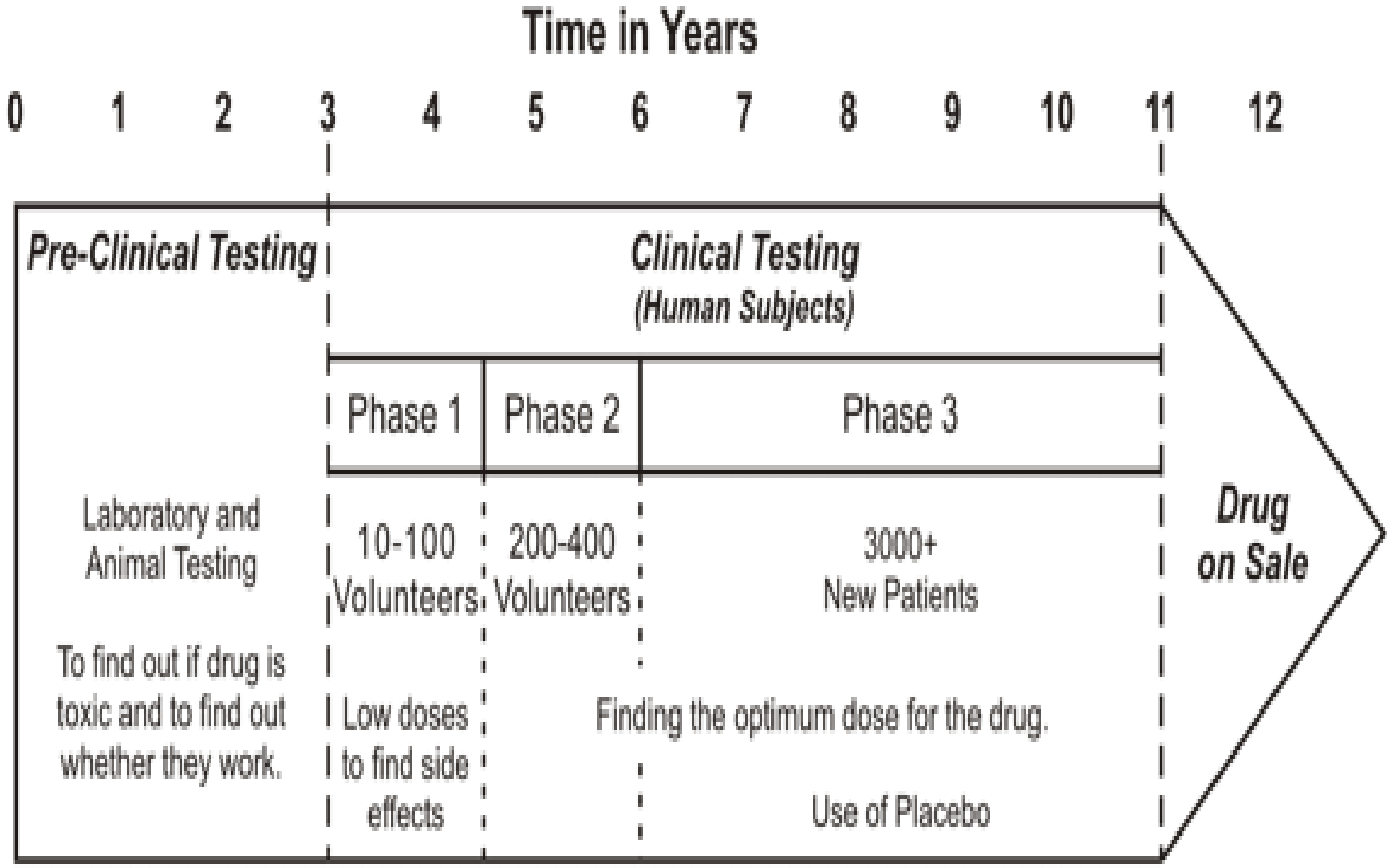
	Patient Aware of Treatment	Physician Aware of Treatment
Open label (Nonblind).	✓	✓
Single-blind.	—	✓
Double-blind.	—	—

Drug Development Process

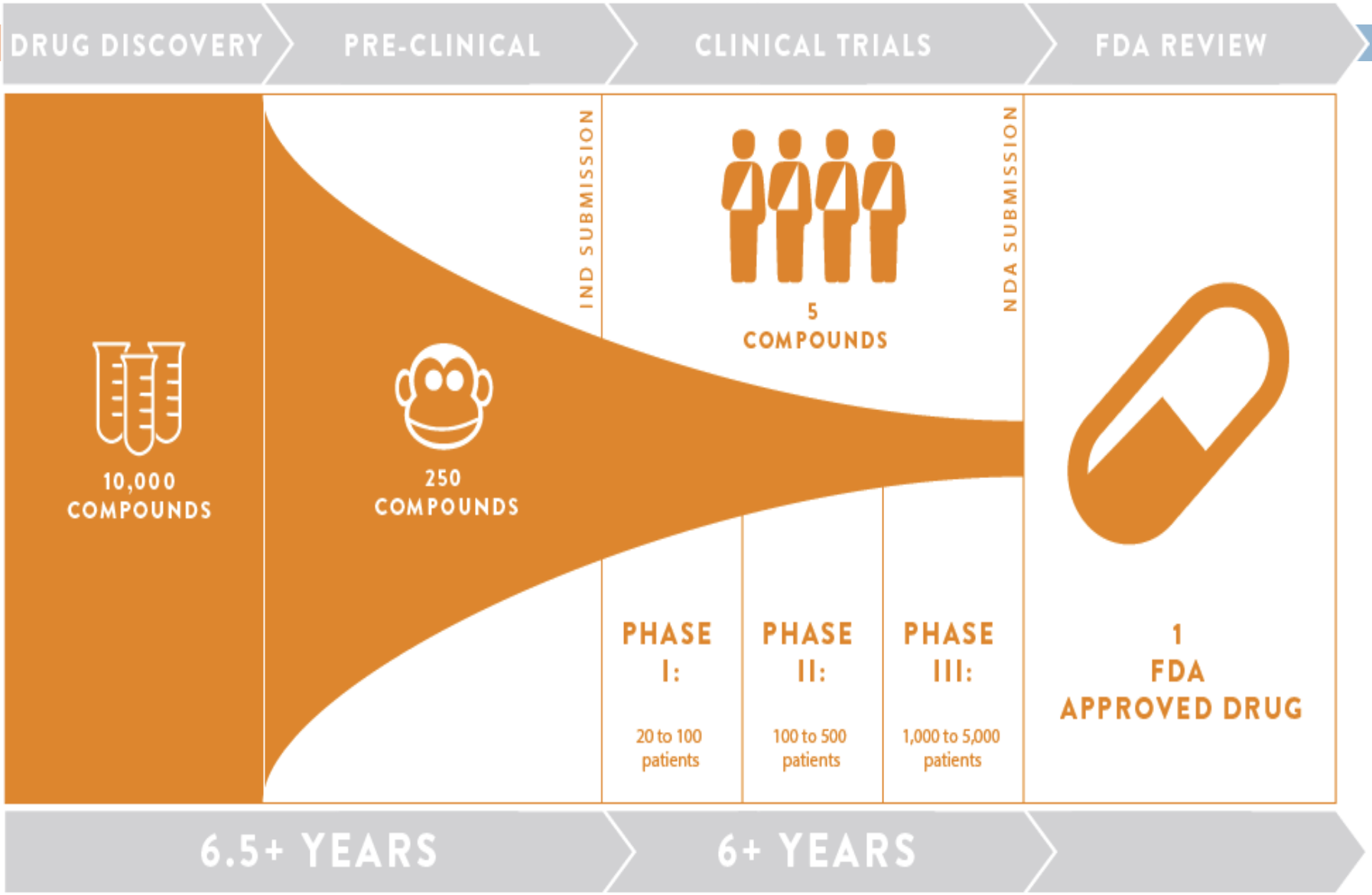


Adapted from US Food and Drug Administration; The CDER Handbook

Drug Development



DRUG DEVELOPMENT PROCESS



HUMAN STUDIES

CONFOUNDIND FACTORS

- Variable natural history of most diseases
- Presence of other diseases and risk factors
- Subjective and observer bias : “placebo “

Stage of Development	Phase 1	Phase 2	Phase 3	Phase 4
End Point	Safety	Efficacy	Efficacy	Efficacy
Specific End Point	Safety Profile	Cardiac Output	Reduction in Mortality Rate	Reduction in Mortality Rate
Types of Studies	Different Indications; Single or Multiple Dose	Placebo Controlled; Dose Escalation	Placebo Controlled; Long Term Follow Up	Comparative; New Indications

HUMAN STUDIES

IND (Notice of Claimed Investigational Exemption for a New Drug) === with FDA

- Involves information about

1. Composition and source of drugs
2. Chemistry and manufacturing of drugs
3. All data from animal studies
4. Proposed clinical plans and protocols
5. Data of research pharmacologists
6. Bio information

HUMAN STUDIES

PHASE 0 (ZERO) CLINICAL TRIALS

- Not designed to be therapeutic
- Limited number of low doses
- Biomarkers and plausible mechanism of action
- Resource management
- Avoiding a waste of efforts and time

HUMAN STUDIES

PHASE 1 CLINICAL TRIALS

- 20 to 100 healthy volunteers
- Safety === to prevent severe toxicity
- AIDS and cancer == diseased volunteers
- Safe clinical dosage range
- Mostly “open”
- May be “blinded” or “placebo controlled”
- Research centers, clinical pharmacologists
- Predictable toxicities, pharmacokinetics

HUMAN STUDIES

PHASE 2 CLINICAL TRIALS

- The study may be blinded or open label
- “proof of concept” = in diseased
- Doses to be used in any follow on trials
- 100 to 200 patients; generally carried out at 2-4 centers.
- ‘Single blind’ with ‘positive control’ drug and a placebo drug
- Special clinical centers like tertiary care hospitals
- Broader range of toxicities/ drug failures

HUMAN STUDIES

PHASE 2 CLINICAL TRIALS

- Conducted by trained physicians on selected patients
- Selected according to specific inclusion and exclusion criteria.
- The primary aim is establishment of therapeutic efficacy, dose range in a controlled setting.
- Tolerability and pharmacokinetics are studied as extension of phase I.

HUMAN STUDIES

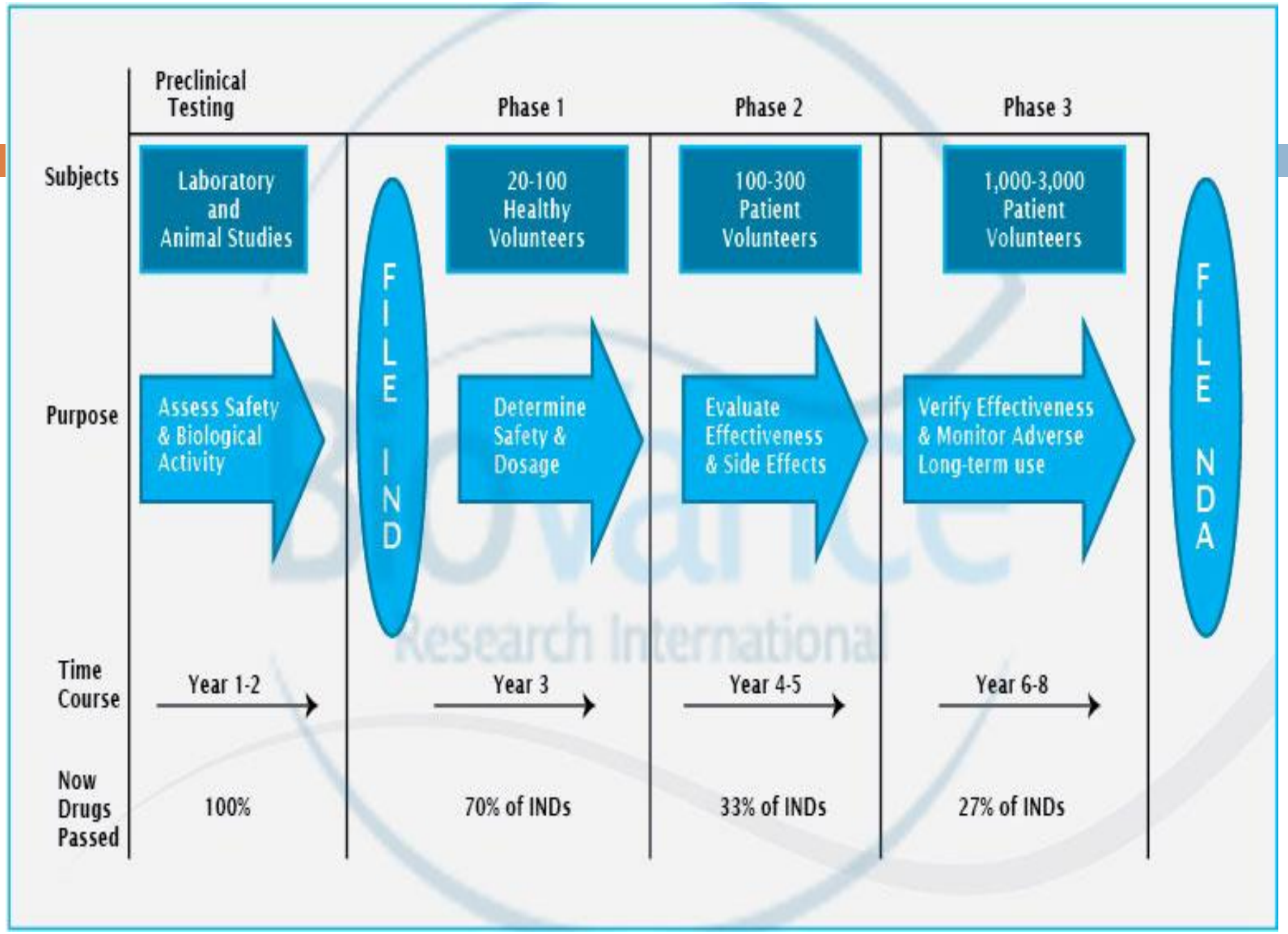
PHASE 3 CLINICAL TRIALS

- Further establish and confirm toxicities, safety and efficacy
- “double blind” or “cross over” techniques
- 500 to > 1000 patients, clinicians
- Difficult to design and execute, expensive
- large data, difficult analysis
- Rare adverse effects, 5 years after IND

HUMAN STUDIES

PHASE 3 CLINICAL TRIALS

- The aim is to establish the value of the drug in relation to existing therapy.
- Safety, tolerability and possible drug interactions are assessed on a wider scale
- Additional pharmacokinetic data may be obtained.
- Indications are finalized and guidelines for therapeutic use are formulated
- A ‘new drug application’ (NDA) is submitted to the licensing authority, who if convinced give marketing permission.


Preclinical Testing
Phase 1
Phase 2
Phase 3
Subjects
Laboratory and Animal Studies
20-100 Healthy Volunteers
100-300 Patient Volunteers
1,000-3,000 Patient Volunteers
Purpose
Assess Safety & Biological Activity
Determine Safety & Dosage
Evaluate Effectiveness & Side Effects
Verify Effectiveness & Monitor Adverse Long-term use
FILE IND
FILE NDA
Time Course
Year 1-2
Year 3
Year 4-5
Year 6-8
Now Drugs Passed
100%
70% of INDs
33% of INDs
27% of INDs

HUMAN STUDIES

New Drug Application (NDA)

Biological License Application (BLA)

- Full report of all preclinical and clinical data
- More than 5000 patients for novel drugs
- Median priority approval time = 6 months
- 50% early controlled marketing
- Approval for launching new drug

HUMAN STUDIES

PHASE 4 CLINICAL TRIALS

- Post marketing surveillance
- Use in the market
- Low incidence adverse effects reported
- Patent = for twenty years after initial application; 14 year after NDA…… ANDA
- Generic

POSTMARKETING SURVEILLANCE / STUDIES

Practicing physicians are identified through whom data are collected

- On structured proforma about the efficacy, acceptability and adverse effects of the drug in large population
- Uncommon/idiosyncratic adverse are detected at this stage.
- Further therapeutic trials involve groups like children, elderly, pregnant/lactating women, patients with renal/hepatic disease, etc.

  (which are generally excluded during clinical trials)
- Modified release dosage forms, additional routes of administration, fixed dose drug combinations, etc. may be explored.

	Preclinical Testing		Phase I	Phase II	Phase III		FDA		Phase IV
Years	3.5		1	2	3		2.5	12 Total	
Test Population	Laboratory and animal studies	File IND at FDA	20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers	File NDA at FDA			
Purpose	Assess safety and biological activity		Determine safety and dosage	Evaluate effectiveness, look for side effects	Verify effectiveness, monitor adverse reactions from long-term use		Review process/ Approval		Additional Post marketing testing required by FDA
Success Rate	5,000 compounds evaluated		5 enter trials				1 approved		

Pre-clinical:
Promising new agents first undergo pre-clinical testing in animals and are designated by the U.S. Food and Drug Administration (FDA) as an Investigational New Drug (IND) if the pre-clinical data is positive. Research then moves on to clinical testing in people through phase I, II and III clinical trials.

Phase I:
Is it safe? This phase determines how the drug works in healthy study participants. Researchers examine the mode of action (how the drug exerts its effects), safety and side effects. The overall safety of the medication in patients is not established at this phase.

Phase II:
Is it effective? This phase determines if a drug's clinical activity may be beneficial against a particular disease or condition. A drug reaches phase II only after the FDA has reviewed the phase I data and concludes the drug is safe enough for patients to proceed with further testing. At this point, a larger group of patients, such as more than 100, is enrolled and rating scales specific to a condition or disease are used to record data.

Phase III:
Can it be used in more patients? At this point, the medication is ready to be studied in a larger population, such as 1,000 patients, with even more advanced rating scales and clinical measures. In recent years, the trend has been to include "real world" measurements—for example, how patients' activities of daily living are improving.

FDA Review: Companies file their New Drug Application (NDA) with the FDA for its review and approval, based on the clinical data supplied from the Phase I-III Clinical Trials.

Phase IV:
Can it be used in different types of patients? At this phase, the FDA has already granted approval, but the study may identify an additional use or gather more safety information from a larger group of patients. These studies can also provide information on how the drug may be best used or best combined with other treatments. Sometimes phase IV studies establish effectiveness in a subgroup of patients, such as patients over age 65.

Years	# Compounds
3.5	5,000
1	5 enter trials
2	
3	
2	1 passed

source: National Psoriasis Organization, www.psoriasis.org/research/pipeline/phases.php

NEW DRUG DEVELOPMENT.

- SYNTHESIS/ISOLATION OF COMPOUND :. → PLANT – Animal. – Molecular modelling.
  - chemical Synthesis – Biotechnology.
  - Rational Approach –

- PRECLINICAL TRIAL → Animals → Test → Screening Test – Toxicity Test.
  - Mechanism of Action
  - Systemic Pharmacology.
  - Pharmacokinetics
- CLINICAL TRIAL → ?

- Phase I (Human Pharmacology and Safety) → open label – (20–40) Patient
- Phase II (Therapeutic exploration and dose ranging) → Blinded or. open label – (100–300) "
- Phase III (Therapeutic Confermation / Comparison) → Double Blinded. – (1000–5000) "
  - → NDA → licencing → Marketing.
- Phase IV (Post marketing Surveillance Studies).

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Email address for queries on the topic

drshams11@hotmail.com