General Pharmacology

Drug development and clinical trials

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Drug Development

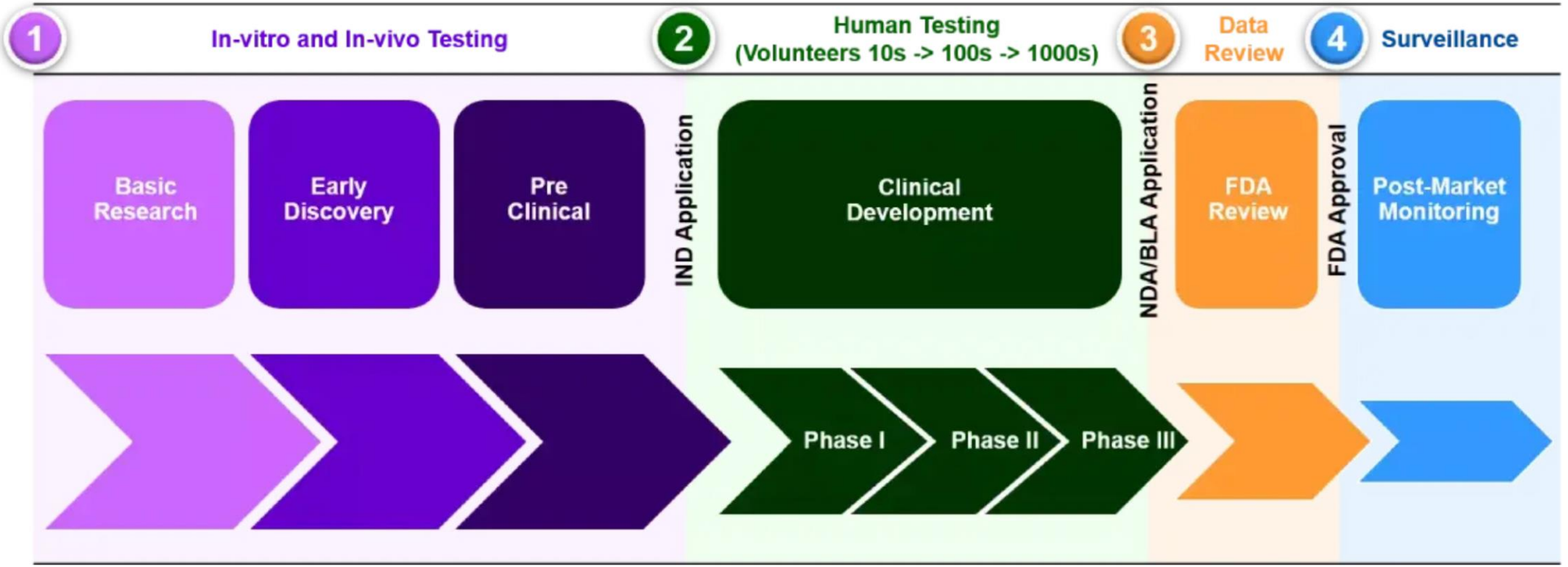
- Drug development is the process of getting a new medication molecule into clinical practice. This includes all phases of the research process, from identifying a potential molecular subsequent assistance with the drug's introduction to the marketplace.
- Drug discovery research is the process by which novel drugs are found. Historically, drug research, design, and development began with the identification of active components in traditional medicines or by chance.
- Later, traditional pharmacology was employed to search **chemical libraries for small molecules, natural products, or plant extracts** having medicinal properties.
- Since the sequencing of the human DNA, reverse pharmacology has used cutting-edge testing to find treatments for diseases that already exist.

Drug Development

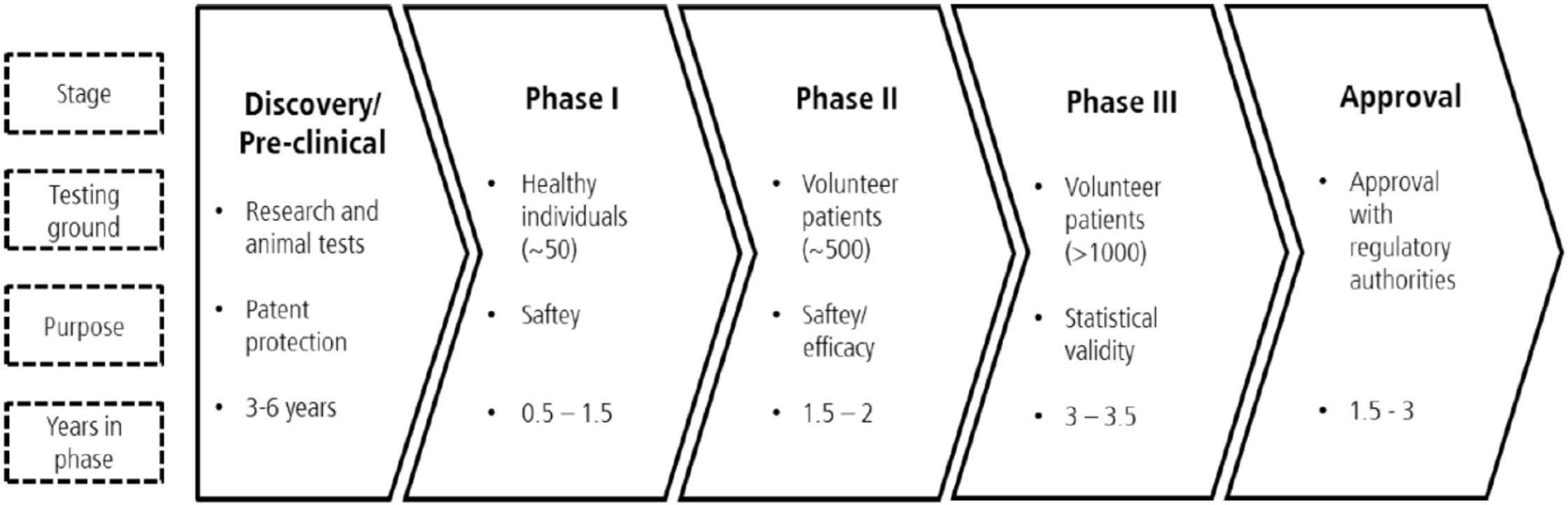
High - risk / high-cost business:

- The process of discovering a new drug and conducting clinical trials to ensure it is safe and effective is estimated to take **15 years** and cost **$2.6 billion** on average!!!
- During the discovery process it takes 5,000-10,000 compounds to get just 5 that will be worthy advancing into the clinical development process (human studies)
- For the 5 compounds that make it into clinical trials, the likelihood of receiving FDA approval is about **12% .**

Drug Development



Drug Development



5 stages of drug Development

Step 1: Drug discovery and development

Target selection

- **Target selection**: is the decision to focus on finding an agent with a specific biological action that is expected to be useful for therapy based on a complex combination of scientific, medical, and strategic factors.

- **Target identification**: to identify molecular targets that are involve in disease progressions.

- **Target validation**: to prove that manipulating the molecular target can provide therapeutic benefit for patients.

Target selection

1. Cellular and genetic target: Drugs are designed to target cellular or genetic substances in the body that are thought to cause disease. Scientists use a variety of methods to uncover and isolate specific targets in order to understand more about their function and disease impact.

2. Genomics: The study of genes and their function. Single nucleotide polymorphism (SNP) libraries are used to compare the genomes from both healthy and sick people and to identify where their genomes vary.

3. Proteomics: Proteomics separates and characterizes proteins in biological systems. Proteomics identifies targets by comparing normal and abnormal tissue protein levels.

4. Bioinformatics:

Bioinformatics is a branch of molecular biology that involves extensive analysis of biological data using computers, for the purpose of enhancing biological research.

Lead discovery

- In the lab, 5 to 50000 compounds are examined, but only 100 to 200 are finalized and tested on in vitro and in vivo systems. **Once the therapeutic target is identified, scientists must identify one or more leads (e.g., chemical compounds or molecules) that interact with it to elicit therapeutic effects.** Compounds should have therapeutic effects on the target. The compounds are next evaluated for toxicity and bioavailability in vivo.
- This data allows medical chemists to change the structure of specific molecules or compounds through screening, resulting in structural analogues.

Step 2: Preclinical Research

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- Preclinical trials examine the new drug's efficacy, toxicity, and pharmacokinetic data in nonhuman subjects. Scientists undertake these trials in vitro and in vivo with unrestricted dosages
- **Researchers discover the following facts regarding the drug:**

1. Data on absorption, distribution, metabolization, and excretion
2. Potential advantages and action mechanisms
3. The best dosage and route of administration
4. Adverse events/side effects
5. Gender, racial, or ethnicity effects
6. Interaction with other medications
7. Efficacy in comparison to comparable medications

Step 3: Clinical trials

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- **Clinical trial**: a prospectively planned experiment for the purpose of evaluating potentially beneficial therapies or treatments
- In general, these studies are conducted under **as many controlled conditions as possible** so that they provide definitive answers to pre-determined, well-defined questions.
- Clinical trials are the **most definitive method to ultimately determine treatment effectiveness.**
- Clinical trials **help determine incidence of side effects and complications.**

Elements of Clinical Protocols

- **Objectives – Primary and Secondary**
- **Biostatistics**
- **Patient selection criteria – Inclusion/Exclusion**
- **Therapeutic Intervention**
  - **Dose and Schedule and Mechanism/Route of Delivery**
- **Clinical Work-up and Follow-up Assessment**
- **Toxicity**
  - **Toxicity criteria**
  - **Dose modifications**
- **Efficacy**
  - **Clinical, pharmacodynamic (PD) and QOL**
- **Analysis and interpretation**
  - **Primary & secondary endpoints**
  - **Correlative studies**

Definitions

- **Single Blind Study**: A clinical trial where the participant does not know the identity of the treatment received
- **Double Blind Study**: A clinical trial in which neither the patient nor the treating investigators know the identity of the treatment being administered.
- **Placebo:**
  - Used as a control treatment

    1. An inert substance made up to physically resemble a treatment being investigated
    2. Best standard of care if “placebo” unethical
    3. “Sham control”
    4. Used in Randomized trials
- **Adverse event:**
  - An incident in which harm resulted to a person receiving health care.

Phase I Trial

This phase is the **first time the drug is tested on humans**

Healthy volunteers: less than 100 volunteers will help researchers **assess the safety and pharmacokinetics.**

Double-blind, randomized, placebo controlled

Investigate:

- Safety/tolerability and identify maximally tolerated dose (MTD)
- Possible drug-drug interactions (DDI)
- Food interactions and absorption

Phase I Trial

Risk-Benefit Ratio

- Some toxicities can be managed and may be acceptable while others are not:

Treatment of aggressive cancers vs treatment of hypertension

- Pharmacogenomics: patients with certain genetic predisposition

e.g., Patients with the HLA-B*1502 genetic variant can lead to Stevens-Johnson syndrome (severe skin disorder) when treated with carbamazepine

Phase II Trial

WHO

- Group of patients with the disease or disorder being studied

HOW MANY

- Several hundred participants in common disorders
- May enroll 30-80 in rare disease

WHERE

- A few locations
  - Hospitals
  - Clinics

Phase II Trial (efficacy)

- Further assess safety of the drug in a larger group of patients.
- Gather preliminary information on safety and potential efficacy for the dose(s) being studied, to know if it is appropriate for a larger Phase 3 clinical trial.
- To accurately compare safety and effectiveness while on and off the drug, includes a comparison group such as placebo (no drug) or active comparators (already approved drug).
- Does it relieve, reverse or stop the progression of the condition?
- **Approximately 33% of drugs move to the next phase**

Phase III Trial

WHO

- Group of patients with the disease or disorder being studied

HOW MANY

- Several hundred to thousand patients
- May be ~70-150 in rare diseases

WHERE

- Many locations (multi-center)
  - Hospitals / Clinics
- Possibly several countries

Phase III Trial (conformation)

- Demonstrate whether or not a product offers benefit to a specific population of people.
- Compare product to other treatments (or placebo) to see if it is more effective, less effective or the same
- Provide more safety information in a larger group of patients
- Treatment is longer in duration to monitor maintenance of efficacy and show any longer-term or rare side effects.
- **Approximately 25-30% of drugs move to the next phase**

Step 4: FDA Approval

FDA Approval

- Once the new drug has been formulated for its best efficacy and safety, and the results from clinical trials are available, it's advanced forward for FDA review.
- At this time, the FDA reviews and approves, or does not approve, the drug application submitted by the drug development company.
- **Regulatory Approval Timeline**
- The new drug regulatory approval timeline may be standard, fast track, breakthrough, accelerated approval, or priority review depending on its applications and necessity for patients
- **IND Application**
- IND applications are submitted to the FDA before starting clinical trials.
- **NDA / ANDA / BLA Applications**
- An NDA abbreviated new drug application (ANDA), or BLA is submitted to the FDA after clinical trials demonstrate drug safety and efficacy.

FDA Approval

- **Orphan Drug**
- An orphan drug is intended to treat disease so rare that financial sponsors are unwilling to develop it under standard marketing conditions.

- Recognizing the difficulty of clinical trials in rare patient populations, the US Congress passed the Orphan Drug Act to facilitate development of treatments for rare disorders

- **Accelerated Approval**
- New drugs may be granted accelerated approval if there is strong evidence of positive impact on a surrogate endpoint instead of evidence of impact on actual clinical benefits the drug provides. Expedition of approval means the medication can help treat severe or life-threatening conditions.

Reasons For Drug Failure

- **Toxicity**: If the toxicity of a new drug is too high in human or animal patients, the drug may be rejected due to safety concerns about its use following manufacture.
- **Efficacy**: If a new drug's efficacy is not high enough or evidence is inconclusive, the FDA may reject it.
- **Pharmacokinetics Properties**: poor bioavailability due to low aqueous solubility, or high first-pass metabolism, or inadequate action duration, or unanticipated human drug interactions may cause a drug to fail FDA review.
- **Inadequate Drug Performance**: If the new drug performs the desired function, but only at a shallow level, the FDA may reject the application in favor of a formulation that performs better.

Step 5: Post-Market Monitoring

Post-Market Monitoring

- Following drug approval and manufacturing, the FDA requires drug companies to monitor the safety of its drug using the FDA Adverse Event Reporting System (FAERS) database.
- FAERS helps FDA implement its post-marketing safety surveillance program.
- Through this program, manufacturers, health professionals, and consumers report problems with approved drugs.

Summary of the FDA drug approval process