New drugs: development &evaluation

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Introduction

- New drug development is a **lengthy (12-30 years), coasty (2 billion dollars)**, **multi-stage process** .
- These **candidate drugs** then undergo rigorous **clinical trials** in **humans** to assess **safety** and **effectiveness**, leading to a **formal regulatory submission for approval.**
- If approved, the drug **enters post-market surveillance** to monitor its **ongoing safety** and real-world **performance**.

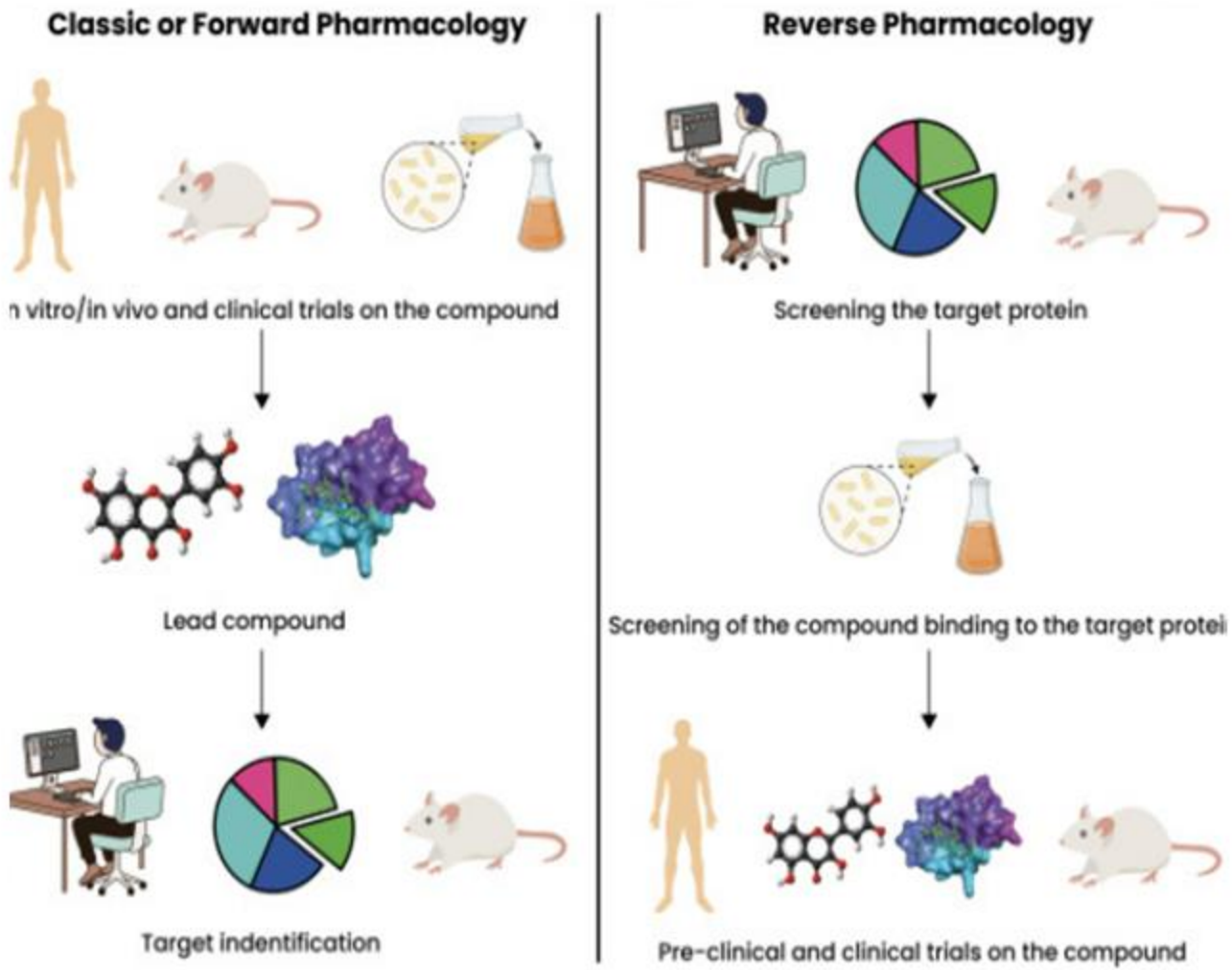
Stages of New Drug Development

- **The Five Main Stages of New Drug Development:**
- 1- Discovery and Development
- 2- Preclinical Research
- 3- Clinical Research
- 4- FDA Review
- 5- Post-Market Safety Monitoring

1- Discovery and Development

- This initial phase involves **extensive research to understand the biology of a disease** and **identify potential molecular targets**.
- Researchers then **screen thousands of compounds** in the laboratory to find those that show promise in affecting the target.
- **The goal** is to **identify a "lead compound"** that can then be refined.
- **Lead compounds** are chemical compounds that show desired pharmacologic activity against therapeutically relevant targets and can be used as base structures for drug optimization

Scientific methods (approaches) of drug discovery



Reverse pharmacology approach(clinic-to-lab) (target-based)

- A method for drug discovery that **starts with clinical observations and traditional knowledge** and **then moves to the laboratory**
- **Advantages:**
- 1- Less time consuming
- 2- Less cost
- 3- Suitable more for natural products
- **Example:**
- Using traditional remedies like the **Indian snakeroot plant** to develop modern drugs like **reserpine,** an antihypertensive and tranquilizing agent.

Target-based Drug Discovery: reverse pharmacology approach

- Drugs typically act by engaging a molecular target.
- **Defining a specific target is the first step** and by far, the richest source of targets for drugs are **protein targets** which play a key role in disease pathogenesis.
- This approach involves **screening of compounds for specific activity against known targets** associated with disease pathogenesis.

Forward pharmacology (lab-to-clinic) approach

- **A traditional drug discovery method** that **screens compounds to find ones with a desired therapeutic effect in an organism or cell**.
- After a **"hit" compound** is identified based on its overall effect, researchers then work **backward** to determine its **specific biological target**
- **Disadvantages**: time consuming and expensive
- **Examples:**
- Aspirin from willow bark
- Morphine from the opium poppy

Willow plant

Willow park

Opium poppy

Forward pharmacology approach

- **Candidate products are chosen according to their pharmacological actions, through:**
- **1- Random screening:** **blind process** in which **new compound** (natural or synthetic) subjected to **pharmacological screening** to find its pharmacological activities: **animal studies**: models of human diseases and isolated organs.
- **Disadvantages**: time-consuming and expensive
- **Advantages**: **valuable** as many drugs were discovered this way: morphine, atropine, digitalis and quinidine

Forward pharmacology approach

- **2- Serendipity (happy observation):**
- **A new use is discovered for old drug** or **its side effect has a new therapeutic use:**
- **Lidocaine**: local anesthetic used as antiarrhythmic
- **Methotrexate:** anticancer used for psoriasis

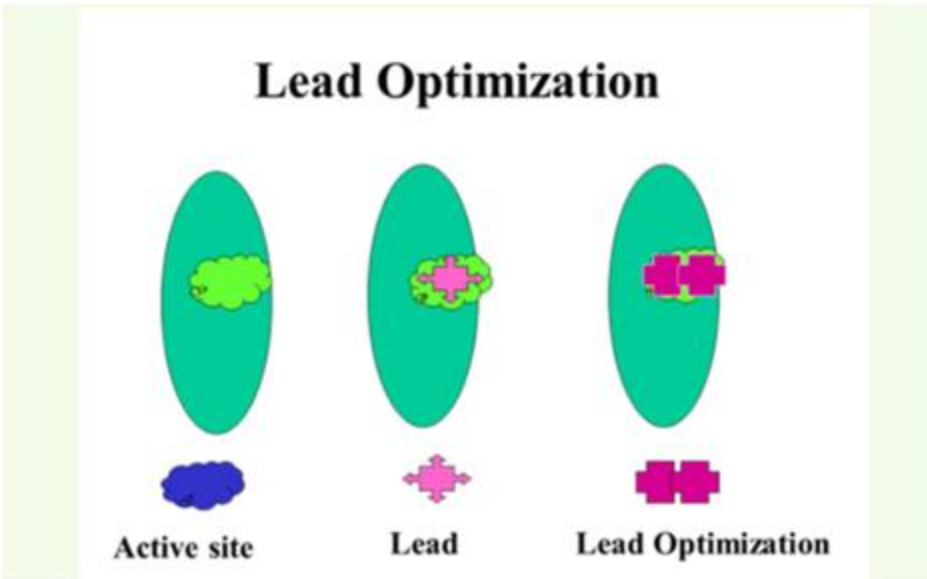
Forward pharmacology approach

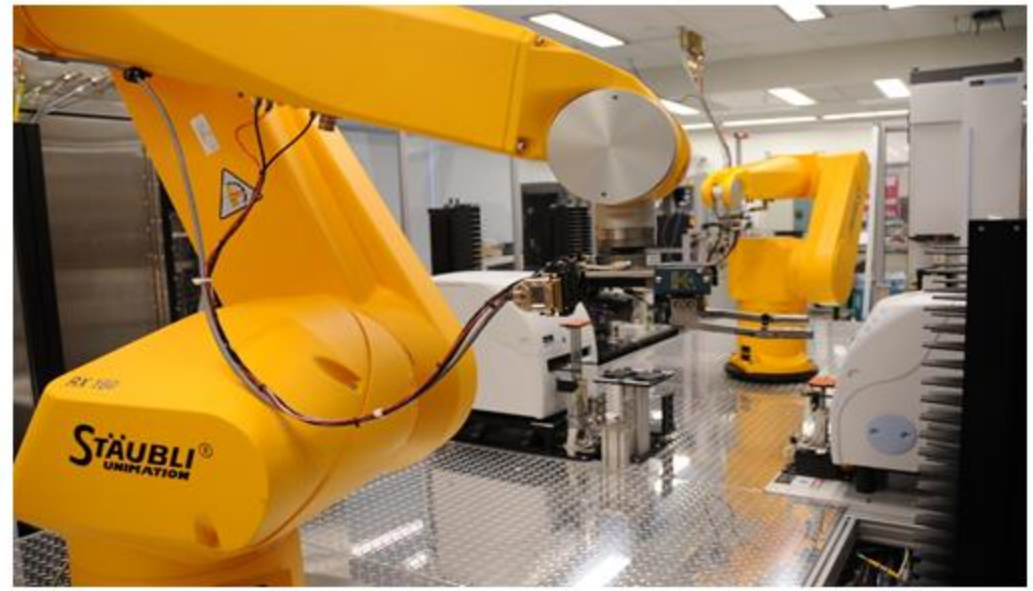
- **3- Rational drug designing by 2 approaches:**
- **Compound-centered approach**: obtaining **lead product** from **natural source**: penicillin from the fungus: penicillium notatum
- **Target-cenetred approach**: obtaining **lead product** from **synthetic product**: beta blockers are based on propranolol structure

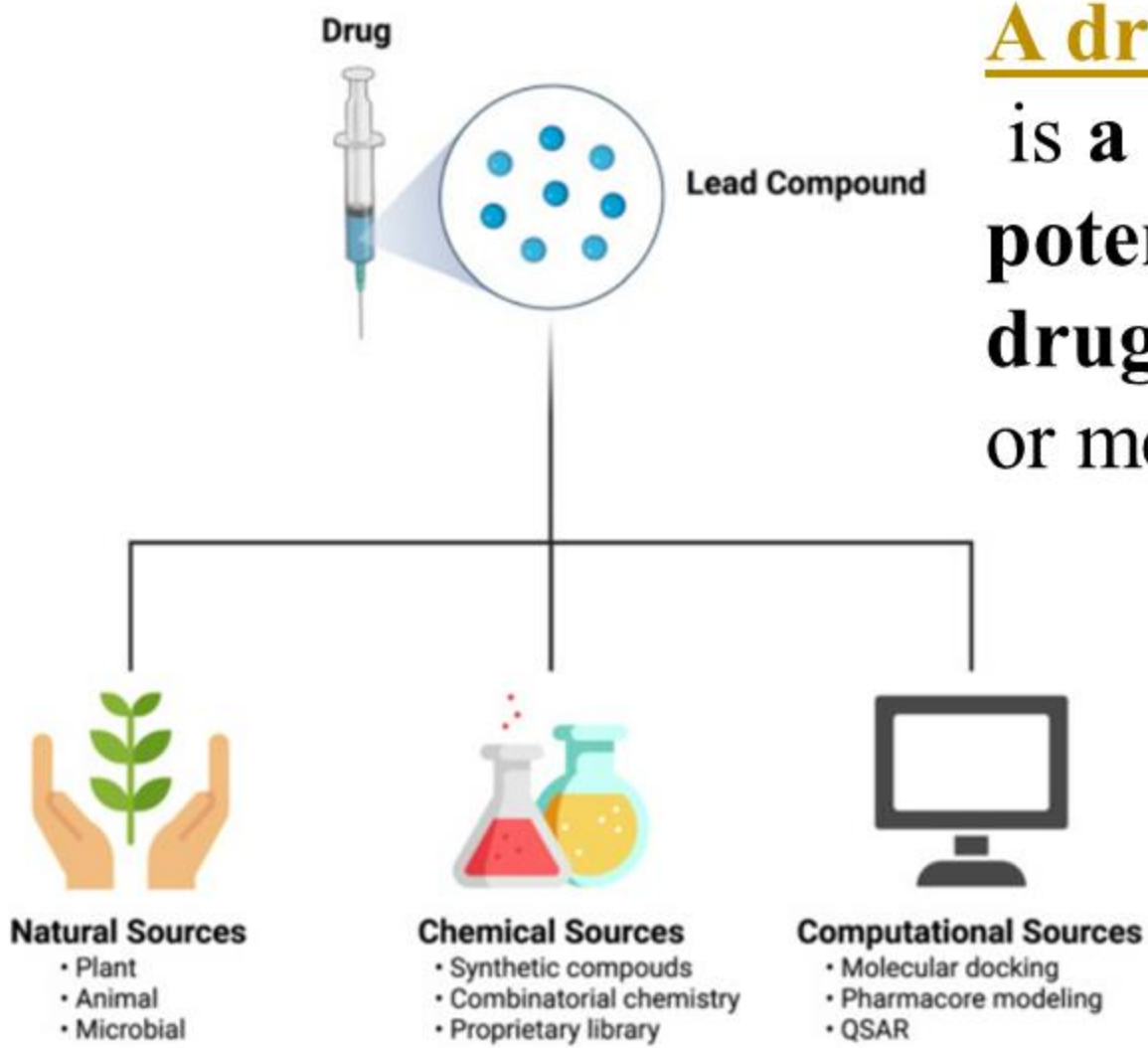
•**Lead optimization:**

•to identify **one or two drug candidates** suitable for further investigation by:

•**High-throughput screening (HTS)** is one of the newest techniques used in drug design applied by robots, detectors and software .







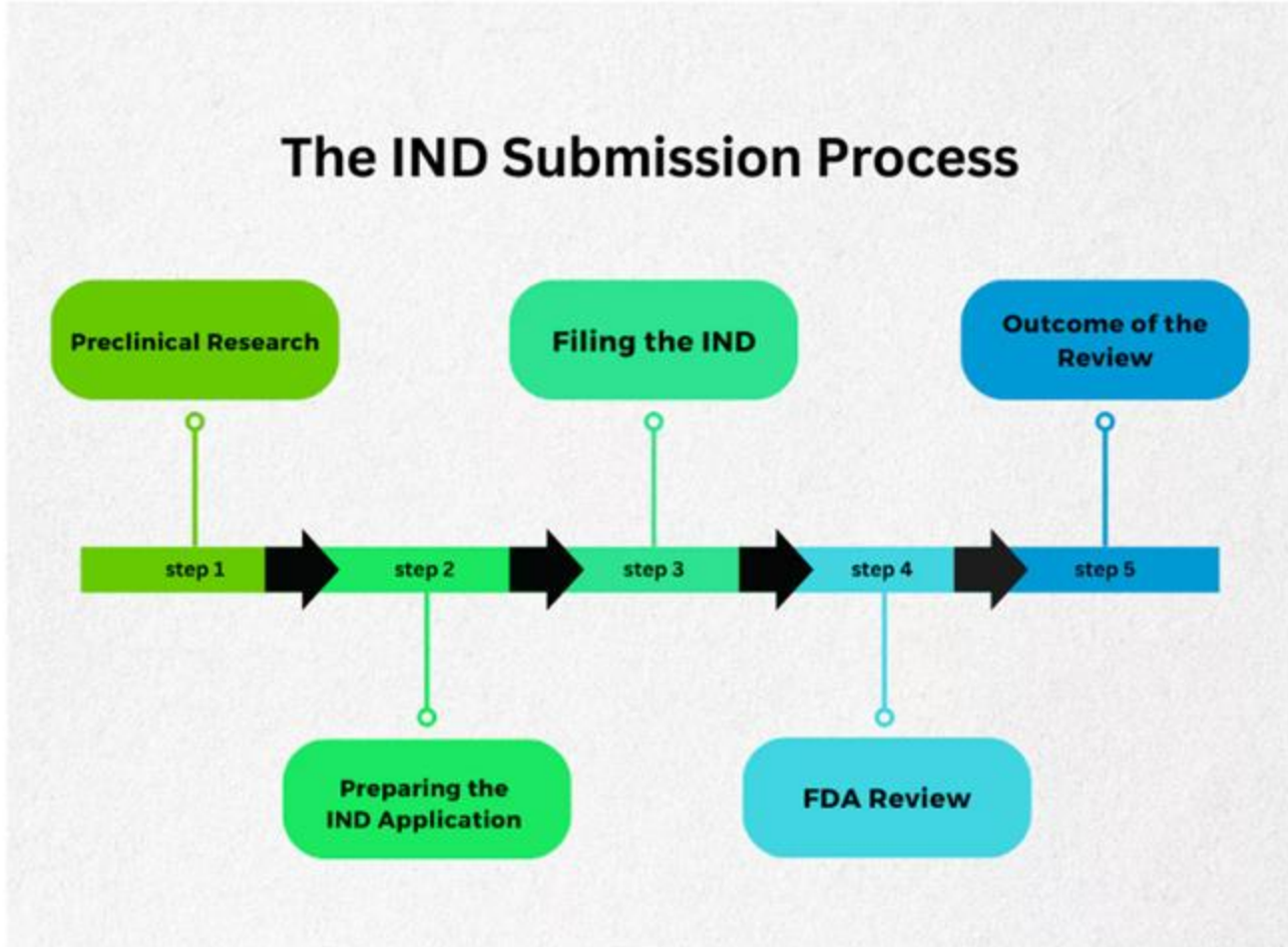
A drug candidate:

is **a molecule that has shown potential to become a therapeutic drug** for treating a particular disease or medical condition.

2- Preclinical Research

- The **lead compounds and candidate drug(s)** are tested both **in vitro and in vivo – experimental models** (cell cultures and animal studies) **(animal models).**
- Once fully characterized, the most promising **lead compounds** become **drug candidates.**
- **This stage evaluates:**
- Drug's safety
- Drug's toxicities
- Drug's effectiveness
- **Before any human trials begin**.

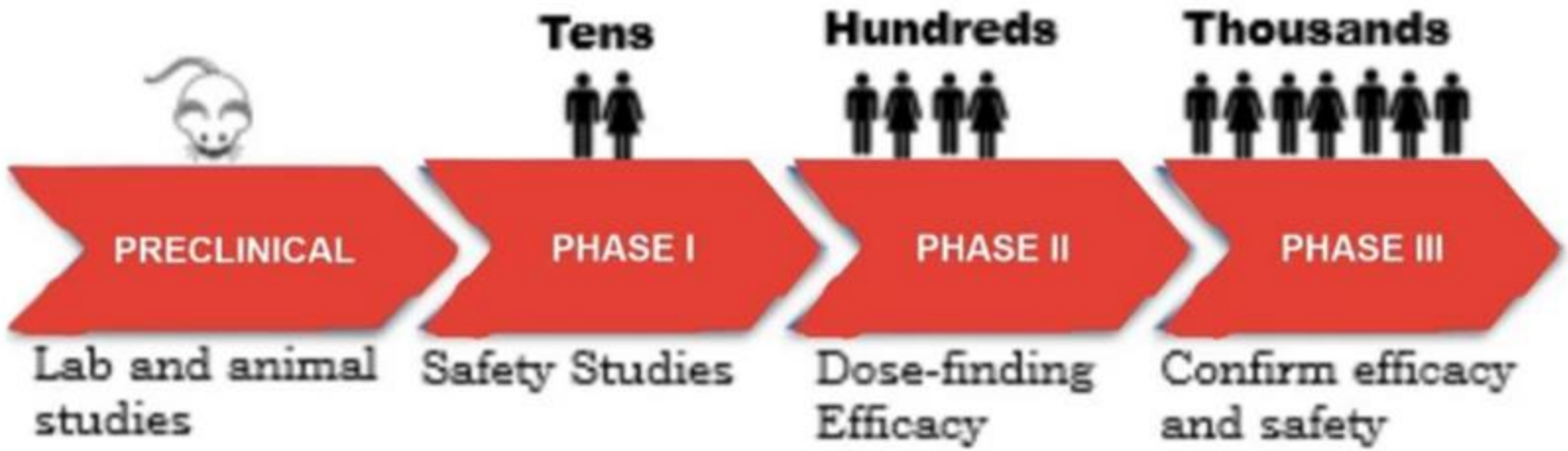
- **The discovery phase and the preclinical phase can take 4-7 years.**
- After completion of the preclinical tests, developers will **apply for permission to proceed with clinical – in-human – studies**.
- This is done either through an ***Investigational New Drug (IND)* application** in the US or a ***Clinical Trial Application* (CTA)** in the EU.
- The **respective regulator authority** then examines all available data and decides whether to approve the clinical studies:
- **FDA**: Food and Drug Administration in US
- **JFAD**: Jordan Food and Drug Administration
- **EDA**: Egyptian Drug Authority


The IND Submission Process
Preclinical Research
Filing the IND
Outcome of the Review
step 1
step 2
step 3
step 4
step 5
Preparing the IND Application
FDA Review

3- Clinical Research

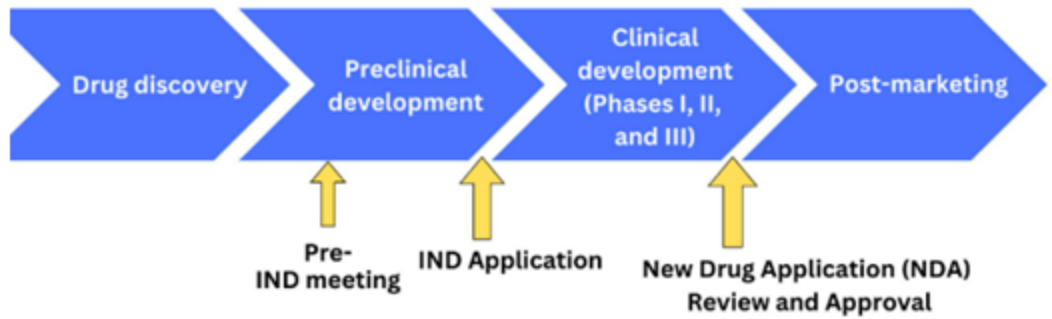
- If the preclinical data suggests the compound is **safe enough**, the developer files an **Investigational New Drug (IND) application** with regulatory agencies like the U.S. Food and Drug Administration (FDA).
- **Clinical trials**, conducted in a **controlled manner on human subjects**, assess the drug's **safety** and **effectiveness**.
- **These trials are typically divided into phases:**
- **Phase I**: **Small** group (20-80) of **healthy volunteers** to assess **safety and dosage**. (**1 year**)
- **Phase II**: **Larger group** of **patients** (100-300) for **2 years** with the condition to evaluate **effectiveness** and **side effects**.
- **Phase III**: **Large-scale (thousands of patients), long-term trials (1-4 years)** to **confirm effectiveness**, **monitor side effects**, and **compare with existing treatments**.

Phases of Clinical Trials



4- FDA Review

- **After a successful Phase III trial**, **a New Drug Application (NDA)** is submitted to regulatory authorities.
- **The FDA** then conducts a **thorough review** of **all data**, **manufacturing processes**, and **labeling** **to ensure the drug meets safety and efficacy standards for market approval**.
- Preparing the application documentation can take several months, followed by about 6-10 months for the authorities to process the application.



Market launch

•If the regulatory authorities approve an application, the candidate – or **medicine (drug) as it is now called – is ready for market launch.**

•At this point, **price negotiations** begin between the principal and the potential buyers (government agencies or insurance companies, depending on the healthcare system).

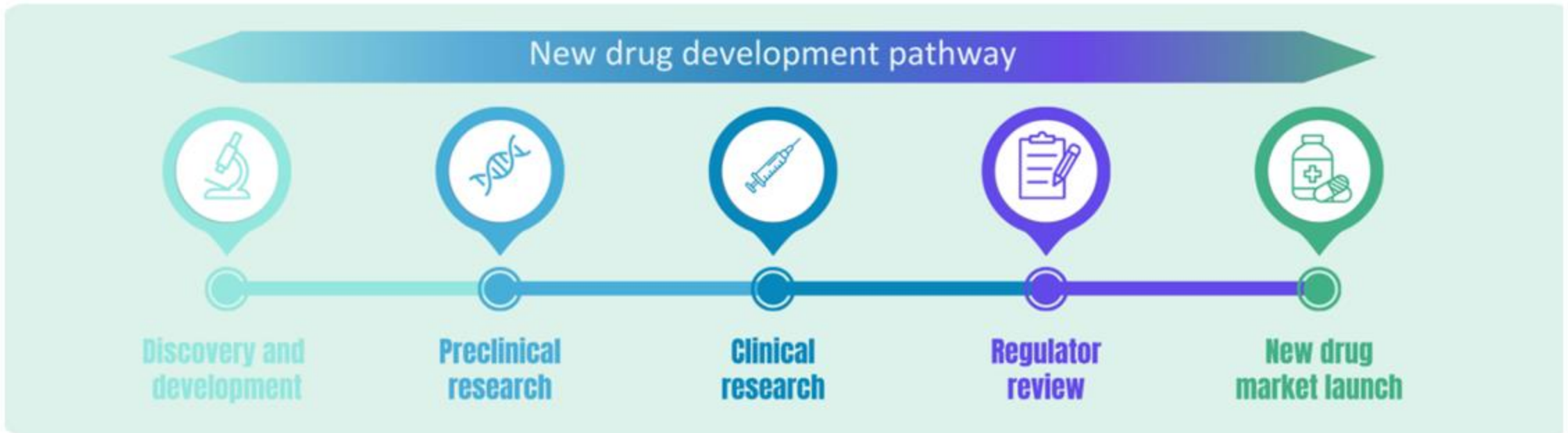
• The price negotiation process can differ greatly from country to country.

5- Post-Market Safety Monitoring (phase IV)

- **Even after approval**, the drug continues to be **monitored for safety** in the general population.
- **This involves:**
- Collecting feedback from **doctors** and **patients** to **identify any long-term adverse effects or other issues.**
- Additionally, phase IV studies may be relevant for drugs that will treat **rare conditions**, which had a limited number of patients in phases I-III.

Examples of drugs withdrawn from the market

- **Trovafloxacin (fluoroquinolone antibiotic):**
- **Withdrawn worldwide in 2016:** serious hepatotoxicity leading to liver transplant or death.
- **Phenformin (antidiabetic drug): in 1977**: sever lactic acidosis
- **Ranitidine (decreasing stomach HCL production)**: **worldwide 2020**: Found to spontaneously break down into the carcinogen
- **Rofecoxib (Vioxx) (analgesic): worldwide 2004**: myocardial infarction and stroke
- **Terfenadine (antihistaminic)**: **1998**: prolong Q-T interval: ventricular tachycardia
- **Thalidomide: 1961**: teratogenicity


New drug development pathway
Discovery and development
Preclinical research
Clinical research
Regulator review
New drug market launch

Stages of drug discovery

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Thank you