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Integrated ADME Approaches in Rational Drug Design and Development

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Abstract: ADME studies are essential to the successful development of pharmaceutical compounds and offer detailed insights into a drug's pharmacokinetic profile. These important determinants collectively known as Absorption, Distribution, Metabolism, Excretion (ADME) play a critical role in the assessment of new compound safety and efficacy and therapeutic performance. The present review provides an in-depth analysis of the role and importance of ADME studies from discovery to development of new drugs. These studies encompass drug absorption, distribution, metabolism, bioavailability excretion allowing the use of knowledge for the purposes of optimizing drug design, improving bioavailability and reducing toxicity thereby predicting drug-drug interactions. In the present scenario of pharmaceutical research, ADME profiling is employed both in preclinical and clinical stages so that desired result showing candidate get select with favourable dose. Early identification of error or unfavourable pharmacokinetic properties reduces the risk of attrition during stages of drug development thereby save time, money and resources. Moreover, ADME studies contribute to the development of safer and effective therapeutic agents by ensuring an appropriate balance between pharmacological activity and systemic exposure. Overall, ADME evaluation remains an important strategy for advancing drug candidates from discovery to clinical application

Keywords: *Absorption, Distribution, Metabolism, Excretion, Drug-Drug Interaction, Candidate Selection, Optimised Drug Design.*

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I. INTRODUCTION

Additionally, ADME studies—a scientific discipline including Absorption, Distribution Metabolism and Excretion—represent an important part of the drug development process by predicting the in vivo behaviour of a drug candidate impacting its eventual safety and efficacy At the beginning of drug discovery many compounds show biological activity but only few are able to advance into well-tolerated drugs due to restrictive pharmacokinetic properties . Absorption describes how a drug enters the bloodstream, particularly important for oral drugs where factors like solubility, permeability, and gastrointestinal conditions affect bioavailability. Once absorbed, the drug undergoes distribution, where it is transported through the bloodstream to different tissues and organs, influenced by blood flow, plasma protein binding, and lipophilicity, ultimately determining whether it reaches its target site in effective concentrations. Drugs are converted into more water-soluble metabolites for removal by metabolism, which mostly takes place in the liver through enzymes like cytochrome P450. This process can either inactivate drugs, activate prodrugs, or occasionally produce toxic intermediates, making it a crucial factor in determining the safety and duration of action of drugs. The drug and its metabolites are eliminated from the body by excretion, primarily through the kidneys or bile, and effective removal is required to avoid buildup and toxicity. [1].

Together, these processes define the pharmacokinetic profile of a drug and guide important decisions in lead optimization, where chemical modifications are made to improve bioavailability, reduce toxicity, and enhance stability. ADME studies also help predict drug–drug interactions, understand variability among patients, and support dose selection during clinical trials. In addition, the efficacy of ADME evaluation has been enhanced by contemporary techniques like microdosing, high-throughput screening, and in silico modeling. Before approving new medications, regulatory bodies need thorough ADME data to be sure they are both safe and effective. All things considered, ADME investigations work as a link between in vitro activity and clinical success, guaranteeing that a drug candidate has both pharmacological activity and the qualities required to function well in the human body [2].

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II. ABSORPTION

The way foreign chemicals (xenobiotics) entering the body's bloodstream. The main spot is the gut, but it can also happen through skin (our key shield from the outside world) lungs (especially for gases, vapours, sprays, or dust). No matter the entry point, these chemicals must pass through cell membranes to reach circulation—and this happens via one of two basic mechanisms**.** [3] Small, fat-loving (lipophilic) chemicals slip through cell membranes easily via passive diffusion, driven by a concentration difference from high to low. This process speeds up with a steeper gradient and the chemical's higher oil-to-water preference. Chemicals that are charged, larger, or water-loving (polar) cannot accomplish this on their own. For active transportation across a membrane, they depend on unique carrier proteins.[4].

➢ *Bioavailability*

The portion of a drug dose that reaches the bloodstream unchanged after administration. It affects the dosage needed based on the drug and delivery method. An intravenous (IV) dose provides 100% bioavailability since it directly enters the bloodstream.[5]

➢ *First Pass Metabolism*

After absorption, drugs can get broken down (metabolized) right in the gut wall before heading to the liver through the hepatic portal vein. Liver cells (hepatocytes) handle most drug metabolism, often zapping a lot of the compound before it hits the bloodstream.[6] First-pass elimination is the amount of a drug that is absorbed from the gut but gets broken down by the gut or liver before it reaches the heart.[7]

➢ *Classification of Mechanism of Drug Intestinal Membrane Transport*

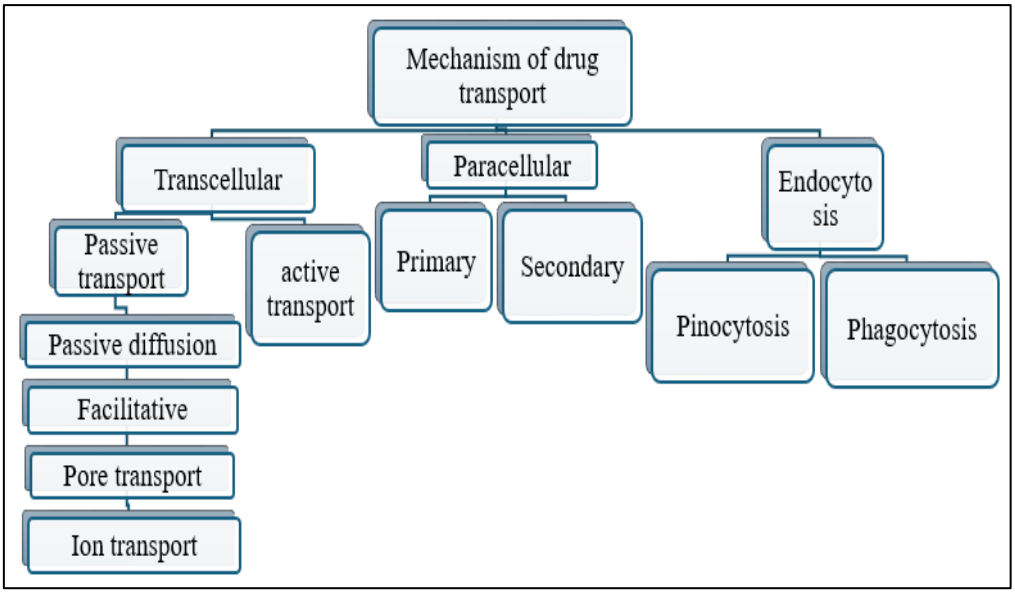

Fig 1 Classification of Drug Transportation

➢ *Passive Diffusion*

- Molecules move from an area of higher concentration to an area of lower concentration without using energy.
- Drugs must be lipid-soluble to cross the phospholipid bilayer.
- Fick's law states that the rate increases as the concentration gradient increases.

➢ *Carrier-Mediated Processes*

Drugs must closely mimic natural ligands to bind carrier proteins, allowing passive or active membrane crossing.

➢ *Facilitated Diffusion*

- Passive process that uses no energy.
- Faster than simple diffusion but still follows the concentration gradient; limited by carrier protein availability.

➢ *Active Transport*

- Energy-dependent: Carrier proteins hydrolyse ATP to power a pump.
- Moves drugs against the concentration gradient.

➢ *Ion Channel Passage*

- Membrane pores are highly selective (leak channels, voltage-gated, ligand-gated, and mechanically gated).
- It requires a concentration gradient and small molecule size (less than 100 Da)

➢ *Pinocytosis*

- The membrane folds inward to surround the molecule and nearby fluid, forming a vesicle for uptake.
- This process is suitable for larger molecules. [8]

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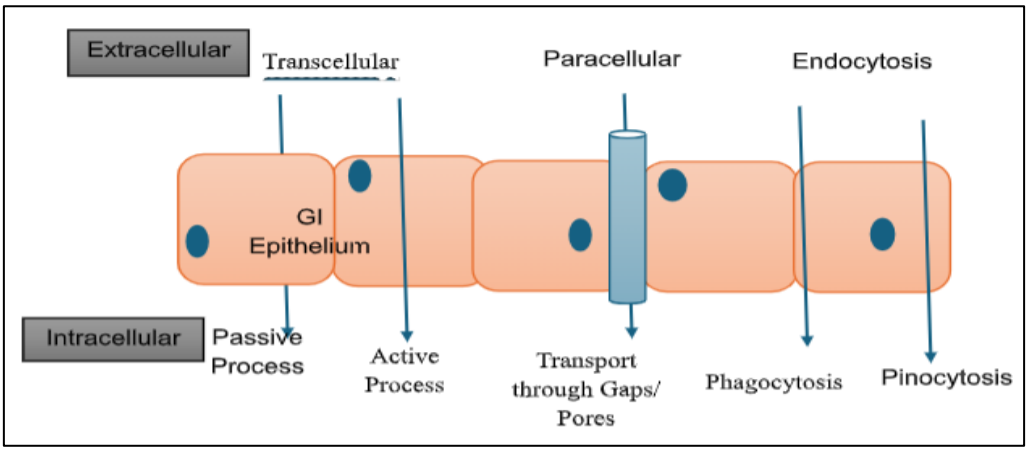

Fig 2 Types of Drug Transport Across Cell Membrane

III. DISTRIBUTION

After a drug enters the bloodstream, its distribution to body tissues depends on blood flow to those areas, passive diffusion across fatty membranes, active transport by specific transporters, and its binding to proteins in the blood or tissues. Most tissue barriers act like lipid walls, letting small fat-soluble molecules pass freely. Bigger or more water-soluble substances can't slip through passively—they need special transporters to get in. [9}

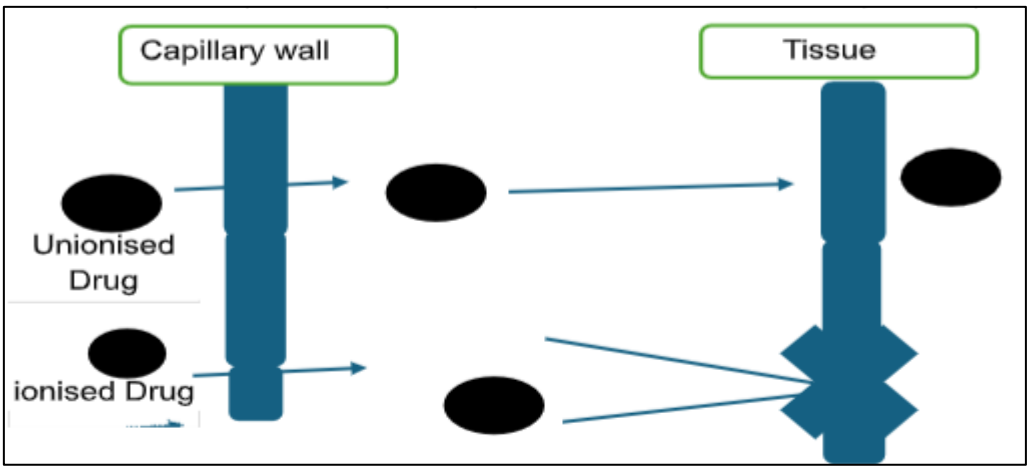

Fig 3 Distribution of Ionised/Unionised Drug

➢ *Protein Binding*

Human serum albumin (HSA), with a molecular weight of 66 kDa, is the main transport protein in blood, despite many molecules binding to other blood proteins like blood cells and serum proteins. It has a high capacity to bind both natural and foreign compounds in plasma (10). HSA binds with acidic or basic drugs (like warfarin, ibuprofen, and diazepam) and natural plasma substances through van der Waals forces, hydrophobic interactions, hydrogen bonds, ionic bonds, and other attractive forces (11).

In contrast, α-1 acidic glycoprotein (AGP), an acute-phase protein, mainly binds to basic compounds, while lipoproteins bind to both basic and neutral drugs. However, some acidic drugs can also bind to AGP[12].

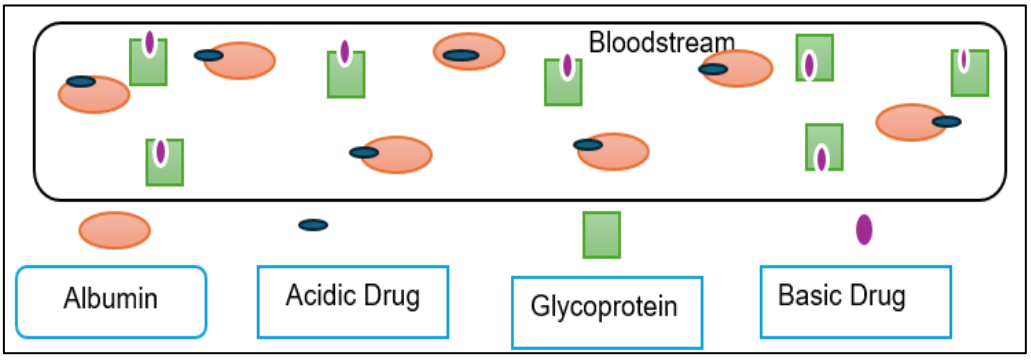

Fig 4 Binding of Drug with Different Types of Proteins

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➢ *Tissue Binding*

Several binding agents besides albumin disrupt drug binding to different tissues. The impact of tissue binding varies with each tissue's volume—for instance, since muscle makes up roughly 40% of body mass, muscle binding often drives overall tissue binding. Furthermore, muscle binding could be just as significant as plasma binding (13).

In tissues, ligandin—a major anion and binding protein—interacts with corticosteroid binder I and Y protein. It has a molecular weight of 42 kDa and makes up about 4% of rat liver protein, with significant amounts also found in kidney tubule cells and small intestine mucosal cells. Ligandin binds endogenous and exogenous substances noncovalently, showing varying strengths of binding [14]. Theoretical calculations of how much anionic drugs bind to plasma and tissue samples in the lab closely matched the actual tissue-plasma ratios seen in living organisms. However, lipophilic cationic drugs showed significant differences between the predicted and observed tissue-plasma ratios (15).

IV. METABOLISM

The metabolism of a new chemical entity by the host system is essential in shaping its pharmacokinetic profile. For most xenobiotics, metabolic transformation paves the way for their elimination from the body. Thus, any factor influencing the speed or degree of metabolism can significantly change the xenobiotic's overall disposition. Typically, metabolism inactivates drugs, but it can also produce active metabolites that drive all or part of the pharmacological effect. [16] Drug metabolism reactions fall into two main categories: Phase I and Phase II.

➢ *Phase I Reactions*

Modify molecules by adding polar groups. This includes breaking down ester or amide groups into acids and alcohols or amines, adding hydroxyl groups to aromatic or aliphatic carbons, removing alkyl groups from heteroatoms in secondary or tertiary amines, ethers, and thioethers, and oxidizing nitrogen or sulfur atoms. The resulting Phase I metabolites can either be excreted directly or further processed in Phase II before elimination. The main enzymes involved in Phase I are the cytochrome P450 (CYP) family, flavin-containing monooxygenases, esterases, and amidases.

➢ *Phase II Reactions*

Modify the parent molecule or its Phase I metabolite by adding polar groups, creating conjugates that are more water-soluble and easier to eliminate. Common Phase II processes include glucuronidation, sulfation, and glutathione conjugation. Some compounds, like ibuprofen, which already contain polar groups, can undergo conjugation directly.

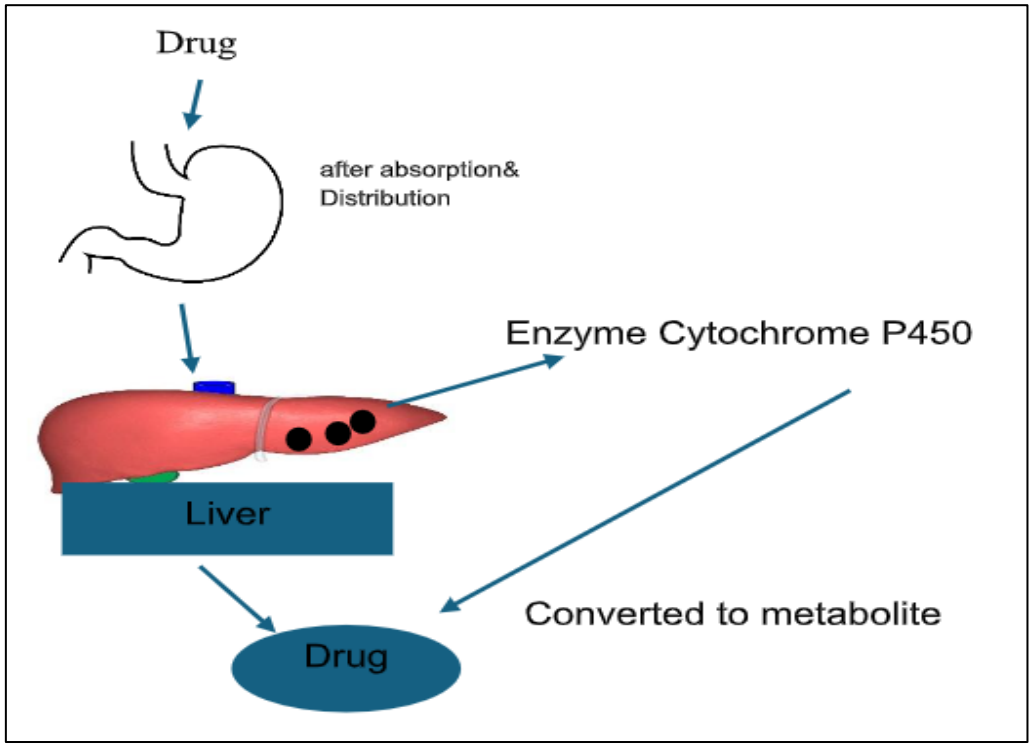

Fig 5 Metabolism of Drug

- *Enzymes*

Cytochrome P450 enzymes are a large family of heme including proteins that act as monooxygenases. They can handle a large variety of substrate. [17,18] They help break down natural body substances like bile acids, steroids and cholesterol, and foreign compounds such as drugs, pollutants and food componentsThese enzymes perform key reactions, including adding hydroxyl groups to carbon chains (aliphatic or aromatic), forming epoxides on double bonds, oxidizing heteroatoms or removing alkyl groups, and dehydrogenation. [19,20] CYP enzymes in the superfamily are grouped into subfamilies based on similarities in their amino acid sequences. The ones that metabolize drugs are mainly found in subfamilies 1, 2, 3, and 4.[17]

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V. EXCRETION

The human organism disposes of xenobiotics and their metabolites in two major ways. Both the kidneys and liver more readily excrete polar (water soluble) compounds than lipophilic (fat soluble) compounds. Therefore, fat soluble compounds are not easily eliminated unless they are first converted into more polar, water-soluble forms. Renal excretions are in three processes:

➢ *Filtration*

Clearance of polar or charged substances with low plasma protein binding is predominantly by glomerular filtration. Examples are aminoglycoside antibiotics and vancomycin. By contrast, compounds that bind tightly to plasma proteins remain in the blood and are not or only minimally filtered.

➢ *Secretion*

Some drugs are cleared from the plasma and actively transported into the proximal tubules by the cells of the tubular walls. This is done by transport systems which separate compounds based on charge. One system deals with weak acids, such as drug conjugates produced by the liver, penicillin, and many thiazide diuretics[21].

➢ *Reabsorption*

Lipid-soluble compounds are heavily reabsorbed in the tubules and poorly eliminated by the kidney. This occurs through concentration gradient from tubular fluid to plasma. The reabsorption of weak electrolytes is very much dependent upon urine ph. Alkaline urine ionizes weak acids more and enhances their excretion.[22] Acidic urine will promote the reabsorption of weak acids and decrease their excretion as the acidic urine will prevent their ionization. For weak bases the effect is opposite. Urine pH varies widely in the general population, as does the excretion rate of weak electrolytes.

➢ *Biliary Excretion*

Small, polar compounds with low protein binding are typically excreted in urine, while larger, lipophilic ones—often heavily protein-bound—are eliminated via bile [30]. Several factors affect how much of a xenobiotic gets excreted into bile. For example, molecular size (usually measured by molecular weight), the number of polar groups, and the compound's chemical structure all influence biliary excretion rates.[23]

➢ *Other Route of Excretion*

The removal of anaesthetic gases and vapors is mostly dependent on pulmonary excretion. Some medications and their metabolites also depart in trace levels. The lungs may eliminate lipophilic substances, in contrast with the kidney or liver. Additionally, some xenobiotics are eliminated via breast milk, sweat, and saliva.[24] Breast milk is important since these harmful substances can harm a breastfeeding infant, even if it's not the major route.

➢ *Drug Development*

New medication development is expensive, dangerous, and usually takes ten to fifteen years. According to a 2001 Tufts Center study, a new prescription medication typically cost $802 million[25] Every new medicine must prove it works safely for people of different ages, races, and ethnic backgrounds, and then pass strict global regulations. After approval, the drug must also be accepted in different countries with varying healthcare systems and cultures. Interestingly, many people think pharmaceutical companies discover only about a quarter of new drugs, but the industry is responsible for over 90% of them.[26]

- *Steps Involved in Drug Development*

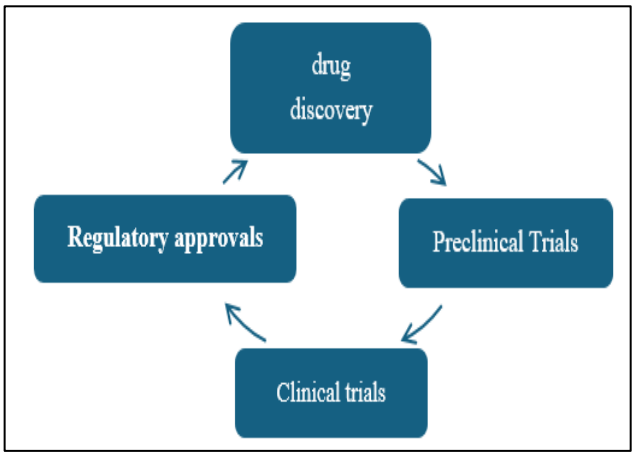

Fig 6 Drug Development Phases

➢ *Drug Discovery Procedure*

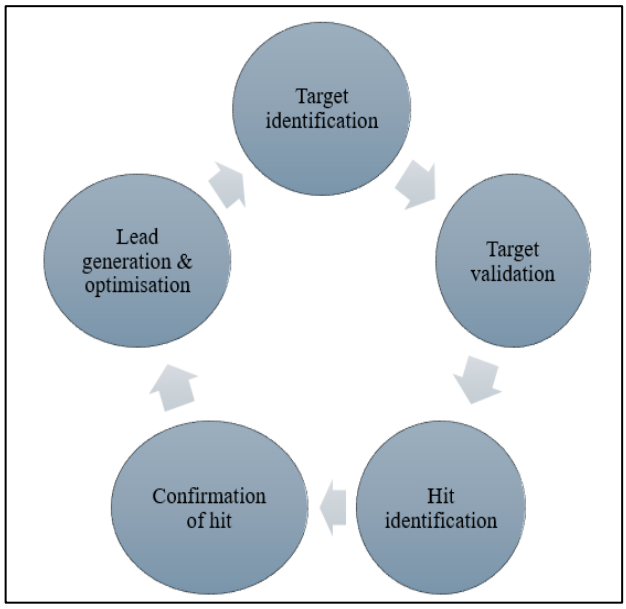

Fig 7 Different Phases of Drug Discovery

- *Target Identification*

Whether they are big antibodies or tiny chemical molecules, biologically active substances function by binding to bodily structures. These structures are referred to as "targets" in the drug discovery process. Enzymes, receptors, metabolites, substrates, ion channels, transport proteins, DNA, RNA, and even ribosomes are examples of targets.[27]

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26may1240

- *Target Validation*

After scientists identify a possible drug target, they need to confirm that it really plays a role in the disease. This step is called validation. One common way to do this is by using antisense technology. In this approach, researchers design short pieces of single-stranded DNA or RNA that match a specific part of the messenger RNA (mRNA) for the target gene. When these pieces bind to the mRNA, they block it from being translated into a protein. As a result, the protein is not made, which helps scientists see how important that protein is in the disease process.[28]

- *Hit Identification*

Finding "hits"—compounds that exhibit the intended effect in a screening test—comes next after a therapeutic target has been verified. High-throughput screening (HTS) is a popular method for doing this. Large libraries of drug-like compounds—up to a million at times—are rapidly tested against the target in HTS. This can be carried out in a cell-based assay (if the target) or a biochemical test (which might require less protein). The process relies on advanced automation, such as robotic systems that handle liquids.

In HTS, researchers usually don't know beforehand what chemical structures will work, so the screening is broad and exploratory. The outcome is that a few compounds may show promising activity, often with measurable potency in the micromolar range (IC50 values). However, HTS has some drawbacks:[29]

- *Confirmation of Hits*

Once hits are identified, they are retested under the same assay conditions to verify the findings. It's crucial to confirm that the activity actually results from the anticipated mechanism rather than from artifacts or mistakes in the experiment. Frequent or promiscuous hitters—compounds that exhibit activity too frequently or in unconnected ways are eliminated.

To detect false positives, researchers use a counter-screening assay. In this test, the hits are checked against a related protein under the same conditions. If a compound shows similar activity there too, it's likely not specific and is considered a false positive.[30]

- *Lead Generation & Generation*

The goal of lead generation, also known as the hit-to-lead phase, is to strengthen lead compounds by refining earlier hits. To make sure representative compounds are "drug-like," researchers also look at their physicochemical characteristics. The Lipinski Rule of 5, which forecasts a molecule's likelihood of being absorbed by the body, is used to evaluate novel compounds because oral delivery is the most popular method. This rule states that if a substance satisfies specific requirements for size, solubility, and chemical structure, it is more likely to be membrane-permeable and orally accessible.[31]

- ✓ It has a molecular mass of less than 500 Daltons.
- ✓ Its lipophilicity, measured by logP, has a lower than 5.
- ✓ There are less than 5 hydrogen bond donors.
- ✓ There are fewer than ten hydrogen bond acceptors. Because solubility affects both in vitro and in vivo tests as well as intestinal absorption, solubility tests are also carried out. The goal of medical chemists is to obtain compounds with a solubility of 60 μg/mL [32].

The in vitro ADME characteristics of substances—how the body might absorb, distribute, metabolize, and excrete them—are being studied by researchers. Important tests consist of:

- ✓ Testing permeability with the Caco-2 cell line, which serves as an intestine absorption model.[33]

Metabolic stability studies with human liver microsomes, to measure how quickly the compound is broken down (intrinsic clearance).[34]

- ✓ Cytochrome P450 (CYP) inhibition and induction tests, to check if the compound might interfere with the metabolism of other drugs taken at the same time.[35]
- ✓ Plasma protein binding assays, which show how much of the compound binds to proteins in the blood—this affects drug distribution and overall activity in the body.[36]
- ✓ Early in the drug discovery process, it's critical to assess a compound's potential for toxicity. For this, a few vitro tests utilizing human cell lines are employed:
- ✓ Cytotoxicity assays → test whether compounds harm cell survival.[37]
- ✓ hERG inhibition assays → predict risk of heart rhythm problems (QT interval prolongation).[38]
- ✓ Hepatotoxicity assays → use liver cells, slices, or fractions to check for liver damage.[39]
- ✓ Micronucleus assays → detect genetic damage, such as structural changes in chromosomes (clastogenic activity) or changes in chromosome number (aneugenic activity).[40].

- *Other Helpful Features Include:*

- ✓ Polar surface area under 140 Å² (better absorption) [41]
- ✓ Good permeability (>2–3 × 10^{-6} cm/s) for oral drugs [42]
- ✓ Microsomal stability half-life >45–60 minutes (resists breakdown in the liver)

- *In Preclinical Testing, Promising Compounds Usually Show:*

- ✓ Oral bioavailability >30%
- ✓ Half-life of 4–6 hours or more
- ✓ Clearance less than 25% of liver blood flow [45,46]
- ✓ Additionally, formulation studies are employed to enhance absorption and solubility, guided by the biopharmaceutical classification system (BCS). [43,44]

Over the past 20 years, drug failures caused by poor "drug-like" properties have dropped a lot, showing that scientists are using better strategies to optimize these properties.[47] But even with these improvements, Clinical drug development still has an extremely low overall success rate (around 10–15%).

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One reason is that the way drugs are chosen for clinical trials often relies too heavily on plasma pharmacokinetics (how the drug behaves in the blood). Typically, drugs with higher plasma exposure are advanced, while those with lower exposure are dropped. But this can be misleading. [47,48].

VI. PRECLINICAL DRUG DEVELOPMENT

A number of development efforts follow the selection of a medication as the preclinical candidate. The beginning of the first human trials and the discovery stage are connected by these activities[49]. Preclinical studies are done before testing a drug in humans. Their main goal is to check if the drug seems safe and effective. These studies look at how the drug works in the body, often using both lab tests (in vitro) and animal tests (in vivo). To make sure the results are trustworthy, they must follow strict rules called Good Laboratory Practice. [49]

- *In Vitro Studies – Studying the Drug in a Petri Dish*

In vitro studies are one of the quickest, easiest, and cheapest ways to test a drug before it's tried in humans. They use cells, tissues, or organs grown in the lab, and sometimes even focus on specific parts like proteins. These experiments allow researchers to tightly control conditions. However, cells in a dish don't behave exactly like they do inside the body, where they interact with millions of other cells. Because of this limitation, in vitro studies alone aren't enough to fully understand a drug's safety. More advanced models, such as animal studies, are needed to build a complete safety profile before moving into human trials.

- *In Vivo Studies*

In vivo studies test drugs in whole living animals, giving a picture of how the compound behaves in a complete organism. Because animals are involved, these studies are strictly regulated, and approval from ethics committees is required to minimize harm. Modern techniques like non-invasive imaging, micro sampling, and remote monitoring have made animal testing more refined.[50]

Studies are typically conducted in both rodents (such as mice, rats, guinea pigs, or hamsters) and non-rodents (generally dogs) to comply with FDA regulations. Sometimes, especially when evaluating larger, more complicated pharmacological compounds, primates are employed.[51]

Mice are one of the most used animals in drug testing because their genes are very similar to humans—about 99% overlap. It's also relatively easy to modify their genes for experiments. Still, there are important differences between mice and humans, such as how their immune systems respond, how they process drugs, and how tumours behave. These differences mean that results from mice don't always predict how well a drug will work in people.[52]

- *In Silico Studies*

Thanks to advances in bioinformatics, in silico studies (computer-based simulations) have become an important part of drug testing. These studies often come before or support lab (in vitro) and animal (in vivo) experiments. By running simulations, researchers can predict how a drug might behave in later tests. However, building these models requires not only powerful technology but also deep expertise in biochemistry and molecular biology.

- *Pharmacokinetic & Metabolism Studies*

Researchers must comprehend how a medicine is absorbed, transported, metabolized, and excreted from the body in order to determine the appropriate dosage and frequency of administration in safety and toxicity investigations. This information also aids in determining the initial dose for human studies and in understanding toxicological data.[53]

Early pharmacokinetic (PK) studies mainly look at how the drug is absorbed and excreted. Later studies compare how the drug and its metabolites spread through tissues in humans versus animals, so the right animal species can be chosen for toxicology testing. Metabolism studies are usually done in vitro (outside the body) using liver microsomes, cytosol, or hepatocyte cultures from different species. These investigations assist evaluate the hazards of drug-drug interactions, particularly those involving cytochrome P450 enzymes, in addition to demonstrating what metabolites are produced.[54]

- *Drug -Drug Interaction*

Doctors often use more than one drug to treat diseases because combination therapy usually works better than single-drug treatment [55,56]. For example, cancer patients may receive a mix of doxorubicin, cyclophosphamide, vincristine, and prednisone. [57,58] Similarly, tuberculosis treatment uses several drugs together to improve effectiveness and slow down resistance.[59]

Drug-drug interactions (DDIs) are more likely to occur while taking many medications.(60) In actuality, a large percentage of older persons use five or more drugs, and many of them are at considerable risk for DDIs.(61) These interactions may occur between medications or between medications and food, bodily substances, or diagnostic tools [62]. DDIs can be detrimental, neutral, or beneficial (synergistic).(63).Three primary categories comprise DDIs: [64]

Pharmaceutical interactions: Chemical reactions before drugs enter the body.[65] Drugs that act on the same receptor and have additive, blocking, or synergistic effects are known as pharmacodynamic (PD) interactions.[66]

Pharmacokinetic (PK) interactions: When drugs affect each other's absorption, metabolism, or elimination, changing blood levels. [67], That's why computational models are now being used to predict DDIs more efficiently. These models can screen large numbers of drugs and highlight combinations likely to interact, helping researchers and doctors make safer choices.

- *Impact of Metabolising Enzyme on Drug-Drug Interaction*

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✓ *CYP3A Inducers*

Table 1 Impact of Enzyme Inducers

Drug	Drug Type& indication	Effect on other CYPs	Comments
Apalutamide	Nonsteroidal antiandrogen nonmetastatic, castration-resistant prostate cancer	Strong inducer of CYP2C19; weak inducer of CYP2C9	Increased risk of seizure; increased incidence of fall and fractures
Carbamazepine	Anti-convulsant	Strong inducer of CYP2B6 Weak inducer of CYP2C9	Dose titration recommended to mitigate side effects
Phenytoin	Sodium channel blocker	Strong inducer of CYP2C19	Preferred perpetrator
Rifabutin	Anti-bacterial	Weak inducer	MHRA recommendation

✓ *OATP1B Inhibitors*

Table 2 Impact of Enzyme Inhibitors

Drug	Drug Type & indication	Effect
Clarithromycin	Semisynethic antibiotic	Strong inhibitor of CYP3A4
Cyclosporine	Arthritis, Immunosuppressant	Inhibitor CYP3A4

➢ *Improving Bioavailability & Stability*

Low oral bioavailability usually happens because a drug doesn't dissolve well in the stomach or can't easily pass through the gut wall. Researchers have studied these problems in detail and developed new ways to overcome them.

- *Techniques Used to Enhance Bioavailability*

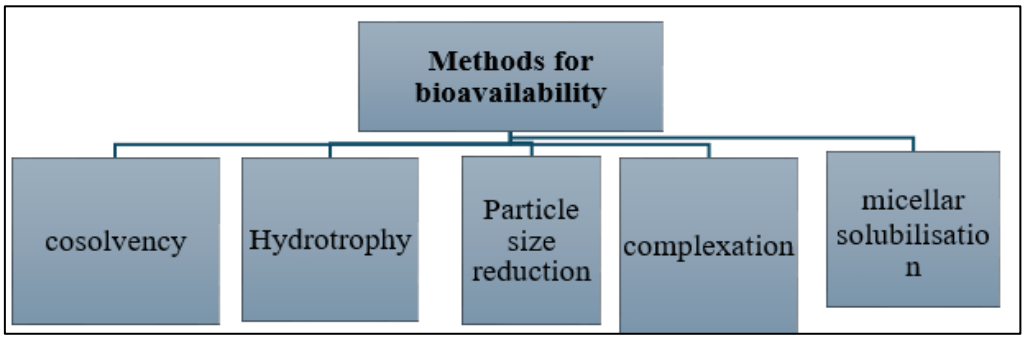

Fig 8 Different Types of Method for Improving Bioavailability

- *Co-Solvency*

A drug that doesn't dissolve well in water can be made more soluble by mixing it with a water-friendly solvent, called a cosolvent.[68] Cosolvents are blends of water and other solvents that help dissolve drugs that normally don't dissolve well. Common cosolvents include PEG 300, propylene glycol, and ethanol.

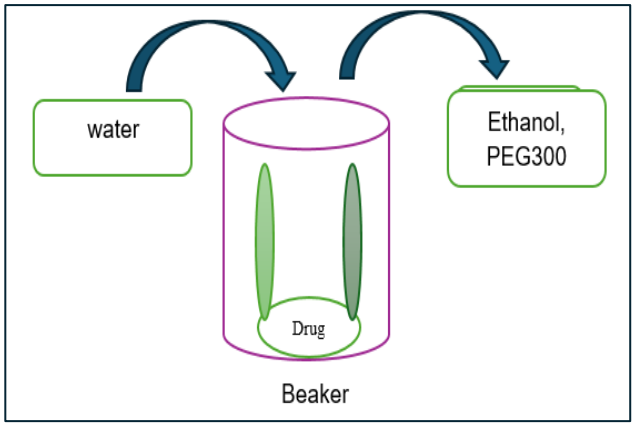

Fig 9 Co-Solvency Method of Bioavailability

- *Particle Size Reduction*

The degree of drug absorption is influenced by the size of the drug particles. Because they contain more surface area, smaller particles dissolve more quickly and have higher bioavailability. Jet mills and colloid mills are two milling techniques that can be used to reduce particle size. However, because decreasing size does not alter the drug's maximal solubility, this method is ineffective for medications that must be taken in large quantities.[69]

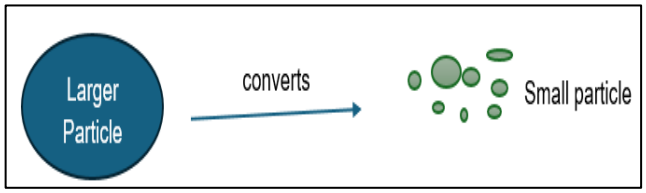

Fig 10 Particle Size Reduction Technique of Bioavailability

- *Complexation*

Cyclodextrins (CDs) are one method of increasing the solubility of medications that don't dissolve well in water. These are starch-based compounds with a ring form. [70, 71]

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They have an interior chamber that can contain medication molecules and an exterior surface that loves water. A drug's solubility, rate of dissolution, stability, and bioavailability can all be enhanced when it fits inside this cavity.

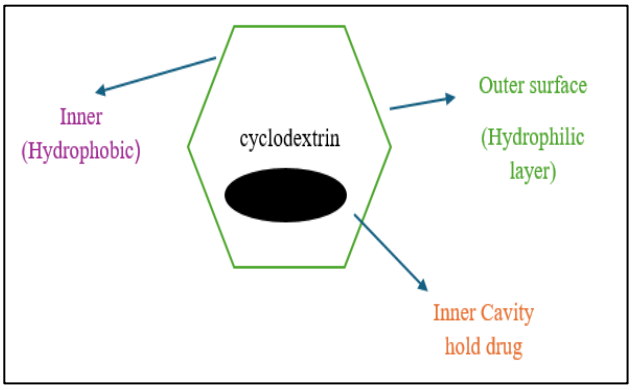

Fig 11 Complexation Method of Bioavailability

➢ *Toxicology Studies*

Before testing a new drug in people, researchers need to answer two key questions:

- Is the medication safe enough for people to take?
- What is the maximum safe dosage to begin with?

Even though toxicology has advanced a lot, the main way to answer these questions is still through animal studies, usually in both rodents and non-rodents [72]

- *Systemic Toxicology Studies*

These studies aim to determine the potential short-term toxicity of drugs. The drug is tested by giving it through a vein (IV) and by the same route planned for patients. Animals are monitored for 14 days following dosage to look for indications of poisoning, changes in body weight, obvious organ damage, and microscopic alterations in impacted tissues. The maximum tolerated dosage (MTD), the minimum lethal dose (MLD), and, if feasible, the primary organ impacted by toxicity are all determined by researchers. Although some regulators still want it, measuring the LD-50—the dose that kills half the animals—is no longer necessary. [73, 74]

- *Repeated Dose / Chronic Dose Toxicity*

Finding safe medication levels while animals are repeatedly exposed is the aim of repeated-dose experiments. The No Observed Adverse Effect Level (NOAEL), which is essential for determining the first dose in people, is identified by this research. These investigations should typically be as long as or longer than the anticipated human clinical trials. Rarely, trials may last longer than the toxicity studies if significant therapeutic advantages are demonstrated. [73, 74]

✓ *In Studies Using Repeated Doses:*

- Visible toxicity should result from the highest dose.
- The smallest dose should be close or greater than the approved human dose while showing no harm.
- A logarithmic scale is frequently used to determine the median dose between the two. [73, 74]

Researchers keep an eye on a variety of factors, including body weight, food intake, blood and urine tests, organ weights, microscopic tissue analysis, and external indicators of intoxication (behaviour, activity, and appearance). Tests like as ECG and eye examinations are also included in non-rodent species. [73, 74]

- *Local Toxicities Studies*

If the medication will be administered to humans by an individual path (anything other than oral), local tolerance trials are necessary. The medication is administered to the appropriate location in the right animal species, based on the route, to check for any negative local effects. [73, 74] For drugs given by injection (intravenous, intramuscular, subcutaneous, or intradermal), the injection sites must be carefully examined—both visibly and under the microscope—during systemic toxicity studies. [73,74]

➢ *Prediction of Drug Toxicity*

Determining the potential toxicity of new medications to people is one of the main challenges in their development. According to a study by Lasser and colleagues, approximately 3% of approved medications had to be taken off the market due to severe side effects during the previous 40 years. Seven medications have been taken off the market since 1993 after being connected to over 1,000 fatalities. [76]

They also reported that between 1975 and 1999, about 10% of approved drugs later needed strong safety warnings (called “black box warnings”).

When a drug must be withdrawn, the consequences are huge: companies lose the enormous investment of time and money (developing a single drug can cost around $800 million and take 12–15 years), [75] they lose potential profits, their reputation suffers, and—most importantly—patients are harmed. Examples of medications that were taken off the market because of unanticipated side effects.

Table 3 Adverse Effect of Drug Which Recall from Market

Drug	Indication	Adverse Effects	Year approved	Year Withdrawn
Propulsid (cisapride)	Gastric reflux	Cardiotoxicity	1993	2000
Rezulin (Troglitazone)	Type 2 Diabetes	Hepatotoxicity	1997	2000
Duract(bromfenac)	Analgesic	Hepatotoxicity	1997	1998
Posicor (mibefradil)	Calcium channel blocker	Drug-Drug Interactions	1997	1998
Baycol (cerivastatin)	Cholesterol Lowering	Rhabdomyolysis	1997	2001
Lotronex (aldosterone)	IBS	Ischemic Colitis	2000	2000

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➢ *Reasons the Prediction of Human Medication Toxicity Has Failed*

To improve drug safety, we first need to understand why predicting human toxicity often fails. Looking at the usual drug development process gives some clues. Safety testing starts in animals—commonly mice, rats, and dogs. The results are sent to the FDA to get permission (called IND status) to begin human trials.

This system seems logical: test in animals first, then in people. If a drug is toxic to both animals and humans, it should be caught early. If it's only toxic to humans, clinical trials should reveal it. But in practice, this process has weaknesses. Some toxic effects slip through, meaning harmful drugs can still reach patients.

- Animal Studies don't Always Match what Happens in Humans Because our Bodies Process Drugs Differently.

✓ The systems that make a drug toxic—or that help detoxify it—can vary between species. For example, a drug might seem safe in rats but be harmful in people if humans produce a toxic byproduct that rats don't, or if humans lack a detoxifying mechanism that rats have. It's common knowledge that human and animal drug-metabolizing enzymes differ. One obvious example is the blood thinner coumarin, which is broken down by people into a molecule known as 7 hydroxycoumarin, while rats do not make this metabolite at all [76].

✓ Animals and humans don't always react the same way to toxic drugs—not just because they process drugs differently, but also because their cells vary in sensitivity. Some species' cells are naturally more vulnerable. For instance, DNA is harmed by bezels, a potent anticancer medication. Even in the absence of metabolism, tests revealed that mouse bone marrow cells were roughly 1,000 times more sensitive to it than human or dog cells.[77] This means that differences in toxicity between species can come not only from how drugs are metabolized, but also from how sensitive the target cells themselves are.

- It's not always true that all drug toxicities in humans will be caught during clinical trials. There are several reasons for this:
- Limited ways to check toxicity in humans: In animal studies, researchers can examine tissues directly, but in humans only non-invasive methods are allowed (like blood tests or obvious symptoms). These methods mostly detect serious or short-term toxicity, not subtle or long-term effects.
- Small number of participants: Clinical trials involve hundreds or maybe thousands of people, but once a drug is marketed, millions may take it. Rare side effects (like those affecting fewer than 1 in 5,000 patients) often don't show up until after approval.
- Trial population doesn't represent everyone: Real-world patients may have conditions, take other drugs, eat certain foods, or carry rare genetic traits that weren't included in trials. These factors can increase toxicity but are hard to model beforehand.
- Changes after approval: Sometimes the drug's formulation changes—like a new dosage form or one that makes the drug more easily absorbed. These changes can cause unexpected side effects, though careful labelling and monitoring can help manage this risk.

➢ *Safety Pharmacology Studies*

According to ICH GCP Guidelines, the Investigator's Brochure must include data on both primary pharmacodynamics and safety pharmacology.[78]

- Primary pharmacodynamic studies look at how a drug works and what effects it has on its intended target.
- These studies are usually done early in drug discovery and help researchers understand the drug's mechanism of action.
- The results are important for deciding the right dose to use in both animal (nonclinical) and human (clinical) studies.[79]

➢ *Route/Dose & Duration*

The medication is often administered using the same route intended for clinical usage in safety pharmacology studies. The dosage is selected to expose the body to higher concentrations of the medication and its primary metabolites than what is typically experienced by humans. A single dosage is frequently used in these investigations. However, if certain effects only appear after longer treatment, or if safety concerns are seen in repeated-dose studies (in animals or humans), then the study duration is adjusted accordingly. [81,80]

➢ *Timing of Safety Pharmacology Studies*

You don't need to finish all safety pharmacology studies before filing an IND (Investigational New Drug application).

- Before testing a drug in humans, the core set of safety studies must be done, plus any extra studies if there's a specific concern.
- Sometimes, information from toxicology studies can replace or reduce the need for separate safety pharmacology studies.
- If animals or humans show unexpected side effects, more studies may be required later during clinical trials [81,80].
- In general, safety effects on all major body systems must be checked before a drug is approved.
- If some studies aren't done, the company must provide a clear justification for why they were skipped

VII. PHASES OF CLINICAL TRIALS

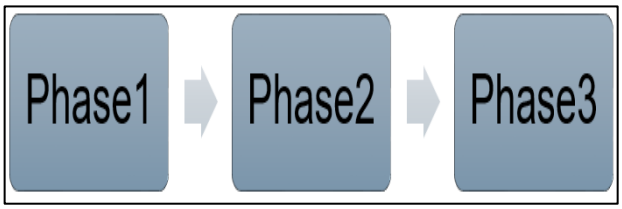

Fig 12 Phases of Clinical Trials

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➢ *Phase I*

This is the first occasion that a novel medication is administered to people. Except for cancer medications and other extremely toxic medications, which are tested on patients directly, this stage often involves healthy volunteers. Here, the primary objectives are safety (is it tolerated?), pharmacodynamics (drug effects on the body, such as variations in blood pressure or heart rate), and pharmacokinetics (drug effects on the body, such as absorption, breakdown, and elimination).These studies are carried out in special research units within hospitals, with trained doctors and full emergency facilities available. Approval from ethics committees and regulators is required before starting. Companies in the United States are required to file an Investigational New Drug (IND) application with the FDA, which contains all preclinical information and production specifics. For their participation, volunteers are typically compensated. The medication is discontinued if it exhibits issues, such as being cleared too soon or too slowly, having poor absorption, or producing severe side effects. Very modest doses are tested first, then gradually raised. Strict guidelines prevent dose increases in the event of harmful side effects or unusual test results [82].

➢ *Phase II*

Once a new drug has passed Phase I trials, meaning it has been tested in healthy volunteers (or in patients for toxic drugs like cancer treatments) and shown to be safe enough to continue, the next step is Phase II. At this point, researchers start testing the medication on real patients who have the illness it is intended to treat. Patients with hypertension will participate in Phase II trials, for instance, if the medication is intended to lower blood pressure.

- *Phase II's Primary Goal is to Provide Answers to Two Major Questions:*

✓ Does the drug really work in patients?
✓ What is the best dose that balances effectiveness and safety?

- *Phase II is Usually Divided into Two Parts:*

✓ *Phase IIa (Proof of Concept):*

This is the first time the drug is given to patients with the disease. The group is small, usually between 12 and 100 people. Researchers test one dose level, often the highest dose that was tolerated in Phase I, to see if the drug shows signs of working. This stage is sometimes called “proof of concept” because it provides the first evidence that the drug might help patients.

✓ *Phase II b (Dose-Ranging Studies):*

The next step is to test multiple doses in a wider patient population if Phase IIa shows potential. Finding the minimum effective dose—the smallest quantity that still works—and identifying dosages that are ineffective or have too many negative effects been the objectives. Researchers can determine the best dose to continue into Phase III studies by comparing several dose levels [83].

➢ *Phase III Trial*

Phase III trial are the last step before a drug can be approved. In this stage, researchers confirm the right dose, how often it should be taken, and the best timing for patients. Because Phase III studies are very expensive, the company running them should already be very confident that the drug is safe, works well in the intended patients, and that the dose range chosen is appropriate. Phase III trials are mainly designed to prove that the drug works (efficacy). At the same time, researchers carefully track side effects to weigh the overall benefits against the risks. Using new or experimental measures (called *novel endpoints*) in Phase III is risky, but it can help show advantages compared to other treatments. However, these new measures must first be tested in Phase II and agreed upon with regulators before Phase III begins. Clinical studies that measure death (mortality) or serious illness (morbidity) often need very large patient groups and can take years to finish Ways to prove efficacy include:

- Showing the drug works better than a placebo.
- Showing it works better than another active treatment.
- Or showing it is about the same as a reference treatment.
- About 70% of phase III trials are successful, although they can cost up to $100 million. Because it indicates a high likelihood of drug approval, a successful Phase III trial frequently raises the sponsor's share price [84].

VIII. REGULATORY APPROVAL

The sponsor starts compiling all the data to present to regulatory bodies after Phase III studies are successfully finished. Typically, this procedure takes many months. A New Drug Application (NDA) evaluation in the United States may take up to 15 months. The evaluation process can be expedited for medications that treat serious medical conditions (such as HIV or cancer). The business files a Biologics License Application (BLA) rather than an NDA if the medication is a biologic.

The sponsor submits a Marketing Authorization Application (MAA) in Europe. The centralized process, which is applicable throughout the EU, or mutual recognition, which extends permission from one nation to another, are the two methods of granting approval.

When regulatory agencies review a new drug application, they often send questions back to the sponsor. To handle this quickly, the sponsor usually sets up a rapid response team. During the review, the drug label is also negotiated. Regulators may ask for additional studies after approval if they have safety concerns.

The company must also demonstrate how it will identify, evaluate, and report side effects. Pharmacovigilance is the term used in Europe to describe this continuous post-approval monitoring of drug safety, which is required of all companies that commercialize drugs. Once the medication is on the market, the manufacturer is also required to provide frequent safety update reports. Phase IV clinical trials, often known as post-marketing trials, are investigations conducted following a drug's approval and release onto the market. The

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main goals of these trials are to keep an eye on safety and search for potentially dangerous side effects. The medication may be taken off the market if major dangers are found (85).

IX. CONCLUSION

The integration of ADME investigations into drug development is far more than a regulatory formality; it is a scientific imperative for turning promising compounds into safe, effective medicines. Through structured assessment of absorption, distribution, metabolism, and excretion, scientists obtain crucial information on a drug's pharmacokinetic behaviour, which underpins rational dose selection, formulation design, and risk management.

Across the continuum from early discovery and preclinical testing to all stages of clinical trials, ADME findings form the foundation for anticipating human responses, refining therapeutic windows, and reducing adverse effects. Regulatory authorities worldwide regard thorough ADME characterization as central to the approval pathway, reflecting its importance in protecting public health and upholding scientific standards.

In essence, ADME research connects molecular discovery with real-world clinical use. It shifts drug development from empirical trial-and-error to a predictive, data-driven process, shortening development timelines while improving patient safety. As drug discovery advances with new computational tools, biomarkers, and translational approaches, ADME studies will remain critical in directing the future of pharmacotherapy.

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