PHARMACEUTICAL
REGULATORY AFFAIRS

CHAPTER 01

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Abstract

New Drug Discovery and Development:

New drug discovery is the process of identifying and developing new medications. It involves various stages from initial research to clinical trials and regulatory approval.

Stages of Drug Discovery:

1. Target Identification and Validation: Identifying a biological target involved in a disease process and validating its relevance.
2. Lead Discovery and Optimization: Finding compounds (leads) that interact with the target and optimizing their properties.
3. Preclinical Research: Evaluating lead compounds in laboratory and animal studies to assess safety and efficacy.

Drug Development Process:

1. Preclinical Development: Conducting non-clinical studies to gather data on safety and efficacy before testing in humans.
2. Clinical Development: Testing the drug in humans through several phases (I, II, III) to determine safety, efficacy, dosage, and side effects.
3. Regulatory Review: Submitting data to regulatory authorities for approval to market the drug.

Pre-clinical Studies:

These studies involve laboratory and animal testing to gather initial data on a drug's safety profile and biological activity before human trials.

Non-clinical Activities: Activities in drug development that occur before clinical trials, including pharmacology, toxicology, and formulation studies.

Clinical Studies:

Testing drugs in humans to evaluate safety (Phase I), efficacy and side effects (Phase II), and broader safety and effectiveness (Phase III).

Innovator and Generics:

- Innovator Drugs: Developed by pharmaceutical companies through extensive research and clinical trials, typically protected by patents.
- Generic Drugs: Copies of innovator drugs that are produced after the patent expires, containing the same active ingredients and meeting regulatory standards for safety and efficacy.

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Concept of Generics:

Generic drugs are bioequivalent to innovator drugs in terms of dosage, strength, route of administration, quality, performance characteristics, and intended use. They provide cost-effective alternatives once patents expire.

Generic Drug Product Development:

Involves demonstrating bioequivalence to the innovator drug through comparative studies, optimizing formulation and manufacturing processes, and meeting regulatory requirements for approval and market entry.

These topics encompass the essential steps and concepts involved in drug discovery, development, and the introduction of generic medications into the market.

New Drug Discovery and developments

Background

Drug discovery is a complex and multi-step process that involves identifying chemical compounds for potential therapeutic use in treating and managing various diseases. This process encompasses the identification of drug candidates, synthesis, characterization, screening, and efficacy testing through various assays. Once a molecule demonstrates satisfactory results in these stages, it moves on to drug development and clinical trials.

The journey of drug discovery and development is notably costly, primarily due to the extensive research and development (R&D) and the clinical trials required. It typically takes about 12-15 years for a new drug molecule to progress from discovery to market availability. The average cost for developing an effective drug ranges from $900 million to $2 billion, factoring in the costs of numerous failures along the way. For every 5,000 to 10,000 compounds that enter the research and development pipeline, only one ultimately gains approval.

These figures highlight the significant challenges involved, but understanding the R&D process helps explain the high attrition rate and the extensive effort required to bring a single medication to patients. Success in this field demands substantial resources, including top-tier scientific and analytical talent, advanced laboratories and technology, and comprehensive project management. Persistence and a bit of luck also play crucial roles. Ultimately, the drug discovery process brings hope and relief to millions of patients worldwide.

Stages of Drug Discovery and Development Process

In the pharmaceutical industry, numerous mandatory processes must be completed before a drug can be sold in the market. The stages necessary to obtain market authorization for a new drug from the Food and Drug Administration (FDA) are as follows:

1. Target Identification
2. Target Validation
3. Lead Identification
4. Lead Optimization
5. Product Characterization
6. Formulation and Development
7. Pre-Clinical Research
8. Investigational New Drug (IND) Application

9. Clinical Trials
10. New Drug Application (NDA) and Approval

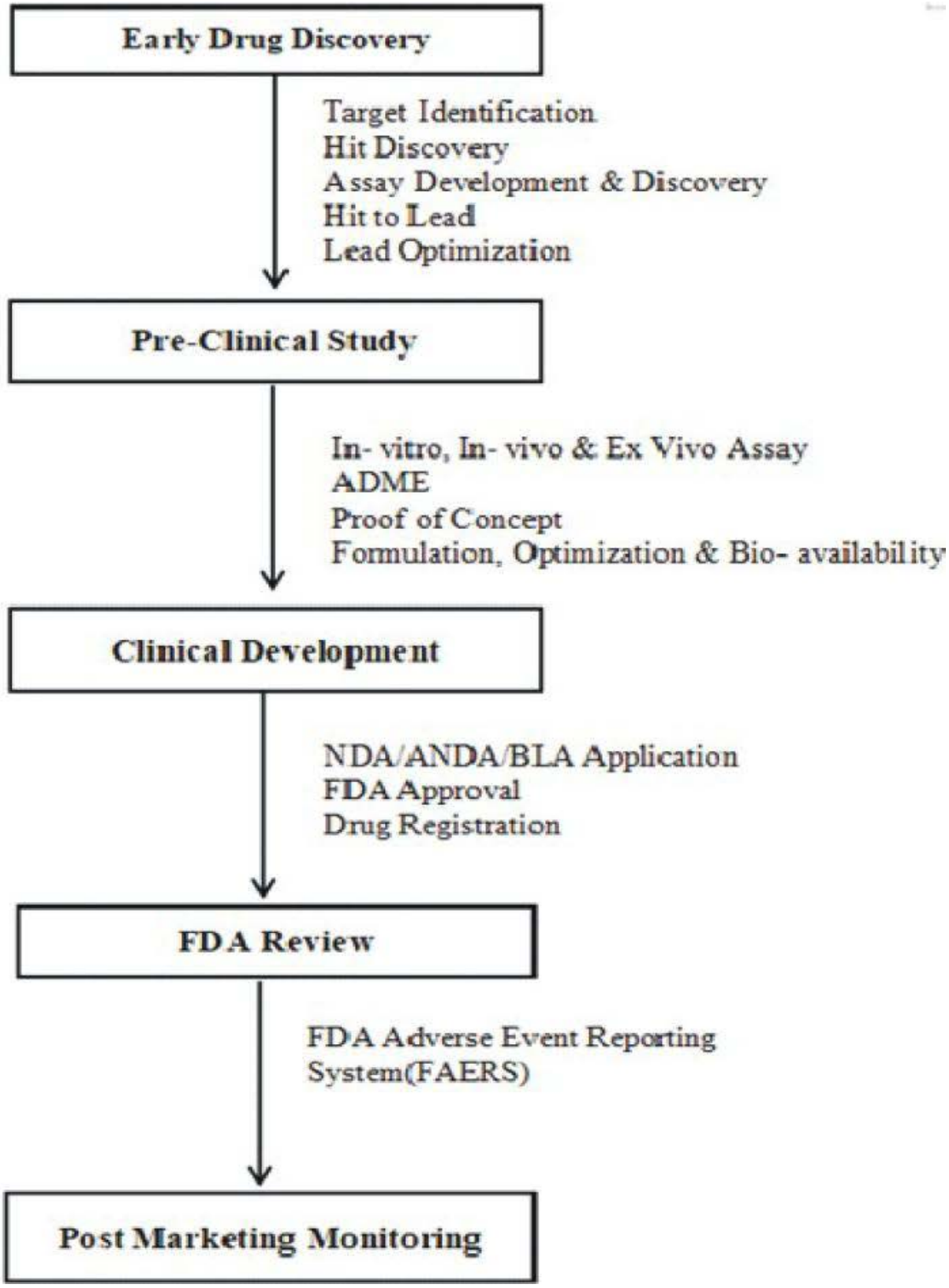

Figure 1: Stages of drug discovery and development process

1. Target Identification

Each year, high-throughput screening leads to the discovery of thousands of molecules, aiding in target identification. By interacting with these targets, potential drugs are evaluated. Lead compounds undergo further screening to assess their properties and activities, ultimately aiming to develop safe and effective medications.

The initial step in drug discovery involves identifying the biological origin of a disease and potential intervention targets. This process starts by isolating the function of a possible therapeutic target (gene, nucleic acid, or protein) and understanding its role in the disease. Following target identification, the molecular mechanisms it addresses are characterized. An ideal target should be effective, safe, meet clinical and commercial requirements, and be "druggable." Techniques for target identification may include molecular biology, biochemistry, genetics, biophysics, or other scientific principles.

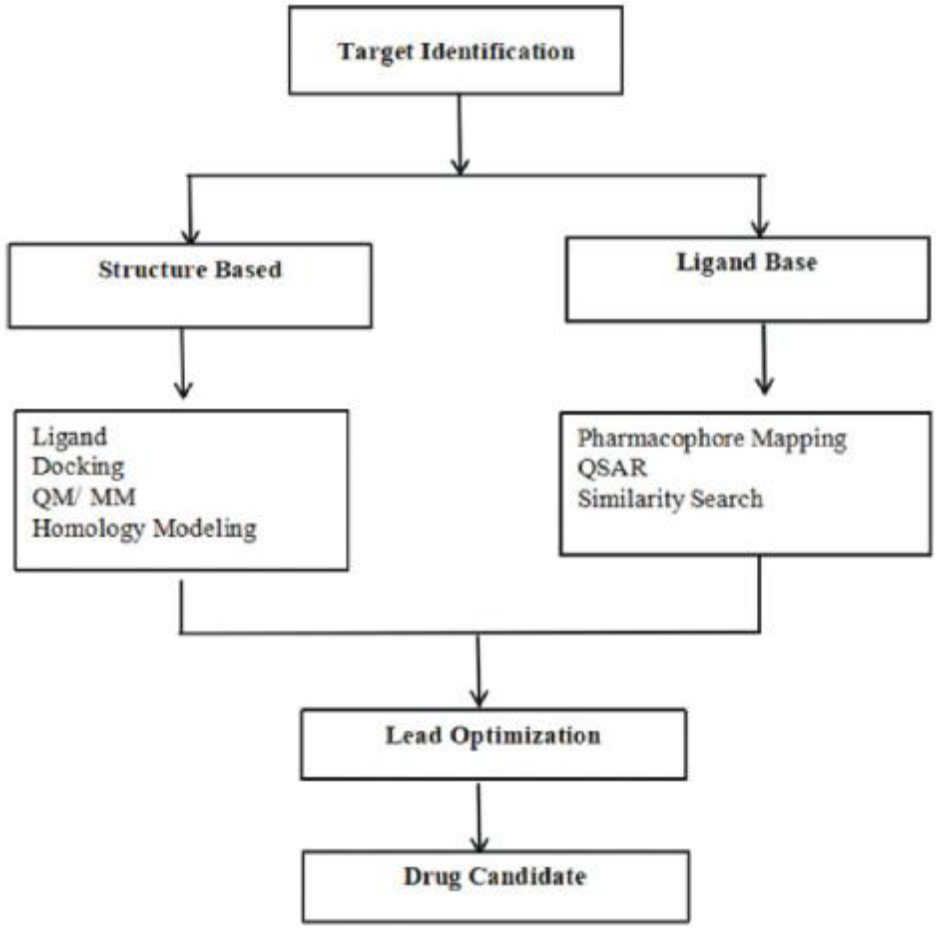

Figure 2: Target Identification

Approaches:

1. Bioinformatics-driven data mining
2. Identification, selection, and prioritization of potential disease targets
3. Genetic association studies
4. Investigation of genetic polymorphisms and their links to diseases
5. Analysis of expression profiles
6. Examination of changes in mRNA and protein levels
7. Pathway and phenotypic analysis through in vitro cell-based mechanistic studies
8. Functional screening techniques
9. Use of knockdown, knockout, or other target-specific tools

2. Target Validation

Target validation involves confirming the intended molecular target, such as a gene, protein, or nucleic acid affected by a small molecule. This process includes several steps: analyzing the structure-activity relationship (SAR) of analogs of the small molecule, creating drug-resistant mutants of the presumed target, manipulating the expression levels of the presumed target through knockdown or overexpression, and observing the signaling pathways downstream of the presumed target. Ultimately, target validation aims to establish the functional role of the identified target in the disease phenotype. While testing a drug's efficacy and safety in various disease-relevant cell and animal models is crucial, the definitive assessment lies in its performance in clinical trials.

Figure 3 : Target Validation

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Validation can be broken down in to two key steps.

- **Reproducibility** After identifying a drug target, whether through a specific technique or literature review, the initial step involves repeating the experiment to verify reproducibility. Techniques for target validation include affinity chromatography, expression cloning, protein microarrays, reverse transfection cell microarrays, biochemical suppression, siRNA, DNA microarrays, systems biology, and studying existing drugs.
- **Introducing Variation to the Ligand-Target-Environment** Manipulation of target genes through genetic techniques such as gene knockdown (using shRNA, siRNA, miRNA), gene knockout (CRISPR), or gene insertion (viral transfection of mutant genes). Antibodies can also interact with the target with high affinity to block further interactions. Chemical genomics involves using chemical approaches against proteins encoded by the genome.
- **Identification of Lead** A chemical lead refers to a synthetically stable, feasible, and drug-like molecule that demonstrates activity in primary and secondary assays, with acceptable specificity, affinity, and selectivity for the target receptor. This process involves defining structure-activity relationships, assessing synthetic feasibility, and gathering preliminary evidence of in vivo efficacy and target engagement. Characteristics of a chemical lead include defined structure-activity relationships (SAR), preliminary toxicity assessments, feasibility of synthesis, specific mechanistic assays, in vitro evaluation for drug resistance and efflux potential, evidence of in vivo efficacy within the chemical class, and preliminary pharmacokinetic/toxicity profiles based on toxicity studies or computational modeling.

The characteristics of a developmental candidate, or chemical lead, include:

i. **Defined Structure-Activity Relationship (SAR)**: Clear understanding of how chemical structure relates to biological activity.

ii. **Drug Ability**: Evaluation of preliminary toxicity and assessment of potential cardiac toxicity (hERG).

iii. **Synthetic Feasibility**: Feasibility of synthesizing the compound on a scale suitable for drug development.

iv. **Select Mechanistic Assays**: Specific assays to understand the mechanism of action of the compound.

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v. **In Vitro Assessment of Drug Resistance and Efflux Potential**: Testing to determine if the compound may face resistance mechanisms or efflux from cells.
vi. **Evidence of In Vivo Efficacy of Chemical Class**: Initial evidence showing the compound's effectiveness in animal models or relevant biological systems.
vii. **Pharmacokinetics (PK) and Toxicity**: Preliminary understanding of how the compound behaves in terms of absorption, distribution, metabolism, excretion (ADME), and toxicity based on early studies, including in silico predictions.
These characteristics collectively help in identifying and advancing promising compounds towards drug development.

To minimize the number of compounds failing in drug development, a crucial step involves conducting a drug ability assessment. This assessment plays a vital role in advancing a compound from a lead molecule to a potential drug. For a compound to be deemed druggable, it must demonstrate the ability to bind effectively to a specific target. Equally important is assessing the compound's pharmacokinetic profile, which includes understanding its absorption, distribution, metabolism, and excretion (ADME).

Additionally, other assays are employed to evaluate the compound's potential toxicity. Screening tests like the Ames test, which assesses mutagenicity, and cytotoxicity assays, which evaluate the compound's impact on cell viability, provide essential data to gauge the safety and viability of the compound as a drug candidate. These evaluations collectively inform decisions on whether to progress a compound further in the drug development pipeline.

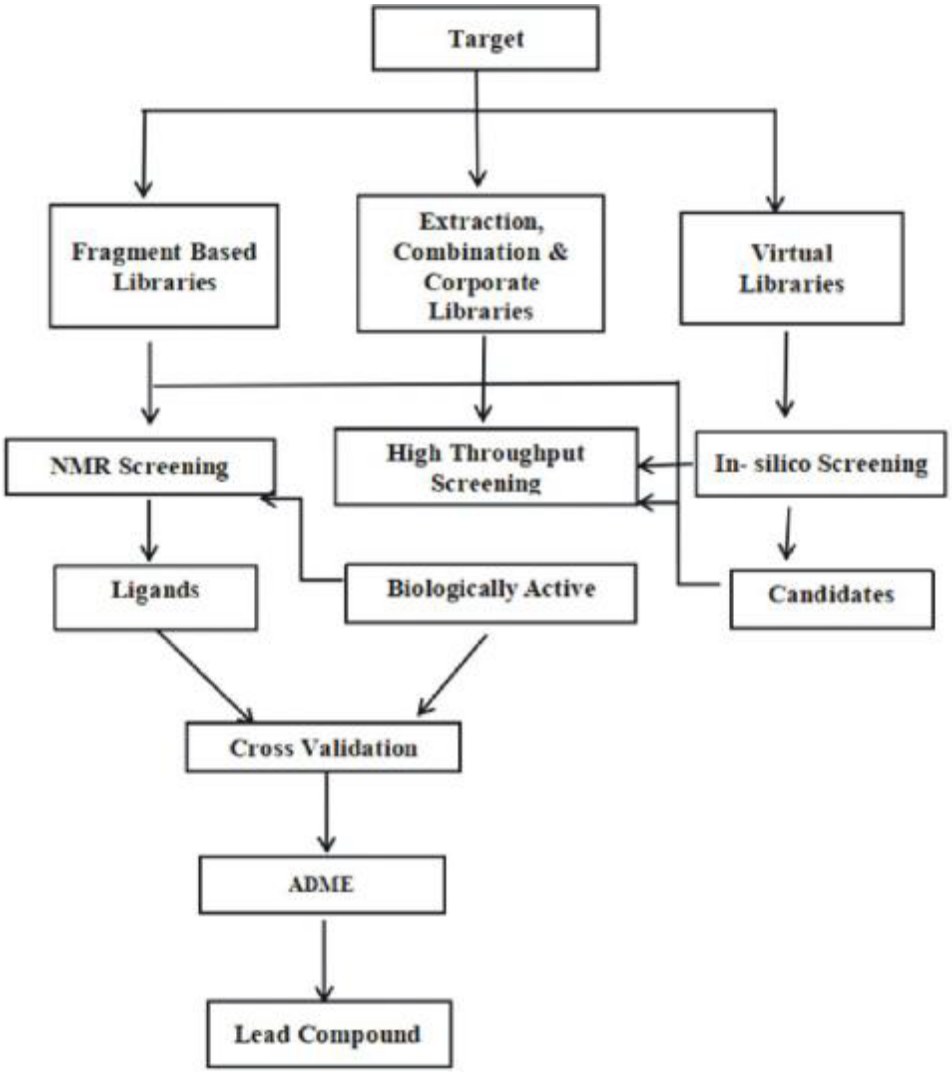

Figure 4 : Lead Identification

4. Lead Optimization

Lead optimization is the critical phase following the identification of an initial lead compound in drug development. This iterative process entails synthesizing and characterizing potential drug candidates to refine their chemical structures and activities. The goal is to systematically build a comprehensive understanding of how the compound interacts with its targets and undergoes metabolism. This process refines the compound's pharmacological profile, aiming to enhance efficacy, minimize side effects, and improve other critical pharmacokinetic properties.

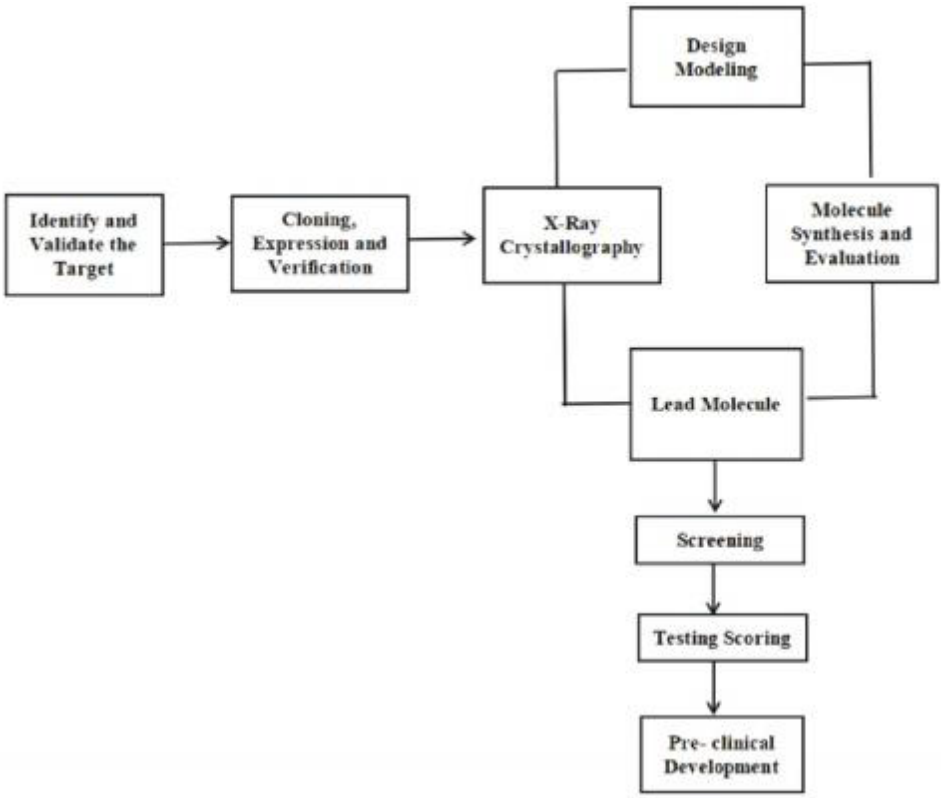

Figure 5 : Lead Optimization

In early drug discovery, after identifying potential leads through high throughput screening tests, the focus shifts to lead optimization. This stage aims to enhance promising compounds by improving their selectivity and binding mechanisms. The goal is to retain favorable properties while addressing any structural deficiencies. Alterations to the chemical structures of lead compounds, whether small molecules or biologics, are crucial for enhancing target specificity, selectivity, and other pharmacological properties. Evaluations encompass pharmacodynamic and pharmacokinetic parameters, as well as toxicological properties to characterize the compound thoroughly and guide optimization pathways.

For efficient downstream profiling and further investigation of drug candidates, drug discovery researchers increasingly rely on high throughput DMPK screens. These screens are integral in predicting in vivo pharmacokinetics through in vitro tests, facilitating the selection of drug candidates with improved potency and safety profiles. Automation in screening systems has become pivotal in pharmaceutical and biopharmaceutical labs, enhancing the efficiency of drug discovery processes. Mass spectrometry plays a critical role in detecting and quantifying metabolites, while MALDI imaging provides rapid and precise evaluation of drug candidates and their metabolites within tissue structures. Moreover, NMR Fragment-based Screening (FBS) has emerged as a widely adopted method in the pharmaceutical

industry for the discovery and optimization of lead molecules in targeted screening campaigns.

5. Product Characterization

When a new drug molecule demonstrates promising therapeutic effects, it undergoes characterization based on its dimensions, form, efficacy, limitations, applications, toxicity, and biological impact. Early pharmacological investigations play a crucial role in understanding the compound's mechanism of action.

6. Formulation and Development

Formulation and Development in pharmaceuticals involve characterizing the physicochemical properties of active pharmaceutical ingredients (APIs) to create a stable, bioavailable dosage form suitable for specific administration routes. During pre-formulation studies, the following parameters are assessed:

- Solubility in different media and solvents
- Dissolution of the active pharmaceutical ingredient (API)
- Accelerated stability testing under various conditions
- Solid-state properties such as polymorphs, particle size, and shape
- Formulation services and capabilities
- Formulation development for new chemical entities (NCEs)
- Optimization of existing formulations
- Process development for selected dosage forms
- Novel formulations for enhanced delivery of existing dosage forms
- Controlled release and sustained release formulations
- Self-emulsifying drug delivery systems
- Colloidal drug delivery systems
- Sub-micron and nano-emulsions

7. Pre- clinical Testing

Pre-clinical testing in the drug development process entails evaluating the safety and effectiveness of a drug in animal species, with findings that inform potential human outcomes. These trials require approval from relevant regulatory authorities, which ensure their safe and ethical conduct, and authorize drugs proven to be both safe and effective. The

International Council for Harmonisation (ICH) has established guidelines outlining the technical requirements for acceptable preclinical drug development.

The pre-clinical trials can be conducted using two primary methods: General pharmacology and Toxicology. Pharmacology involves studying the pharmacokinetic and pharmacodynamic parameters of a drug. It is crucial to identify potential adverse pharmacological effects using appropriate animal models and to monitor these effects in toxicological studies. Pharmacokinetic studies are particularly important for determining the safety and efficacy parameters related to absorption, distribution, metabolism, and excretion. These studies provide information on absorption rates for various routes of administration, aiding in the selection of dosage forms, distribution patterns, metabolic rates, and elimination processes, which collectively influence the drug's half-life. Understanding a drug's half-life is essential for establishing its safety profile, a requirement for regulatory approval. Drug distribution mechanisms clarify the therapeutic effectiveness of the drug, influenced by its bioavailability and affinity. Drug metabolism studies reveal the pathways and metabolites formed during biotransformation processes, shedding light on enzymatic reactions involved.

Toxicological studies of a drug can be conducted through both in vitro and in vivo tests to assess its potential adverse effects. In vitro studies examine direct effects on cell proliferation and phenotype, while in vivo studies provide qualitative and quantitative assessments of toxicological effects. Given that many drugs exhibit species-specific responses, selecting appropriate animal models is critical for conducting reliable toxicity studies. In vivo studies are also valuable for evaluating pharmacological and toxicological actions, including the mode of action, thereby supporting the rationale for the drug's proposed use in clinical trials.

8. The Investigational New Drug Process (IND)

Before initiating clinical research, drug developers are required to submit an Investigational New Drug (IND) application to the FDA. This application must include:

- Preclinical and toxicity study data
- Drug manufacturing information
- Clinical research protocols outlining the studies to be conducted
- Previous clinical research data, if available
- Information about the investigator or developer

9. Clinical Research

Clinical trials involve the participation of volunteers and aim to address specific questions regarding the safety and effectiveness of drugs, vaccines, therapies, or new uses for existing treatments. Each clinical trial follows a detailed study protocol developed by the researcher, investigator, or manufacturer. Prior to initiating a clinical trial, developers undergo the Investigational New Drug (IND) process, which is mandatory.

Before commencing a clinical trial, researchers thoroughly review existing information about the drug to establish research questions and objectives. They then determine:

- Participant selection criteria
- Number of participants involved in the study
- Study duration
- Dosage and administration route
- Parameters to be assessed
- Methods for data collection and analysis

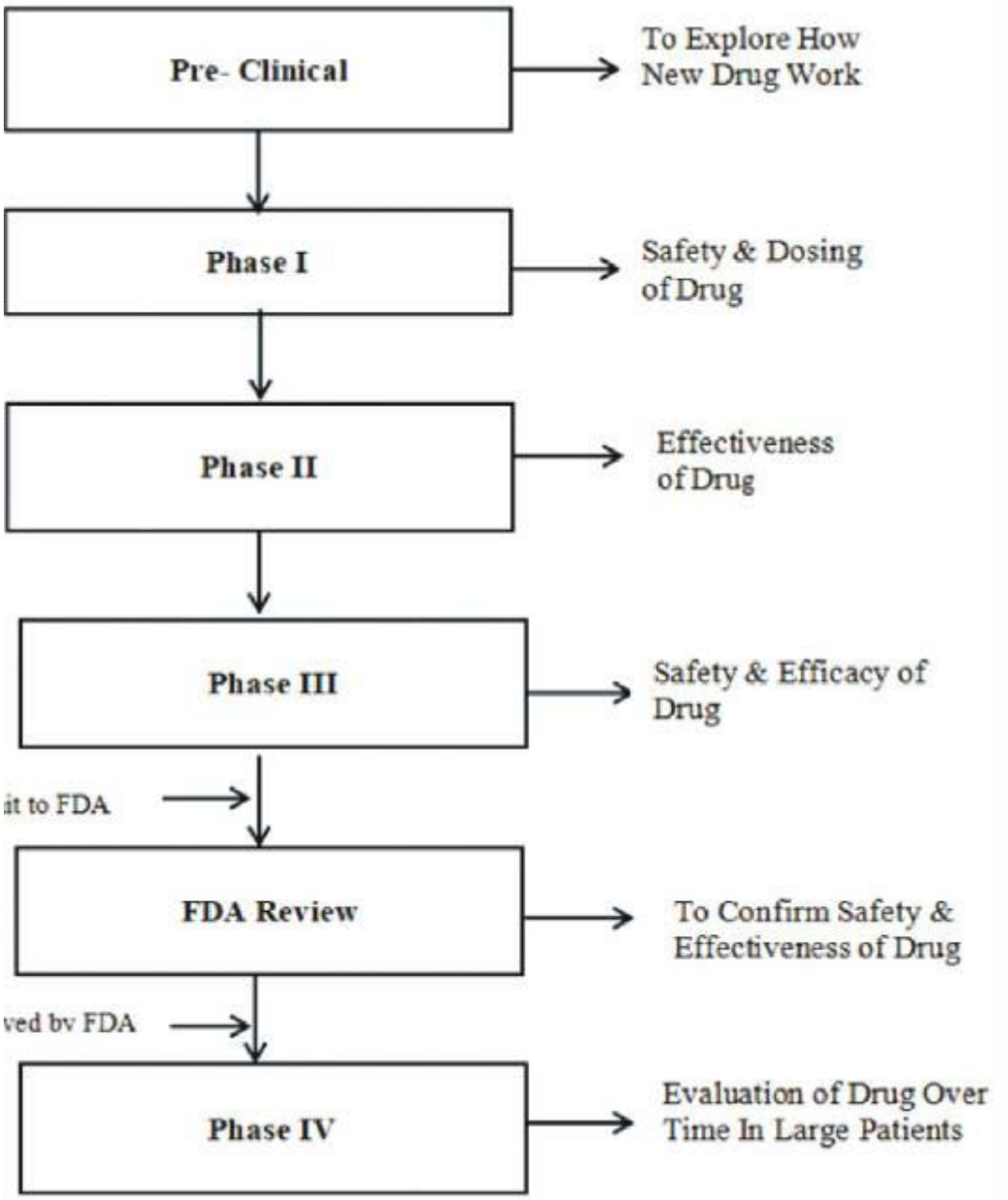

Figure 6 : Phases of clinical trials

i. Phase 0- clinical trial

Phase 0 clinical trials, also known as first-in-human (FIH) trials, adhere to FDA guidelines and involve investigative research. These trials, sometimes referred to as human micro-dose studies, administer single sub-therapeutic doses to 10 to 15 volunteers. Their primary goal is to gather pharmacokinetic data or assist in imaging specific targets without eliciting pharmacological effects. Pharmaceutical companies conduct Phase 0 studies to determine which of their drug candidates exhibit the most favorable pharmacokinetic profiles in humans.

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ii. Phase 1- Safety and dosage

Phase I trials represent the initial stage of testing for a drug involving a small number of healthy human volunteers, typically ranging from 20 to 80 individuals. If the drug's mechanism suggests it may not be well-tolerated by healthy subjects, patients with the specific condition may be included, such as diabetes patients for a diabetes drug. These trials focus on closely monitoring pharmacodynamics in humans, adjusting dosages based on animal study data to determine tolerable levels and acute side effects. Throughout Phase 1, researchers gather data on the drug's mechanism of action, dose-related side effects, and preliminary effectiveness, crucial for designing Phase 2 studies. Approximately 70% of drugs advance to the next phase following Phase 1.

iii. Phase 2- Efficacy and side effects

Phase II trials involve larger groups of patients, typically in the hundreds, focusing on assessing both the efficacy of the drug and confirming safety after Phase I evaluations. However, these trials alone do not conclusively determine the therapeutic potential of the drug. They provide researchers with additional safety data, which helps refine research questions, develop methodologies, and design Phase III protocols. Approximately 33% of drugs advance to Phase III. Notably, Phase II clinical studies are crucial for establishing therapeutic doses needed for larger-scale Phase III trials.

iv. Phase 3- Efficacy and adverse drug reactions monitoring

Phase III studies, also known as pivotal studies, are designed by researchers to determine whether a product provides a therapeutic benefit to specific populations. These trials typically involve 300 to 3,000 volunteers and primarily focus on evaluating efficacy and monitoring adverse drug reactions. Unlike earlier phases, Phase III studies are conducted on a larger scale and over a longer duration, making them more likely to detect rare or long-term side effects that may not have been identified in previous stages. Approximately 25-30% of drugs progress to the next phase of clinical research following successful Phase III trials.

Once a drug developer accumulates sufficient data from preclinical and clinical trials indicating that a drug is safe and effective for its intended use, they can submit a New Drug Application (NDA) to seek approval for marketing from regulatory bodies such as the FDA. The NDA provides a comprehensive overview of the drug, including preclinical findings and

data from all phases of clinical trials up to Phase III. It must include detailed reports on study outcomes.

- Proposed labeling
- Safety updates
- Drug abuse information
- Patent information Institutional review board compliance information
- Directions for use

v. FDA Review

After the FDA receives a complete New Drug Application (NDA), their review team typically takes between 6 to 10 months to decide whether to approve it. If the NDA is incomplete, the FDA review team will reject it.

If the FDA determines that a drug is safe and effective for its intended use, they collaborate with the developer to update the prescribing information, known as labeling. Labeling specifies the approval basis and provides guidance on how to use the drug. However, any remaining issues must be addressed before the drug can be approved for marketing. In some cases, additional studies may be required by the FDA. In such situations, the developer can decide whether to proceed with further development. If a developer disagrees with an FDA decision, there are formal appeal processes available.

vi. Phase 4- Post-Market Drug Safety Monitoring

Phase 4 trials are initiated following FDA approval of a drug or device. These trials, also known as post-marketing surveillance, involve ongoing monitoring of pharmacovigilance and technical support after approval. Phase 4 trials employ various observational strategies and assessment methods to evaluate the effectiveness, cost-effectiveness, and safety of the intervention in real-world settings. Regulatory authorities may mandate Phase 4 studies to update labeling or implement risk management plans, while sponsoring companies may conduct them for competitive reasons or other purposes. Therefore, understanding a drug's safety profile requires continuous monitoring over months or years of its market presence. The FDA monitors reports of adverse effects associated with both prescription and over-the-counter drugs, and may adjust dosage recommendations or usage guidelines in response to serious adverse reactions.

10. A New Drug Application and Approval

A New Drug Application (NDA) is a detailed submission required by the U.S. Food and Drug Administration (FDA) to seek approval for marketing a new drug in the United States.

The process of obtaining new drug approval involves two phases: first, non-clinical studies are conducted to establish the efficacy and safety of the drug. Subsequently, an application for conducting clinical trials is submitted to the relevant regulatory authority. Following approval, clinical trials (Phase I to Phase IV) are conducted to further assess the drug's efficacy, safety, and optimal dosage in humans.

Once clinical studies are completed, an application for marketing approval is submitted to the regulatory authority. Approval for marketing is granted if the drug is deemed safe and effective, or if its benefits outweigh its risks. Post-approval, ongoing monitoring is crucial to detect any unforeseen side effects when the drug is used in larger populations. This includes monitoring interactions with other drugs that may not have been assessed in pre-marketing trials, and identifying adverse effects in specific populations.

"Innovator and Generic Drugs

A drug refers to any substance or pharmaceutical product designed for human use to modify or address physiological systems or pathological conditions for the recipient's benefit.

Innovator Product: The innovator product typically denotes the first version authorized for market release, often under patent protection. Over time, identifying the original innovator pharmaceutical product may become challenging.

Generic Drug: A generic drug is a pharmaceutical product intended to be interchangeable with the innovator product, launched after the patent or exclusivity rights have expired. These products can be marketed under the approved nonproprietary name or a brand name. They may also be available in different dosage forms and strengths compared to the innovator products."

Concept of Generics and Generic Drug Product Development

"Definitions of Generic Drugs

The global field of generic and biosimilar drugs often causes confusion due to varying definitions used by authorities across different regions. This confusion can stem from

different interpretations of terms and misunderstandings about the nature, characteristics, research methods, and manufacturing processes of generic and biological products.

To enhance public understanding and clarity, GaBI Online has taken steps to compile tables of definitions used in various countries and regions. Table 1 presents a glossary of terms relevant to biosimilars as defined by the World Health Organization (WHO)."

WHO Definitions Relevant to Generics

- **Active Pharmaceutical Ingredient (API):** The chemical substance within a product responsible for its effect, referred to as 'substance' in this guide.
- **Bioequivalence:** Two pharmaceutical products are considered bioequivalent if they are pharmaceutically identical and their rates and extents of absorption (bioavailabilities), when administered at the same molar dose, are sufficiently similar that their effects can be expected to be essentially the same.
- **Brand Name:** The name given to a pharmaceutical product by its manufacturer. For instance, Valium is the original brand name (also known as a trade name) for diazepam. This name is exclusively reserved for the owner, distinct from the generic name, such as diazepam. Brand names may also be used for generic products, known as 'branded generics,' which differ from innovator brand names. See generic medicine.
- **Comparator:** A term used to denote a pharmaceutical product intended to be interchangeable with a new product in clinical practice. In any specific market, the comparator should typically be:
  - The product for which efficacy, safety, and quality have been thoroughly established (often the innovator).
  - A leading product authorized for marketing following an assessment process.
  - A legally marketed leading product that has not undergone pre-marketing authorization assessment.
- **Dispensing Fee:** Typically a fixed fee charged by pharmacies per prescribed item, either instead of or in addition to a percentage mark-up. This fee more accurately reflects the effort involved in dispensing a prescription, whereas a percentage mark-up ties profit to the cost of expensive medicines.
- **Dosage Form:** The form in which a pharmaceutical product is administered, such as tablet, capsule, suspension, or injection. Also known as 'dose form' or 'dosing unit'.

- **Drug:** Any dosage form containing an approved substance used for disease prevention and treatment. The term 'medicine' is increasingly used to differentiate it from drugs that are misused. See also Pharmaceutical product.
- **Essential Medicines:** Medicines intended to be consistently available within functional health systems in adequate quantities, appropriate dosage forms, assured quality, with sufficient information, and at prices affordable to individuals and communities. The WHO model list of essential medicines is designed to be adaptable across various contexts, with specific definitions determined at the national level.
- **Excipient:** Any component of a finished dosage form other than the claimed therapeutic ingredient(s).
- **Finished Product:** A product that has undergone all stages of production, including packaging in its final container and labeling.
- **Formulation:** The formulation of a dosage form encompasses the composition of its components, the properties of raw materials, and the procedures involved in its manufacturing.
- **A generic medicine**, also known as a multi-source product, is typically designed to be interchangeable with the original branded product. It is manufactured once the patent or exclusivity rights of the original manufacturer have expired, without requiring a license from them. Generic medicines are often marketed under their non-proprietary names (e.g., diazepam) or occasionally under another approved name, rather than a specific brand name. However, they can also be marketed under brand names, known as 'branded generics.' In many countries, multiple branded generic versions of the same medicine can be found alongside the original branded product.

According to the manual 'Marketing Authorization of Pharmaceutical Products with Special Reference to Multi-source (Generic) Products (WHO/DMP/RGS/98.5),' the term 'multi-source pharmaceutical product' encompasses generic products, including the original branded product whose patent has expired. While this definition is used in certain countries, the manual makes a distinction between the original branded product, regardless of patent status, and the lowest-priced generic equivalents.

Innovator brand

International non-proprietary name (INN)

A common, standardized name chosen by designated experts to clearly identify a new pharmaceutical substance. This selection process adheres to guidelines established by the World Health Assembly and aims for global acceptance. International Nonproprietary Names (INNs) are universally recommended and serve as public property names, distinct from proprietary brand names. They were introduced by the WHO in 1950 to uniquely identify each pharmaceutical substance or active ingredient, such as diazepam. It's important that brand names (trade names) do not directly derive from the INN.

Interchangeable pharmaceutical products

Interchangeable pharmaceutical products are those within the same therapeutic class but containing different active ingredients that produce equivalent therapeutic effects.

Medicine refers to any form of dosage containing a substance approved for preventing or treating diseases. This term is increasingly used to distinguish it from drugs that may be misused. See also Pharmaceutical Product.

Originator pharmaceutical products, also known as originator brands, are typically the first products authorized globally for marketing, often under patent protection. These products demonstrate efficacy, safety, and quality based on the requirements at the time of authorization, like Valium. Originator products always have a brand name, which may vary across countries.

Some substances, such as prednisolone and isoniazid, are so old that their original patent holders cannot be identified, and patents were likely never claimed.

A patent is an official title granted by public authorities, providing temporary monopoly rights to the inventor who discloses, fully describes, and claims this invention.

Patient co-payments refer to fixed amounts patients pay per prescribed medicine, irrespective of whether they receive reimbursement.

Pharmaceutical equivalence pertains to medicines containing identical amounts of the same active ingredient, in the same dosage form and route of administration, meeting standards for strength, quality, purity, and identity.

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A pharmaceutical product is any medicine intended for human use, presented in its final dosage form and subject to regulation under pharmaceutical laws (registered). Such products may be marketed under a brand name (e.g., Valium) or a generic name (e.g., diazepam).

Stability denotes the capability of an active ingredient or drug product to maintain its properties within specified limits throughout its shelf life. Stability considerations encompass chemical, physical, microbiological, and biopharmaceutical aspects.

Trade name is synonymous with brand name.

Generic Drug Product Development

A generic drug is identical in chemical composition to a branded drug and is sold under its chemical name. Generic drugs enter the market after the exclusivity period of the branded product ends, when the patent holder relinquishes rights, or when FDA requirements are met. The FDA aims to enhance its pre-application interactions with drug applicants, providing resources and guidance to assist in the development of generic drugs and the preparation and submission of abbreviated new drug applications (ANDAs), ensuring stakeholders are well-informed throughout the process.

a. **Specific Guidance for Generic Drug Development** To promote the availability of generic drug products and support the generic pharmaceutical industry, the FDA regularly issues product-specific guidance documents. These documents outline the FDA's current recommendations and expectations regarding the development of therapeutic equivalents to specific reference listed drugs.

b. **Approval of Generic Drug**s The FDA maintains an updated list of initial approvals for generic drugs. To access information on all generic drug approvals and tentative approvals, users can utilize the "Drug Approval Reports by Month" feature on Drugs FDA. For details on generic drug approvals, select "Original Abbreviated New Drug Approvals (ANDAs) by Month," or choose "Tentative Approvals by Month" for tentative approvals. This database is updated daily.

c. **Pre-ANDA Program The Pre-ANDA Program** serves as a valuable resource for applicants seeking to develop generic drugs. It offers assistance in product development

and includes pre-submission meetings as well as mid-review cycle meetings to clarify regulatory expectations early in the development process and during application review.

d. **List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic** The FDA maintains a list of drug products that were approved under new drug applications (NDAs), are no longer protected by patents or exclusivities, and have not yet been approved as generic equivalents through an Abbreviated New Drug Application (ANDA).

e. **Authorized Generic Drugs** Updated quarterly, the FDA's List of Authorized Generic Drugs includes details such as the trade name of the drug, the manufacturer of the brand-name drug, and the date the authorized generic entered the market.

f. **Quality by Design (QbD)** QbD is a proactive, scientific approach to pharmaceutical development that emphasizes risk management and deliberate design efforts to optimize product performance. The FDA has published examples of QbD reports, including: a. Inactive Ingredient Database This database provides information on inactive ingredients found in FDA-approved drug products, aiding in the development of generic drugs. b. Hatch-Waxman Letters These letters reflect FDA decisions concerning matters like 180-day exclusivity and other issues related to generic drug approvals.

g. **FDA Letters to Industry** This series of letters informs manufacturers of generic drug products about policy and procedural developments under the Drug Price Competition and Patent Term Restoration Act of 1984.

h. **Bioequivalence Study Retention Samples** The FDA mandates requirements for retaining samples of drug products used in bioavailability and bioequivalence testing. According to regulations, applicants must retain reserve samples of tested products administered to study subjects and provide these samples to the FDA upon request.

Educational Resources

The FDA's Center for Drug Evaluation and Research Small Business & Industry Assistance program provides a range of multimedia educational resources. The CDER SBIA Learn webpage features numerous beneficial courses and recordings specifically in the "Generic Drugs" category.

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Process of generic product development

The process of developing generic products begins with the physical formulation of the product, which involves several key steps:

1. Selecting from available types of excipients.
2. Choosing appropriate manufacturing processes.
3. Using similar equipment and facilities that comply with relevant regulations.

Despite persistent beliefs that generic products are inferior to brand-name counterparts, the reality is different:

- Generic products are required to meet identical quality standards as brand-name products.
- Their equivalence to the reference product must be demonstrated through bioequivalence studies.
- Manufacturing facilities and processes for generics must adhere to the same cGMP (current Good Manufacturing Practice) standards as those for brand-name products.

It's acknowledged that both excellent and subpar development practices exist across both brand-name and generic pharmaceutical companies. Fortunately, stricter regulatory requirements and thorough process validation have increasingly eliminated poorly developed products. This underscores the critical importance of robust formulation development.

While the focus here primarily concerns solid oral dosage forms, many of the principles discussed are applicable to generic semi-solid or liquid products as well.

Prior to Development

A product for development must be chosen with input from various disciplines such as R&D, Regulatory Affairs, Legal, Marketing & Sales, Finance, etc. Once selected, detailed information about the product should be documented, including:

- Innovator Product Description and Dosage Form
- Innovator Product Packaging Description
- Innovator Product Sales
- Generic Product Description and Dosage Form
- Generic Product Packaging Description

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- Generic Sales Forecasts
- Intended Manufacturing Site
- Intended Production Batch Size
- Any other relevant information

The project scheduling and management should be based on factors like patent expiry, product exclusivity, forecasts, availability of the active ingredient, etc. The goal is to ensure the project progresses effectively to become the first generic drug manufacturer for that specific product in the market.

Pre-formulation

Before proceeding with the development of actual trial formulations, it is essential to conduct preliminary "pre-formulation" work aimed at gathering comprehensive information about both the reference product and the drug substance. Typical pre-formulation activities include:

1. Reviewing the product selection document.
2. Examining relevant patent information.
3. Acquiring samples of the reference product and its packaging.
4. Assessing the physical characteristics of the reference product.
5. Determining the release characteristics of the reference drug through in-vitro dissolution profiling.
6. Characterizing the drug substance to identify its form (crystalline, powder, amorphous), solubility, polymorphism, particle size, bulk density, flow properties, chemical properties (such as pKa and functional groups), absorption characteristics (pharmacokinetics), incompatibilities, and sensitivities (to light, heat, moisture), among other factors.
7. Establishing a suitable dissolution procedure that correlates with relevant in-vitro/in-vivo relationships.

Once these pre-formulation activities are completed, informed decisions can be made regarding the type of formulation and development process to pursue. The dosage form and strength are determined by both the reference product itself and the specifications outlined in the product selection document.

There are three general processes used to produce tablets and capsules, as follows:

Direct Mix:

This method involves blending the drug substance with excipients and then compressing the mixture into tablets or filling it into capsule shells.

Dry Granulation:

In this process, the drug substance and excipients are processed using a "slugging" or "compaction" technique. This is followed by granulation sizing and final blending with additional excipients before tablet compression or capsule shell filling.

Wet Granulation:

This process entails mixing the drug substance with excipients and a solvent, which may contain a binder dissolved to form a granulation. Afterward, the granulation is dried, sized, and blended with additional excipients prior to tablet compression or capsule shell filling.

When feasible or practical, initial consideration is given to the direct mixing process due to its simplicity and cost-effectiveness in producing solid pharmaceutical dosage forms. However, the specific dosage requirements, physical characteristics of the drug, and attributes of the reference product will ultimately dictate the most suitable process.

A tablet or capsule dosage form typically includes the following components:

- **Active Ingredient (Drug Substance):** The primary pharmaceutical ingredient.
- **Binder:** Holds filler and drug particles together to form granules or tablets/capsule slugs.
- **Solvent:** Used in wet granulations as the granulating medium.
- **Fillers/Diluents:** Provide bulk or weight to tablets and capsules to achieve practical sizes for administration.
- **Disintegrating Agent:** Facilitates the breakup of tablets or capsule contents to enhance drug substance dissolution and absorption.
- **Glidant:** Reduces friction between particles to improve flow characteristics.
- **Anti-adherent:** Prevents adhesion to equipment surfaces (used in combination with lubricants).
- **Lubricant:** Prevents powders from sticking to equipment used for tablet compression or capsule filling.

- **Others:** Includes dyes for coloring tablets, sweetening agents and flavors for chewable tablets, wetting agents to enhance solubility, acidifying agents, buffers, stabilizers, etc., to ensure stability and efficacy.
- **Film Coating Preparations:** Components for tablet film coatings, including a polymeric film-former, plasticizer, opacifying agent, dispersing agent, dyes, etc.

The range of excipients available serves various functions in tablet and capsule formulations, tailored to specific requirements and roles within the final pharmaceutical product.

Therefore, only some of the most common excipients and their suggested use levels are listed as follows:

It looks like you've provided a detailed list of binders, solvents, fillers/diluents, disintegrating agents, glidants/lubricants/antiadherents, and other excipients commonly used in pharmaceutical formulations. These substances play crucial roles in ensuring the stability, efficacy, and manufacturability of tablets and capsules. Here's a summarized breakdown:

Binders:

- **Polyvinylpyrrolidone (PVP)**: 0.5-5%
- **Pregelatinized starch**: 5-10% (wet), 5-20% (direct)
- **Starch paste**: 5-25% w/w
- **Microcrystalline cellulose**: 5-25% (wet), 5-25% (direct)
- **Sucrose**: 50-70% solution
- **Hydroxypropyl cellulose**: 4-6%
- **Ethylcellulose**: 5% solution
- **Methylcellulose**: 1-5% solution (depending on viscosity grade)
- **Acacia**: 1-5%

Solvents:

- **Purified water**
- **Ethanol**
- **Purified water/ethanol**
- **Other organic solvents** (e.g., Methylene Chloride)

Fillers/Diluents:

- **Microcrystalline cellulose**
- **Lactose**

- **Starch/pregelatinized starch**
- **Dicalcium phosphate**
- **Calcium carbonate**
- **Compressible sugars** (e.g., Mannitol, Sorbitol)

Disintegrating Agents:

- **Sodium starch glycolate**: 4-8%
- **Croscarmellose sodium**: 3-6%
- **Pregelatinized starch**: 5-10%
- **Starch**: 5-10%
- **Microcrystalline cellulose**: 5-15%
- **Cross-linked polyvinylpyrrolidone**: 2-5%
- **Alginic Acid**: 5-10%

Glidants/Lubricants/Antiadherents:

- **Fumed silicon dioxide** (glidant): 0.1-0.5%
- **Talc** (anti-adherent): 1-4%
- **Magnesium stearate**: 0.25-1.5%
- **Stearic acid**: 0.5-3%
- **Hydrogenated vegetable oils**: 2-5%
- **Sodium lauryl sulfate**: 1-3%
- **Mineral oil**: 1-3%

Others:

- **Dyes**: Typically aluminum lakes, used for coloration.
- **Sweetening Agents & Flavours**: Compressible sugars/alcohols and various flavoring agents.
- **Wetting Agents**: e.g., Sodium lauryl sulfate, Polysorbate 80.
- **Acidifying Agents, Buffers, Stabilizers, etc.**: e.g., Citric acid, Sodium citrate (dihydrate), Sodium phosphate monobasic.

These excipients serve diverse functions such as binding, filling, disintegrating, lubricating, coloring, flavoring, and stabilizing, essential for formulating tablets and capsules with desired properties and performance characteristics.

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Considerations for Selecting Excipients in a Formulation:

1. **Composition of Reference Product**: When available, reference sources like PDR, CPS, or product labels provide qualitative compositions of formulations.
2. **Requirement for Specific Excipient**: Begin formulations with a simple composition, integrating specialized excipients through experimental trials as necessary.
3. **Drug/Excipient Incompatibilities**: Prior drug characterization and pre-formulation studies may necessitate excluding certain excipients due to potential compatibility or stability issues.
4. **Excipient Characteristics and Effect on Drug Substance Release**: Depending on the drug substance, select excipients that enhance or retard drug release to achieve the desired in-vitro dissolution profile.
5. **Formulation Process**: Differentiate excipients suitable for direct mixing processes from those more appropriate for wet granulation processes.
6. **Availability**: Prefer readily available excipients over equally adequate alternatives that are less accessible.
7. **Experience**: Formulators typically prefer excipients they are familiar with, despite equivalent alternatives being available.
8. **Cost**: When faced with functionally equivalent and equally available excipients, opt for the more cost-effective option.
9. **Formulation Development:** After completing pre-formulation work and establishing a development strategy, the next step involves conducting a series of small-scale trials. These trials entail processing the drug substance with selected excipients using the chosen process to create a dosage form that aligns with the specified strength and appearance outlined in the product selection document. Subsequently, the dosage form undergoes thorough physical and chemical evaluation to assess its acceptability compared to the reference product.

The various types of testing conducted on tablet and capsule formulations during development include:

Blends:

- **Physical Testing:** Bulk and tapped density, particle size distribution, flow index, angle of repose, moisture and/or loss on drying.
- **Chemical Testing:** Blend uniformity.

Tablets:

- **Physical Testing:** Appearance, average weight and weight variation, hardness, thickness, friability, disintegration time.
- **Chemical Testing:** Dissolution profiles compared to a reference product, assay, content uniformity, chemical identification, impurities and related substances, ICH stability.

Capsules:

- **Physical Testing:** Appearance, average weight and weight variation, disintegration time.
- **Chemical Testing:** Dissolution profiles compared to a reference product, assay, content uniformity, chemical identification, impurities and related substances, ICH stability.

Development trials continue until achieving a formulation with a dissolution profile matching the reference product in one or more dissolution media. This formulation is then scaled-up slightly, and the resulting dosage form is packaged and subjected to accelerated stability testing. Meanwhile, additional trials are conducted to optimize formulation and process parameters, which are crucial to:

- Gaining experience with the new formulation and process.
- Identifying limitations by testing various process parameters.
- Gathering additional data necessary for setting meaningful specifications.
- Addressing significant formulation or processing issues before finalizing the product formulation and process (before bioequivalency testing).

If the product maintains acceptable physical and chemical characteristics, it undergoes further scaling-up under GMP conditions as the "test batch" for in-vivo bioequivalency testing against the reference product. Should the product prove non-bioequivalent, reformulation may be necessary, assuming economic viability despite delays.

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Upon demonstrating bioequivalence, a submission package is compiled and submitted to the relevant regulatory agency for review and approval. Successful generic product development goes beyond bioequivalency and approval; it entails ensuring consistent manufacturing under various conditions without issues.

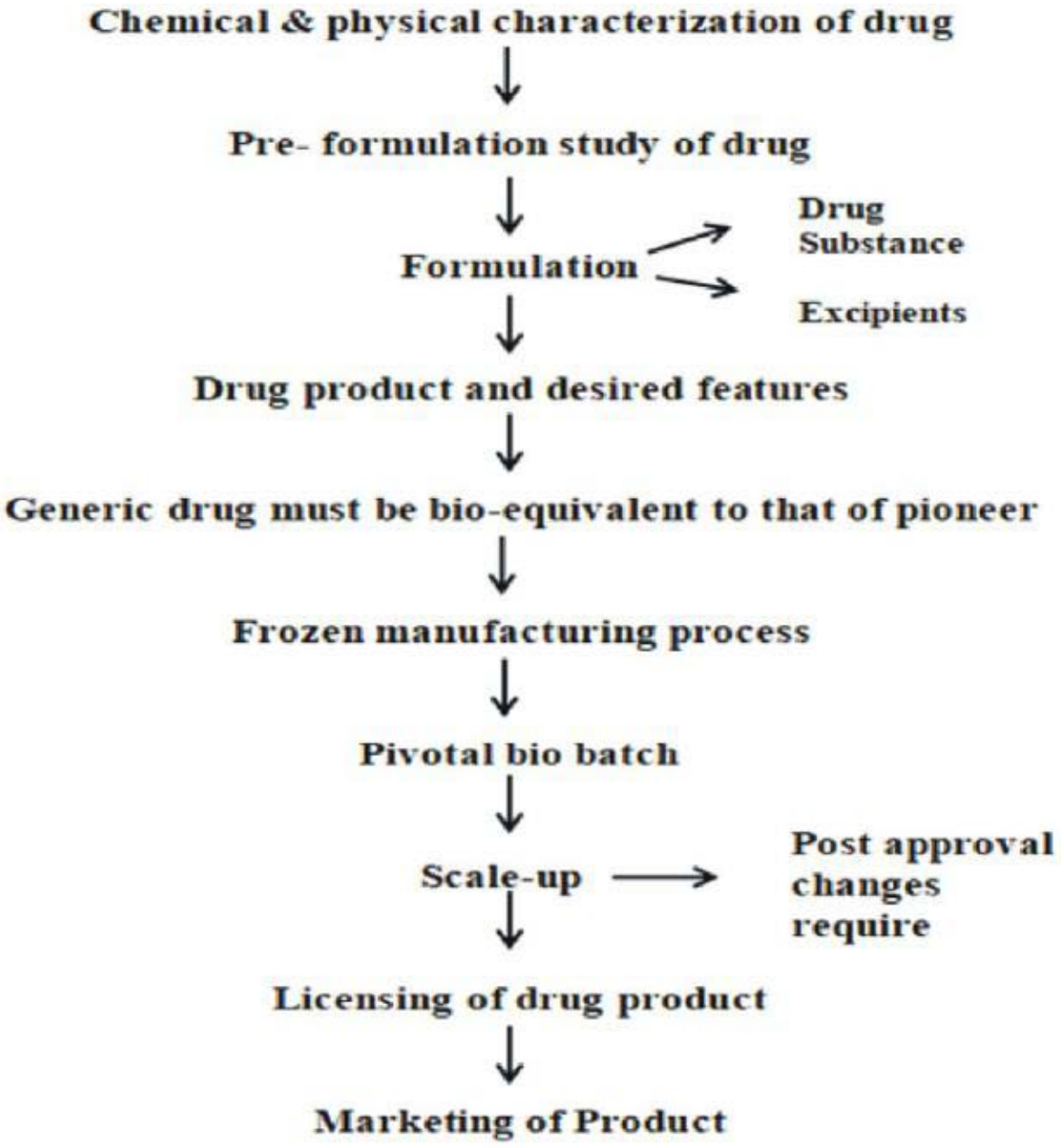

Figure 7 : Generic Drug Product Development