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Research Article

Study on Formulation and Development with New Drug Application and Investigational New Drug Application Process

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Abstract

The formulation and development of pharmaceutical dosage forms are critical stages in the path from medication discovery to market availability. This study focuses on the manufacturing and approval processes related with the development of a new pharmaceutical dosage form. It explores into the complexities of production, quality control, and regulatory compliance to assure the safe and effective distribution of a medicine to patients. The investigation begins with the selection of an active pharmaceutical ingredient (API) and the optimization of its formulation to suit therapeutic criteria. Following that, the emphasis moves to translating this formulation into a scalable production method. To establish a repeatable, cost-effective, and high-quality dosage form, several production processes such as granulation, extrusion, and tableting are investigated. Throughout the production process, stringent quality control methods are undertaken to ensure uniformity in drug content, dissolving rates, and physical features. These actions are critical for meeting severe regulatory criteria and obtaining regulatory clearances. The study further highlights the importance of regulatory affairs in the pharmaceutical business. It goes on regulatory processes, current Good Manufacturing Practices (cGMP), and preparing dossiers for submission to regulatory agencies. The fact that these authorities approved the designed dosage form attests to its safety, effectiveness, and quality. Ultimately, this study emphasizes the need of thorough planning and execution in the pharmaceutical dosage form formulation, production, and approval procedures. A complete understanding of these processes is required to bring novel and safe drug delivery systems to market, eventually helping patients and improving the pharmaceutical sector.

Keywords: Investigation; API; Regulatory Compliance; Clearances; cGMP; Emphasizes; Novel

Introduction

Formulation and development are key stages in various fields, including pharmaceuticals, cosmetics, food, and product manufacturing. These processes involve creating and refining products, from initial concept to final production. It is iterative processes that require collaboration among various departments, including research and development, marketing, and regulatory affairs. Effective communication and project management are essential to ensure a successful outcome.

Pharmaceutical formulation is the multi step process where the active drug is mixed with all other components by considering the factors of particle size, polymorphic, pH, and solubility and becomes the final beneficial medicinal product. Benefits and constraints of the active pharmaceutical ingredients (API), valuable excitements, associated interactions, and manufacturing procedure are the four basic components for a successful pharmaceutical formulation. The formulation often functions in a way that includes different dosage forms. The dosage form is the pharmaceutical

drug product as marketed for use with a specific mixture of active ingredients and inactive components. It has to be a particular configuration(capsule shell, for example) and distributed into a particular dose. Some of the widely used formulation are:

- **Tablets, Capsules, and Liquids:** These formulations allow for accurate dosing, ease of administration, and extended shelf life.
- **Trans dermal Patches:** Provide controlled drug release over time, reducing the need for frequent dosing.
- **Inhalers:** Effective delivery of drugs directly to the respiratory system for conditions like asthma.

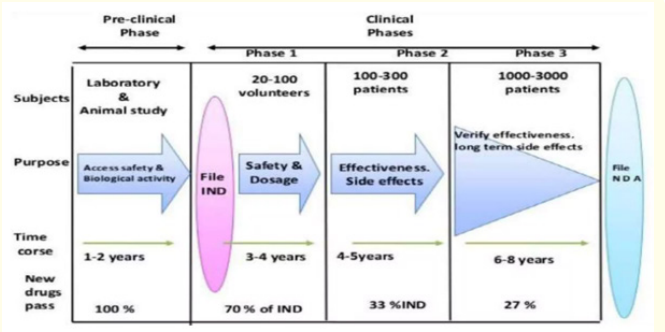

Figure 1: Drug development stages.

Formulation is the process of designing and developing a mixture or combination of substances to create a specific product with desired properties.

Whether you are formulating pharmaceuticals, cosmetics, food products, or chemicals, the process typically involves several key steps:

- **Define Objectives:** Determine the purpose of the formulation, including the product's intended use, target market, and desired properties (e.g., appearance, texture, efficacy, taste).
- **Select Ingredients:** Identify and select the raw materials and ingredients that will be used in the formulation. Consider factors like the quality, purity, compatibility, and availability of these ingredients.
- **Establish Formulation Parameters:** Set specific criteria and parameters for the formulation, including ingredient proportions, concentrations, and any constraints or limitations (e.g., regulatory requirements, cost limitations).
- **Preliminary Formulation:** Create an initial formulation by combining the selected ingredients according to the established parameters. This preliminary formulation serves as a starting point for further development.
- **Testing and Evaluation:** Conduct various tests and evaluations to assess the preliminary formulation's properties. This may include physical tests (e.g., viscosity, pH, color), chemical analysis, stability testing, and sensory evaluations (e.g., taste, smell, texture).
- **Iterative Adjustments:** Based on the test results and feedback, make adjustments to the formulation. Modify ingredient proportions, processing methods, or other variables as needed to achieve the desired product attributes.
- **Optimization:** Continue to refine and optimize the formulation through multiple iterations until it meets all the established criteria and provides consistent results.
- **Stability Testing:** Conduct stability testing to assess how the formulation performs over time under various environmental conditions (e.g., temperature, humidity) to ensure product longevity.
- **Scale-Up:** If the formulation is for commercial production, scale up the process to produce larger quantities. Ensure that the formulation remains consistent and cost-effective during scale-up.
- **Quality Control:** Develop and implement quality control measures to ensure that each batch of the formulated product meets the desired specifications and quality standards.
- **Regulatory Compliance:** If applicable, ensure that the formulation and final product comply with relevant regulations and safety standards, such as those imposed by government agencies like the FDA.
- **Documentation:** Maintain detailed records of the formulation process, including ingredient specifications, batch records, and testing data. This documentation is crucial for consistency and regulatory compliance.
- **Final Validation:** Validate the final formulation to ensure that it consistently meets all predetermined criteria and is ready for production
- **Production and Commercialization:** Begin large-scale production of the formulated product. Develop packaging, labelling, and marketing strategies for commercialization.
- **Continuous Monitoring:** After commercial launch, continuously monitor the product's performance, gather customer feedback, and make necessary adjustments or improvements as needed.

Formulation development is an iterative and systematic process that requires careful planning, testing, and refinement to create a product that meets consumer expectations and industry standards. Each step should be well-documented and carried out with precision to ensure the success of the formulated product. Development in the pharmaceutical industry involves the systematic process of turning a drug candidate into a safe, effective, and market-ready medication. This process is highly regulated and can take many years and significant financial investments.

History

The history of the formulation of pharmaceuticals is a story of continuous innovation and progress in the field of medicine and pharmacy. Pharmaceutical formulation refers to the process of creating a specific dosage form or preparation of a drug that is suitable for administration to patients. Here is an overview of the historical milestones and developments in the formulation of pharmaceuticals.

Ancient Formulations (Antiquity - Middle Ages)

- Early civilizations, such as the Egyptians, Greeks, and Chinese, developed herbal and plant-based remedies for various ailments.
- Formulations often took the form of decoctions, infusions, or ointments.

Arab and Islamic Contributions (8th - 13th Century)

- Arab scholars made significant contributions to pharmaceutical knowledge, including the development of drug formulations.
- The "Canon of Medicine" by Avicenna (Ibn Sina) included formulations for various drugs.

Medieval European Apothecaries (13th - 16th Century)

- Apothecaries played a crucial role in preparing and compounding medicines.
- Formulations included herbal extracts, tinctures, and salves.

Scientific Revolution and Alchemy (17th - 18th Century)

- The emergence of modern chemistry and the understanding of chemical reactions contributed to the development of more precise pharmaceutical formulations.
- Alchemical practices laid the groundwork for pharmaceutical compounding techniques.

Pharmacopoeias (17th Century - Present)

- The publication of pharmacopoeias, such as the London Pharmacopoeia in 1618 and the United States Pharmacopeia (USP) in 1820, standardized drug formulations and dosages.

Emergence of Pharmaceutical Industry (19th Century)

- The industrial revolution facilitated the mass production of pharmaceuticals.
- Innovations like tablet compression machines, encapsulation techniques, and sterile drug manufacturing improved drug formulation.

Antibiotics and Modern Pharmaceuticals (20th Century)

The discovery of antibiotics like penicillin in the 20th century revolutionized medicine and led to the development of various pharmaceutical formulations.

The pharmaceutical industry expanded rapidly, leading to the development of tablets, capsules, injectables, and more.

Biotechnology and Advanced Formulations (Late 20th Century - Present)

- Advancements in biotechnology have led to the development of biologics and gene therapies with complex formulations.
- Formulations now include sustained-release dosage forms, transdermal patches, and controlled-release technologies.

Personalized Medicine (21st Century)

Advances in genomics and pharmacogenomics have paved the way for personalized medicine, where drug formulations can be tailored to an individual's genetic makeup.

Regulatory Oversight (20th Century - Present)

The establishment of regulatory agencies like the FDA (Food and Drug Administration) in the United States has led to rigorous testing and approval processes for pharmaceutical formulations, ensuring safety and efficacy.

The history of pharmaceutical formulation is marked by a continuous quest for safer, more effective, and better-tolerated medi-

cations. It has evolved from simple herbal remedies to complex, precision-engineered drug formulations that play a vital role in modern healthcare. The future of pharmaceutical formulation continues to be shaped by advancements in science and technology, as well as the growing emphasis on personalized medicine.

Research in drug discovery

Research in drug discovery is a multifaceted and complex process that involves identifying, designing, and developing new drugs or therapies to treat or prevent diseases.

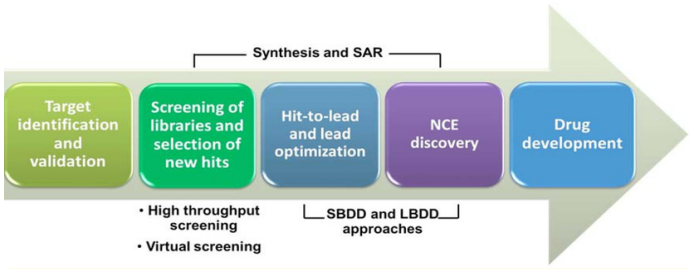

Figure 2: Steps in research.

The drug discovery process typically encompasses several key stages:

Identification of a biological target

The first stage is to identify a particular molecule related with an illness, which is often a protein, gene, or biological pathway. This target is often selected because it is important in the etiology of the illness.

Identification of biological sources refers to the process of discovering the origin or source of biological samples, organisms, or materials in scientific study, notably in domains such as microbiology, genetics, and drug development. This identification is critical for a variety of applications, including research, diagnostics, and quality control. Here are some examples of frequent contexts and strategies for identifying biological sources in research.

Microbial identification

Microbiologists frequently need to identify bacteria, fungus, and other microorganisms. Methods that are commonly used include:

Phenotypic methods

These include examining and characterizing the microorganism's physical and biological features, such as colony shape and biochemical assays.

Genotypic methods

Microorganisms can be identified using genetic methods such as Polymerase Chain Reaction (PCR) and DNA sequencing, such as 16S rRNA sequencing for bacteria.

- **Species Identification:** Identifying species within a group may be required by researchers in a variety of subjects, including ecology and conservation biology. DNA barcoding using particular gene markers is a frequent technique.
- **Sample Origin Verification:** The origin of a biological sample can be critical in forensic and food safety investigations. DNA fingerprinting and isotopic analysis can assist in determining a sample's geographic or genetic origin.
- **Genomic Sequencing:** Next-generation sequencing (NGS) technologies are used in genetics and genomics research to sequence and identify genes and other genomic components in biological samples. This is essential for comprehending genetic variation and function.
- **Drug Development:** Identifying the biological origins of active chemicals or prospective medications is critical in pharmaceutical research. To identify the active chemicals in natural goods such as plant extracts, researchers may employ methods such as nuclear magnetic resonance (NMR) and mass spectrometry.
- **Cell Line Authentication:** Researchers in cell biology and biotechnology must validate the identification of cell lines to guarantee they are dealing with the proper cells. For this aim, Short Tandem Repeat (STR) analysis is often utilized.
- **Forensic Science:** In forensic investigations, DNA profiling is used to identify individuals or to match biological evidence to a specific person or source.
- **Quality Control in Biotechnology:** Companies in biotechnology and pharmaceuticals must assure the uniformity and purity of biological resources such cell cultures, antibodies, and recombinant proteins. To validate the source and quality of these components, several analytical procedures are used.

- **Food and Environmental Testing:** The detection of biological contaminants, diseases, or pollutants is critical in food safety and environmental studies. This can be accomplished by the use of molecular approaches, immunoassays, and other techniques.
- **Taxonomy and Classification:** The detection of biological contaminants, diseases, or pollutants is critical in food safety and environmental studies. This can be accomplished by the use of molecular approaches, immunoassays, and other techniques.

Validation

Researchers must validate that modifying this target will have a meaningful impact on the disease. This involves using various techniques, including genetic studies and *in vitro* assays, to confirm the target's relevance.

The basic goal of validation is to establish the reliability and dependability of research findings. Here is a overview of many areas of study validation:

- Data Validation.
    - Data Collection Validation.
    - Data Entry Validation.
    - Data Quality Control.
- Method Validation.
- Instrument Validation.
- Statistical Validation.
    - Assumption Checking.
    - Model Validation.
    - Cross-Validation.
- Validation of Findings.
- Peer Review.
- Ethical and Legal Validation.
- Validation of Assumptions.
- Validation of Software and Tools.
- External Validation.

Hit generation

After a target has been verified, researchers seek to identify or create small molecules, biologics, or other chemicals that can interact with the target and alter its activity. These earliest compounds are referred to as "hits."

Researchers find or generate possible compounds that have the potential to interact with a certain biological target linked with a disease during the hit generation stage of the drug discovery process. These substances are frequently referred to as "hits." The objective is to identify a starting point for medication development. Here's an in-depth look of the hit creation process:

Target selection and validation

A specific biological target must be chosen and confirmed before hit generation may commence. Typically, this target is a protein, gene, or cellular pathway thought to be implicated in the illness of concern. Validation verifies that changing this target will have a therapeutic impact.

Compound library development

Researchers generate a list of substances that may be tested for potential hits. These chemicals can originate from a variety of sources, including:

- **Natural Products:** Compounds extracted from plants, microorganisms, or marine organisms.
- **Chemical Libraries:** Collections of synthetic compounds.
- **Virtual Libraries:** Computational approaches that generate potential drug-like compounds.

High-throughput screening (HTS)

HTS is a critical approach for testing the ability of compounds in the library to interact with the target. It entails automated systems that can swiftly test hundreds, if not millions, of chemicals for their anti-target activity.

Assays are utilized, which are particular assays designed to evaluate the interaction of the chemical with the target. Enzyme activity tests, receptor binding assays, and cell-based assays are examples of assays.

Hits are determined by their capacity to influence the target's activity or function. Positive hits are chemicals that interact well with the target.

Hit confirmation

- Hits found by HTS must be validated by subsequent tests. Researchers must guarantee that the effects they see are consistent and repeatable.

- Dose-response experiments are frequently carried out in order to discover the concentration at which the drug is most effective.

Chemical optimization

Hit compounds are usually beginning points that need to be chemically optimized. Medicinal chemists seek to alter the hit compound's chemical structure in order to increase its drug-like effects. The goal of this optimization method is to:

- Enhance potency (the compound's ability to affect the target).
- Increase selectivity (the compound's ability to interact with the target without affecting unrelated proteins).
- Improve pharmacokinetic properties (how the body absorbs, distributes, metabolizes, and excretes the compound).
- Reduce toxicity and adverse effects.

Lead identification

After several rounds of chemical optimization, a molecule with good features that is suitable for future development is designated as the "lead compound." It is the foundation for the medication development process.

Structural biology and computational chemistry

These methods can be utilized to obtain insight into the molecular interactions between the lead drug and the target. This information aids in further improving the structure of the chemical.

Hit-to-lead optimization

Researchers are working to improve the blockbuster chemicals' qualities. This entails improving their structure in order to improve potency, selectivity, and other drug-like qualities while limiting toxicity.

"Hit-to-Lead Optimization" is an important stage in drug discovery that bridges the gap between identifying potential therapeutic candidates (hits) and selecting a lead molecule for future development. This procedure entails refining and enhancing hit compounds in order to produce a lead molecule suitable for medication development. The Hit-to-Lead Optimization process in research is explained in depth here:

- **Selection of Hits:** Hit compounds are chosen based on their initial contact with a biological target of interest that demonstrates potential therapeutic efficacy. High-throughput screening, virtual screening, and other technologies are commonly used to identify these hits.
- **Biological Activity Assessment:** The initial stage in hit-to-lead optimization is to evaluate and confirm the biological activity of the selected hits. This frequently entails doing more extensive experiments to confirm their efficiency in modifying the target.
- **Medicinal Chemistry and Structural Activity Relationship (SAR) Studies:** Medicinal chemists investigate the structure-activity relationship (SAR) of the hit compounds to learn how structural alterations impact biological activity.
- SAR investigations aid in the identification of important functional groups and regions of hit compounds that are essential for their activity.
- **Optimization of Chemical Structure:** Medicinal chemists work on improving the pharmacological characteristics of pharmaceutical molecules by altering their chemical structure, which includes:
    - **Potency:** Enhancing the compound's ability to interact with the target.
    - **Selectivity:** Reducing the compound's interaction with unintended targets.
    - **Pharmacokinetics:** Improving how the compound is absorbed, distributed, metabolized, and excreted in the body.
    - **Toxicity:** Minimizing harmful effects on normal cells or organs.
- **ADME (Absorption, Distribution, Metabolism, and Excretion) Profiling:** The ADME features of the lead candidates are being evaluated by researchers in order to better understand how the chemicals will behave in the human body. This involves determining bioavailability, solubility, metabolism, and excretion.
- **Toxicology Studies:** To assess the safety of lead compounds, preclinical toxicological studies are carried out. This involves defining safe dose levels and identifying potential harmful consequences.
- **Formulation and Delivery:** Scientists are working on converting the lead compounds into an appropriate dosage form (e.g., pills, capsules, injections) for patient administration. It is critical to consider medication delivery and bioavailability.

- **Pharmacodynamic and Pharmacokinetic Profiling:** Researchers investigate how the lead compounds impact the target's activity (pharmacodynamics) as well as how the chemical is processed by the body (pharmacokinetics). This information aids in the formulation of dosage regimens.
- ***In Vivo* Studies:** Animal models are used to evaluate the effectiveness, safety, and therapeutic potential of the lead compounds. These investigations shed light on how the chemicals could act in people.
- **Lead Selection:** Lead compounds are assessed for their entire profile, which includes effectiveness, safety, and ADME characteristics, after extensive optimization. The most promising lead candidate is chosen for preclinical development.
- **4.4.k Intellectual Property Protection:** To protect the generated compounds, it is critical to acquire intellectual property through patents throughout the hit-to-lead optimization process.

Lead compound selection

A lead drug is chosen for continued research from among the optimized hits based on its efficacy, safety, and other pertinent characteristics.

The process of selecting lead compounds in research is an important stage in drug development. It entails selecting the most promising compound from a pool of lead candidates that have been heavily optimized throughout the hit-to-lead stage. The following is a full explanation of the lead compound selection procedure:

- **Lead Candidate Pool:** The lead compound selection process starts with a pool of lead candidates identified during the hit-to-lead optimization phase. To improve their pharmacological qualities, several lead candidates have been chemically changed and improved.
- **Evaluation of Pharmacological Activity:** To evaluate biological activity, the lead candidates are subjected to extensive pharmacological testing. This entails evaluating the compounds against the chosen therapeutic target to ensure that they can affect it.
- **Pharmacological Profiling :**The pharmacological characteristics of lead candidates are thoroughly evaluated by researchers. This includes the following:
    - Considering the efficacy of the chemicals against the target.
    - Determining lead chemical selectivity to guarantee minimal interaction with off-target proteins.
    - Evaluating the mechanism of action of the chemicals to ensure that they work as planned.
- **Safety and Toxicity Evaluation:** To discover any possible side effects, lead candidates are subjected to extensive safety and toxicity investigations. These investigations involve *in vitro* and *in vivo* evaluations to identify the safety profile of the chemicals, possible organ toxicity, and any other safety issues.
- **ADME Profiling:** To analyse their pharmacokinetic features, lead compounds are subjected to ADME (Absorption, Distribution, Metabolism, and Excretion) investigations. These researches look at the compound's:
    - The bioavailability of a chemical (the amount to which it reaches systemic circulation).
    - Metabolism and bodily stability.
    - Targeted tissue and organ distribution.
    - Expulsion from the body.
- **Formulation and Delivery:** Researchers are working on producing acceptable formulations for the lead compounds so that they can be administered to patients successfully. This might entail developing pills, capsules, injections, or other dose forms to improve bioavailability and patient compliance.
- ***In Vivo* Studies:** Animal models are used to test lead candidates' therapeutic effectiveness, safety, and overall performance in a live system. *In vivo* investigations give important information about how chemicals function in a complicated biological context.
- **Dose-Response and Efficacy Studies:** To identify the best dosage range for lead compounds, researchers conduct dose-response experiments. Efficacy studies assess the therapeutic benefits of substances at various dosage levels.
- **Selection Criteria:** The selection of the lead compound is based on a combination of factors, including:
- **Efficacy:** The lead compound should exhibit significant therapeutic effects in relevant disease models.
- **Safety:** The compound should demonstrate an acceptable safety profile and minimal toxicity.

- **Pharmacokinetics:** The lead compound should possess desirable ADME properties for effective drug delivery.
- **Selectivity:** It should display high selectivity for the target and minimal interaction with off-target proteins.
- **Formulation:** The feasibility of formulating the compound for administration to patients.
- **Intellectual Property:** Considerations for patent protection to secure the compound's exclusivity.

Intellectual property protection

To preserve the investment in medication research, the selected lead molecule and accompanying intellectual property are protected by patents.

- Copyright
- Trademarks
- Patents
- Trade Secrets
- Industrial Design Rights
- Utility Model.

Pre-clinical study

Pre-clinical studies refer to the early stages of research and testing that are conducted before a new medical treatment or drug is tested on humans in clinical trials. These studies are essential for evaluating the safety and efficacy of a new drug or medical intervention.

Pre-clinical testing

In vitro (in the lab), *in vivo* (animal), in silico (software) studies are conducted to assess a drug candidate's safety, efficacy, and toxicity. This phase helps determine whether the drug is suitable for human testing.

After synthesize/identifying a prospective compound it is tested on animal to expose the whole pharmacological profile.

Experiments are generally performed on a rodent (Mouse, rate, guinea pig, hamster rabbit).

Larger animals (cat, dog, monkey).

As the evaluation progresses, unfavourable compounds get rejected at each step so that only a few out of thousands reach the stage when administration to man is considered.

Tests are preformed, like:

- **Screening test:** These are simple and rapidly performed tests to indicated presence or absence of a particular pharmacodynamic activity. i.e., analgesic and hypoglycaemia activity.
- **Tests on isolated organs bacterial cultures:** These also are preliminary tests to detect specific activity, such as antihistamine, anti secretory vasodilation, antibacterial etc.
- **Tests on animal models of human disease:** Such as kindled seizures in rats spontaneous (genetically) hypertensive rats, experimental tuberculosis in mouse, alloxan induced diabetes in rat or dog etc.
- **Confirmatory trusts and analogous activities:** Compound found for detailed study by more elaborate tests which confirm and characterize the activity other related activities. i.e. antipyretic and anti-inflammatory an analgesic are tested.
- **Systemic pharmacology:** It is irrespective of the primary action of the drug.
- Its effects on major organs system. i.e., nervous system, cardiovascular, respiratory, renal, GIT are worked out.
- **Quantitative tests:** The dose response relationship maximal effect and comparative potency/efficacy with exiting drug is ascertained.
- **Pharmacokinetics:** The absorption, volume of distribution metabolism, excreation pattern of tissue distribution and plasma half-life of the drug are quantified.

Toxicity tests: Aim is to determine safety least 2 animal species.

- One rodent (mouse/rat) and one no-rodent (dog/cat)
- Dose: oral and parenteral.
- Mechanism of action, including additional mechanism.
- e.g., alpha-adrenergic blockade, calcium camel blocked nitrovasodilation etc in a Beta-adrenergic blocker hyperventilate are elucidated.

Formulation development

Pre-clinical research may involve developing the drug formulation, such as pills, injections, or topical preparations, that will be

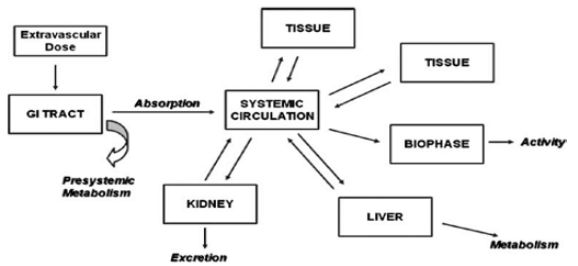

Figure 3: Pharmacokinetic in pre-clinical.

used in human trials. Formulation is important for ensuring the drug's stability and effectiveness.

Investigation new drug (IND) application

Before conducting clinical trials in humans, pharmaceutical companies must submit an IND application to the regulatory authority (e.g., FDA,CDSCO in the United States and India). The application includes per-clinical data, proposed clinical trial plans, and safety information.

An Investigation New Drug (IND) application is a critical step in the drug development process in the United States. It is a submission to the U.S. Food and Drug Administration (FDA) that requests permission to begin clinical trials of a new drug or biologic (such as a vaccine or gene therapy) in humans. The IND application provides the FDA with comprehensive information about the drug, including its chemistry, manufacturing, pharmacology, toxicology, and proposed clinical study protocols. Here are the key details about the IND application.

The purpose of the guidance is to assist sponsor-investigation in preparing and submitting complete investigation new drug application.

- CDER centre for drug evaluation and research
- CBER centre for biologic evaluation and research
- Food and drug administration "FDA"
- Sponsor investigators seeking to do clinical research after do not have the regulatory knowledge or the resource to hire experts to help with IND submission process.
- Exhaustive step by step instruction manual this guidance.
- This guidance also discuses the IND review process and general responsibility of sponsor-investigators related to clinical investigations.
- Sponsor -investigation should review in full these requirement, which are described in the code of federal regulation (CFR)
- Many section of the regulation the apply to INDS I.e., CFR parts 50,56 and 312.
- This Guidance has been present by the office of ND in CDER in cooperation with the centre for biologic evaluation and research (CBER) at the FDA.
- CFR (Code of federal regulation); total parts 21 to 312.
- its general and permanent rules pretested in the federal register by executive industry/agency federal governments.
- 50 titles that represent broad areas subj to federal regulation, CFR reference that related to the IND.
- This guidance is directed primary at these sponsor-investigator who are seeking to evaluate a drug that is either currently approved or is being investigated under an existing IND for a different indication.
- This guidance is not intended for developing a drug for commercial purpose(seeking market approval or license) does not focus on certain regulatory requirements that involve exchange of information or material.
- This guidance is not response to CDER and CBER is only to marketing and exchange exposes license approve for FDA.
- It is a general FDA guidance is CFR part 50 protection of human subject.
- 56 institutional review boards code of federal regulation.
- Part 312; procedures and requirements governing use IND submission to review by FDA
- Parts 21; FDA, it is general FDA guidance documents do not establish legally enforceable responsibilities instead guidance.

Background

- Generally FDA regulation sponsors including sponsor-investigation. Who wise to evaluate a drug or biological product in humans to submit an IND to the FDA (21 CFR part 312).

- FDA primary reviewing an IND are to help protect the right and safety of subject and in phase 2 and phase 3 ensure the quality of the clinical trail is adequate to evaluate the drugs effectiveness and safety

Biological devices

- Biological licence access FDA guidance is establish legally.

- CDER - drug
- CB-ER-88 vaccine, blood compound ceteris DNA material and IND is not apply cable to marketing exchange access.

NDA Application types

- **An Investigator IND:** Is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- **Emergency use of IND:** Allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR, Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- **Treatment IND:** Is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

Commercial

Collect the data needed drug to market for FDA.

Non commercial; physician submitted INDA research for new indication, instead their clinical research for efficacy for new indication.

Number: Regulation

- 21 CFR part 201: Drug labelling.
- 21CFR part 54: Financial disclosure by clinical investigators.
- 21CFR part 58: Animals studies (non clinical)
- 21CFR part 314: INDA and NDA for FDA marketing a NDA.
- 21CFR part 56: Institutional review boards.
- 21CFR part312: Investigation NDA.
- 21CFR part 316: Orphan Drugs.
- 21 CFR part 50: Protection of human subjects.

The primary purpose of an IND application is to obtain FDA authorization to conduct clinical trials of a new drug in humans.

These clinical trials are typically conducted in three phases, each with specific objectives and increasing numbers of participants.

- **Phase 0:** Some companies conduct Phase 0 studies in a small number of humans to gather initial pharmacokinetic and pharmacodynamic data.
- **Phase I:** Safety and dosage testing in a small number of healthy volunteers.
- **Phase II:** Efficacy and side effects testing in a larger group of patients with the targeted disease or condition.
- **Phase III:** Large-scale testing to confirm efficacy, monitor side effects, and gather additional information about the drug's risks and benefits.
- **Phase IV:** Post marketing surveillance.

Sponsorship

- The IND application is typically submitted by the sponsor, which is usually the company or organization responsible for developing and conducting the clinical trials of the investigational drug.
- The sponsor is responsible for ensuring that the drug is safe and effective, conducting the trials according to FDA regulations, and providing ongoing reports to the FDA.

Contents of the IND application

Chemistry, Manufacturing, and Control (CMC) Information: Detailed information about the drug's composition, manufacturing processes, quality control, and stability.

- **Preclinical Data:** Comprehensive data from laboratory and animal studies, including pharmacology, toxicology, and any other relevant information.
- **Clinical Study Protocols:** Detailed plans for the proposed clinical trials, including study design, objectives, patient populations, and endpoints.
- **Investigator Information:** Background and qualifications of the clinical investigators who will conduct the trials.
- **Human Subject Protection Information:** Plans to ensure the ethical treatment of study participants and protection of their rights and safety.
- **Regulatory Requirements:** Information about the regulatory requirements for conducting clinical trials and the sponsor's commitment to complying with them.

Review process

- The FDA reviews the IND application to assess the safety and scientific rationale for the proposed clinical trials.
- If the FDA finds the IND application satisfactory, they issue an IND number, allowing the sponsor to proceed with clinical trials.
- The FDA may request additional information or clarification during the review process, and the sponsor is expected to respond promptly.

IND phases

- After receiving IND approval, the sponsor can proceed with Phase I clinical trials.
- The sponsor must submit additional IND amendments to the FDA for each subsequent phase of clinical testing.
- The FDA closely monitors the progress of clinical trials through periodic reports submitted by the sponsor.

Ongoing reporting

The sponsor is required to provide the FDA with regular updates on the status of clinical trials, including adverse events, safety data, and any changes to the study protocols.

IND termination

- The FDA can suspend or terminate an IND if safety concerns arise during the clinical trials.
- If the clinical trials demonstrate that the drug is safe and effective, the sponsor may proceed with a New Drug Application (NDA) to seek FDA approval for marketing the drug.
- The IND application process is a critical regulatory step in bringing new drugs to market. It ensures that potential new treatments are thoroughly evaluated for safety and efficacy before they can be made available to the public. The FDA's oversight during this process helps protect the welfare of patients and the integrity of the drug development process.

Clinical trials

When a compound deserving trail in man is identified by animal studies, the regulatory authorities are approached who on satisfaction issue an 'IND' licence. The drug id formulated into a suitable dosage form and clinical trials are treated with only relevant monitoring.

Standards for the design, ethics, conduct, monitoring, auditing, recording and analysing data reporting of clinical trails have been laid down in the form of 'Good Clinical Practice'.

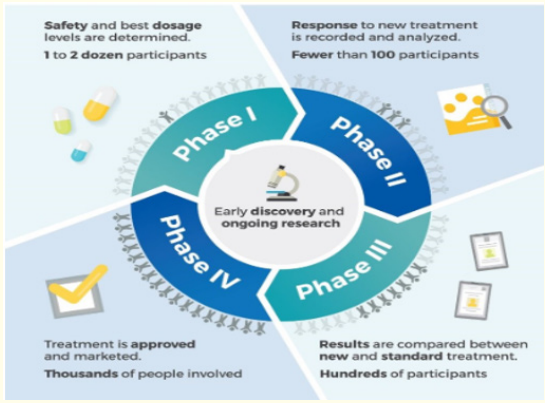

Figure 4: Stages in clinical trail.

Phase I

A Phase 1 clinical trial is the first stage in the process of testing a new drug or medical treatment in humans. These trials are conducted to evaluate the safety, dosage, and potential side effects of the experimental treatment. Here are the key details of a Phase 1 clinical trial:

- **Preclinical Research:** Before a drug or treatment can advance to Phase 1, it typically undergoes extensive preclinical testing in laboratories and on animals. This research helps establish the potential safety and efficacy of the treatment.
- **Study Design:** Phase 1 trials are typically small-scale, involving a relatively small number of healthy volunteers(20-80) or, in some cases, patients with the condition the treatment is intended to address. The primary objective is to assess safety, dosage, and side effects.
- **Safety Evaluation:** The primary goal of Phase 1 trials is to determine the safety of the treatment. Researchers look for adverse effects, both expected and unexpected. Dose escalation, starting with a very low dose, is often used to gradually increase the dose to assess toxicity.
- **Dosing:** Researchers start with a low dose of the experimental treatment and gradually increase it in cohorts of participants. This process helps determine the highest dose that can be given without causing unacceptable side effects.

- **Informed Consent:** All participants in the trial must provide informed consent, meaning they are fully informed about the potential risks and benefits of the treatment and willingly agree to participate.
- **Monitoring:** Participants are closely monitored throughout the trial. This includes regular medical check-ups, blood tests, and other assessments to detect any adverse effects.
- **Duration:** Phase 1 trials are typically shorter in duration compared to later-phase trials, often lasting several months.
- **Endpoint:** The primary endpoint of Phase 1 trials is safety. However, researchers may also collect preliminary data on how the treatment is metabolized and how it affects the body.
- **Dose-Limiting Toxicities (DLTs):** DLTs are significant, unacceptable side effects that can limit the dosage of a treatment. Researchers closely monitor for DLTs in Phase 1 trials.
- **Patient Population:** In some Phase 1 trials, especially for cancer treatments, patients with the target condition may be included, but healthy volunteers are typically involved initially.
- **Data Analysis:** The data collected from Phase 1 trials are analyzed to determine if the treatment is safe and to identify the recommended Phase 2 dose.
- **Regulatory Oversight:** Phase 1 trials are subject to regulatory oversight to ensure that they adhere to ethical and safety standards. In the United States, the Food and Drug Administration (FDA) regulates Phase 1 trials.
- **Phase Advancement:** If the treatment is found to be safe and tolerable in Phase 1, it may progress to Phase 2 trials, where its effectiveness is further assessed in a larger group of patients.

Phase II

- A Phase 2 clinical trial is the second stage in the process of testing a new drug or medical treatment in humans. In Phase 2, the primary focus shifts from primarily assessing safety, as in Phase 1, to evaluating the treatment's effectiveness and further understanding its side effects. Here are the key details of a Phase 2 clinical trial:
- **Study Design:** Phase 2 trials are larger in scale compared to Phase 1 and typically involve a larger number of patients(200-500) who have the condition the experimental treatment is intended to address. The goal is to assess the treatment's efficacy and gather more information on its safety and dosing.
- **Patient Population:** Participants in Phase 2 trials have the condition or disease that the experimental treatment is designed to treat. The trial may enroll a specific patient population, such as those with a particular stage of the disease.
- **Randomization:** In some Phase 2 trials, patients may be randomly assigned to different treatment groups. This helps ensure that the results are not biased and can be compared fairly.
- **Control Group:** In many Phase 2 trials, there may be a control group that receives either a standard treatment or a placebo for comparison. This helps determine whether the experimental treatment is more effective than existing options.
- **Dosage:** Researchers have typically identified the recommended Phase 2 dose (RP2D) based on the Phase 1 trial results. Phase 2 trials often use this dose to evaluate the treatment's effectiveness.
- **Endpoints:** Phase 2 trials have specific endpoints, which are predefined measures used to assess the treatment's effectiveness. These can include changes in disease symptoms, tumor size, laboratory markers, or other relevant outcomes.
- **Duration:** Phase 2 trials can vary in duration but are generally longer than Phase 1 trials. They may last several months to a few years, depending on the nature of the condition being studied.
- **Data Collection:** Detailed data are collected on the treatment's effectiveness, safety, and side effects. This includes regular medical check-ups, diagnostic tests, and patient-reported outcomes.
- **Statistical Analysis:** The data collected are analyzed to determine whether the treatment demonstrates statistically significant improvements in comparison to the control group or other relevant benchmarks.
- **Safety Monitoring:** Although Phase 2 trials primarily focus on effectiveness, safety remains an important consideration. Any significant adverse events or side effects are carefully documented and assessed.

- **Regulatory Oversight:** Phase 2 trials are subject to regulatory oversight to ensure that they adhere to ethical and safety standards. In the United States, the Food and Drug Administration (FDA) regulates Phase 2 trials.
- **Phase Advancement:** If the treatment shows promising results in terms of efficacy and an acceptable safety profile in Phase 2, it may progress to Phase 3 trials, which are larger, more extensive trials designed to provide further evidence of safety and efficacy for regulatory approval.

Phase III

- A Phase 3 clinical trial is the third and final stage in the process of testing a new drug or medical treatment in humans before it can be considered for regulatory approval. Phase 3 trials are designed to confirm and expand upon the efficacy and safety data obtained in earlier phases (Phase 1 and Phase 2). Here are the key details of a Phase 3 clinical trial:

- **Study Design:** Phase 3 trials are larger and more extensive than Phase 2 trials, often involving a larger number of patients. These trials are conducted in a controlled, clinical research setting to assess the treatment's effectiveness, safety, and side effects.
- **Patient Population:** Participants in Phase 3 trials are individuals who have the condition or disease that the experimental treatment is designed to treat. This phase often includes a more diverse patient population to better represent the real-world patient group that would use the treatment.
- **Randomization and Control Group:** In many Phase 3 trials, patients are randomly assigned to different treatment groups, including a control group that receives either a standard treatment or a placebo for comparison. Randomization helps ensure that the results are unbiased and statistically valid.
- **Blindness:** Many Phase 3 trials are double-blind, meaning both the participants and the researchers are unaware of which treatment each participant is receiving. This helps minimize bias in the results.
- **Dosing:** Phase 3 trials typically use the recommended Phase 2 dose (RP2D) determined from earlier phases to evaluate the treatment's efficacy and safety.
- **Endpoints:** Phase 3 trials have well-defined endpoints, which are predefined measures used to assess the treatment's effectiveness. These endpoints are often based on clinical or patient-related outcomes.
- **Duration:** Phase 3 trials are longer in duration than Phase 1 and Phase 2 trials, lasting several years in some cases. This allows for a more extended assessment of the treatment's long-term effects.
- **Data Collection:** Rigorous data collection continues during Phase 3, including regular medical check-ups, diagnostic tests, and patient-reported outcomes. Large amounts of data are collected to ensure a comprehensive evaluation.
- **Statistical Analysis:** The data collected in Phase 3 trials are subjected to rigorous statistical analysis to determine whether the treatment demonstrates statistically significant improvements in comparison to the control group or existing therapies.
- **Safety Monitoring:** Safety remains a critical focus in Phase 3 trials, and any significant adverse events or side effects are documented and assessed.
- **Regulatory Oversight:** Phase 3 trials are closely monitored by regulatory authorities to ensure adherence to ethical standards and the safety of participants. These authorities vary by country but often include the FDA in the United States.
- **Post-Marketing Commitments:** In some cases, regulatory authorities may require post-marketing studies (Phase 4) to continue monitoring the treatment's safety and efficacy after it is approved and in general use.

Phase IV (Post-marketing)

- A Phase 4 clinical trial, often referred to as post-marketing surveillance or post-marketing studies, is a stage in the process of drug or medical treatment development that occurs after a treatment has been approved for use by regulatory authorities (e.g., the FDA in the United States). Phase 4 trials are designed to continue monitoring the treatment's safety, effectiveness, and long-term impacts in a real-world setting. Phase 4 occurs after a drug or treatment has received regulatory approval, meaning it is now available to the general population. Phase 4 studies are conducted in the real-world clinical setting. Here are the key details of a Phase 4 clinical trial:

- **Monitoring Safety:** Continuously assessing and monitoring the long-term safety of the treatment, including rare or unexpected side effects.
- **Effectiveness in a Broader Population:** Expanding the understanding of the treatment's effectiveness and safety in a larger, more diverse patient population.

- **Comparative Studies:** Comparing the approved treatment with other available treatments to assess its advantages and disadvantages.
- **Long-Term Outcomes:** Evaluating the treatment's long-term outcomes, including patient survival, quality of life, and disease progression.
- **Study Design:** Phase 4 studies can vary widely in design. They may be observational, meaning data is collected from real-world use without intervention, or they may involve specific interventions or sub-studies designed to answer particular questions.
- **Patient Population:** The patient population in Phase 4 trials typically reflects the broader, real-world population who will use the treatment. This includes patients with various disease stages, comorbidities, and demographics.
- **Duration:** Phase 4 studies are often long-term, as they aim to monitor outcomes over an extended period. They can continue for several years or even decades.
- **Data Collection:** Extensive data is collected from real-world patients, including electronic health records, patient-reported outcomes, and healthcare utilization information.
- **Safety Monitoring:** Continuous safety monitoring remains a priority, and any new safety concerns or adverse events are closely tracked.
- **Comparative Research:** Some Phase 4 studies may include head-to-head comparisons with other treatments to determine whether the approved treatment is more effective, safer, or cost-effective.
- **Regulatory Oversight:** Regulatory authorities may require or suggest Phase 4 studies as part of the post-marketing commitment, and they continue to oversee the safety and efficacy of the treatment during this phase.
- **Labeling and Guidelines:** Phase 4 studies may lead to updates in treatment labeling, guidelines, or recommendations. New information may be used to refine dosing recommendations, contraindications, and other aspects of treatment use.
- **Real-World Evidence:** Phase 4 studies contribute to the body of real-world evidence that informs clinical practice and healthcare decision-making.

New drug application (NDA)

Every medicine on the market must be authorized by the Food and drugs Administration (FDA). The "New Drug Application" (NDA) collects drug information such as clinical trial findings, animal study results, ingredients, how the medicine works in the body, and how the drug is made, processed, and packaged. The primary goal of the NDA is to give enough information to the FDA to establish that the medicine is safe and effective for the intended use in the population. Depending on the type of medicine being produced, there are numerous regulatory processes for drug approval.

In the United States, the Food and Drug Administration (FDA) authorizes new drug products for sale and marketing based on clinical trial data demonstrating a medicine's safety and efficacy for a proposed indication. A drug's sponsor (for example, a company, a research institution, or the government) seeks approval by submitting a new drug application (NDA) [1] to the FDA, which must include documentation and analyses of all animal and human trial data, as well as information about the drug's ingredients, clinical pharmacology, manufacturing, processing, and packaging. In the NDA, the FDA expects sponsors to provide all data, including entire protocols, protocol changes, and data from failed studies.

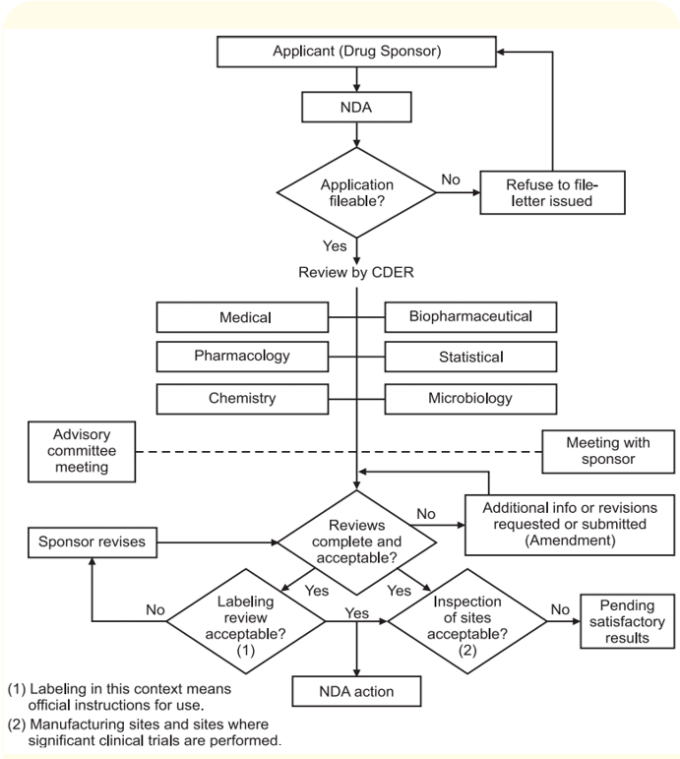

Figure 5: NDA procedure.

After successful clinical trials, a full NDA is prepared and submitted to the regulatory agency.

The NDA includes:

- Detailed information about the drug and formulation.
- Data from preclinical and clinical studies.
- Manufacturing and quality control information.
- Proposed labelling, including instructions for use.
- Detailed analyses of risks and benefits.
- Proposed post-approval plans for monitoring and additional studies.
-

Abbreviated new drug application

An application for a license to market a generic (or a duplicate) version of a drug that has already been granted an approval under a full NDA (i.e. the drug has already met the statutory standards for safety and effectiveness**.**

Regulatory review

The regulatory agency (e.g., the FDA) reviews the NDA. The review includes a thorough the assessment of the drug, safety, efficacy, manufacturing process, labelling, and risk-benefit profile.

Advisory committee meeting (if applicable)

In some cases, the regulatory agency may convene an advisory committee of external experts to provide recommendations regarding approval.

Approval decision

The regulatory agency decides whether to approve the drug based on the submitted data and reviews. The decision may result in one of the following outcomes:

- **Approval:** The drug is granted marketing authorization.
- **Complete Response Letter:** If deficiencies or concerns are identified, the regulatory agency issues a complete response letter, and the applicant must address these issues before approval.
- **Refusal to File:** If the application lacks essential information, the regulatory agency may refuse to accept the NDA.
- **Post-Approval Activities:** Once a drug is approved, post-marketing commitments and requirements may be imposed, including additional studies, safety monitoring, or label updates.
- **Market Launch:** If the NDA is approved, the drug can be marketed and made available to patients.

The NDA process is highly regulated and can be lengthy, expensive, and complex. Success requires a combination of rigorous research, effective clinical trials, and thorough documentation to demonstrate a drug's safety and efficacy, making it a vital process for ensuring public health and safety.

Conclusion

To summarize, pharmaceutical formulation and development is a complicated and dynamic process that is critical in bringing safe and effective treatments to market. Pharmaceutical businesses attempt to generate breakthrough formulations that meet unmet medical needs and enhance patient outcomes by using a systematic strategy that incorporates scientific knowledge, technical improvements, and regulatory compliance.

Pharmaceutical formulation and development success is dependent on multidisciplinary collaboration among professionals in chemistry, biology, pharmacology, and engineering. These groups collaborate to create medication formulations with the highest bioavailability, stability, and therapeutic effectiveness. Furthermore, advances in medication delivery techniques, such as nanotechnology and targeted distribution, lead to improved therapeutic performance and fewer adverse effects. Finally, pharmaceutical formulation and development are critical in tackling global health concerns and increasing patient quality of life. As science and technology progress, the pharmaceutical sector will play an increasingly important role in pushing the frontiers of innovation, delivering breakthrough treatment solutions, and determining the future of healthcare [2-37].

Bibliography

1. Gita Chaurasia. "A review on pharmaceutical formulation studies in formulation and development of new drug molecules". *International Journal of Pharmaceutical Sciences and Research, IJPSR* 7.6 (2016).

2. James M Butler., *et al*. "The Developability Classification System: Application of Biopharmaceutics Concept to Formulation Development". *Journal of Pharmaceutical Sciences* 99 (2016).

3. William F Salminen., *et al*. "Streamlining nonclinical drug development using the FDA 505 (b) (2) NDA regulatory pathway". *Drug Discovery Today* 24.1 (2019): 46-56.

4. Feroz Jameel and Susan Hershenson. "Formulation and process development strategies for manufacturing biopharmaceuticals". John wiley and sons (2010).

5. Gunter Jagschies., *et al*. "Biopharmaceutical processing: development, design, and implementation of manufacturing process". Elsevier (2018).

6. T O'Connor and S Lee. "Emerging technology for modernizing pharmaceutical production: continuous manufacturing". *Developing Solid and Oral Dosage Forms* (2017): 1031-1046.

7. Malcolm Rowland and Christian R Note. "Impact of the pharmaceutical sciences on health care: a reflection over the past 50 year". *Journal of Pharmaceutical Sciences* 101.11 (2012): 4075-4099.

8. OV Krylova and TM Litvinova. "History of the paster-based drug formulation development". *Journal of Pharmaceutical Sciences and Research* 10.9 (2018): 2212-2215.

9. Feroz Jameel and Susan Hershenson. "Formulation and process development strategies for manufacturing biopharmaceuticals". John Wiley and Sons (2010).

10. Johnathan D Adams and KP Flora. "Taxol: a history of pharmaceutical development and current pharmaceutical concerns, Journal of the national cancer institute". *Monographs* (1993): 141-147.

11. Donglu Zhang and Gang Luo. "Preclinical experimental models of drug metabolism & disposition in drug discovery and development". *Acta Pharmaceutica Sinica B* 2.6 (2012): 549-561.

12. Jayme L Dahlin., *et al*. "Mitigating risk in academic preclinical drug discovery". *Nature Reviews Drug Discovery* 14.4 (2015): 279-294.

13. Lalage Wakefield and Seema Agarwal. "Preclinical models for drug discovery for metastatic disease". *Cell* 186.8 (2023): 1792-1813.

14. Diana W Shineman and Garibay S Basi. "Accelerating drug discovery for Alzheimer's disease: best practices for preclinical animal studies" (2011).

15. "Accelerating drug discovery for Alzheimer's disease: best practices for preclinical animal studies". *Alzheimer's Research and Therapy* 3 (2011): 1-13.

16. ME Blair Holbein. "Understanding FDA regulatory requirements for investigational new drug applications for sponsor investigators". *Journal of Investigative Medicines* 57.6 (2009): 688-694.

17. Emil J Freireich. "The investigational new drug application-who benefits?". *Nature Clinical Practice Oncology* 3.2 (2006): 62-63.

18. Davy Chiodin and Erica M Cox. "Regulatory affairs 101: introduction to investigations new drug applications and clinical trial applications". *Clinical and Translational Science* 12.4 (2019): 334-342.

19. Larissa Lapteva and Anne R Parister. "Investigational new drug applications: a 1-year pilot study on rates and reasons for clinical hold". *Journal of Investigative Medicine* 64.2 (2016): 376-382.

20. Brenda Wright. "Clinical trial phases, A comprehensive and practical guide to clinical trials". (2016): 11-15.

21. Philip Sedgwick. "What are the four phases of clinical research trials?" *BMJ* 348 (2014).

22. Vu Nguyen and Burgunda V Sweet. "Defining the phases of clinical trials". *American Journal of Health-System Pharmacy* 63.8 (2006): 710-711.

23. Genevieve Decoster and Marc Buyse. "Phase IV clinical trials: purpose, design, and a limited place for good clinical practice". *Drug Information Journal* 29.1 (1995): 79-86.

24. Say-Beng Tan and David Machin. "Phase II clinical trials, Pharmaceutical Sciences". *Encyclopedia: Drug Discovery, Development, and Manufacturing* (2010): 1-24.

25. Carlos R Ayers. "Conducting Phase III and Phase IV Clinical Trials". *Drug Development* (2019): 175-184.

26. Eric H Rubin and D Gary Gilliland. "Drug development and clinical trials—the path to an approved cancer drug". *Nature Reviews Clinical Oncology* 9.4 (2012): 215-222.

27. John Orloff., *et al*. "The future of drug development: advancing clinical trial design". *Nature Reviews Drug Discovery* 8.12 (2009): 949-957.

28. Peter L Bonita. "Clinical trial simulation in drug development". *Pharmaceutical Research* 17 (2000): 252-256.

29. EA Eisenhauer., *et al*. *Journal of Clinical Oncology* 18.3 (2000): 684-684.

30. Arup K Basak., *et al*. "Pharmaceutical impurities: regulatory perspective for abbreviated new drug applications". *Advanced Drug Delivery Reviews* 59.1 (2007): 64-72.

31. Joseph A DilMasi. "New drug innovation and pharmaceutical industry structure: trends in the output of pharmaceutical firms". *Drug Information Journal: DIJ/Drug Information Association* 34 (2000): 1169-1194.

32. Jingjing Yu., *et al*. "Drug disposition and drug-drug interaction data in 2013 FDA new drug applications: a systematic review". *Drug Metabolism and Disposition* 42.12 (2014): 1991-2001.

33. William F Salminen., *et al*. "Streamlining nonclinical drug development using the FDA 505 (b) (2) new drug application regulatory pathway". *Drug Discovery Today* 24.1 (2019): 46-56.

34. John J Sunderland. "The academic NDA: justification, process, and lessons learned". J*ournal of Nuclear Medicine* 61.4 (2020): 480-487.

35. Marian F Henriquez Abramuk. "New drug application". *Translational Sports Medicine* (2023): 425-427.

36. Daniel Bobo., *et al*. "Nanoparticle-based medicines: a review of FDA-approved materials and clinical trials to date". *Pharmaceutical Research* 33 (2016): 2373-2387.

37. Eric Patridge., *et al*. "An analysis of FDA-approved drugs: natural products and their derivatives". *Drug Discovery Today* 21.2 (2016): 204-207.