Drug Discovery and Its Process

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ABSTRACT:

Drug discovery is a process which aims at identifying a compound therapeutically useful in curing and treating disease. This process involves the identification of candidates, synthesis, characterization, validation, optimization, screening and assays for therapeutic efficacy. Once a compound has shown its significance in these investigations, it will initiate the process of drug development earlier to clinical trials. New drug development process must continue through several stages in order to make a medicine that is safe, effective, and has approved all regulatory requirements. The process of drug design and discovery stands as the cornerstone of modern medicine, offering a ray of hope for the treatment of various diseases. This article explores the critical stages of drug development, emphasizing their paramount importance in bringing novel therapeutics to the forefront of healthcare. The journey commences with Pre Discovery, a phase characterized by exhaustive target identification and validation, underscoring the necessity of robust preclinical research. Subsequently, the Hit to Lead Discovery stage emerges, focusing on the identification and optimization of lead compounds with promising pharmacological properties. As these leads evolve, Preclinical Studies play an indispensable role in evaluating safety, efficacy, and pharmacokinetics, bridging the gap between laboratory findings and clinical applications. Finally, the Drug Development phase encapsulates the regulatory procedures and clinical trials necessary for transforming promising molecules into market-ready pharmaceuticals. In this dynamic field, the intersection of cutting-edge technology and scientific innovation continually redefines the boundaries of therapeutic possibilities. Understanding the nuances and significance of each stage is pivotal for researchers, pharmaceutical companies, and healthcare professionals, as they collectively endeavor to address the ever-evolving healthcare challenges of our time.

Keywords: Drug discovery, Drug development, Clinical trials, Pre Discovery, Target identification, Lead compounds, Preclinical Studies, Safety evaluation, Drug Development phase.

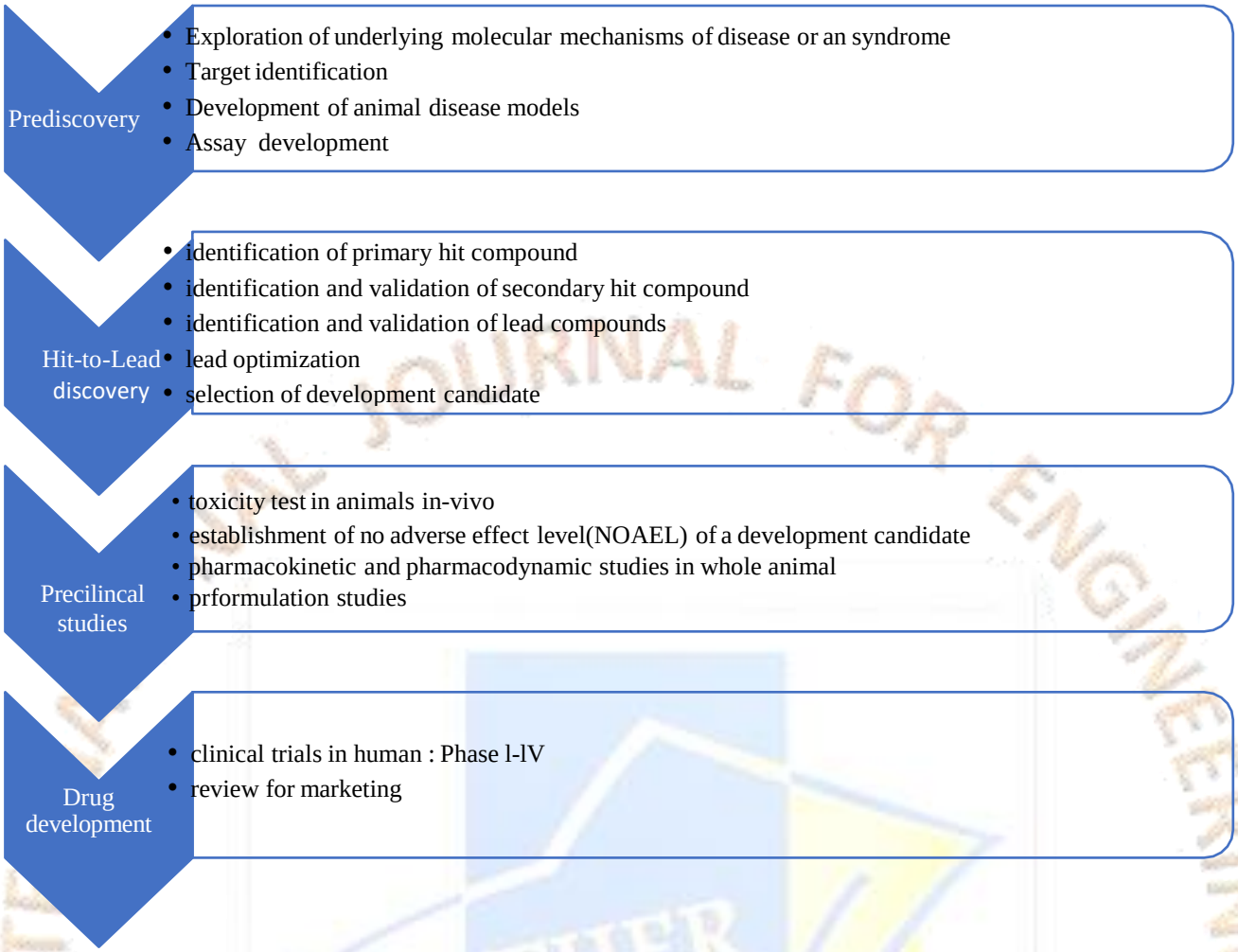
INTRODUCTION:

Drug discovery is a complex process that entails finding a medication molecule that is therapeutically effective in treating and managing a disease condition. New insights into a disease process that enable investigators to create a pharmaceutical to stall or counteract the symptoms of the sickness are often how researchers discover new drugs . The consequences of drug discoveries were felt in all facets of the human race, most notably the notable enhancements in life quality and the enhanced longevity that allowed people to live considerably longer than ever before [1]. Beginning in the 1980s, fewer novel therapeutic compounds were entering the pipeline for drug research and development [2]. The drug discovery process comprises the identification of drug candidates, synthesis, characterization, screening, and therapeutic efficacy assays . Several variables contribute to medication development efficacy problems. First and foremost, it is becoming increasingly clear that the old "one drug-one target" approach is no longer effective [3]. Furthermore, efficacy may be reduced if the level of physiological redundancy in biological networks is underestimated [4]. Many pharmacological targets function in biological processes that are unrelated to the drug's intended effects, causing to unexpected toxicities [5-8]. In-silico techniques to drug design and discovery are used to explore the biological effects of a large range of tiny molecular weight molecules on a wide range of macromolecular targets [9]. Excellent drug targets are being identified at an increasing rate as bioinformatics advances. These targets' genes can be rapidly cloned, and the protein can be produced and purified to homogeneity. Automation at all phases, more powerful synchrotron radiation, and new advancements in phase determination have decreased the timetable for determining structures in high-throughput crystallography. Nuclear magnetic resonance (NMR) structure determination has also undergone a lot of breakthroughs in recent years, including magnet and probe enhancements, automated assignment [10-12], and novel experimental approaches to detect bigger structures [13]. It is also important to note that structure-based drug design guides the development of a drug lead, which is a chemical having at least micromolar affinity for a target but is not a therapeutic product [14]

PRINCIPLE:

During lead discovery, an exhaustive search is conducted to identify a drug-like small molecule or biological therapy, commonly referred to as a development candidate, that will advance onto preclinical testing and, if successful, clinical development, and eventually become a sold medicine. The identification of screening hits, medicinal chemistry, and optimization of those hits to boost affinity, selectivity (to lower the risk for adverse effects), efficacy/potency, metabolic stability (to increase the half-life), and oral bioavailability are all part of modern drug discovery. Once a molecule that meets all of these criteria has been identified, the drug development processwill commence prior to clinical trials [15].

- **STAGES OF DRUG DISCOVERY AND DEVELOPMENT PROCESS:**



Target Identification:

The first step in drug discovery is determining the biological cause of a disease and potential targets for intervention. Isolating the function of a potential therapeutic target (gene/nucleic acid/protein) and its significance in the disease is the first step in target discovery [16]. Target identification approaches may be based on ideas from molecular biology, biochemistry, genetics, biophysics, or other areas [17].

Target Validation:

Target validation is the process of certifying the intended molecular target of a tiny molecule, such as a gene, protein, or nucleic acid. Determine the structure activity relationship (SAR) of small molecule analogues; generate a drug-resistant mutant of the presumed target; knockdown or overexpression of the presumed target; and monitor the known signaling systems downstream of the presumed target [18].

Assay development:

To construct so-called biochemical tests in the recombinant era, the majority of assays in use within the industry rely on the production of stable mammalian cell lines over-expressing the target of interest or on the overexpression and purification of recombinant protein. despite the fact that the number of studies documenting the use of primary cell systems for chemical screening has increased in recent years [19]. The biology of the drug target protein, the equipment infrastructure in the host laboratory, the experience of the scientists in that laboratory, whether an inhibitor or activator molecule is sought, and the scale of the chemical screen all influence the format of the test. Whatever test format is chosen, it is essential that the following factors be considered:

1. The assay's pharmacological utility. Studies should be undertaken using known ligands with activity at the target under research, if available, to evaluate if the assay pharmacology is predictive of disease state and to demonstrate that the assay is capable of finding compounds with the necessary potency and mechanism of action. The test's reproducibility. It is a need in a compound screening setting that the assay be repeatable across assay plates, screen days, and, in a programme that may continue for several years, across the entire drug discovery programme.
2. The expense of the assay. Microtiter plates are commonly used for compound screening tests. Assays in academia are often

designed in 96-well or 384-well microtiter plates for relatively small amounts of compounds, but assays in industrial or HTS applications are formatted in 384-well or 1536-well microtiter plates in assay volumes as small as a few microliters. In each example, assaychemicals and assay volumes are chosen to reduce assay costs.

3. Assay precision. The Z' factor is commonly used to determine assay quality [20].

HIT-TO-LEAD-PHASE:

The goal of this step of the work is to refine each hit series in order to develop more powerful and selective compounds with acceptable PK characteristics to test their efficacy in any accessible in vivo models. Structure-based drug design approaches based on molecular modelling and technologies like as X-ray crystallography and NMR can be utilized to build SARs more quickly and precisely. Once a lot of hits have been discovered using virtual screening or HTS, the drug discovery team's first task is to choose which molecules are the best to work on. The next step in the initial refining procedure is to produce dose-response curves for each hit in the primary experiment, preferably using a fresh sample of the chemical. Obtaining a dose-response curve enables the calculation of a half maximum inhibitory concentration, which is then used to compare the potencies of prospective drugs. Once valid dose-response curves for the target have been obtained in the first assay, the stage is set to investigate the surviving hits in a secondary assay, if one is available, for the target of choice. This does not have to be a high-throughput test, but it will involve examining the influence of the chemicals on a functional response, such as in a second messenger assay or a tissue- or cell-based bioassay. Key compounds that are beginning to approach goal potency and selectivity, as well as the majority of physicochemical and ADME targets, should be tested for PK in rats.

Identification of Lead:

A synthetically stable, viable, and drug-like molecule active in primary and secondary assays with adequate specificity, affinity, and selectivity for the target receptor is referred to as a chemical lead. This necessitates the establishment of the structure-activity relationship, as well as the identification of synthetic feasibility and preliminary proof of in vivo efficacy and target engagement [21].

LEAD OPTIMIZATION:

To progress from a lead to a therapeutic candidate, the lead is utilized as a starting point for the synthesis of hundreds, if not thousands, of derivatives in a process known as "Lead Optimization." If the lead ingredient comes from a plentiful natural source, it may be easier to isolate and purify the component for subsequent therapeutic development. A synthetic chemical method is frequently used for novel drug discovery in order to conserve natural resources and manage purity and yield. If full synthesis is not possible, a key precursor may be extracted and purified for future use [22, 23]. To create a pre-clinical therapeutic candidate, the chemical structures of lead compounds (small molecules or biologics) must be altered in order to increase target specificity and selectivity. Pharmacodynamic and pharmacokinetic characteristics, as wellas toxicological properties, are all assessed [24].

Preclinical studies:

Pre-clinical research in the drug development process entails assessing a medicine's safety and efficacy in animal models, which leads to a potential human outcome. Pre-clinical experiments must also be approved by the appropriate regulatory authorities. The regulatory authorities must ensure that studies are conducted in a safe and ethical manner, and they must only approve pharmaceuticals that have been proven to be safe and effective. The International Conference on Harmonisation (ICH) has created a fundamental guideline for the technical requirements of acceptable preclinical drug development. Unwanted pharmacological effects must be investigated in appropriate animal models and monitored in toxicological studies[25].

In-vivo Studies:

Because in vitro studies cannot completely anticipate the drug's effect on organs and organ systems, or even its combination with other medications, in vivo investigations are required to clarify facts concerning therapeutic drugs before clinical trials are conducted. In vivo studies allow for the long-term monitoring and observation of the drug's effects, as well as assessing bioequivalency, safety, dosing regimen, positive and negative effects, and drug-drug interactions in a living system.

In vitro studies provide relevant information on drug mechanism of action, which is useful for making hazard-based decisions and informing decision-making in the drug development process; however, the relevance to human exposure scenarios and risk assessment is limitedwithout linking in vitro toxicodynamic measurements to in vivo toxicokinetics [26].

PHARMACOKINETIC STUDIES:

Animal models have been quite beneficial in describing the links between tissue concentrations and serum or plasma concentrations. The interstitial compartment and the intracellular compartment are different regions, and medication distribution in these two compartments often differs. Another pharmacokinetic aspect that can affect antibacterial activity is serum protein binding. Numerous investigations have shown that only the free or unbound component of the medication is available for antibacterial activity . Protein binding has little influence on the half-life of medicines removed via tubular secretion, but it can significantly decrease the clearance of medications eliminated primarily through glomerular filtration [27]. One of the most significant differences in pharmacokinetics between animals and humans is the rate of medication clearance in animals [28, 29]. In vitro and animal studies can both be used to investigate the influence of drug exposure on organism growth following drug exposure. Only in vivo animal models, however, can assess the temporal course of activity at the site of infection, as well as the possible impact of host immunological variables on antimicrobial activity. Both models have been extensively used for the majority of antibacterial classes and many

antifungals. The persistence of these post-antibiotic effects is frequently longer than when assessed in vitro [30].

Preformulation studies:

Preformulation is the study of the chemical and physical properties of the medication components prior to the formulation's compounding procedure. The study's goal is to better understand the nature and properties of each component and to optimize manufacturing conditions for dosage forms. Preformulation data must be generated before formulation development to facilitate the development process, and the physicochemical parameters must be determined. The interaction of the medication components and the excipient utilized in the formulation is often included in the study, resulting in intelligent excipient selection. The study includes preliminary medication degradation profiles to assist the creation of a stable product. The analytical features of the component (analytical profiles) are also mentioned. A study of this topic contributes in the establishment of the monitoring procedure during the formulation development process.

Need for a Preformulation Study:

The following are scientific and regulatory motivations for collecting preformulation data.

1. Development of medication requirements for toxicologic testing and clinical supplypreparations
2. Development of clinical supplies and development of preliminary requirements
3. Providing scientific data to aid in the formulation of dosage forms and the evaluation of product efficacy, quality, stability, and bioavailability
4. Stability testing of early designed dosage forms
5. Compliance with the CMC portion of the IND and subsequent NDA or ANDA.

Preformulation Study for Drugs and Health-Care Products:

The preformulation research guidelines and forms presented in this chapter are usually relevant to a variety of health-care items, including conventional medication products, biotechnology-derived products, and dietary supplements. Because of the goods' particular physicochemical character and physiological activity, it may be necessary to modify the study in order to acquire useful data for the development of prospective products and/or dosage forms.

In the pharmaceutical industry, various products are manufactured based on thefollowing classifications.

- Regulatory classification, such as prescription drug, generic drug, over-the-counter (OTC) product, biotechnology product, and nutritional supplement
- Physical classification, for example, solids, oral liquids, semisolids, and parenteralpreparations.
- Classification of dosage forms based on whether they are intended for human or animalconsumption.

The following sections list pharmaceutical goods in the regulatory classification. Their various concepts, as well as related preformulation investigations, are discussed.

1. Ethical, or Prescription, Products

Ethical or prescription product manufacturers are R&D-based, innovative product development organizations. The majority of pharmaceutical firms fall into the category of brand-name product (a distinct brand name may be assigned to a certain product), which generates significant revenue for the sector. The FDA approval of the NDA, a lengthy and costly process, is required for the market debut of a brand-name product. The manufacturingprocess is governed by cGMP.

2. Generic or Multisource Products:

More than one company may frequently receive approval to market the same product, which is known as a "multisource product." Following ANDA clearance, the Waxman-Hatch Act of 1984 authorizes pharmaceutical medicines to be manufactured and marketed by corporations other than the original developer. Because the chemical name rather than the brand name of the original product is used, this type of product is commonly referred to as "generic." A generic product must use the same active component and mode of administration as the innovator medication. Although no clinical trials are necessary, bioequivalence of the generic product to the novel product must be demonstrated and reported in the ANDA. The introduction of generic pharmaceuticals allows competition among some drug items on the market, resulting in lower costs with minimal quality compromise. A generic house or an inventive product producer, such as a big ethical pharmaceutical house, may manufacture generic products, including human or animal pharmaceuticals. The tasks for preformulation studies for generic medications are simpler than those for original prescription products. The innovator drug product may have been sold for a long period by the time the generic equivalent is released.

3. Biotechnology Products:

Biotechnology goods are pharmaceuticals created by industrial procedures that employ biological systems such as fermentation or tissue culture. Some industries employ genetically modified organisms in these procedures. Recombinant DNA, monoclonal antibody/hybridoma, continuous cell lines, and cellular treatment technology are commonly used in product development. With the exception of short-chain peptides, biotechnology- derived medicinal compounds are primarily protein or peptide or long-chain molecules that can be degraded via hydrolysis or other denaturation mechanisms. As a result, stability is a major concern in the

handling, formulation, and storage of these materials. To some extent, knowledge about pharmacologic characteristics and toxicity, as well as clinical experience with the isolated protein or peptide, may be available. Following FDA approval, two alternative processes may deliver the biotechnology product to the market. A biological license application (BLA) is necessary for some well-characterized biotechnology and synthetic biology products in order to acquire market distribution permission. Four categories are defined for this process:

a) Therapeutic DNA plasmid product
b) Therapeutic synthetic peptide of 40 or fewer amino acids
c) Monoclonal antibody products for in vivo use
d) Therapeutic recombinant DNA-derived products

4. Over-the-Counter Products:

OTC, or nonprescription, drugs are self-treatment medications that are available without a doctor's prescription. These products are meant to treat minor discomfort, illness, or injury symptoms. Analgesic pills, first-aid treatments, cough suppressants, antifungal agents, and antiperspirants are examples of OTC medications. In general, no preformulation research is necessary because most OTC product formulations are simply an extension of the marketed product with a change in the active component content.

5. Dietary supplement product:

A dietary supplement product is a dose form that includes dietary elements including vitamins, minerals, herbs, and amino acids, as well as things like enzymes, organ tissues, metabolites, extracts, or concentrates. Dietary supplements, particularly herbal products, have grown in popularity since the passage of the Dietary Supplements Education and Health Act (DSEHA) in 1996. Natural herbal products (also known as botanicals, nutraceuticals, or phytochemicals) exist. Historically, there has been minimal scientific documentation of the constituent amounts, chemical structures, pharmacologic and toxicologic data, and clinical indications of these products. Herbal crude materials come in a variety of forms, including dried materials, powder extracts, and liquid concentrates. According to the DSEHA, the manufacture or distribution of dietary supplements does not necessitate prior FDA registration or approval. However, the product must be labelled as a "dietary supplement," and the label contents must adhere to FDA guidelines. Dietary supplement ingredients are chemical components having features and effects similar to synthetic medications. The preformulation research should follow the same format as conventional pharmaceutical trials. Some herbal products' formats may be updated in response to the particular role and qualities of plants.

6. Animal Health Products:

Animal health or veterinary drug products include pharmaceuticals used in animal feeds and are meant for animals other than humans. These drugs may be the same as human drugs approved through the NDA, but commercialization requires approval of a new animal drugs application (NADA). Additional requirements for "animals for food" include environmental consequences, human toxicity, and residual levels in meat used for food. Because most animal dose forms are comparable to those for human products, the preformulation study should be the same or minimally adjusted if difficulties such as mixing homogeneity or "premix" instability occur.

7. Special or Novel Drug-Delivery Systems:

Special or novel drug-delivery systems (DDS) are dosage forms created using new drug manufacturing technologies (as opposed to traditional goods like tablets, capsules, cream, ointments, injectables, and suppositories). The convenience of patients, avoiding the medication delivery issues of conventional products, and line extensions, particularly for generic competition, are the business advantages of selling these items.

8. Other Health-Care Products:

Diagnostic items, medical gadgets, and radiopharmaceuticals are examples of pharmaceutical-related products. Although they should have specific preformulation studiesdeveloped, they will not be detailed in this chapter [31].

DRUG DEVELOPMENT:

CLINICAL TRIALS:

Clinical trials are undertaken in individuals (volunteers) and are designed to answer specific questions about the safety and efficacy of medications, vaccines, other therapies, or new ways of utilizing established treatments. As the developers construct the clinical study, they will evaluate what they intend to complete for each of the four Clinical Research Phases and initiate the Investigational New Drug Process (IND), a process that must be completed before clinical research can commence.

Phase 0 clinical trial.

Phase 0 refers to first-in-human (FIH) trials that are done in accordance with FDA criteria. Phase 0 trials, often known as human micro dosage studies, consist of single sub therapeutic doses administered to 10 to 15 volunteers and provide pharmacokinetic data or assistance with imaging specific targets without imposing pharmacological activities [32].

Phase 1: Safety and dosage.

Phase I trials are the initial studies of a medication on a small group of healthy human volunteers. Phase 1 typically involves 20 to 80 healthy volunteers with the disease/condition. Patients are often utilized only when the mechanism of action of a medicine indicates that it will be intolerable in healthy persons. As a Phase 1 trial progresses, researchers learn more about the mechanism of action, the side effects associated with increased dosage, and information about effectiveness. This is critical for Phase 2 study design. Almost 70% of medications continue to the next stage.

Phase 2: Efficacy and side effects.

Phase II trials are done on bigger groups of patients (a few hundred) and are designed to test the efficacy of the medicine as well as to withstand the Phase I safety checks. These trials are insufficient to determine if the medicine will be effective. Phase 2 trials offer researchers with more safety data. These data are used by researchers to improve study topics, develop research techniques, and create new Phase 3 research protocols. Approximately 33% of medicines progress to the next level. Most notably, Phase II clinical investigations contribute inthe discovery of therapeutic dosages for large-scale Phase III studies.

Phase 3: Efficacy and adverse drug reactions monitoring.

The majority of the safety data comes from phase 3 research. The prior study may have missed less common adverse effects. Researchers intend to conduct Phase 3 research to determine whether a product provides an action advantage to a specific group of people. Thesestudies, often known as pivotal studies, have 300 to 3,000 people.

The FDA review panel thoroughly examines all provided data on the drug beforedeciding whether or not to approve it.

Phase 4: Post-Market Drug Safety Monitoring.

Phase 4 trials are undertaken after the FDA has authorized the medicine or device. These trials are also considered post-marketing surveillance, which includes pharmacovigilance and ongoing technical support following authorization. Regulatory agencies may mandate Phase IV studies, or the sponsoring corporation may conduct them for competitive or other reasons. As a result, the genuine demonstration of a drug's safety essentially necessitates throughout the months and even years that constitute a drug's commercial lifecycle [33].

Conclusion:

Drug design and delivery is a complex and crucial process in the field of pharmaceuticals. It encompasses various stages, each with its unique importance. In the prediscovery phase, extensive research and target identification lay the foundation for future drug development efforts. This stage is vital as it determines the direction of subsequent research and resource allocation. The transition from hit discovery to lead discovery is pivotal, as it narrows down potential compounds for further investigation. Identifying promising drug candidates is a critical step in ensuring the efficiency of the drug development process.

Preclinical studies are essential for assessing the safety and efficacy of potential drugs. These studies help eliminate unsafe candidates early in the process, saving both time and resources. Finally, drug development brings together all the preceding efforts to refine and produce a market-ready medication. This stage is the culmination of years of research and serves as the bridge between scientific innovation and patient care. In summary, every stage of drug design and delivery plays a crucial role in bringing new treatments to the market. It is a collaborative effort involving scientists, researchers, and pharmaceutical companies, all working towards thecommon goal of improving health and well-being through innovative drug therapies.

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