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Chapter 8: From Discovery to Drug Development: Processes and Challenges in Creating New Medicines

8.1. Introduction

The creation of novel medicinal molecules, transforming them into pharmaceutical formulations, and introducing them into human health systems, is one of the most complex activities undertaken by scientists of diverse disciplines. Though it represents the utilization of research ideas and the application of testing procedures common to many sciences, its primary objective is to address and amend health deficits in humans. This is an activity founded on a century and a half of scientific research into the basic biological mechanism of human metabolism and diseases, as well as research into the means to use those mechanisms. It is an activity that requires regulatory pathways and compliance with a structure that places the patient's safety above all concerns. It is an activity, most importantly, that aims to correct disease processes in living humans. The process is driven by both public and private interests, with input from public health activity design, patent legislation, research funding, and fostering business environments (Davis et al., 2023; Harrison et al., 2024; Martinez et al., 2025).

The activity utilizes a corporate model to finance and organize resources necessary for its achievement. Resources and work necessary to enable clinical testing of consumer products are offered for validation in the marketplace by small business groups as well as multinational conglomerates, and filled with patent-protected medicinal molecules the results from their effort. The successful passage of a drug from discovery to approval at a regulatory agency is a rare event, requiring many years of work, a hundred-fold return on investment, and sometimes some fortunate lapses in consistency. During that time, thousands of new drug designs would have been generated, with numerous potential medicinal qualities. Many may have been produced during phases of the early drug development process that were many years in the making, included along with the

numerous mistakes that were necessary for the passing-of-time learning process. This book will endeavor to offer a step-by-step description of the activities and accumulated knowledge that have constituted the incorporation of drug discovery into drug development (Patel et al., 2023; O'Connor et al., 2024).

8.1.1. Overview of Drug Discovery

In the modern era of pharmaceutical development, the creation of medicines to combat diseases is typically governed by a series of well-defined steps, each orchestrated by specific departments with designated goals of its own. This well-coordinated division of labor enables pharmaceutical companies to successfully move promising new drugs from an initial phase of discovery to the final development of an actionable therapeutic product. The entire journey from discovery to medicine launch and commercialization can take more than 10 years and at least 2 billion dollars of investment. While the various phases in drug research and development are immensely costly and require vast investment resources, the associated risks are comparably high, particularly during certain critical steps in the process. This risk can potentially be mitigated by the early and clear identification of viable drug discovery and development candidates. In parallel, it is critical to combine sound business strategy and decision-making along each phase in the drug development process in order to de-risk the investments made. Such strategies and best practices are shared across different disciplines and against the backdrop of a wealth of real-life drug discovery and development examples.

The creation of a new medicine takes years of arduous work by teams of researchers and clinicians from many interrelated disciplines, including biological and chemical sciences, pharmacology, clinical medicine, industrial manufacturing, and distribution. Considerable resources are required to take a new drug from concept through the long and tortuous regulatory approval process before reaching the patients who most need it. An innovative new drug that successfully navigates the entire journey can provide years of improvement in disease management, and lessen human suffering on a grand scale. New medicines also provide new options for patients and physicians to manage the many diseases that afflict humans. Successful development of new medicines can also reward drug developers financially, enabling them to continue their efforts in drug discovery and help provide new medicines for the future.

8.2. The Drug Discovery Process

The drug discovery process is a complex, multidisciplinary undertaking that seeks to take advantage of novel mechanistic insights and emerging technologies to discover new drug candidates. The process is rarely linear and often requires iterative experimentation

to overcome unexpected challenges. The completion of one successful drug discovery program does not ensure success in future programs. Rather, the variability of the drug discovery process can create a gap between the efficacy, speed, and cost-effectiveness of developing new drug candidates and the demands and expectations of patients and physicians. Herein we review the essential steps of the drug discovery process, emphasizing the challenge of translating basic scientific discovery into actionable strategies for drug discovery, selecting and optimizing drug candidates with attractive pharmaceutical properties, and the latest technological advancements that identify new molecular entities that enter clinical testing.

The drug discovery process begins with the identification of a drug target, which is typically a purified or recombinant protein involved in a disease-relevant mechanism that can be functionally modulated by drug-like small molecules or biological molecules. The mechanism needs to be druggable, and a chemical or biological tool should help dissect the biological mechanism explored in the drug discovery process, which ideally links the drug target to a disease-relevant cellular or animal model. This is a crucial step because it sets the rationale for the entire drug discovery process. Scientists develop pharmacological tools to either activate or inhibit the drug target in collaboration with medicinal chemists.

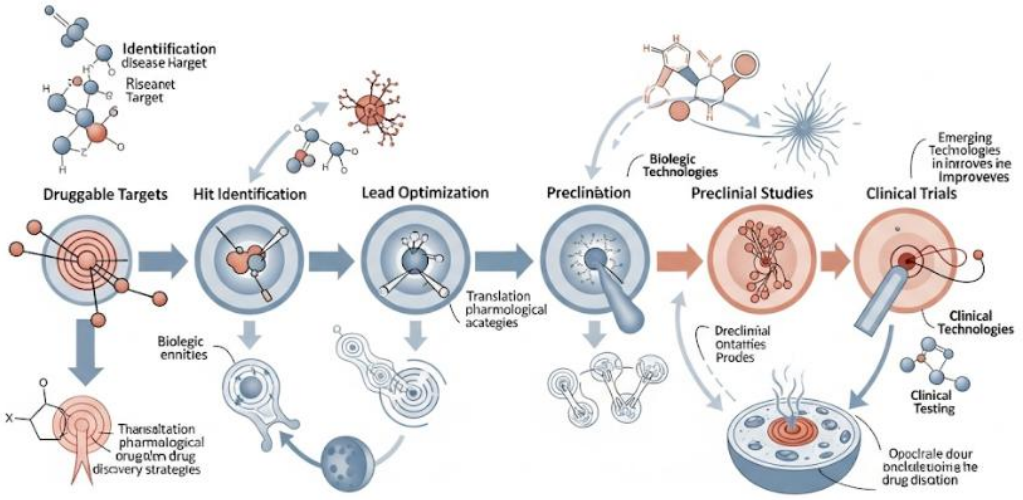

Fig 8 . 1 : The Drug Discovery Process

8.2.1. Identifying Drug Targets

The first step in drug discovery is identifying the biological target for new medicine. A target is a protein, enzyme, or molecular pathway typically involved in a disease mechanism. Drug discovery has 2 aspects; discovery of a specific target, i.e. target

discovery, which is related to the underlying biology of a disease, and generation of a druggable target, i.e. target validation. New druggable targets are generated based on target engagement showing the target is relevant to a clinical indication and providing evidence that this can be manipulated with a small molecule modulator or a Biological with clinical efficacy. In addition to this "assayable" aspect, factors such as market size, and societal and market needs also play a key role in making a target druggable. Providing druggable targets requires interdisciplinary collaboration between biologists, chemists, pharmacologists, pharmacogenomics experts, bioinformatics analysis, and clinical experts to understand target validation in the setting of efficacy and safety in subjects with genomics modulation of the target and disease mechanisms. This collaborative effort is required for iterating novel druggable targets that provide the potential for deviants in the mechanisms affected by modulation of that druggable target. Clinical insights to do with exploiting specific diseases or patient populations are critical for guiding biology. Examples of how this collaboration effort yields new druggable targets include specific target goals. In addition to these newly drugable targets, many others were made.

8.2.2. High-Throughput Screening

The methodology used in this stage of drug development is High-Throughput Screening (HTS), a technology used to rapidly test the biological or pharmacological activity of thousands of compounds in a shorter time than traditional assays permit. A standard screen optionally evaluates millions of compounds, screening against a specific target to identify those that interact. For GPCRs, HTS of ligands is now commonplace, with clear applications in drug discovery. While the vast majority of screens seek ligands that bind GPCRs, it is also possible to screen for ligands that modulate receptor activity (activate or inhibit receptor signaling). As we will elaborate, HTS is now used, with important caveats, to identify ligands that modulate GPCR activity. Like all first-generation screens, HTS is information-poor, identifying only crude molecules that show weak binding or are relatively weak modulators of hormone-stimulated receptor signaling with no information regarding specificity relative to other receptors or other targets.

Because HTS screens target hundreds of thousands to millions of compounds, they rely on the purification of the target and the development of an assay that can be tested in a format that allows millions of parallel evaluations in a single day. The GPCR at the assay’s center needs to be purified, either via approaches designed to generate a particularly stable protein or via an affinity tag system. These facilitate direct enzyme-linked immunosorbent assays or purification-based detection. This is an important assay limitation but one that can be overcome, to some extent, by developing parallel assays. Therefore, HTS can take longer than expected, making it challenging to obtain ligand-

directed modulators. We are only beginning to understand how to develop assays that directly detect the modulators desired.

8.2.3. Lead Compound Identification

Highly complex biological systems involving genes, proteins, and metabolites are modulated by small-molecule drugs on their way to a desired effect on their disease target. The desired modulation is understood in a biological context, through the understanding of biological complex function, or a mechanistic or spatial-kinetic approach, which guides further optimization towards a more defined and modulated activity. The information towards optimization is gained from initial small molecules with good activity towards already-defined or guesstimated selectivity but, more often than not, from an in-depth but not necessarily complete understanding of the biological context. The forward-looking drug design of active compounds for unmodulated targets is guided by knowledge of the cellular location of the target and of the biochemical and biophysical processes involved. Information gained from extensive crystallization and molecular modeling of spaces near proteins comprising the target, and previous experience or heuristics is vital to the ease of compound identification. Compound chemical space is nearly infinite, so initial activity toward the target is not necessarily a good guide, although activity towards protein/ionic interactions may help identify possible chemical motifs. The tasks of identifying the lead compound and optimizing it towards a defined activity modulating a disease mechanism, with the best adjuvant properties, then fall to the medicinal chemists, or more often the pharmaceutical industry and academic drug discovery collaborations as pharmaceutical houses specialize more.

8.3. Preclinical Development

The preclinical phase covers the critical bench work necessary to develop methods for putting the drug and dosage form together as intended for human administration. It also involves the completion of pharmacokinetic, stability, and toxicity studies that will allow the initiation of a clinical study in humans. Some of the work will be repetitive for different routes of administration if the formulation is intended for more than one route; however, the need for dose optimization is critical, particularly if the compound will require food intake or other special patient-specific aspects for appropriate bioavailability.

Preclinical work can take several months but may be accomplished relatively quickly when preclinical studies are compiled with previous work. Every applicant must demonstrate and provide proof of the safety of their drug application. The required studies aid the understanding of the effect of serious and probable adverse reactions on

individuals exposed to the test drug. Toxicology studies form an integral and necessary part of the data package that supports the shipment of an investigational agent and its testing in humans. Toxicology science is based on the understanding that the drug action manifests sequentially. Just like the drug action, the toxic side effects also depend on three basic parameters: a dose, some specific time lag, and a unique reaction. For each drug administered, there is a relationship distinguishing the dose versus the ratio of observable adverse effects. Quantitatively, the ratio of effects is compared to the control group that did not receive the drug. The model is used to understand and lessen the chances of observing these toxic drug side effects when testing for drugs for human conditions.

8.3.1. In Vitro Studies

Following the identification of a drug candidate from a high-throughput screening effort, further drug evaluation and testing are carried out in vivo and in vitro, respectively, before advancing the candidate to the project's preclinical or clinical phases. Various in vitro tests such as radio-inhibition assays, nucleotide triphosphates hydrolysis assays, competition binding assays, and reporter-gene assays are designed and performed to confirm whether the activity of drug candidates is involved with the inhibition of specific enzymes or receptors. The most dependable assay is the hydrolysis assay which measures the ability of a drug candidate to block the hydrolysis of high-energy molecules by an enzyme of interest. If the compound is tidal and inhibits the enzyme compared to a compound known to be inactive in a cell-free environment, it is confirmed that the compound inhibits the enzyme; if not, it is inferred that the compound likely does not inhibit the enzyme. Radio-inhibition and competition assays are designed to confer drugs that have a high affinity for the target by assessing whether the drug candidate can displace a ligand bound to the specific enzyme or receptor.

Specialized in vitro cellular assays are established to confirm either the tidal effect of the drug candidate on a specific virus or the preventive anti-viral effect of the candidate and the compound's selectivity index, a measure of the selectivity of a drug for virus-infected cells. The therapeutic dose of the drug candidate is determined using the selectivity index value. Thereafter, a study of important parameters, such as cytotoxicity, effectiveness, and mechanism of the anti-viral activity, is conducted. To finalize the therapeutic dose of the drug candidate, both animal model studies and in vitro cellular assays are performed. The unique aspects of the candidate's mechanism of action must be further characterized using various enzymatic assays as well as cellular and recombinant virus assays to confirm the drug action, not only on its desired target but also on other cellular pathways or viral targets. For testing specificity, surrogate mutant viruses could be used.

If the tidal activity of the drug candidate is validated by the cellular assays, regulatory approval for human clinical trials can be applied.

8.3.2. In Vivo Studies

Animal studies can be conducted to measure drug absorption, distribution, metabolism, efficacy, toxicity, and interaction with other drugs. The physiological and metabolic processes in animals are similar to those in humans. Furthermore, animals are more predictive of potential human effects than some assays. Animal studies often use different species specific to the disease being treated or those that correlate the best to the human condition. For example, mouse models can be utilized for approximately 90% of available diseases, including cancer, arthritis, diabetes, obesity, multiple sclerosis, cardiovascular diseases, and thermogenesis. Although some prediction knowledge has increased, the translatability of animal studies to humans still lacks complete correlation for many compounds.

The FDA introduced the "Animal Rule" to provide regulatory flexibility in drug development when clinical efficacy studies are not feasible. The rationale relies on animal pathology and the drug or vaccine effect being shown to predict clinical benefit in humans. Other conditions pertain to the reaction being life-threatening, no available effective alternative treatment and the proposed drug for efficacy validation supports a well-marked therapeutic effect in animals. The animal model used should adequately mimic the potential human adverse pathological effects to make the proposed animal efficacy results translatable to humans. All requisite efficacy studies need to be completed. There are currently 40 products for humans approved based on these criteria, specifically vaccines, and treatments for various diseases.

8.3.3. Toxicology Assessments

In these studies, the compounds intended for treatments are administered to animals, such as rats or dogs, to look for dose-limiting toxicity or the highest doses in which drug administration is not lethal. The main goal is to determine the MTD for the clinical dose selection and justification, as well as to understand the onset and nature of adverse drug-related reactions. These results may require an extensive number of animals and a long period for conclusions and therefore the alternatives for the long periods of traditional in vivo toxicology studies are being investigated. In these techniques, tissues or organs are removed from the animal and analyzed using advanced imaging methods, such as computed tomography or magnetic resonance imaging. Using in vivo imaging to assess adverse drug reactions diminishes the number of animals used and the time needed to analyze the drug's impact on the subjects. These in vivo imaging methods could be used

in combination with non-invasive imaging methods, enabling the identification of various drug-induced responses, including pharmacokinetic, pharmacologic, and toxicologic events in the same rodents.

While several governmental agencies provide guidelines on the requirements for preclinical toxicology studies, individual sponsors must work with agency officials to finalize a specific plan. It is common for drugs to have some differences in the requirements for preclinical toxicologic studies due to the nature of the drug product, indication for use, or development stage. Therefore, there cannot be a one-size-fits-all plan for any molecule. Understanding the important aspects of the toxicology assessments and preparing for any issues that may arise can improve overall study conduct for more successful outcomes.

8.4. Clinical Trials

On one hand, preclinical studies explore safety and efficacy, providing essential information on suitable routes of administration, biologic activity, pharmacokinetics, and toxicity profiles that guide clinical development and identify likely candidates for success in the clinic. On the other hand, it is commonly acknowledged that preclinical studies are not always predictive of success in clinical studies. Factors responsible for this widened gap between preclinical and clinical testing include inappropriate choice of dosage, formulation, route of administration, or delivery method, and subtle differences in biological activity between model systems. Consequentially, clinical testing has its own rules, challenges, and issues to address, explaining the high attrition rates in drug development. Clinical trials are designed to test the safety and efficacy of the compound in human subjects, which were shown to be predictive of probable benefit-risk ratios in an initial indication.

Clinical development points towards three stages denoted as phases I, II, and III. Phase I trials address pharmacokinetics, usually adopting single ascending dose and/or multiple ascending dose escalation designs to assess maximal tolerated dose and dose-limiting toxicities associated with an investigational medicinal product in healthy subjects or sicker patients, who have already exhausted all available treatment options and are at risk of experiencing major symptomatic benefit without escaping the chance of serious adverse events. Clinical pharmacodynamic studies may run simultaneously, usually investigating food-drug or drug-drug interactions. Patients recruited for phase I trials belong to specific subgroups or risk groups, which are more likely to develop side effects or show specific responses, although severe problematic adverse events are potential concerns. Phase I studies attempt to target specific populations with special safety considerations, employing exploratory clinical designs that may target signal detection such as proof-of-mechanism evaluation, studies, special population studies, or drug-drug

interaction considerations. Nearly all pharmaceutical companies developing innovative medicines have developed clinical compounds reaching the requisite standards of safety and efficacy information to initiate studies in humans.

8.4.1. Phase I Trials

Early clinical trials identify the point at which a drug is no longer safe to administer. They are intended to determine safety and tolerability and to explore the interrelationship of dose, pharmacokinetics, and drug-related effects. These initial trials involve a small number of healthy volunteers and are designed to evaluate the potential effects of the drug on the volunteers. These effects include dose response, pharmacokinetics, excretion, safety and/or tolerability, and exploration of the effects of the drug on specific endpoints of interest like QT interval. Phase I trials are the first exposure of humans to the drug under study and are normally conducted under the auspices of the sponsor to evaluate the safety and/or tolerability of the drug. The sponsor is also responsible for the risk to the volunteers. In most cases, this responsibility becomes absolute once the first human dose is administered. These trials typically involve fewer than 100 subjects. When a healthy population may not be appropriate, a small number of patients with the disease will be included. These studies only assess the potential benefits of a drug relative to risk when the volunteers are exposed to danger. Once this safety assessment has been made, safety reports must explain the occurrence and nature of serious adverse events to potential volunteers in subsequent studies. Written consent should be available.

8.4.2. Phase II Trials

Phase II trials are the initial clinical trials conducted in patients with the target disease. They are designed to assess the further effectiveness of the drug candidate in a small cohort of patients after initial safety assessment in the healthy volunteer Phase I trial and can vary dramatically in length, duration, and cost. Generally, Phase II trials range from a few months to a year, are conducted with several hundred patients, and cost between $2 million and $25 million. Consequently, Phase II fail rates often approach or exceed 50%, usually because of a lack of efficacy signals. A Phase II trial can be further divided into a Phase IIa trial (which evaluates pharmacology and preliminary signs of efficacy) and a Phase IIb trial (which assesses preliminary efficacy). Historically, Phase II trials have not relied upon patients with the target disease because of the lack of available drugs; however, an increasing number of Phase I trials are now assessing patients with the disease, so hybrid Phase I/II designs have been created that have shortened the timelines for Phase II efficacy assessments.

Like Phase I protocol, a Phase II protocol must be carefully designed and detail the rationale for patient selection, number of patients, duration, and timing of treatment for and after the trial, the statistical design, endpoints describing preliminary efficacy, as well as detailed safety parameters; however, it also must define the rationale for the selected endpoint. The biological effects should ideally happen while the drug is still being administered in the trial. In assessing the preliminary effect, these endpoints must also balance the need for an immediate effect with the risk of accelerating a benign disease. More practical considerations also factor into selecting the endpoint: the expense and ease of monitoring, the expected time frame for observing an effect, reliability, the ability to define the responder, and the seriousness of the consequences when making an error.

8.4.3. Phase III Trials

Phase III studies, comprising a series of trials, are the indispensable next stage of clinical development after the initial positiveness of Phase II. These are high-risk, high-reward trials, which determine sales potential or whether the clinic can terminate development and submit a New Drug Application to the regulatory agency. Testing a new drug on a sufficiently large number of patients in a prospective double-blind, randomized comparison with simultaneous control, which could be a placebo or agent in the same class, is essential to provide clinically significant endpoints of safety and efficacy. These endpoints also necessitate a high likelihood of patient compliance, because dropout affects the interpretation of the trial, especially in regard to the number of endpoints reached and the benefit-risk equation. Accurate analysis of efficacy responders, adverse events frequencies, risk factors, and drug-drug interaction effects in the actual population that will use the drug is vital. Therefore, trials in a probabilistically relevant study population, generally without replication, often comprising several thousands of patients with long-term follow-up, are done to provide sufficient statistical significance. The accomplishments are used for labeling and promotion decision-making and are essential for the regulators to ensure a unique product profile. A key consideration is whether the dosing and duration of treatment can be matched to its usual clinical application.

Phase III testing today, with its very large cohorts and elaborate statistical maneuvers, often utilizing sophisticated biomarkers and population pharmacokinetic pharmacodynamic evaluations, molecular genotyping, and target enrichment, grew out of the earliest importance of Phase IIb studies but with the discovery of analysis disruption by investigator and patient stratagems to toggle between safety search and benefit measurement difficulties, especially in rare disorders with damaged incentives. Conducted majorly in the USA, this sunny opto-cousin of the multi-country Phase IIa prevents witching from uncontrolled to controlled response-based exploration of

efficacy. But the design and execution are now also much alive in specialist and expert investigator sites in Europe and Japan for experiences evolving validation and regulatory confirmation.

8.4.4. Regulatory Considerations

Considerable interdependence exists between regulatory approval and the successful execution of clinical trials. On the one hand, investigators are obliged to conduct research that adheres to the letter and spirit of the protocols reviewed and approved by an Institution Review Board. On the other hand, regulatory agencies have recognized that the future of clinical research and the development of new medicines lies in the hands of clinical investigators and the IRBs they represent. Accordingly, the desire to support and not interfere with or impede the progress of clinical research is the motivation for the concept of the circumvention research model. Under the circumvention paradigm, an IRB can approve a clinical study design that deviates from traditional regulatory standards. What this means is that before the safety and efficacy of an investigational medicine for a specific disease are established by clinical trials, a clinical investigator can conduct clinical research on patients with that disease using an investigational medicine that has not been approved for such use. Regulatory guidelines permit an IRB to approve the use of an investigational treatment even when, according to regulatory standards, it is being used noncompassionately. An investigational drug may be considered noncompassionate in that it is being tested for its ability to prevent, diagnose, or help treat the disease for which it was investigated. With the growth in market size and opportunities for commercializing therapeutic products, a growing regulatory environment and issues are also coming to the forefront. For therapeutics, which typically represent the largest medical expense in the United States, the premarket approval process is especially extensive. The drug development process includes exploratory studies, preclinical trials, clinical trials, and post-market surveillance.

8.5. Regulatory Approval

In the United States, new medicines cannot be marketed without prior approval from the Food and Drug Administration. The agency regulates drug development through the Office of New Drugs and the Center for Drug Evaluation and Research, both of which are part of the FDA. The Center develops related policies and regulations under Title 21, Parts 312 and 314 of the Code of Federal Regulations. The drafting and implementation of these regulations are based on expertise in the field, input from stakeholders and the public, practical experience, and public health considerations.

The regulatory submission influencing the clinical development plan is the Investigational New Drug Application, while the regulatory submission needed for marketing authorization is the New Drug Application. They are both complex and lengthy documents that enable the regulatory agencies to review and determine whether the study or the data contained in the application meets the approval standards and can impact public health. The IND is a comprehensive application consisting of detailed descriptions of the drug, preclinical studies, clinical study protocols, and informed consent documents. It must be submitted to the FDA before commencing first-in-human studies. The NDA contains data from all clinical studies conducted on the drug, as well as all information to support the FDA review of the preclinical and clinical program. Because the drugs are intended to be administered to humans, due care and caution must be implemented during the development of the IND and NDA.

8.5.1. FDA Submission Process

The ultimate regulatory approval of a new drug is granted by the FDA in the form of a marketing application, or license. The license application must demonstrate through evidence provided in the sponsor's submission to the FDA, either in a NDA or BLA, that the drug is safe and effective for the product's intended use. The extensive nonclinical and clinical research and the compilation of its data and findings into a concise, readable document are rare and remarkable achievements. Most global drug development programs submit a NDA to the FDA in a Common Technical Document format.

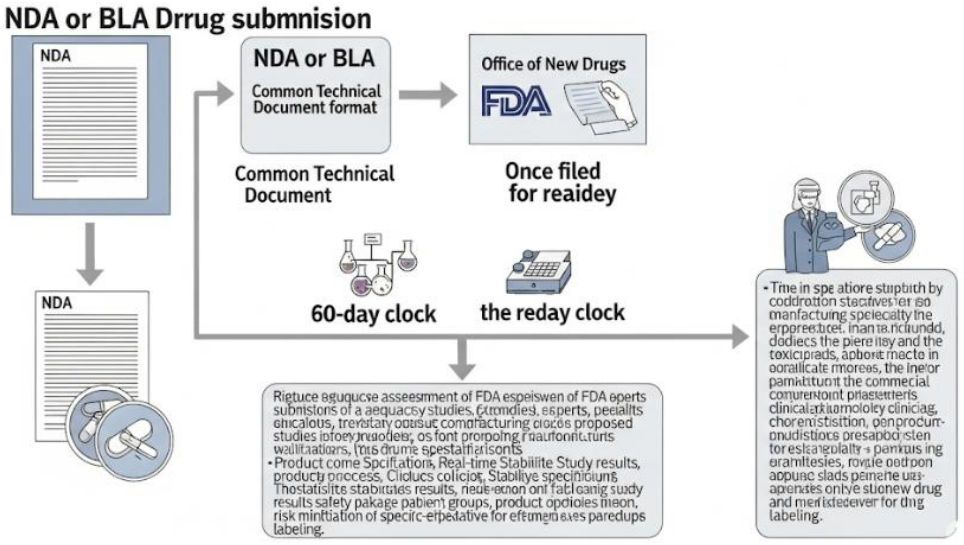

Fig 8 . 2 : NDA or BLA Drug Submission

Once the NDA is submitted, and the FDA's Office of New Drugs formally receives it, a team of administrative, review, and regulatory experts review the submission to determine if the NDA is receipt ready and accepts the NDA for filing. If the NDA is sufficiently complete to permit a substantive review and the designed product has timings on safety and efficacy, the NDA is filed. A 60-day clock considers the filing review of the NDA. Once filed, the NDA undergoes comprehensive assessment by a team of agency scientists representing the key areas of new drug development: Chemistry, Manufacturing, Controls, Toxicology, Clinical Pharmacology, Clinical, Biostatistics, and Microbiology. They assess the adequacy of the studies and data submitted, supportability of the proposed commercial manufacturing process, processes' validation, product specifications, real-time stability study results, safety package, description of risk and risk mitigation for special patient populations, and product labeling.

8.5.2. International Regulatory Bodies

The principal international agency concerned with global health issues is the main intergovernmental organization in directing and coordinating international health. It meets twice a year and gives final approval to products that countries can use to lay the groundwork for the future development of international medicines. The Prequalification Program aims to supplement the availability of quality-assured medicines for treating diseases in resource-limited settings through a rigorous quality-assurance process, serving as a valuable guideline for countries.

An organization works to develop guidelines that facilitate the trade of medicines between countries. The aim is to achieve greater harmonization between different regions; a company can request marketing authorization through a centralized procedure; an applicant who obtains a positive opinion from a committee can market its medicines in all member states and associated countries.

The agency is responsible for approving the marketing of medicines. The company submits a file that responds to the requirements set by recommendations, and the committee evaluates the safety, efficacy, and quality of medicine, ensuring adherence to current guidelines, with each country’s ethics committee granting final approval. The operations guide is revised and updated frequently. A national agency participates in the clinical review, inspections, and pharmacovigilance activities usually outsourced to it. Worldwide, regarding external matters for pharmaceutical companies, a significant percentage of pharmaceutical sales are owned by foreign affiliates.

8.6. Post-Marketing Surveillance

1. Adverse Event Reporting

Shortly after the FDA approves an NDA and a drug is marketed, the FDA begins post-marketing surveillance, called Phase IV clinical trials. This surveillance is the responsibility of the drug manufacturer, who is required to submit every adverse event report received to the FDA. The FDA provides a database housing these reports and updates it weekly. This responsibility does not end when the drug is no longer marketed, nor does it end if a second manufacturer is permitted to market the drug generically. The manufacturer continues to collect adverse event reports and update the FDA.

Many of the reports are sent in by patients and physicians taking action to help other people, but this surveillance is also incomplete; most adverse events go unreported. Efforts have been made to provide better coverage but, as always, the net will never have a 100% catch. Although physicians are aware of the potential dangers of new drugs, reports of adverse events due to newly marketed drugs can be affected by the publicity given to the drug, and how many patients are treated with it during the general treatment of a given disease state. Regardless, it is obvious that surveillance cannot guarantee safety, or even that maintenance of a drug's efficacy needs no further studies. Most new drugs are variations of already existing drugs but unique to themselves.

2. Long-Term Efficacy Studies

To address this very situation for large populations, the FDA can mandate existing long-term studies. For safety data approval and to address efficacy over a broader patient population, long-term studies are necessary and often mandated after a new drug is marketed; some randomized-controlled studies also have been mandated. The average patient will take medications prescribed for months or years, but in various drug studies, most drug patients are monitored for only a few weeks or months. If an adverse effect happens after that time, or if drug interactions occur over time with concomitant medications also prescribed, these problems are not addressed in many drug studies before marketing. Further, as noted previously, changes in drug metabolism come with age. The mean population age now is many years greater than in previous decades. Although these late-onset adverse effects may not occur as frequently as others, they can be debilitating to the patient, impose chronic withdrawal problems, or even cause death as with certain adverse effects.

8.6.1. Adverse Event Reporting

Once a medicine is on the market, it is the responsibility of the health care professionals to maintain safety surveillance by reporting to the manufacturer and the relevant health

authorities any suspected adverse events that occur in patients treated with it. The drug company is mandated by law to record and investigate these reports, which are then used to generate a summary of product characteristics that help identify potential safety concerns that may require a risk management plan. All incidences of non-serious events, serious events that are not life-threatening, and other serious adverse events must be recorded for the duration of time the affected patient is being treated and for an additional 30 days afterward for clinical medicines. However, only serious adverse events must be reported to health authorities within 15 days for clinical medicines. The same time frames apply for preclinical medicines, but as additional safety measures need to be put in place, the risk of loss of life to patients while being treated is considered greater.

Moreover, spontaneous reporting is also carried out by health authorities. Given that people often face unique medical circumstances, not all adverse events occurring among patients on a particular medication may be detected. Case reports and publications in scientific journals are invaluable ways for exposing previously unrecognized safety concerns, signaling that increased regulatory vigilance may be required in examining long-term safety data and adverse event reports received from post-marketed sources. Identifying previously unknown risks after a treatment is on the market is especially important. The number of people taking a drug for several years can be enormously greater than the number of clinical trial volunteers. It is vital to continually monitor this information, in addition to surveillance provided by physicians and other health care professionals in the course of routine patient care. Spontaneous reporting typically relies on voluntary reporting by healthcare professionals and patients.

8.6.2. Long-Term Efficacy Studies

For some drug classes, approval is not the endpoint for the long procedure that allowed us to investigate their safety and efficacy. For example, certain vaccines and cancer immunomodulators require long-term efficacy studies continuing to monitor patients for up to 10 years. These long-term efficacy studies can clarify whether the effect observed during the evaluation of the product can last many years and if there is a certain period in which the drug is totally or partially ineffective. In the case of products for which long-term protection is very relevant, these efficacy studies are generally carried out at the expense of the sponsor.

Very commonly, however, post-marketing requirement studies are safety studies even if they can also be led to evaluate the efficacy in the post-marketing phase. In some cases, even pharmaceutical companies express concerns about long-term efficacy, often regarding the need to demonstrate long-term efficacy for new product combinations or for new vaccines or immunomodulators that could potentially be less effective than those already in the market. Post-marketing requirement studies are safety studies using

patients treated with the product during the post-marketing authorization and that may or may not compare two or more treatment groups. A post-marketing requirement could serve as an efficacy study in rare diseases where the randomized controlled trial would be unfeasible during the pre-marketing phase. Similarly, rare events discovered during Phase IV studies could serve as the basis for regulatory agencies or sponsor ethical boards to confirm the commercial phase in the post-marketing requirement. In summary, the main goal of the long-term studies that a pharmaceutical company has to conduct during the marketing phase remains the assessment of the benefit-risk ratio that the drug produces.

8.7. Challenges in Drug Development

Drug development is a costly enterprise, and not all products result in commercial success, which drives up the cost of those that do succeed. However, the average capitalized cost of developing a drug intended to treat an infectious disease is about $165 million. In comparison, pharmaceutical companies can expect to recover their investment in drugs for more prevalent diseases, such as cardiovascular and metabolic disorders, neurodegenerative diseases, and cancer. The transition from drug discovery to drug development also comes with high scientific uncertainties. Many potential drug candidates fail during preclinical development and the clinical testing phases of drug development for reasons other than safety concerns, including poor pharmacokinetics, inadequate target engagement, poor patient selection, and lack of therapeutic effect. As a result, many drug candidates fail later in the development process, which further increases the costs of drug development. Multiple clinical trials may be required to establish the safety and efficacy for specific populations. More than 50% of new drug candidates undergo at least one late-stage clinical trial failure. Others simply don’t work as well as marketed alternatives. The virulence of the current pandemic illustrates the speed at which companies can develop new medicines.

Another major hurdle in drug development is market competition. As drug development has become increasingly expensive, it has created more disparities in drug accessibility, particularly between rich and poor nations. As a result, the critical need for effective medicines has yet to be fulfilled in many diseases for which there is currently no acceptable treatment. After such a large investment in development, companies may be reluctant to sell their product at prices that are low enough to meet the needs of consumers in those less developed countries, particularly for neglected diseases.

8.7.1. Financial Constraints

Beyond the lab, there are many forces at work to keep new medicines safely in their pipelines. Too many medicines fail to make the leap from the lab to the pharmacy shelf not for lack of merit, but for lack of resources. With the average cost of developing a new medicine exceeding $1 billion and the average length of the development process lasting more than a decade, pharmaceutical companies must have sound financial models with which to secure the needed investment during this perilous period. The heavy capital investment required to undergo the many stages of development and test for the many variables demanded by the regulatory authorities exists in no other industry. Short operational histories and the unpredictable outcomes of carefully designed but risky health science technology investments force the pharmaceutical industry to rely on external debt and equity financing, but few sources of capital are experienced in and capable of analyzing the specialized risk/return parameters of drug development.

The need for capital and launching medicine in the market once the extended drug development process has been completed explains the logic behind the way the pharmaceutical industry is organized — the ways that it obtains, allocates, and manages its various kinds of resources. Many resourceful business people outside the industry realize the danger of reducing pharmaceutical development to a collection of largely random early-stage innovations producing molecules with various degrees of promise to be secured and licensed to a chosen few established pharmaceutical companies for further development and commercialization. Such a strategy implies no coherent life-cycle flow of resources, the idea of a pharmaceutical empire extending from gene and protein discovery to the design and distribution of new drugs curing old and new diseases.

8.7.2. Scientific Uncertainties

Drug Research & Development (R&D) involves endeavors based on pioneering scientific exploration. Discoveries in basic and applied science, such as drug targets, molecular scaffolds, drug formulations, and delivery routes, and the technology to develop and manufacture new drugs are critical to enabling drug development. In this dynamic world of science and technology, the unpredictability of the R&D outcomes of any individual project and the uncertainty of timing amplify the risk of an overall drug R&D investment portfolio. In particular, practical matters of ongoing project management, interface with regulatory bodies, and collaboration with profit-oriented commercial entities further constrain drug research and development activities. This chapter reviews some of the key issues in drug research and development concerning scientific uncertainties, financial constraints, and market competition, and discusses real-world examples of these issues.

Although fundamental discoveries in basic science form the bedrock for new drug development, drug R&D also depends on emerging technologies in trial design, conceptualization of new delivery methods and manufacturing processes, quantitative analysis, etc. However, the R&D outcome is uncertain for every drug under development, ranging from pessimistic to optimistic, due both to the unknowns associated with the target biology and the drug properties, and also to the degree of reliance on new technologies not previously validated by drug approval. The risk of puddle-hopping is particularly salient as drug R&D moves from the laboratories of academic or small biotech companies with sufficient funding and scientific expertise, to the more competitive and risk-averse environment of larger players. Commercial companies release, produce, and distribute new drugs only after careful consideration of the research, education, and "puddle-hopping" drug development sequence, that is, the scientific subjects in biotechnology and pharmaceutical research.

8.7.3. Market Competition

Market competition happens not only during the regnant of a product but also during the innovation phase. New drug development commands legions of skilled personnel—scientists, engineering technicians, and patent attorneys—who usually direct their efforts toward projects that promise the biggest payoff. Consequently, scientists with experience in the applied technology of drug development gravitate toward a relatively small number of firms. There their productivity is multiplied by investment, not only by full-scale drug development but also by investment in the specialized technology for short periods needed to evaluate essentially different therapeutic agents for a large number of diseases.

Little wonder, then, that there is a concentration of development resources on a few major therapeutic areas. The new product times, after regulatory approvals, in these fields can be achieved by many firms with relatively limited resources. Outside them are long times to the markets for chemical or biological agents for many of the major diseases—closer to 15 years for rheumatology, cardiovascular or metabolic disorders, allergy, or forerunners of AIDS—for which the upside payoff is low about the investment of people and money. There is little epidemiological justification for product diversity, and in some areas, only a small number of companies could be expected to be effectively involved in either development or marketing. Competition is dulled by the high barrier of entry; the payoff is diminished because of the time it takes for any single company to bring a product up to market and past the regulatory hurdles.

The duration of time from product discovery to market entry may vary depending on several factors; these include company strategies, therapeutic areas, regulatory environments, and product types. New drug development by small innovative

companies, particularly for platform-based products, that do not have the cell culture facilities needed for drug development but do have the necessary financial resources to bring them to market as viable commercial products is increasingly done by large pharmaceutical companies, using their unique development and surveillance ability and resources.

8.8. Innovations in Drug Development

Searching for a new drug is an extremely long and expensive process. In this search, pharmaceutical companies have to adapt to a number of realities: a gradually shrinking pipeline of innovative molecules, too many clinical trials that fail, an increasing regulatory burden, and rising research costs. The need for innovation became paramount. The relationship between the public and pharmaceutical companies become increasingly negative. The increase in costs associated with creating a new drug, together with the advances in Information and Communication Technologies, gave rise to Business Process Outsourcing, the establishment of close partnerships with academic institutions, biopharmaceutical start-ups, collaborative drug and product development, and the establishment of affiliations along pharmaceutical development. Given the current public problems in creating new medicines, there was increased pressure on pharmaceutical companies to utilize new scientific advances in the areas of molecular biology, structural biology, immuno-oncology, clinical trials, and the use of new technologies to optimize the process of drug development.

Biotechnology is a sector of the economy that uses biological processes or organisms to design products or technological processes for use or commercial exploitation. Technological innovation in this field is particularly well developed because of the high demands of research and development in the health sector, which require medium- and long-term investment. In the various phases, the investment has to be supported by public and private funding to leverage the existing university resources and favor an adequate push for technology transfer, allowing for quick commercialization.

8.8.1. Biotechnology Advances

During the past two decades, a great number of science and technological advances have propelled the field of research and drug development forward in unprecedented ways. The sequencing of the human genome, in combination with new capabilities in such areas as genetic engineering, gene cloning, protein engineering, high-throughput screening, cellular targeting, and systems and synthetic biology are paving the way to new generations of biologics, shortened timelines, and greater affordability of needed medicines. Some of the biotechnology milestones that have opened important new

illness models to medical research, but especially drug discovery and development, are briefly listed here.

Among or even at the top of milestones of biotechnological research are purposely generated knockout mice and genetically modified mice -both of which also serve as important illness models. These biotechnological tools paved the way for a large number of patents covering genetically modified mice, with leading companies making antibody discoveries based on monoclonal mouse technology including many with humanization or chimeric strategies. Broadly engineered antibody specificities strengthen the flexibility, future, and utility of biopharmaceutical antibody modalities. Transgenic mice also support the co-development of antibody-drug conjugate modalities. Based on these technologies, the body of patents pending/patents granted is an area of hyperactivity worth over a billion U.S. dollars/year.

Other notable advances enabling drug development within less predictable but important experience-driven timelines, and possibly at greatly reduced pricing levels, are disruptions to the fields of protein and even enzyme development. Additionally, digital solutions are enabling the sourcing of neoantigens for personalized cancer vaccine approaches and novel therapeutic developments with platform development.

8.8.2. Personalized Medicine

Thanks to advances in genetics and genomics research, we have been reminded that patients are as different from each other, as the pathogens that infect them. Personalized medicine or precision medicine is a novel approach to the treatment and prevention of disease that uses the personal characteristics of each patient to match them with prevention and treatment strategies that are most likely to be effective for them without unnecessary adverse effects. Personalized medicine uses large datasets covering clinical history and outcomes, biochemical data, and social data to determine the most effective strategies for each patient within treatment and prevention options used by doctors. Personalized medicine is used even before clinical presentation, where genomic data is utilized in pharmacogenomics to tailor drug types and dosages during treatment. Several personalized medicine approaches are already being used for selected indications in oncology.

The sequencing revolution has transformed genomics from a research tool into a clinical tool, providing precision diagnostics to patients afflicted with genetic diseases. The availability of large mutation databases has ensured the broad clinical availability of whole exome and genome sequencing. Catalyzed by the success story of trisomy 21 identification during pregnancy using amniocentesis and chorionic villus sampling to ploidy assessment based on fetal DNA circulating in maternal plasma, the clinical

translation of nascent whole exome sequencing technology has led to a tenfold reduction in turnaround time for identifying mutations in congenital deafness and other monogenetic diseases of children with neurological problems.

8.8.3. Digital Health Technologies

The integration of medicine and technology in a coherent manner has produced Digital Health Technologies (DHT). With a flourishing ubiquitous infrastructure of mobile computing devices linked to the Internet through the cloud, a novel cascade of possibilities has emerged for recovering Health Data derived from human beings on a continuous basis in both passive and real-time manners. DHT acts both as a complement and a logistical collaborator to facilitate the existing traditional healthcare ecosystem. DHT includes information and communication technology that focus on health and well-being and has the potential to profoundly impact the quality and cost of healthcare, including:

1. Sensor systems that enhance diagnosis weighing the true cost/benefit of large population screening.

2. Devices that facilitate treatment adherence cost-effectively.

3. Technologies that empower patients to manage their health, paving the way for preventive medicine and the next stage of personalized medicine.

4. Digital Devices and Mobile Health Apps that allow patients to reveal their reactions to treatment promptly, facilitate preventive medicine, allow for a more rapid response to adverse events, and the next stage of personalized medicine—connected and sharing with other patients.

5. Data transfer, mining, and analysis algorithms that allow for the proper exploitation of physiological and medical information on a mass scale without compromising privacy and confidentiality.

6. Robotics that assist doctors and patients alike, allowing fast and precise diagnosis at clinics and homes, and DHT training response and new prosthetic limbs for the patients.

The impact that these tools may have on the drug development industry should not be underestimated—streamlining processes, bringing down costs, speeding up the time to patient response to drug therapy, and redefining the concept of clinical trial. Consequently, they are seen as a potential panacea for the inefficiencies and issues currently faced by the drug development industry.

8.9. Conclusion

After decades of research into the development of target-specific, new medicines, little seems to get done faster. To reap all possible benefits from scientific insights and new technologies, others must get involved in the value chain, with help with planning first-in-human studies and bringing products rapidly through the various phases of development. The financial burden of advancing torturous molecules through clinical testing should not be for an individual company, which then bears the entire risk that a product will be successful or quickly take care of losing money. Early cooperation with a partner sympathetic to the goal of accelerating drug development is key. Take time to prepare a program management MAP dictating what each partner will do in the discovery and development phase and with clear times for transfer points and data packages which will automatically trigger a go/no-go decision.

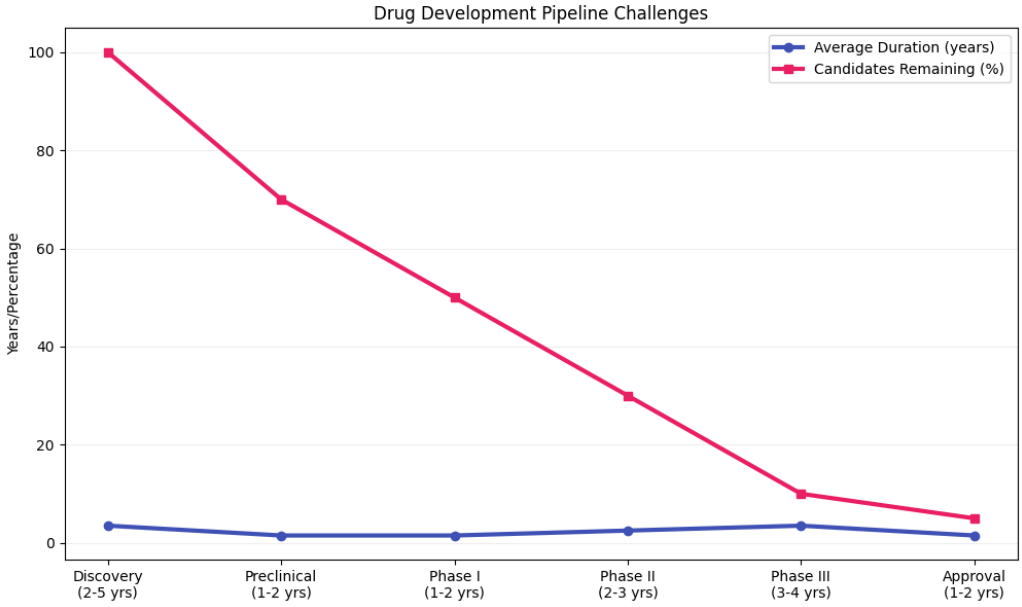

Fig 8 . 3 : Drug Development Pipeline Challenges

Bringing new medicines to market is an increasingly difficult task that is often beset by failures and complications. Yet it is a task that is a requirement in modern society and one that is not without reward. How can we ensure faster progress to market for these important new treatments? The drug discovery and development process is a complex system, in which many different players play a role. The pharmacological, technological, as well as financial requirements during discovery and development must be in sync with the system's drivers, processes, and requirements to prevent losing money over and over again. Here, by systematically addressing the major components within the research, drug discovery, and development system, we have outlined a few potential paths towards a more efficient drug discovery and development system that would allow society to

reap the benefits of modern pharmaceutical research into curing diseases and enabling healthy living.

8.9.1. Key Takeaways and Future Directions

We have highlighted critical milestones in the various stages of drug discovery and development, as well as potential challenges and limitations to successful progression in transiting these gatekeeper processes. The major conclusion is that the future of how new medicines are developed, and how they become accessible to those for whom they were created, is at a critical intersection caused by rapidly developing new technologies spanning innovative biology through reasoning artificial intelligence, and machine learning. These tools are being matched by other discoveries in chemistry, manufacturing, and control that will allow for reductions in cost, risk, and time to approval. While the overwhelming challenge is focusing on therapeutically and commercially valuable questions, rather than those of academic curiosity, this changing landscape is becoming populated by an increasing number of successful, nimble, private entrepreneurs. The pharmaceutical industry and regulatory authorities must rethink how they partner with these innovators to address the pressing, unmet medical needs of the global population so that the resulting products are perceived as credible across different stakeholders, including life science entrepreneurs, investor communities, Big Pharma, and global regulators.

The demands for compelling new interventions to improve the health of the world's population – especially those of high economic and commercial cost – will only continue to increase. Addressing these challenges within the new landscape of drug discovery and development will allow for better prioritization and resource allocation across disease areas and correction of deficiencies, thus minimizing the cost and burden of failed innovation. In summary, while the current processes are beginning to divert, the final destination for each of the parallel roads is the same: providing new solutions to pressing unmet medical needs for patients worldwide in a timely, efficient, and safe manner.

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