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From Idea to Market: The Drug Design, Development & Approval Process

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ABSTRACT

A new drug discovery, design and development is a complex series of processes. It involves a lot of stakeholders, astronomical amounts of funds, a lot of time and energy. Though, the process of drug development involves much effort by the researchers, there is very less probability that a new gets approval from the regulatory authorities like US FDA. This review article discusses the complexities involved and various challenges of new drug development and approval processes.

INTRODUCTION

A new drug to be developed into an active pharmaceutical from its inactive form generally takes minimum of ten years to maximum of 15 years and costs astronomical amounts to the research organizations. Before being developed and marketed 5000 to 10000 chemical compounds are studied but a few of them only get approval from the US FDA to be prescribed or used in other medical applications^[1, 2]. A variety of complex medical cases and advent of new kind pathogens and their drug resistance in recent years led the pharmaceutical research teams to consider various parameters like demographics of patients, life cycles of causative organisms, disease profiles, the duration of the treatment, etc^[3 - 6].

According the IMS statistics related to the annual growth rate and approval rate of new drugs and biologics by the regulatory authorities like US FDA, European Union and PMDA of Japan it can be said that, the pharmaceutical market is one of the most complex businesses. The regulation process in the business is very complex and approval process is quite delayed because of various major differences among the policy frameworks of the regulatory bodies in each country^[7].

Pharmaceutical development process basically includes three distinct stages such as non-clinical, pre-clinical and clinical phases. Each of the above stages proceeds to ensure the quality safety and efficacy of the drug under investigation. Potential drug development starts by the studies of biochemistry and physiology of the disease and the development of prodrugs^[8, 9, 10]. However, recent trends in the industry and regulatory bodies suggest developing drugs that offer the value for money. In other words making cost effective pharmaceuticals is very important in order to market them and to be taken up by the health care system^[11].

In the light of the above reasons and in order to develop cost effective and safe drugs the professionals of various fields of science and technology have been working on new methods and systems. Efforts of which led to develop various novel and advanced drugs and drug delivery approaches

such as nanomedicine, molecular engineering and robotics in pharma. Research has been focusing on various areas like high performance computing, prediction studies, advanced data clustering techniques, computational intelligence, etc. to discover, design and develop advanced pharmaceuticals to face the current challenges [12]. Drug discovery has been made easier by inter-disciplinary applications of genomics, proteomics, bioinformatics, and efficient technologies including combinatorial chemistry, High Throughput Screening (HTS), virtual screening, de novo design, *in vitro*, *in silico* ADME screening, and structure-based drug design [13, 14].

Advent of Computer Aided Drug Designing and emergence of nanomedicine, molecular engineering, tissue engineering and stem cell technology offer great many applications in the field of drug development and will provide answers to various problems existing currently [15]. The success of “Magic Bullet” concept in chemotherapeutics to target the specific site gave inspiration to focus on developing the multi-target drugs which will enable the advancements in diagnosis and treatment of complex diseases like Alzheimer’s, HIV, Parkinson’s diseases. These are known as promiscuous drugs i.e. single drug molecule is capable of selectively interacting with multiple receptors in order to diagnose or treat a given disease [16, 17].

Phases in the Drug Development

Pre-clinical Phase

This is the first and foremost step to start with in the development process which involves the review of all the advancements in the relevant fields [16]. Apart from that bio-analytical technique infrastructure, good laboratory practices and validation are the major areas of this stage [17 - 22]. This step facilitates the understanding of various components of the disease process and other parameters in terms of pharmacology, chemistry, computer applications, etc. that will be useful to transform the potential drug agent into a therapeutic agent [23].

Electronic health records have been widely used in modern clinical trial phases in order to alleviate the health care delivery, trial efficiency, cost constraints and quality [24]. This move helps in identifying and enrolling the possible patient groups that fit the particular trial.

Clinical Phase

This phase of the drug development is again divided into four sub phases. A molecular entity that passes preclinical studies must undergo in-vivo tests in animals, generally rodents [25 - 27]. The drug given at approximately effective doses is tested for the potential damage of chromosomes or toxicity in the subject. The results of these tests along with pharmacologic and safety data are used to support the IND application with FDA. However, the threat of irreversible immunogenic reactions caused by some biopharmaceuticals (large molecules) while testing on the subjects may lead to failure of many drug candidates [28].

Phase 1: This stage tests the chemical compounds for appropriate dose, safety and pharmacology, but in a small group (generally 20 to 100) of healthy human volunteers under close supervision [29, 30]. This phase also screens the compounds to check the side effects. However, certain compounds may not show side effects immediately and in some individuals. So phase is followed by phase 2 of the clinical trials to overcome the shortcomings of phase 1. Dose-ranging can also be found at this stage of clinical trials on the subjects of different age groups.

Phase 2: At this stage of clinical trials the researcher without any presumption for the drug to show particular therapeutic effect, studies on a group of 100-300 patients. The study examines the suitable therapeutic dose of the potential drug [31 - 33]. The phase also tests the safety and efficacy of the drug on the subjects.

Phase 3: This stage also continues to study the safety, efficacy and effectiveness of the drug similar to the previous phase but in large number of patients that is 1000 to 2000. Therapeutic dose can

be found and the drug is presumed to show some therapeutic effect [34, 35]. These studies compare the new treatments with the best currently available treatment for the presumed therapeutic effect in terms of dose, target, delivery system, etc [36].

Phase 4: This phase will be carried out after the drug has been proved to show therapeutic effect and has been granted a license [37-39]. The main reasons for running phase 4 trials are to find out-

- More about the side effects and safety of the potential drug
- The long term risks and benefits associated with the drug [40, 41]
- Effects of the wide usage of the drug

New Drug Approval Process

When a drug survives through all the clinical trial phases the researcher applies New Drug Application with the FDA for the review and recommendations, which contains information about pre-clinical and clinical research information in terms of chemical makeup and manufacturing process, pharmacology and toxicity of the compound, human pharmacokinetics, results of the clinical trials, and proposed labeling [42]. The Prescription Drug User Fee Act of 1992 (PDUFA) helps in facilitating the review process by collecting user fee from the pharmaceuticals companies. Once the review is complete, the NDA might be approved or rejected. If the drug is not approved, the applicant is given the reasons why and what information could be provided to make the application acceptable. Sometimes the FDA makes a tentative approval recommendation, requesting that a minor deficiency or labeling issue be corrected before final approval [43, 44]. Once a drug is approved, it can be marketed.

Once the review is plenary, the NDA might be approved or abnegated. If the drug is not approved, the applicant is given the reasons why and what information could be provided to make the application acceptable [45]. Sometimes the FDA makes a tentative approbation recommendation, requesting that a minor deficiency or labeling issue be redressed afore final approbation. Once a drug is approved, it can be marketed [46, 47].

Some approbation contains conditions that must be met after initial marketing, such as conducting supplemental clinical studies [48]. For example, the FDA might request a postmarketing, or phase 4, study to examine the perils and benefits of the incipient drug in a different population or to conduct special monitoring in a high-risk population [49, 50]. Alternatively, a phase 4 study might be initiated by the sponsor to assess such issues as the longer term effects of drug exposure, to optimize the dose for marketing, to evaluate the effects in pediatric patients, or to examine the efficacy of the drug for supplemental designations. Postmarketing surveillance is consequential, because even the most well-designed phase 3 studies might not unearth every quandary that could become ostensible once a product is widely utilized. Furthermore, the incipient product might be more widely utilized by groups that might not have been well studied in the clinical tribulations, such as elderly patients. A crucial element in this process is that medicos report any untoward complications. The FDA has set up a medical reporting program called Medwatch to track earnest adverse events [51]. The manufacturer must report adverse drug reactions at quarterly intervals for the first 3 years after approbation [52] including a special report for any solemn and unexpected adverse reactions.

CONCLUSION

Potential drug development starts by the studies of biochemistry and physiology of the disease and the development of prodrugs [53]. Efforts of which led to develop various novel and advanced drugs and drug delivery approaches such as nanomedicine, molecular engineering and robotics in pharma [54]. Drug discovery has been made easier by inter-disciplinary applications of genomics, proteomics, bioinformatics, and efficient technologies including combinatorial chemistry, High Throughput Screening (HTS), virtual screening, de novo design, in vitro, in silico ADME screening, and structure-based drug design. Advent of Computer Aided Drug Designing and emergence of nanomedicine, molecular

engineering, tissue engineering and stem cell technology offer great many applications in the field of drug development and will provide answers to various problems existing currently [55 - 57].

The discovery, design and development of drugs follows various stages. The clinical phase of the drug development is again divided into sub phases [58 - 60]. At this stage of clinical trials the researcher starts without any presumption for the drug to show particular therapeutic effect [61]. The potential drug is tested on animals and then on healthy volunteers and finally on patients to show the therapeutic effects. The final human phase using patient subjects will be carried out after the drug has been proved to show therapeutic effect and has been granted a license [62 - 64]. When a drug survives through all the clinical trial phases the researcher applies New Drug Application with the FDA for the review and recommendations, which contains information about pre-clinical and clinical research information in terms of chemical makeup and manufacturing process, pharmacology and toxicity of the compound, human pharmacokinetics [65, 66], results of the clinical trials, and proposed labeling. Post-marketing surveillance is consequential, because even the most well-designed phase 3 studies might not unearth every quandary that could become ostensible once a product is widely utilized.

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