Review On Stages of New Drug Discovery Development

RUSHUKESH A. PATIL[1], BHIMASHANKAR S. HUCCHE[2], SHYAMLILA B. BAVAGE[3], NANDKISHOR B. BAVAGE[4]

[1] *B. Pharm Final Year Student, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*

[2] *Department of Pharmaceutics, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*

[3] *Department of Pharmacognosy, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*

[4] *Department of Pharmaceutical Chemistry, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*

Abstract— Drug discovery is a process which objects to recognizing a compound therapeutically useful in preventing and treating diseases. Drug discovery and development studies that add to solving any of the many scientific and processing issues involved in the development process can improve the competence of the process. This method involves the recognizing of nominees, synthesis, characterization, validation, optimization, screening and bio-assays for therapeutic value. Once a new entity or compound has shown its impact in these investigations, it will primary the process of drug development prior to clinical trials. The development of a drug from an initial idea to its entry into the market is a very multifaceted process which can take around 11 to14 years and cost US $1 billion to $2billon. On an average, a million molecules screened but only a single is discovered in late stage of clinical trials and is finally available for patients. This article gives a short blueprint of the cycles of new drug discovery and development.

Index Terms— Drug discovery; Drug development; Clinical research; Clinical trials

I. INTRODUCTION

Drug development process involves rigorous testing and optimization of selected compounds to identify the drug that is most effective. This testing is done in cells (in vitro) and in animals (in vivo) to study the metabolism and to produce a product that is safe and has passed all regulatory requirements. Drug's failure in clinical practice is due in large part to two main reasons. The first reason is if they do not work properly and the second reason is, if they are not safe. The two most important issues to address in drug invention processes are; to identify a target and validation. This may be a protein receptor that is associated with a disease condition, for this reason, it is important to know how the disease occurs at the molecular, cellular and genetic levels. Once the target is identified, then the next step is how the target plays a role in the disease process. This is carried out by testing the target against different known and new compounds to know either one or several compounds that interact with the target and show either to neutralize or slow down the disease process.[1]

The average cost for research and development for each efficacious drug is likely to be $1billion to $2billion. For every 5,000-10,000 compounds that enter the investigation and development pipeline, ultimately only one attains approval. These statistics challenge imagination, but a brief understanding of the R&D process can explain why so many compounds don't make it and why it takes such a large, lengthy effort to get one medicine to patients. [2]. The Success requires immense resources the best scientific and logical minds, highly sophisticated laboratory and technology; and multifaceted project management. It also takes persistence and good fortune. [3]

Stages of drug discovery and development include:

1) Pre discovery

- Target identification
- Validating drug targets
- Identification of lead

- lead optimization
- Product characterization
- Formulation and development

2) Preclinical research
- Investigational New Drug

3) Clinical trials

II. PRE DISCOVERY

There are many different steps in the Drug Discovery process. The main purpose of this practice is to confidently select strong candidates by reducing the large initial number of compounds as we move down the ladder. There are a few different ways these candidates can be reduce

III. TARGET IDENTIFICATION

Identifying a biological target that is 'druggable' – a target is termed 'druggable' if its activity (behaviour or function) can be modulated by a therapeutic – whether it be a small molecule drug, or biologic. Proteins and nucleic acids are both examples of biological targets. But what makes a 'good' target? Properties of a promising drug target…

- The target has a confirmed role in the pathophysiology of a disease and/or is disease-modifying.
- Target expression is not evenly distributed throughout the body.
- The target's 3D-structure is available to assess druggability.
- The target is easily 'assayable' enabling high throughput screening.
- The target possesses a promising toxicity profile, potential adverse effects can be predicted using phenotypic data.

The proposed target has a favourable intellectual property (IP) status. (Relevant for pharma companies).[4]

VALIDATING DRUG TARGETS:

Target validation is the process of demonstrating the functional role of the identified target in the disease phenotype. [5]. whilst the validation of a drug's efficacy and toxicity in numerous disease-relevant cell models and animal models is extremely valuable – the ultimate test is whether the drug works in a clinical setting. [6,7]

Identification of lead

This is the next step after Target Validation. Molecules that comply with the desired activity and can potentially interact with the drug target are called "hits". The identification of these molecules is carried out during High Throughput Screening (HTS) processes. During these studies, important properties such as potency or selectivity of the new drugs are provided as the basis for moving forward to the next level in the Drug Discovery path.

HIT TO LEAD

This stage is also known as lead generation and the molecules coming from the High Throughput Screening are selected for Lead Optimization. During lead generation, drug properties such as potency, selectivity, solubility or stability are analysed and improved to pave the way to Lead Optimization.

Lead Optimization

Once a lead compound has been identified from the previous steps, several events take place during the Lead Optimization process, including refined synthesis and characterization of the promising compound and the study of its different properties. By slightly modifying the chemical structure of the molecules, potential future adverse events may be minimized. Among these properties, it is important to study the selectivity and specificity of the molecule to the target of choice and to evaluate its binding properties.

Identification and quantification of drug metabolites is an important part of the Lead Optimization process. This can also contribute to show potential toxic effects in subsequent clinical trials. Potential safety concerns about some lead compounds can be addressed at this stage by modifying or reducing deficiencies in its structure. Other properties that are favourable are meant to be maintained during this phase. Some advanced tools to study the metabolites found inside the tissues include mass spectrometry (MALDI) and

nuclear magnetic resonance (NMR) fragment-based screening (FBS) tools. These modern automated screening systems are often employed by pharmaceutical companies during these Drug Discovery processes. At the end of the Lead Optimization phase, important key points during the development of a new drug are investigated. Among these key points, the efficacy, potency, toxicity, stability, bioavailability and route of optimization of the chemical compounds or biologics are accurately characterized before entering into Clinical Trials.

Lead Optimization may include *in vitro* and *in vivo* studies that might shed light to metabolic processes using pharmacokinetic and pharmacodynamic approaches. One problem associated with cell-based and biochemical screens is that some important effects that have to do with toxicity or in vivo drug effects may be missing. An *in vivo* model can show up the modulation of a cell niche by a particular drug, rather than the target cell-type directly. [8]

Product Characterization

When any new drug molecule shows a promising therapeutic activity, then the molecule is characterized by its size, shape, strength, weakness, use, toxicity, and biological activity. Early stages of pharmacological studies are helpful to characterize the mechanism of action of the compound.

Formulation and Development

Pharmaceutical formulation is a stage of drug development during which the physicochemical properties of active pharmaceutical ingredients (APIs) are characterized to produce a bioavailable, stable and optimal dosage form for a specific administration route.

Pre-clinical studies

Pre-clinical research in drug development process involves evaluation of drugs safety and efficacy in animal species that conclude to prospective human outcome. The pre-clinical trials also have to acquire approval by corresponding regulatory authorities. The regulatory authorities must ensure that trials are conducted in safe and ethical way and would give approval for only those drugs which are confirm to be safe and effective. ICH has established a basic guideline for technical necessities of acceptable preclinical drug development.[9]

The pre-clinical trials can be conducted in two ways: General pharmacology and Toxicology. Pharmacology deals with the pharmacokinetic and pharmacodynamic parameters of drug. It is essential to explore unwanted pharmacological effects in suitable animal models and monitoring them in toxicological studies. Pharmacokinetic studies are very important to make known the safety and efficacy parameters in terms of absorption, distribution, metabolism and excretion. These studies give information on absorption rate for diverse routes of administration, which helps in selection of dosage form, distribution, rate of metabolism and elimination; which governs the half-life of the drug. Half-life of the drug clarifies the safety outline of the drug which is the obligatory for a drug to get approved by regulatory agencies. The drug distribution mechanism elucidates the therapeutic effectiveness of the drug as it depends on the drugs bioavailability and its affinity. Drug metabolism provides the probability of through phases of biotransformation process and formation of drug metabolites. It also helps in understanding the reactions as well as enzymes involved in biotransformation. [10]

Toxicological studies of the drug can be performed by invitro and in-vivo test which evaluate the toxicological effects of the drug. In-vitro studies can be performed to inspect the direct effects on cell proliferation and phenotype. In-vivo studies can be performed for qualitative and quantitative determination of toxicological effects. As many drugs are species specific, it is essential to select appropriate animal species for toxicity study. In-vivo studies to evaluate pharmacological and toxicological actions, including mode of action, are often used to support the basis of the proposed use of the product in clinical studies. [11]

Investigational New Drug Application

INDA is applied after the Preclinical studies show success and if the INDA submission is accepted the product is further forwarded to the clinical research studies (Phase I - Phase IV studies) [12]

CLINICAL TRIALS

While preclinical research answers basic questions about a drug's safety, it is not a substitute for studies of ways the drug will interact with the human body [13] . "Clinical research" refers to studies, or trials, that are done in people. As the developers design the clinical study, they will consider what they want to accomplish for each of the different Clinical Research Phases and begin the Investigational New Drug Process (IND), a process they must go through before clinical research begins [14-17]

DESIGNING CLINICAL TRIALS

Researchers design clinical trials to answer specific research questions related to a medical product. These trials follow a specific study plan, called a protocol that is developed by the researcher or manufacturer [18-21]. Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives [22]. Then they decide:

- Who qualifies to participate (selection criteria)
- How many people will be part of the study?
- How long the study will last
- Whether there will be a control group and other ways to limit research bias
- How the drug will be given to patients and at what dosage
- What assessments will be conducted, when, and what data will be collected
- How the data will be reviewed and analysed Clinical trials follow a typical series from early, small-scale

Phase 1 studies to late-stage, large scale Phase 3 studies [23-26]

PHASE STUDIES:

Phase 1 (First in Humans)
Trail Design:
Patients: 20 to 100 normal healthy volunteer subjects in a single centre with no benefit to the subjects.
Duration of study: Short – Days to several weeks or months
Type of study: Open label (No Placebo or comparative agent), uncontrolled, single or multiple doses [27-30].
Purpose:

- Mechanism of action (ADME) and PK/PD studies
- Pharmacological effect
- Tolerability, side effects and toxicity at different doses
- Early evidence of efficacy
- Evaluates safety – Identify most likely potential toxicities and most likely dosage range Percentage of Drugs

that Move to the next Phase 70% [31]

Phase 2 (Therapeutic Exploratory)
Trail Design:
Patients: several hundred (100-300) patients with the targeted disease/condition.
Length of Study: Several months to 2 years
Type of study: Randomized, placebo or active control, parallel double blinded study, single or multiple doses, multicentre [32] .

Purpose:

- Dose range finding (Minimum and maximum effective dose) [33]
- Effectiveness for the treatment of the disease or condition for which the drug is intended to use
- Maximum Tolerated Dose (MTD)
- Common short time side effects and risks
- Pharmacokinetics

Percentage of Drugs that Move to the Next Phase 3 [34]

Phase 3 (Therapeutic Confirmatory) – Pivotal Trails
Trail Design:
Patients: Several 1000 to 3,000 patients with the targeted disease/condition [35,36] .
Length of Study: 1 to 4 years
Type of study: Randomized, placebo or active control, parallel double blinded study, multicentre

Purpose [37]

- Effectiveness (Large scale)

- Relative risk/benefit relationship
- Long term safety information – common side effects, drug interactions, age/rate/gender differences
- Dosing (for labelling)
- Assessment of safety and efficacy Percentage of Drugs that Move to the Next Phase 25-30%

After completing the phase III trails the application is filed with the concerned regulatory bodies seeking permission for marketing and after the regulatory bodies grant the required approval, the product is launched into the market [38-40]

Phase 4 (Post-Marketing Therapeutic Use)
Trail Design
Patients: Several hundred to thousand patients with the disease/condition.
Type of study: Randomized, Placebo or active control, Multicentre

Purpose
- Perform Quality of Life Trails (QOL) trails
- Perform pharmacoeconomic trails – Is the drug more effective that other available treatments
- Collection of long-term safety information – Epidemiological studies for safety and additional surveillance for unexpected or rare adverse effects
- Add line extensions – New dosage forms and formulations

CONCLUSION

New drugs are an important part of modern medicine with the emergence of diseases. A few decades ago, a disease such as peptic ulcers were an indication for major surgery [43]. The advent of new pharmacologic treatments and introduction of novel medications have reduced the serious complications of peptic ulcer disease. Similarly, thanks to many new antiviral medications with which the outlook for HIV-infected patients has improved. It is important that physicians understand the process of drug discovery and development [44]. Understanding the process can promote innovation, help physicians assess new products, underline the importance of reporting adverse drug events and provide physicians with the information to educate patients about participating in a clinical trial [45]

REFERENCES

[1] Gamal Osman Elhassa*1 and Khalid Omer Alfarouk2. Introduction of drug development: Stages of Drug Development.

[2] Moffat J, Vincent F, Lee J, Eder J, Prunotto M. Opportunities and challenges in phenotypic drug discovery: an industry perspective. Nature Reviews Drug Discovery, 2017; 16(8):531-543.

[3] DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. Journal of Health Economics, 2003; 151-185.

[4] Gashaw, I., Ellinghaus, P., Sommer, A., & Asadullah, K. (2012). What makes a good drug target? Drug Discovery Today, 17, S24-S30. doi: 10.1016/j.drudis.2011.12.008.

[5] Lindsay, M.A. (2003). Target discovery. Nature Reviews Drug Discovery volume 2, pages 831–838. doi: 10.1038/nrd1202

[6] Wermuth, C., Aldous, D., Raboisson, P., & Rognan, D. (2015). The Practice of Medicinal Chemistry (4th ed., pp. 45-70).

[7] Jain, K. (2004). RNAi and siRNA in target validation. Drug Discovery Today, 9(7), 307-309. doi: 10.1016/s1359-6446(04)03050-8.

[8] www.igi-global.com › chapter › lead-optimization-in

[9] Barile FA. Pri. nciples of Toxicological Testing. CRC Press, USA, 2008.

[10] Friedman LM, Furberg CD, Demets DL. Fundamentals of clinical trials. 4th ed. New York: Springer Science and Business Media LLC; 2010.

[11] Faqi AS. A comprehensive guide to toxicology in preclinical drug development. Waltham, MA: Elsevier; 2013.

[12] Torzewski J, et al. Road Map to Drug Discovery and Development–Inhibiting C-reactive protein for the Treatment of Cardiovascular Disease. J Bioequiv Availab. 2011; S1:001.

[13] Elzahabi HAS. Virtual Screening in Drug Discovery, A Topic between Believe and Reality? Biochem Pharmacol (Los Angel). 2012;1:e103.

[14] Nishant T, et al. Role of Pharmacokinetic Studies in Drug Discovery. J Bioequiv Availab. 2011;3:263-267.

[15] Celikyurt IK. Thought-provoking Molecules for Drug Discovery: antioxidants. Pharm Anal Acta. 2011;S3:001.

[16] Fortuna A, et al. In vitro and In vivo Relevance of the P-glycoprotein Probe Substrates in Drug Discovery and Development: Focus on Rhodamine 123, Digoxin and Talinolol. J Bioequiv Availab. 2011;S2.

[17] Arun B. Challenges in Drug discovery: Can We Improve Drug Development. J Bioanal Biomed. 2009;1:050- 053.

[18] Subudhi BB, et al. Updates in Drug Development Strategies against Peptic ulcer. J Gastrointest Dig Syst. 2016;6:398.

[19] Zhao Y. Towards Structural Based Drug Development for Ebola Virus Disease. J Chem Biol Ther. 2016;1:e101.

[20] Ashok Kumar Panda. Ayurveda Treatment Outcomes for Osteoarthritis. J Homeop Ayurv Med. 2015;4:e115.

[21] Jayram H, et al. Ayurvedic Regimen in Hemorrhagic Ovarian Cyst without Peritoneal Bleeding: A Case Report. J Homeop Ayurv Med. 2014;3:164.

[22] Nazmul Huda Md, et al. Clinical Evaluation of an Ayurvedic Preparation for the Treatment of Iron Deficiency Anemia in Patients. J Homeop Ayurv Med. 2014;3:162.

[23] Banamali D. Concept of Dietetics and its Importance in Ayurveda. J Homeop Ayurv Med. 2014;3:149.

[24] Soluade KO and Do DP. Biosimilars: The New Era of Drug Development? J Bioequiv Availab. 2013;5:e40.

[25] Panda AK. Comprehensive Ayurvedic Care in Type-2 Diabetes. J Homeop Ayurv Med. 2014;3:e111.

[26] Panda AK. Complementary and Alternative Medicine is Mother Medicine. Altern Integr Med. 2013;3:e112.

[27] Hazra J and Panda AK. Concept of Beauty and Ayurveda Medicine. J Clin Exp Dermatol Res. 2013;4:178.

[28] Shintani H. Drug Development and Validation. Pharmaceut Anal Acta. 2013;4:e149.

[29] Huang L. Inhibiting Protease Auto-processing: A Novel Strategy for Anti-HIV-1 Drug Development. Biochem Physiol. 2013;2:e115.

[30] Aliev G, et al. Mitochondria Specific Antioxidants and their Derivatives in the Context of the Drug Development for Neurodegeneration and Cancer. Drug Des. 2013;2:103.

[31] Sun L. Peptide-Based Drug Development. Mod Chem appl. 2013;1:e103.

[32] Amin A and Lowe L. Plant-Based Anticancer Drug Development: Advancements and Hurdles. J Gastroint Dig Syst. 2012;2:e111.

[33] Elsheikha H and Rauch CRedefining the Limits of Biochemistry in Multidrug Resistant Nematodes: Implications for Future Drug Development. J Vet Sci Technol. 2012;3:e110.

[34] Bhattacharyya S. Application of Positron Emission Tomography in Drug Development. Biochem Pharmacol. 2013;1:e128.

[35] Akkol EK. New Strategies for Anti-Inflammatory Drug Development. J Pharmacogenomics Pharmacoproteomics. 2012;3:e118.

[36] Luisa BM, et al. Challenges Faced in the Integration of Pharmacogenetics/Genomics into Drug Development. J Pharmacogenomics Pharmacoproteomics. 2012;3:108.

[37] Panda AK. Evidence based Ayurveda Practice. J Homeop Ayurv Med. 2012;1:e108.

[38] Ansari R. Defining the Role of Single Nucleotide Polymorphic (SNP) in Drug

Development and Toxicity. J Drug Metab Toxicol. 2012;3:e103.

[39] Kummalue T. Difficulties of Drug Development from Thai Herbal Medicine. Pharm Anal Acta. 2012;S15:002.

[40] Khan A and Khan AU. Biomarker Discovery and Drug Development: A Proteomics Approach. J Proteomics Bioinform. 2012;5: 5-6.

[41] Sang N. Biochemistry, Drug Development and Open Access. Biochem Pharmacol. 201;1:e101.

[42] Nicolson TJ, et al. The Post-Transcriptional Regulator EIF2S3 and Gender Differences in the Dog: Implications for Drug Development, Drug Efficacy and Safety Profiles. J Drug Metab Toxicol. 2010;1:101.

[43] Avramidis D, et al. Regrowth Concentration Zero (RC0) as Complementary Endpoint Parameter to Evaluate Compound Candidates During Preclinical Drug Development for Cancer Treatment. J Cancer Sci Ther. 2009;1: 019-024.

[44] Nawab DH. The Pharmaceutical Applications of Next Generation Sequencing in Oncology Drug Designing and Development. Next Generat Sequenc & Applic. 2015;2:116.

[45] Dev Bukhsh Singh. Success, Limitation and Future of Computer Aided Drug Designing. Transcr Open Access 2014;4:e-127.