IJPSR (2023), Volume 14, Issue 7 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 October 2022; received in revised form, 28 November 2022; accepted 30 November 2022; published 01 July 2023

DRUG DISCOVERY AND DEVELOPMENT: A BASIC APPROACH TO IMPROVE THE SUCCESS OF DRUG DISCOVERY

Tarang Varshney [1], Shaily Saini [1] and Aafreen [* 2]

SRMS College of Engineering, Technology & Research Bareilly [1], Department of Pharmaceutics [2], Bareilly - 243202, Uttar Pradesh, India.

Keywords:

Drug discovery, Drug development, Clinical trials, Preclinical trials, New drug application, Preclinical software

Correspondence to Author:
Aafreen
Assistant Professor,
Department of Pharmaceutics,
Bareilly - 243202, Uttar Pradesh, India.

E-mail: aafreen844796@gmail.com

ABSTRACT: Drug discovery is a process that aims at identifying a compound therapeutically useful in curing and treating disease. This process involves the identification of candidates, synthesis, characterization, validation, optimization, screening, and assays for therapeutic efficacy. Once a compound has shown its significance in these investigations, it will initiate the drug development process earlier to clinical trials. The new drug development process must continue through several stages to make a safe, effective medicine that has approved all regulatory requirements. One overall theme of our article is that the process is sufficiently long, complex, and expensive, so many biological targets must be considered for every new medicine ultimately approved for clinical use, and new research tools may be needed to investigate each new target. From initial discovery to a marketable medicine is a long, challenging task. It takes about 12 - 15 years from discovery to the approved medication and requires an investment of about USD 1 billion. This article outlines the processes of new drug discovery and development.

INTRODUCTION: Drug discovery is the process through which potential new medicines are identified. It involves a wide range of scientific disciplines, including biology, chemistry, and pharmacology [1-2]. In the fields of medicine, biotechnology and pharmacology, drug discovery is the process by which new candidate medications are discovered. Historically, drugs were discovered by identifying the active ingredient from traditional remedies or serendipitous discovery, as with penicillin [3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(7).3314-26

This article can be accessed online on www.ijpsr.com

DOI link: http://doi.org/10.13040/IJPSR.0975-8232.14(7).3314-26

The development of new drugs is very complex, costly, and risky. Its success is highly dependent on intensity. Collaboration and interaction between many departments within the drug development organization, external investigators, and service providers, in constant dialogue with regulatory authorities, payers, academic experts, clinicians, and patient organizations. Within the different phases of the drug life cycle, drug development is by far the most crucial part for the initial [4-5].

Periods in Drug Discovery in Development Process: It is roughly estimated that it takes around 5-10 years for the complete drug discovery and development process and for its introduction into the commercial market, and its costs around $1.7 Billion for the complete process to proceed successfully [6-9]. The various periods/phases in the Drug discovery and development process are [10-14].

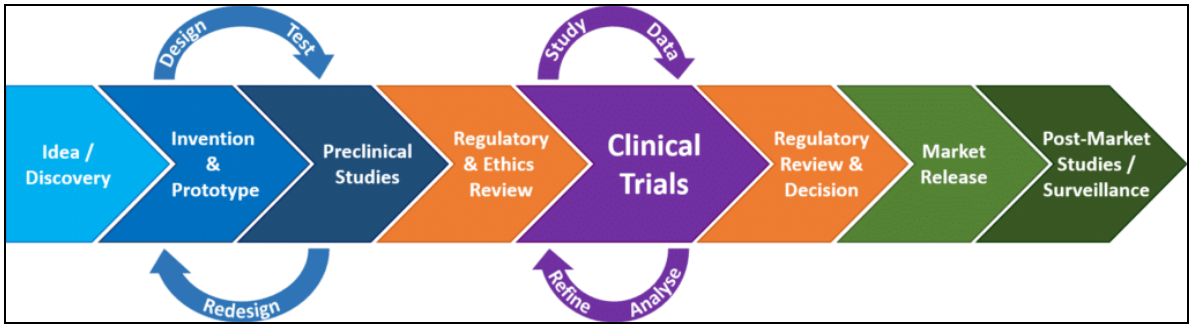

FIG. 1: SYNTHESIS OF DRUG DISCOVERY AND DEVELOPMENT

Objectives of Drug Discovery & Development [15]:

Investigational Drug Success [16]:

- Discovery/Screening: 5000-10,000
- Enter Preclinical Testing: 250
- Enter Clinical Testing: 5
- Approved by Regulatory Bodies: 1

Drug Discovery Period [17]

- ❖ Initiate a drug discovery program
- ❖ Combinatorial chemistry
- ❖ Lead compound series identification
- ❖ Additional compounds are made
- ❖ NCE' s identified

Drug Development & Registration Period [18]

- ➢ IND plan established & initiated
- ➢ IND filed
- ➢ Clinical studies initiated
- ➢ NDA prepared & submitted
- ➢ Drug launched into the market

Drug Marketing & Line Expansion [19]

- ❖ Post-Marketing surveillance initiated
- ❖ New clinical indications pursued
- ❖ New dosage forms and formulations developed
- ❖ Activities conducted to support marketing and the continued success of a drug on the market shown in **Fig. 1.**

Drug Discovery and Development:

Drug Discovery:

- Typically, researchers discover new drugs through.
- New research into a disease process encourages scientists to discover a new product to stop or reverse the effects of the disease [20].
- Many tests of molecular compounds to find possible beneficial effects against any of a large number of diseases.
- Existing treatments that have unanticipated effects [21-24].
- New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material.
- Thousands of compounds may potentially develop as a medical treatment at this stage. After early testing, however, only a few compounds look promising and call for further study [25-26].

Drug Development:

- ❖ Once researchers identify a promising compound for development, they conduct experiments to gather information on :
- ❖ How it is absorbed, distributed, metabolized, and excreted.
- ❖ Its potential benefits and mechanisms of action.
- ❖ The best dosage and best way of administration.
- ❖ Side effects (often referred to as toxicity).

- ❖ How it affects different groups of people (such as by gender, race, or ethnicity) differently.
- ❖ How it interacts with other drugs and treatments.
- ❖ Its effectiveness as compared with similar drug.

Stages of Drug Discovery and Development Include shown in Fig. 2. [27]

- Target identification
- Target validation
- lead identification
- lead optimization
- Product characterization [28]
- Formulation and development
- Preclinical research
- Investigational New Drug
- Clinical trials
- New Drug Application [29]
- Approval

Step 1 Target Identification and Validation: Target identification and validation kicks off the whole drug discovery process. Naturally occurring cellular or modular structures that appear to play an important role in pathogenicity or disease progression are normally targets for therapeutics. A good target needs to be efficacious, safe and be accessible by the drug molecule/meet clinical needs of the prospective patient. Following identification of the drug target, a systematic validation approach should be adhered to for the mode of action of lead candidate to be assessed for efficacy. The approach itself depends on the therapeutic area, but has a set of general principles that include disease association, preclinical evidence in key cells, preclinical evidence in intact systems (i.e. transgenic animals), and literature survey and competitor information [30-34].

Step 2 Hit Identification and Validation: The obvious next step is to identify whether the small molecule leads have the desired effect against the identified targets. There are a number of approaches by which hits can be identified, including high-throughput screening, knowledge-based approaches, and virtual screening. After initial screening, validation of hits is required, and again there are a few options to choose from.

Step 3 Moving from a Hit to a Lead [35-36]: After several hit series has been established, the aim at this point is the refinement of each hit series in order to produce more selective compounds. Multiple series should be worked on in tandem, as it is likely that some hit series will fail, often due to particular characteristics of the series. Focusing on multiple structurally different sets of hit series will help to offset this possibility.

Step 4 Lead Optimization: At this stage, the aim is to maintain the desired properties of lead compounds while improving on possible deficiencies of their structures to produce a preclinical drug candidate. This stage can be used to find out whether your drug metabolizes in the right area of the body or whether there are currently any side effects that are cause for concern. For this process, an integrated approach is recommended. The combination of specialists in computational chemistry, medical chemistry, drug metabolism, and other areas can provide unique insights into this late stage of the process.

Step 5 Late Lead Optimization [37]: Before progression to preclinical and clinical trials, late-stage optimization, in which further pharmacological safety of a lead compound is assessed, is a vital step. If this stage is overlooked, problems in efficacy, pharmacokinetics, and safety are more likely to occur later in drug development. Safety optimization is a core stage; the aims are to identify and progress the leads with the best overall safety profile, remove the most toxic leads, and establish a well-characterized hazard and translational risk profile to enable further *in-vitro* tests.

***In-vitro* Studies:** *In-vitro* drug metabolism studies play a dual role from drug discovery to preclinical development. By analyzing the objectives of each type of study, the question of whether to apply good laboratory practices (GLP) requirements is clarified. This review outlines the various *in-vitro* techniques available and categorizes the goals for which they are applied as either supporting drug

discovery or influencing decisions of clinical safety. Based on this categorization, it is proposed that studies performed to explore the utility of a potential drug candidate be conducted non-GLP, while studies used to support IND and post-IND submissions are considered for GLP.

***In-vivo* Studies:** *In-vivo* studies are crucial in drug development for evaluating a drug's pharmacokinetic and pharmacodynamic characteristics. They are essential because *in-vitro* studies do not possess the ability to provide quantitative results of absorption, distribution, metabolism, and excretion in animal and human models. An animal model should be considered based on the physiological and biochemical similarities between the animal model and humans, in addition to the underlying mechanisms of drug absorption, distribution, metabolism, and excretion in the animal. Many semi-invasive and non-invasive techniques, such as MRI and microdialysis, have recently replaced older techniques, such as skin blistering, for collecting *in-vivo* data. However, much work is still needed to advance animal study data to better resemble human clinical trials.

Stimulation *In-silico*: The term '*in-silico'* is a modern word usually used to mean experimentation performed by a computer and is related to the more commonly known biological terms *in-vivo* and *in-vitro.* The history of the '*in-silico'* term is poorly defined, with several researchers claiming their role in its origination.

However, some of the earliest published examples of the word include the use by Sieburg (1990) and Danchin *et al.* (1991). In a more recent book, Danchin (2002) provides a quotation that offers a concise and cogent depiction of the potential of computational tools in chemistry, biology, and pharmacology:

Informatics is a real aid to discovery when analyzing biological functions. I was convinced of the potential of the computational approach, which I called *in-silico*, to underline its importance as a complement to *in-vivo* and *in-vitro* experimentation. *In-silico* pharmacology (also known as computational therapeutics and computational pharmacology) is a rapidly growing area that globally covers developing techniques for using software to capture, analyze and integrate biological and medical data from diverse sources. More specifically, it defines the use of this information in creating computational models or simulations that can be used to make predictions suggest hypotheses, and ultimately provide discoveries or advances in medicine and therapeutics.

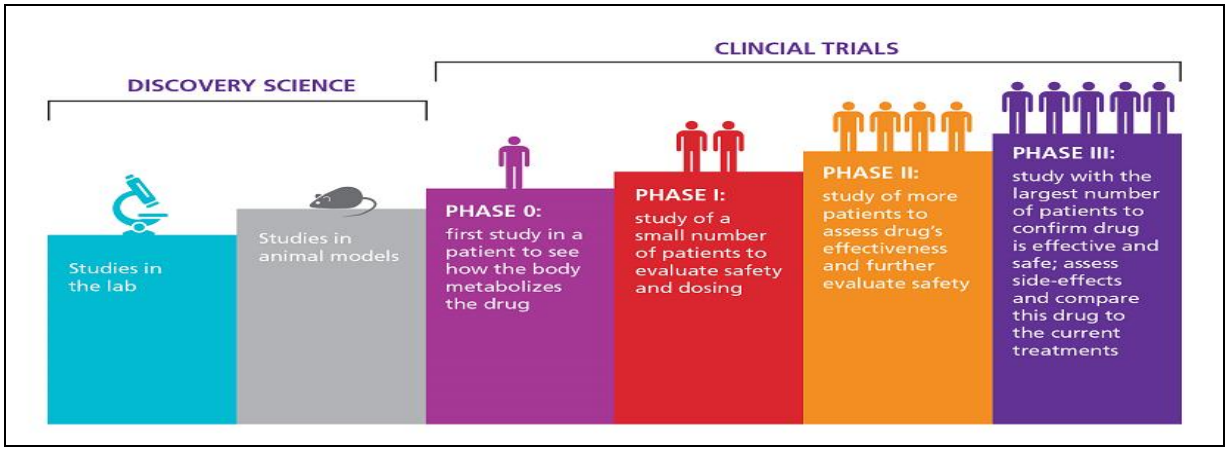

FIG. 2: STAGES OF DRUG DISCOVERY

Preclinical Research:

- Before testing a drug on people, researchers must find out whether it has the potential to cause serious harm to humans.
- The preclinical studies are conducted on animal models under laboratory conditions [38].
- The two types of preclinical research are:
- *In-vitro* these experiments are conducted outside the animals in controlled laboratory conditions shown in **Fig. 3.**

- *In-vivo:* These experiments are conducted inside the animals [39-40].
- Usually, preclinical studies are not very large. However, these studies must provide detailed information on dosing and toxicity levels [41]. After preclinical testing, researchers review their findings and decide whether the drug can be tested on people [42].
- The various experiments conducted during these studies include [43].
- Single dose toxicity studies.
- Repeated dose studies.
- Safety pharmacology studies.
- Carcinogenicity studies.
- Reproductive toxicity studies.

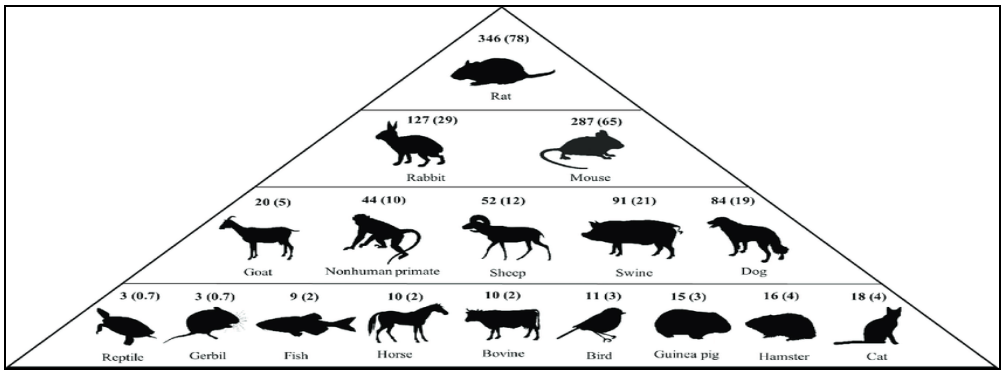

FIG. 3: ANIMALS FOR PRECLINICAL TRIALS

Preclinical Software [44]: The basics of preclinical drug development for neurodegenerative disease indications. After identifying a drug target and candidate compounds, several early activities, such as pharmacology, *in-vivo* efficacy, and experimental toxicology, can contribute to selecting a lead candidate for preclinical development.

These preclinical activities provide the basis for an Investigational New Drug (IND) application to the FDA for permission to initiate clinical testing in humans. ADME - absorption, distribution, metabolism, and excretion; API- active pharmaceutical ingredient; PK - pharmacokinetics; Prep -preparation; Tox - toxicity.

The parallel and inter-related activities contributing to preclinical development are summarized with color coding to denote related components: manufacturing (red), analytical (grey), documentation (orange), safety (blue), clinical (green) [45].

API, active pharmaceutical ingredient; CMC, chemistry, manufacturing, and controls; FDA, US Food and Drug Administration; GLP, good laboratory practice; GMP, good manufacturing practice; ICF, informed consent form; IND, Investigational New Drug; PK, pharmacokinetics [46].

Phase 0 [47]:

- Phase 0 implicates investigative, first-in-human (FIH) trials that are conducted according to FDA guidelines.
- Phase 0 trials besides termed human microdose studies.
- They have single sub-therapeutic doses given to 10 to 15 volunteers and give pharmacokinetic data or help with imaging specific targets without exerting pharmacological actions [48].
- Pharmaceutical industries perform Phase 0 studies to pick which drug applicants have the preeminent pharmacokinetic parameters in humans.

Investigational New Drug Application:

- INDA is applied after the Preclinical studies show success. If the INDA submission is accepted, the product is further forwarded to the clinical research studies (Phase I - Phase IV studies) shown in **Fig. 4.**

The FDA Groups INDs into three Different Types:

- **Investigator:** This is submitted by the physician responsible for initiating and investigating. The same physician will manage the investigational drug's administration and/or dispensing. This type of application is typically requested for the study of an unapproved drug, an approved drug for use in an unlicensed indication, or a different patient population.
- **Emergency:** An emergency use IND enables the regulator (FDA) to authorize the use of an investigational drug in an urgent situation without the obligation to submit an IND by 21 CFR, Sec. 312.23 or Sec. 312.20. This application is used for patients who do not meet existing clinical study criteria, or in situations where an approved clinical protocol doesn't exist [49].
- **Treatment:** This type of IND application is submitted to gain access to an experimental drug that has shown promise in clinical trials for treating a serious or life-threatening condition. The final clinical work is completed, and the FDA reviews the new drug application.
- An IND can be categorized as either "commercial" or "research". For an IND application, key areas must be covered; animal model pharmacology and toxicology studies, manufacturing information, clinical study protocols and investigator information [50].
- The IND sponsor must wait 30 days before starting clinical trials – this delayed period allows regulators to review the information contained within the IND application.

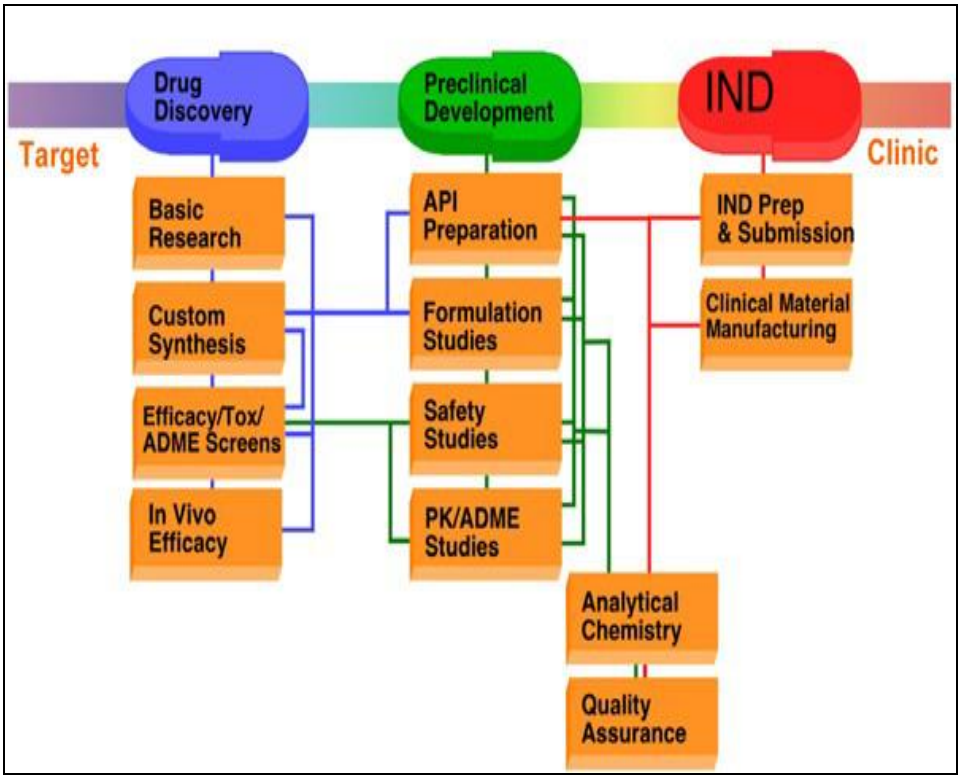

FIG. 4 : INVESTIGATIONAL NEW DRUG APPLICATION

Clinical Research: 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 [51].

"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 clinical research phase and begin the.

Investigational New Drug Process (IND), a process they must go through before clinical research begins [52-54] shown in **Fig. 5.**

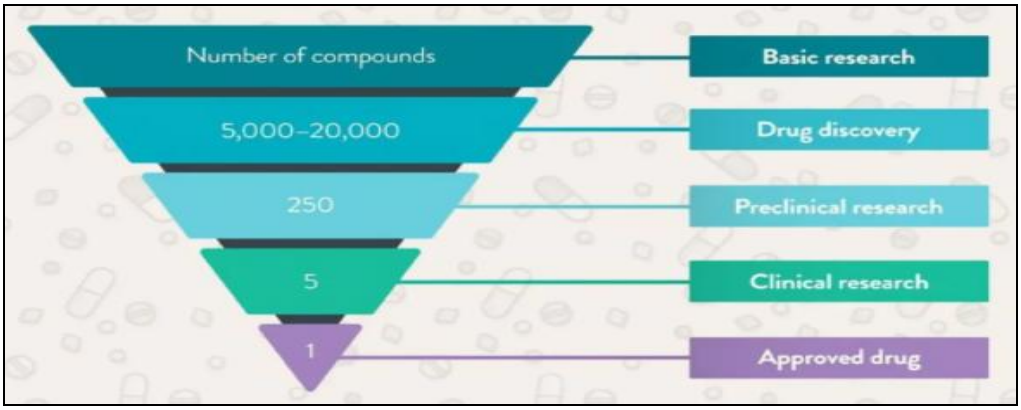

FIG. 5: THE ATTRITION OF COMPOUNDS AS THEY MOVE THROUGH THE DRUG DEVELOPMENT PROCESS

It has concluded with 3 phases:

Phase 1 (First in Humans):

- Trail Design:
- Patients: 20 to 100 normal healthy volunteer subjects in a single center 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 [55].
- 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% [56].

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
- Purpose: Efficacy and side effects
- Type of Study: Randomized, placebo or active control, parallel double-blinded study, single or multiple doses,
- multicenter [57]
- Purpose:
- Dose range finding (Minimum and maximum effective dose) [58]
- 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 33 [59]

Phase 3 (Therapeutic Confirmatory) – Pivotal Trails:

- Trail Design:
- Patients: Several 1000 to 3,000 patients with the targeted disease/condition [60-64].
- Length of Study: 1 to 4 years.
- Type of Study: Randomized, placebo or active control, parallel double-blinded study, multicenter.
- Purpose [65].

- Effectiveness (Large scale).
- Relative risk/benefit relationship.
- Long-term safety information – common side effects, drug interactions, age/rate/gender differences.
- Dosing (for labeling) is shown in **Fig. 6.**
- 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 [66].

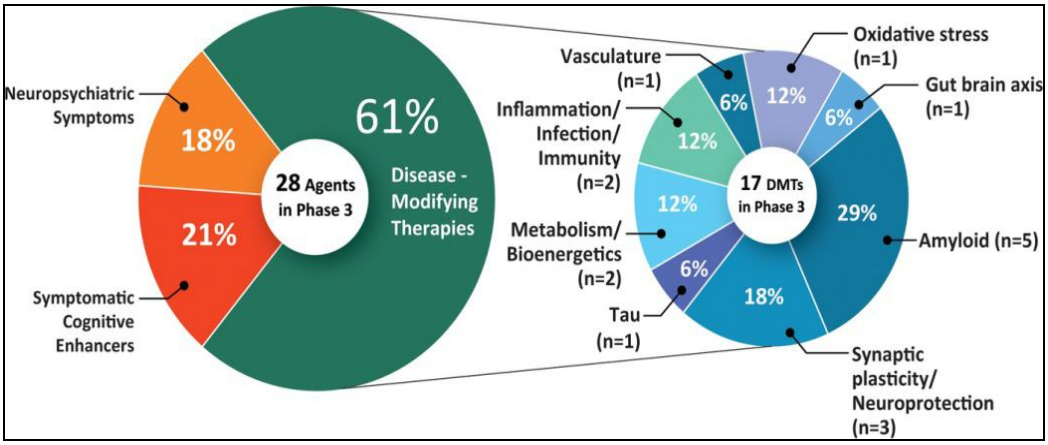

FIG. 6: SHOWING PHASE III DISTRIBUTION

New Drug Application:

- When a drug is developed with evidence throughout its history of research to show it is safe and effective for the intended use in the United States, the company can apply – the New Drug Application (NDA) – to have the drug commercialized and available for clinical application.
- NDA status enables the FDA to examine all submitted data on the drug to determine whether to approve or not approve the drug candidate based on its safety, specificity of effect, and efficacy of doses.
- Researchers design clinical trials to answer specific research questions about a medical product.
- These trials follow a specific study plan, called a protocol developed by the researcher or manufacturer [67].
- Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives. 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 analyzed.
- Clinical trials follow a typical series from early, small-scale Phase 1 studies to late-stage.

The application process for marketing authorization in the USA is known as a New Drug Application (NDA). In the European Union and other countries worldwide, this same process is referred to as a Marketing Authorisation Application (MAA) [68]. The regulatory authority is responsible for the scientific evaluation of the NDA or MAA. The goal of the application is to provide the regulator with enough information – gathered during preclinical and clinical studies – for them to be able to determine if:

- The drug is safe and effective as a treatment for the condition it has been developed for.
- The drug's therapeutic benefits outweigh the risks [69].
- The drug's labeling is fit-for-purpose and whether all required details are included.
- The methods used to manufacture the drug and measures to ensure the drug's quality are satisfactory.

Biologics License Application: The approval of biological products in the USA falls under the provisions of the Public Health Service (PHS) Act. The Act requires the manufacturer of the biologic to hold a license for that product. A Biologics License Application (BLA) must be submitted for therapeutic biological products including (but not limited to); monoclonal antibodies (for *in-vivo* use), cytokines, growth factors, enzymes, immunomodulators, [70] proteins and non-vaccine therapeutic immunotherapies.

Product Launch: Once the drug receives approval from the relevant regulatory authority, numerous activities will need to be initiated to prepare for the product launch. These include:

- Manufacturing scale-up and serialization.
- Printing of final product label information, packaging and artwork.
- Product storage, shipping and distribution arrangements.
- Production staff and quality team availability.

Regulatory Review, Approval and Post-Marketing Safety Surveillance:

Post-marketing Safety Surveillance: Post-marketing safety surveillance is the term used for the monitoring of a drug after it has received approval and has reached the market. It is designed to evaluate the long-term safety and efficacy of a drug, potential "real-world" problems with formulation, and use for unapproved conditions or "off-label" (e.g. use in an age group or at a dosage outside of that advised in the product label).

Phase IV: Phase IV studies are conducted after approval of the drug has been granted.

Number of Participants: Several thousand. The volunteers will be diagnosed with the condition/disease the drug is approved to treat. The purpose of a Phase IV study is to obtain additional information about the long-term risks and benefits of taking a drug now that it is being more widely used. The "real-world" data can also help determine if there is scope to develop the drug further, for example, [71]:

- To explore the use of the drug for additional indications/ additional age groups.
- To develop an alternative route of administration.

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, Multicenter
- Purpose
- Perform Quality of Life Trails (QOL) trails
- Perform pharmaco-economic trials. Is the drug more effective than 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
- Pharmaceutical industries perform Phase 0 studies to pick which drug applicants have the preeminent pharmacokinetic parameters in humans [72].

Primary cell lines, patient-derived cell lines, and whole animal models. These screens are designed to find compounds that reverse a disease phenotype, such as death, protein aggregation, mutant protein expression, or cell proliferation, as examples in a more holistic cell model or organism.

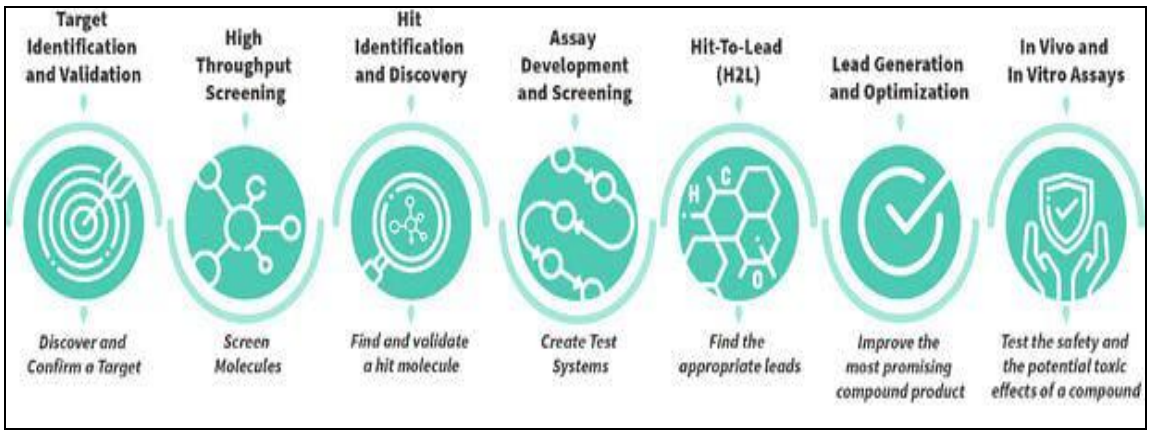

FIG. 7: DIFFERENT STEPS INVOLVED IN THE DEVELOPMENT OF THE DRUG

In many cases, the exact mechanism of action of hits from these screens is unknown and may require extensive target de-convolution experiments to ascertain. The growth of chemoproteomics has provided numerous strategies to identify drug targets in these cases [73].

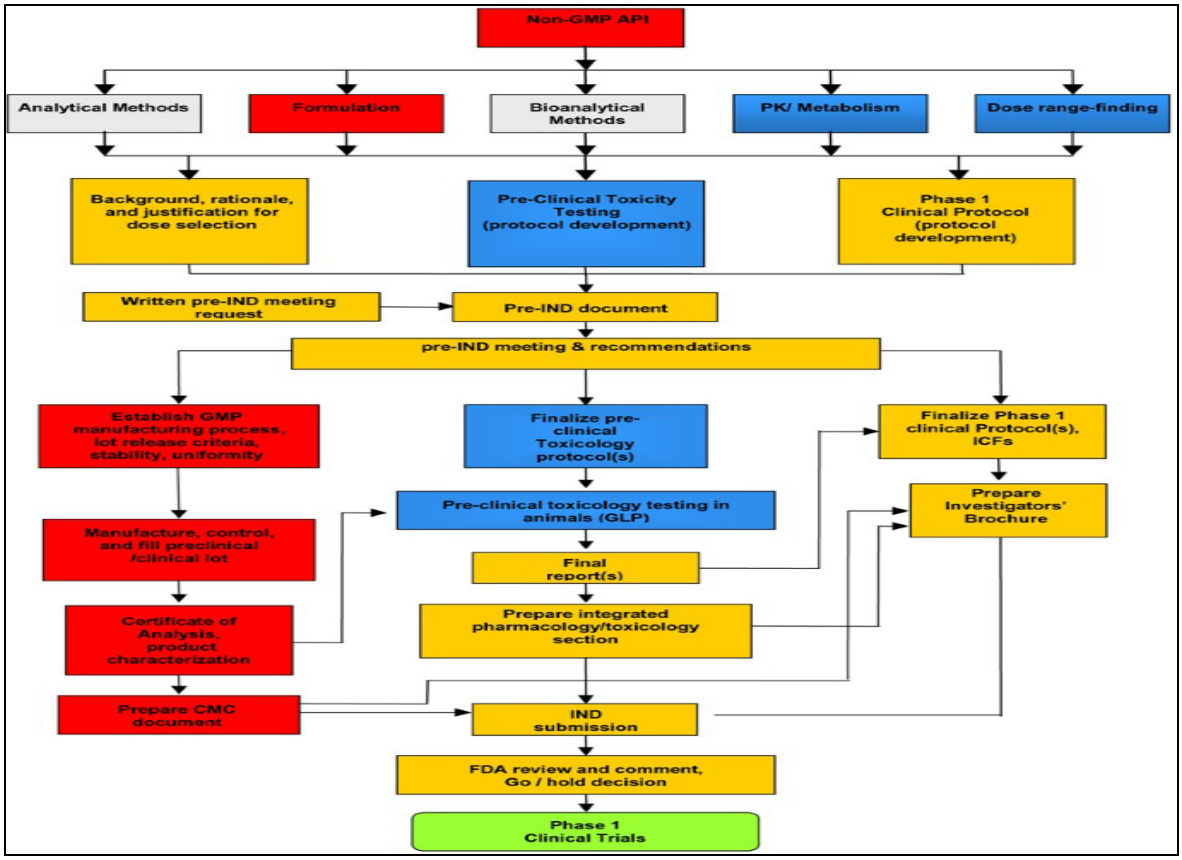

FIG. 8: APPROVAL PROCESS

Once a lead compound series has been established with sufficient target potency, selectivity, and favourable drug-like properties, one or two compounds will be proposed for drug development. The lead compound is the best, while the other will be designated as the "backup" [74-75].

Computational modelling innovations generally support these decisions.

CONCLUSION: The drug discovery and development of new medicines is a long, completed process. Research-based pharmaceutical companies are committed to advancing science and bringing new medicines to patients. Increased government and organizational support may help develop safer and cost-effective medicines. New drugs are an important part of modern medicine with the emergence of diseases.

A few decades ago, a disease such as peptic ulcers was an indication for major surgery [76]. The advent of new pharmacologic treatments and the 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. Physicians must understand the process of drug discovery and development. 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.

ACKNOWLEDGMENTS: The authors would like to acknowledge the management of Shri Ram Murti Smarak College of Engineering and Technology (Pharmacy), Bareilly, Uttar Pradesh, for supporting the basic research ideas and also for the resources provided.

CONFLICTS OF INTEREST: The authors declare no conflict of interest.

REFERENCE:

1. Pharmaceutical Research and Manufacturers Association (PREMA) Introduction to drug development process. 30th PREMA Anniversary 2015; 15(8): 48-59.
2. Martin S Lipsky and Lisa K Sharp: From Idea to Market: The Drug Approval Process. J Am Board Fam Med 2017; 21(2): 71-86.
3. Rungsiwiwut R, Virutamasen P & Pruksananonda K: Mesenchymal stem cells for restoring endometrial function: An infertility perspective. Reproductive Medicine and Biology 2021; 20(1): 13–19.
4. Brown C, McKee C, Bakshi S, Walker K, Hakman E, Halassy S, Svinarich D, Dodds R, Govind CK & Chaudhry GR: Mesenchymal stem cells: Cell therapy and regeneration potential. Journal of Tissue Engineering and Regenerative Medicine 2019; 13(9): 1738–1755.
5. Andrzejewska A, Lukomska B & Janowski M: Concise Review: Mesenchymal Stem Cells: From Roots to Boost. Stem Cells (Dayton, Ohio) 2019; 37(7): 855–864.
6. Ling MP, Lee SDS, Farhana A, Alzahrani B & Ali MS: Photoreceptor Therapy: Generation of Neurosphere-like Cells from Human Mesenchymal Stem Cells Expressing Erythropoietin. Sains Malaysiana 2020; 49(1): 113-119.
7. Naji A, Eitoku M, Favier B, Deschaseaux F, Rouas-Freiss N & Suganuma N: Biological functions of mesenchymal stem cells and clinical implications. Cellular and molecular life sciences: CMLS 2019; 76(17): 3323–3348.
8. Cozene B, Sadanandan N, Farooq J, Kingsbury C, Park YJ, Wang ZJ & Borlongan CV: Mesenchymal Stem Cell-Induced Anti-Neuroinflammation Against Traumatic Brain Injury. Cell Transplantation 2021; 30: 09636897211035715.
9. Chen C, Ai Q, Chu S, Zhang Z, Zhou X, Luo P & Chen N: IMM-H004 protects against oxygen-glucose deprivation/reperfusion injury to BV2 microglia partly by modulating CKLF1 involved in microglia polarization. International Immunopharmacology 2019; 70: 69-79.
10. Bacherini D, Maggi L, Sodi A, Vannozzi L, Mazzoni A, Capone M & Liotta F: CD3+ CD4-CD8- Double-Negative Lymphocytes Are Increased In The Aqueous Humour Of Patients Affected By Retinitis Pigmentosa: Their Possible Role In Mediating Inflammation 2022.
11. Antunes MS, Cattelan Souza L, Ladd FVL, Ladd AABL, Moreira AL, Bortolotto VC & Boeira SP: Hesperidin ameliorates anxiety-depressive-like behavior in 6-OHDA model of Parkinson's disease by regulating striatal cytokine and neurotrophic factors levels and dopaminergic innervation loss in the striatum of mice. Molecular Neurobiology 2020; 57(7): 3027-3041.
12. Martínez-Pinilla E, Rico AJ, Rivas-Santisteban R, Lill J, Rod E, Navarro G & Franco R: Expression of GPR55 and either cannabinoid CB1 or CB2 heteroreceptor complexes in the caudate, putamen, and accumbens nuclei of control, parkinsonian, and dyskinetic non-human primates. Brain Structure and Function 2020; 225(7): 2153-2164.
13. Lyu J, Jiang X, Leak RK, Shi Y, Hu X & Chen J: Microglial responses to brain injury and disease: functional diversity and new opportunities. Translational Stroke Research 2021; 12(3): 474-495.
14. Paul R, Nath J, Paul S, Mazumder MK, Phukan BC, Roy R & Borah A: Suggesting 7, 8-dihydroxyflavone as a promising nutraceutical against CNS disorders. Neurochemistry International 2021; 148, 105068.
15. Catorce MN & Gevorkian G: Evaluation of Anti-inflammatory Nutraceuticals in LPS-induced Mouse Neuroinflammation Model: An Update. Current Neuropharmacology 2020; 18(7): 636-654.
16. Kaniowska D, Wenk K, Rademacher P, Weiss R, Fabian C, Schulz I & Jaimes Y: Extracellular Vesicles of Mesenchymal Stromal Cells Can be Taken up by Microglial Cells and Partially Prevent The Stimulation Induced by β-Amyloid. Stem Cell Reviews and Reports 2022; 1-14.
17. Shin JY & Lee PH: Mesenchymal stem cells modulate misfolded α-synuclein in parkinsonian disorders: a multitarget disease-modifying strategy. Stem Cell Research 2020; 47: 101908.
18. Dunbar H, Weiss DJ, Rolandsson Enes S, Laffey JG & English K: The inflammatory lung microenvironment; a key mediator in msc licensing. Cells 2021; 10(11): 2982.
19. Liu Q & Lu D: Mesenchymal stem cells-macrophage crosstalk and the maintenance of inflammatory microenvironment homeostasis. Frontiers in Cell and Developmental Biology 2021; 9: 1628.
20. Song WJ, Li Q, Ryu MO, Nam A, An JH, Jung YC & Youn HY: Canine adipose tissuederived mesenchymal stem cells pre-treated with TNFalpha enhance immunomodulatory effects in inflammatory bowel disease in mice. Research in Veterinary Science 2019; 125: 176-184.
21. An JH, Li Q, Ryu MO, Nam AR, Bhang DH, Jung YC & Youn HY: TSG-6 in extracellular vesicles from canine mesenchymal stem/stromal is a major factor in relieving DSS-induced colitis. PLoS One 2020; 15(2): e0220756.
22. Song W J, Li Q, Ryu MO, Nam A, An J H, Jung YC & Youn HY: Canine adipose tissue-derived mesenchymal stem cells pre-treated with TNF-alpha enhance immunomodulatory effects in inflammatory bowel disease

in mice. Research in Veterinary Science 2019; 125: 176-184.
23. Watanabe Y, Tsuchiya A, Seino S, Kawata Y, Kojima Y, Ikarashi S & Terai S: Mesenchymal stem cells and induced bone marrow-derived macrophages synergistically improve liver fibrosis in mice. Stem Cells Translational Medicine 2019; 8(3): 271-284.
24. Zhang B, Yang L, Zeng Z, Feng Y, Wang X, Wu X & He TC: Leptin potentiates BMP9-induced osteogenic differentiation of mesenchymal stem cells through the activation of JAK/STAT signaling. Stem cells and development 2020; 29(8): 498-510.
25. Hu B, Lv X, Chen H, Xue P, Gao B, Wang X & Cao X: Sensory nerves regulate mesenchymal stromal cell lineage commitment by tuning sympathetic tones. The Journal of Clinical Investigation 2020; 130(7): 3483-3498.
26. Zhang Z, Liu J, Zeng Z, Fan J, Huang S, Zhang L & He TC: lncRNA Rmst acts as an important mediator of BMP9-induced osteogenic differentiation of mesenchymal stem cells (MSCs) by antagonizing Notch-targeting microRNAs. Aging (Albany NY) 2019; 11(24): 12476.
27. Ghasemi A, Saeidi J, Azimi-Nejad M & Hashemy SI: Leptin-induced signaling pathways in cancer cell migration and invasion. Cellular Oncology 2019; 42(3): 243-260.
28. Cetin I & Topçul M: Can mesenchymal stem cells be used to treat COVID 19 induced pneumonia. Biomedical Reports 2020; 13(6): 1-1.
29. Zhou Y, Yamamoto Y, Xiao Z & Ochiya T: The immunomodulatory functions of mesenchymal stromal/stem cells mediated via paracrine activity. Journal of clinical medicine 2019; 8(7): 1025.
30. Zoehler B, Fracaro L, Senegaglia AC & Bicalho MDG: Infusion of mesenchymal stem cells to treat graft versus host disease: the role of HLA-G and the impact of its polymorphisms. Stem Cell Reviews and Reports 2020; 16(3): 459-471.
31. Marino L, Castaldi M A, Rosamilio R, Ragni E, Vitolo R, Fulgione C & Selleri C: Mesenchymal stem cells from the Wharton's jelly of the human umbilical cord: biological properties and therapeutic potential. International Journal of Stem Cells 2019; 12(2): 218.
32. Barrett J & Galipeau J: Mesenchymal Stem Cells: From Bench to Bedside and Back. Cell and Gene Therapies 2019; 219-242.
33. Wang S, Zhu R, Li H, Li J, Han Q & Zhao RC: Mesenchymal stem cells and immune disorders: from basic science to clinical transition. Frontiers of Medicine 2019; 13(2): 138-151.
34. Wang S, Zhu R, Li H, Li J, Han Q & Zhao RC: Mesenchymal stem cells and immune disorders: from basic science to clinical transition. Frontiers of medicine, 2019; 13(2): 138-151.
35. Amor IB, Lainas P, Kassir R, Chenaitia H, Dagher I & Gugenheim J: Treatment of complex recurrent fistula-in-ano by surgery combined to autologous bone marrow–derived mesenchymal stroma cells and platelet-rich plasma injection. Inter J of Color Disea 2019; 34(10): 1795-1799.
36. Salmenkari HANNE, Laitinen A, Forsgård R A, Holappa M, Linden J, Pasanen L & Nystedt J: The use of unlicensed bone marrow–derived platelet lysate–expanded mesenchymal stromal cells in colitis: a pre-clinical study. Cytotherapy 2019; 21(2): 175-188.
37. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall R S & Manson JJ: COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet 2020; 395(10229): 1033-1034.
38. Gundestrup AK, Lynggaard CD, Forner L, Heino TJ, Jakobsen KK, Fischer-Nielsen A & von Buchwald C: Mesenchymal stem cell therapy for osteoradionecrosis of the mandible: a systematic review of preclinical and human studies. Stem Cell Reviews and Reports 2020; 16(6): 1208-1221.
39. Crippa S, Santi L, Bosotti R, Porro G & Bernardo ME: Bone marrow-derived mesenchymal stromal cells: a novel target to optimize hematopoietic stem cell transplantation protocols in hematological malignancies and rare genetic disorders. Journal of Clinical Medicine 2019; 9(1): 2.
40. Mukherjee S, Baidya A & Barik S: New Approaches in Cancer Research: Stem Cell Research, Translational Research, Immunotherapy and Others. In Cancer Diagnostics and Therapeutics 2022; 377-405. Springer Singapore.
41. Farrokhi AS, Zarnani AH & Moazzeni SM: Mesenchymal stem cells induce expansion of regulatory T cells in abortion-prone mice. Reproduction 2021; 161(4): 477-487.
42. de Freitas CL, Polonio CM, Brandão WN, Rossato C, Zanluqui NG, de Oliveira LG & Peron JPS: Human Fallopian Tube–Derived Mesenchymal Stem Cells Inhibit Experimental Autoimmune Encephalomyelitis by Suppressing Th1/Th17 Activation and Migration to Central Nervous System. Stem Cell Reviews and Reports 2021; 1-17.
43. Jia H, He J, Zhao L, Hsu CC, Zhao X, Du Y & Ye H: Combination of stem cell therapy and acupuncture to treat ischemic stroke: a prospective review. Stem Cell Research & Therapy 2022; 13(1): 1-16.
44. Pradeep KV: Importance of ADME and Bioanalysis in the Drug Discovery. J Bioequiv Availab 2013; 5: 31.
45. Baumeister AA: On the Exploitation of Serendipity in Drug Discovery. Clin Exp Pharmacol 2013; 3: 121.
46. Cheng SB. The Nervous System: An Ideal Therapeutic Target for Anti-Schistosomal Drug Discovery. Tropical Medicine & Surgery 2013; 1: 103.
47. Ravindran S: Significance of Biotransformation in Drug Discovery and Development. J Biotechnol Biomaterial 2012; 13-05.
48. Bhakta S: An Integration of Interdisciplinary Translational Research in Anti-TB Drug Discovery: Out of the University Research Laboratories to Combat Mycobacterium tuberculosis. Mol Biol 2013; 2: 108.
49. Pomin VH. Current Status of Fucanomics and Galactanomics in Drug Discovery and Glycomics. J Glycobiol 2013; 2: 104.
50. Cheng F and Vijaykumar S: Applications of Artificial Neural Network Modeling in Drug Discovery. Clin Exp Pharmacol 2012; 2: 113.
51. Deshmukh R. Modeling and Simulation in Drug Discovery and Development. J Bioequiv Availab 2012; 4: 27-28.
52. Persaud-Sharma V and Zhou SF. Drug Repositioning: A Faster Path to Drug Discovery. Adv Pharmacoepidem Drug Safety 2012; 1: 117.
53. Sánchez HEP. Exploitation of Massively Parallel Architectures for Drug Discovery. Drug Des 2012; 2: 108.
54. Young W: Patientspecific Induced Pluripotent Stem Cells as a Platform for Disease Modeling, Drug Discovery and Precision Personalized Medicine. J Stem Cell Res Ther 2012; 10: 010.
55. Yang Z and Marotta F: Pharmacometabolomics in Drug Discovery & Development: Applications and Challenges. Metabolomics 2012; 2: 122.
56. Patil SA: Role of Medicinal Chemist in the Modern Drug Discovery and Development. Organic Chem Curr Res 2012; 1: 110.

57. Medina-Franco JL: Drug Discovery with Novel Chemical Libraries. Drug Des 2012; 1: 105.
58. Liu Y: Renaissance of Marine Natural Product Drug Discovery and Development. J Marine Sci Res Development 2012; 2: 106.
59. Gonzalez-Sabin J: Natural Products: Back to the Future in Drug Discovery. Biochem Pharma Los Angel 2012; 1: 12.
60. Pascu ML: The Laser Use in Generating New Species of Medicines with Antitumor and Antibacterial Properties: New Processes in Drug Discovery. Biochem Pharmacol (Los Angel) 2012; 1: 111.
61. Elzahabi HAS: Virtual Screening in Drug Discovery, A Topic between Believe and Reality. Biochem Pharmacol (Los Angel) 2012; 1: 103.
62. Nishant T: Role of Pharmacokinetic Studies in Drug Discovery. J Bioequiv Availab 2011; 3: 263-267.
63. Celikyurt IK. Thought-provoking Molecules for Drug Discovery: antioxidants. Pharm Anal Acta 2011; 3-001.
64. Fortuna A: *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; 2:224.
65. Torzewski J: Road Map to Drug Discovery and Development–Inhibiting C-reactive protein for the Treatment of Cardiovascular Disease. J Bioequiv Availab 2011; 1:001.
66. "The drug development process: Step 3: Clinical research"."The drug development process: Step 3: Clinical research". Swinney DC, Anthony J (July 2011). "How were new medicines discovered?". Nature Reviews. Drug
67. Jacobson KA (December 2015). "New paradigms in GPCR drug discovery" Rask-Andersen M, Almén MS, Schiöth HB (August 2011). "Trends in the exploitation of novel drug Chen, Ya; Kirchmair, Johannes (6 September 2020). ”Cheminformatics in natural product-baseddrugdiscovery" (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7757247) Molecular Informatics. 39 (12):25-89.
68. Rester U: (July 2008). "From virtuality to reality – Virtual screening in lead discovery and lead optimization: a medicinal chemistry perspective". Current Opinion in Drug Discovery & Development. 11. Borhani DW, Shaw DE (January 2012).
69. Shastri PN: FDA Expedited Drug Development Programs. J Pharmacovigil 2016; 4: 156.
70. Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors for the Treatment of Advanced Non-Small Cell Lung Cancer. Biochem Anal Biochem 2016; 5: 258.
71. Yu X Nagai J & Khakh BS: Improved tools to study astrocytes. Nature Reviews Neuroscience 2020; 21(3): 121-138.
72. Yong HY, Rawji KS, Ghorbani S, Xue M & Yong VW: The benefits of neuroinflammation for the repair of the injured central nervous system. Cellular & Molecular Immunology 2019; 16(6): 540-546
73. Zhao Y: Towards structural based drug development for ebola virus disease. j chem biol ther. geert er: selection strategy of *in-vivo* models for ophthalmic drug development in diabetic retinopathy. J Mol Genet Med 2016; 10: 202.

How to cite this article:
Varshney T, Saini S and Aafreen: Drug discovery and developnment: a basic approches to improve the success of drug discovery. Int J Pharm Sci & Res 2023; 14(7):3314-26. doi: 10.13040/IJPSR.0975-8232.14(7).3314-26.