ORIGINAL RESEARCH

The Drug Development Process: From Discovery to Market

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ABSTRACT
The drug development process is a meticulously structured journey aimed at translating scientific discoveries into safe and effective medications for the benefit of patients. It is a multifaceted and highly regulated endeavor. This article provides a detailed description of the key stages involved in drug development, emphasizing the intricate balance between innovation and rigorous evaluation. The process commences with the identification and validation of therapeutic targets, often specific proteins or biological processes implicated in diseases. Scientists then embark on the discovery of compounds, which may include small molecules, biologics, or gene therapies, with the potential to interact with these targets.
Keywords: Clinical Trials, Drug Development, Therapeutic targets, Validation, New Drug Application, Regulatory Review

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. The drug development process is a complex and highly regulated journey that pharmaceutical companies and researchers undertake to bring new medications and treatments to the market. This process involves multiple stages, rigorous testing, and extensive clinical trials to ensure the safety and efficacy of drugs before they can be prescribed to patients. Research across all the therapeutic domains shows that it typically takes substantially longer than 12 years to produce a new drug, from target identification to approval in the market[1,2].

The process of drug development is a complex and lengthy one that involves several stages, each with its own specific goals and challenges. The key to effective drug development is identifying and capturing the clinical spectrum of disease as well as the precise function that a possible therapeutic target has in the disease[3]. Following more precise research, the LEAD compound—a molecule that binds to the target specifically and selectively and can alter its usual mechanism of action—was chosen. The latter is logically altered to enhance biological activity and ADME (absorption, distribution, metabolism, and excretion): preclinical and clinical phases will begin in the event that a compound deemed promising is discovered during screening. Once the clinical trials are completed, the drug must receive approval from either the European Medicines Agency (EMA) or the Food and Drug Administration (FDA) before it can be sold. Figure 1 shows the schematic representation of the Drug Development process. The Oxford Dictionary of Biochemistry and Molecular Biology defines a drug target as “a biological entity (usually a protein or gene) that interacts with, and whose activity is modulated by, a particular compound.” The drug development process is a testament to human ingenuity and the pursuit of improving healthcare outcomes. In this exploration of the Drug Development Process we will delve into the various stages and key players involved in this journey, shedding light on the rigorous testing, meticulous research, and rigorous regulations that underpin the development of life-changing medications. This topic is not only of interest to scientists and healthcare professionals but also vital for anyone who wants to understand the process behind the pills they take and the treatments they receive.

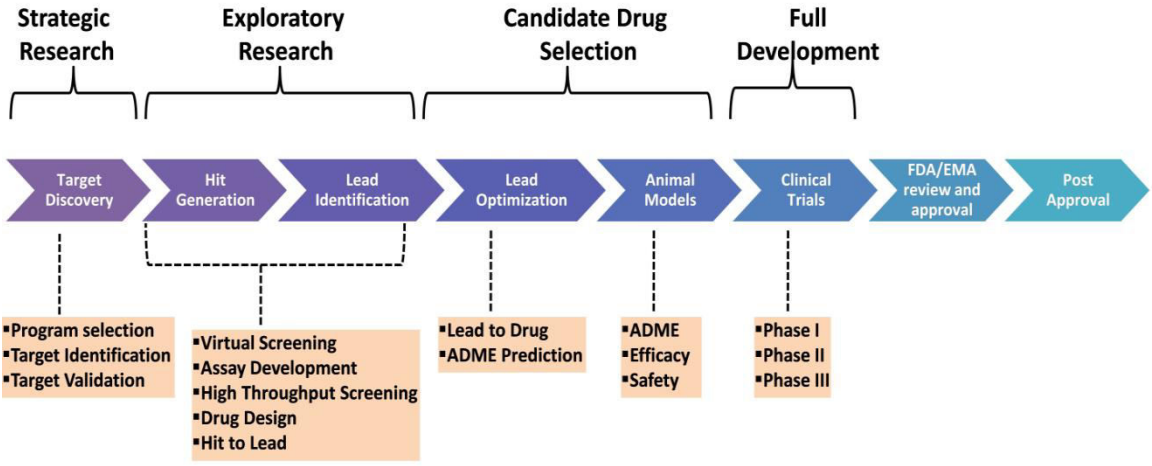


Figure 1: Schematic representation of Drug Discovery Process. (Adapted from Duelen, R. et al (2019). Medicinal Biotechnology for Disease Modeling, Clinical Therapy, and Drug Discovery and Development. In: Matei, F., Zirra, D. (eds) Introduction to Biotech Entrepreneurship: From Idea to Business. Springer, Cham. https://doi.org/10.1007/978-3-030-22141-6_5)

This article deals with the overview of the key stages and considerations involved in drug development process from its inception to clinical application. The article aims to elucidate the various stages involved in the drug development process. By delving into the stages, challenges faced, recent advances, innovations, future trends and prospects we try to provide a comprehensive review on this vital process.

STAGES OF DRUG DEVELOPMENT PROCESS

The drug development process typically consists of several stages, each with its own specific goals, activities, and challenges. These stages are designed to ensure that a new drug is safe and effective before it reaches the market.

DISCOVERY AND PRECLINICAL RESEARCH

This is the essential step which involves identifying potential drug candidates, conducting initial testing in the laboratory and in animal models, and gathering data to support the safety and efficacy of a drug before it can move on to clinical trials in humans. The various steps involved in this stage are:

TARGET IDENTIFICATION AND VALIDATION

Target selection is one of the most important decision and investment which a researcher and companies has to make in the drug development process. The drug candidate is selected based on its broad spectrum applications and its ability to change according to the conditions. Appropriate target identification methods could assist scientists shorten the time and effort they expend at this stage. Currently, the methods for drug target have increased enormously and the desirable drug targets have increased many folds. As a result, there is a need for highly sensitive and specific techniques that can account for the diversity of disease phenotypes in preclinical research before the commencement of expensive clinical trials and enable the early selection of suboptimal drug candidates in the drug discovery process[4,5].

STRATEGIES FOR TARGET IDENTIFICATION

The two major strategies followed by scientists include the deconvolution methods and bottom up strategy. Deconvolution methods play a crucial role in target identification in drug development, particularly in the early stages of drug discovery. It begins with the drug compound and then the targets are identified for it[6] whereas the bottom-up strategy goes through the process of screening of thousands of small drug molecule after the target is identified[7] (Lindsay). In both strategies the methods to be used are extremely important for target identification. These methods are classified into three categories: the scientific literature and databases, biological assay and machine based methods.

a) **Drug Databases:** Drug databases are invaluable resources in the field of pharmaceuticals and healthcare. They are essential for identifying potential drug candidates, understanding their mechanisms of action, and optimizing their properties. The significant drug databases included in Table 1 provided researchers with access to the historical data they require for drug development. These databases contained data on the toxicity, bioactivity, DNA sequences, 3D and 2D structures of the target proteins, and binding affinities of tiny pharmacological compounds.

Table 1: Drug Database and their URL used for Drug Development Process.

S.No.	Drug Database	URL
1.	PubChem	https://pubchem.ncbi.nlm.nih.gov/
2.	ChEMBL	https://www.ebi.ac.uk/chembl/
3.	ChemSpider	http://www.chemspider.com/
4.	DrugBank	https://go.drugbank.com/
5.	ZINC database	https://zinc.docking.org/
6.	ChemBank	https://pubchem.ncbi.nlm.nih.gov/source/ChemBank
7.	PDB (Protein Data Bank)	https://www.rcsb.org/
8.	KEGG (Kyoto Encyclopedia of Genes and Genomes)	https://www.genome.jp/kegg/
9.	Chemical Abstracts Service (CAS) Registry	https://www.cas.org/cas-data/cas-registry
10.	PharmGKB	https://www.pharmgkb.org/
11.	BindingDB	https://www.bindingdb.org/
12.	Comparative toxic genomic database	https://ctdbase.org/
13.	toxin and Toxin target database (T3DB)	http://www.t3db.ca/
14.	canSAR Database	https://cansar.ai/
15.	Therapeutic Target Database (TTD)	https://db.idrblab.net/ttd/
16.	SureChEMBL	https://www.surechembl.org/search/

These databases cater to various aspects of drug discovery, from compound identification and characterization to understanding their interactions with target proteins. Researchers often use a combination of these databases and other tools to streamline the drug discovery process, from target identification to lead optimization and beyond.

b) Biological assay:

Biological assays play a crucial role in target identification in drug development. These assays are designed to assess the activity, function, or interaction of potential drug targets (usually proteins) in response to various compounds. The key consideration for Assay development is three "Rs" (Relevance, Robustness and Reliability/Reproducibility).

Table 2: Commonly Used Biological Assays in Drug Development and their brief description.

S.No.	Biological Assays	Description
1.	**Binding Assays:**	
	Radio ligand Binding Assay[8]	Measures the binding affinity of a compound to a specific receptor or protein by using a radio labeled ligand.
	Fluorescence Polarization (FP) Assay[9]	Detects changes in fluorescence polarization when a fluorescently labeled ligand binds to its target protein.
	Surface Plasmon Resonance (SPR)[10]	Monitors real-time binding interactions by measuring changes in refractive index as molecules bind to a sensor surface.
	Isothermal Titration Calorimetry (ITC)[11]	Measures heat changes when a compound binds to a target protein, providing thermodynamic information about the interaction.
2.	**Enzyme Activity Assays:**	
	Enzyme Inhibition Assays[12,13]	Assess the ability of compounds to inhibit the enzymatic activity of a specific enzyme, often used for target validation.
	Enzyme Activation Assays[12,13]	Measure the ability of compounds to enhance enzyme activity, which can be relevant for certain drug targets.
3.	**Cell-Based Assays[14,15,16]:**	
	Reporter Gene Assays	Use genetically modified cells with reporter genes to assess the activation or inhibition of specific signaling pathways or transcription factors.
	Cell Viability Assays	Determine the effect of compounds on cell viability, often used for cytotoxicity testing.
	Functional Assays	Evaluate the functional response of cells or tissues to compounds, such as changes in ion flux, membrane potential, or cell signaling.
4.	**Protein-Protein Interaction (PPI) Assays:**	
	Co-immunoprecipitation (Co-IP)[17]	Identifies protein-protein interactions by immunoprecipitating a target protein along with its binding partners.
	Yeast Two-Hybrid Assay[18]	Screens for protein-protein interactions in yeast by detecting the

		reconstitution of a transcription factor.
	Bimolecular Fluorescence Complementation (BiFC)[19]	Utilizes split fluorescent proteins to visualize protein-protein interactions in live cells.
5.	**RNA Interference (RNAi) Screens:**	
	siRNA or shRNA Libraries[20]	Use small RNA molecules to selectively knock down gene expression to assess the impact on a cellular phenotype.
	CRISPR-Cas9 Screens[21]	Employ CRISPR technology to create gene knockout or knockdown cell lines for target identification.
6.	**Phenotypic Screens:**	
	High-Content Screening (HCS)[22]	Combines automated microscopy and image analysis to assess the effect of compounds on cellular phenotypes.
	Zebrafish or Drosophila Screens[23,24]	Use model organisms to screen for compounds that affect specific biological processes or pathways.
7.	**Microarray and RNA Sequencing (RNA-Seq)[25]:**	Analyze changes in gene expression profiles upon compound treatment to identify affected pathways or potential target genes.
8.	**Electrophysiological Assays[26]:**	Measure changes in ion channel activity in response to compounds using techniques like patch-clamp electrophysiology.
9.	**Proteomics and Mass Spectrometry[27]:**	Identify protein targets and post-translational modifications in response to compound treatment, providing insights into target engagement.

These biological assays are critical for both target identification and validation in drug development. By evaluating the effects of compounds on specific biological processes, researchers can identify potential drug targets and gain a deeper understanding of their roles in disease pathways. These assays are often used in combination with computational approaches to prioritize and validate targets for further drug discovery efforts.

c) Machine based methods:

Machine-based methods have become increasingly important in target identification in drug development. These methods leverage computational techniques and data analysis to identify potential drug targets based on various biological and chemical data sources.

Table 3: Commonly Used Machine Based Methods in Drug Development and their brief description.

S.No.	Machine Based Methods	Description
1.	**Machine Learning and Data Mining[28]:**	
	Classification Algorithms	Use supervised learning algorithms (e.g., random forests, support vector machines) to classify proteins as potential drug targets based on features such as gene expression patterns, sequence data, or functional annotations.
	Association Rule Mining	Discover associations between drugs, diseases, and biological targets by analyzing large-scale datasets like electronic health records and drug databases.
2.	**Network Analysis[29,30]:**	
	Protein-Protein Interaction (PPI) Networks	Analyze PPI networks to identify hub proteins and their interacting partners. Target proteins closely connected to disease-related proteins are potential drug targets.
	Functional Interaction Networks	Explore functional interactions and pathways by integrating protein interaction data, gene expression data, and pathway information to identify key proteins in disease processes.
3.	**Text Mining and Natural Language Processing (NLP):**	
	Literature Mining	Analyze scientific literature to extract information about disease-gene associations, protein functions, and potential drug targets mentioned in research articles.
	Drug-Target Interaction Prediction	Predict drug-target interactions by mining text from sources like drug labels, scientific publications, and patents.
4.	**Genomic and Transcriptomic Analysis[31]:**	
	Differential Gene Expression Analysis	Identify genes that are differentially expressed in disease versus healthy tissues to pinpoint potential drug targets.

	Pathway Analysis	Analyze pathway enrichment to identify key biological pathways associated with a disease and potential targets within those pathways.
5.	**Structural Biology and Molecular Docking[32]:**	
	Virtual Screening	Use molecular docking simulations to predict the binding affinity of small molecules to target proteins. High-affinity interactions can suggest potential drug candidates.
	Structure-Based Drug Design	Analyze protein structures and identify druggable sites or pockets that can guide the design of small molecule inhibitors.
6.	**Pharmacophore Modeling[33]:**	Develop pharmacophore models based on known drug-target interactions to identify similar compounds that could target the same proteins.
7.	**Deep Neural Networks (DNNs):**	Utilize deep learning models, such as convolutional neural networks (CNNs) and recurrent neural networks (RNNs), to analyze complex biological data, including genomic sequences and protein structures, for target identification.
8.	**Drug Repurposing and Computational Screening[30]:**	
	Virtual Screening	Employ machine learning algorithms to virtually screen large chemical libraries for potential drug candidates that may target specific proteins associated with a disease.
	Drug-Drug Interaction Prediction	Predict potential interactions between existing drugs and proteins associated with a disease, enabling drug repurposing.
9.	**Metabolomics and Metabolic Modeling[34]:**	Analyze metabolomic data to identify altered metabolic pathways in diseases and potential targets within those pathways.
10.	**Quantitative Structure-Activity Relationship (QSAR) Modeling:**	Develop QSAR models to predict the biological activity of chemical compounds against specific protein targets, aiding in target prioritization.

These machine-based methods are valuable for sifting through vast amounts of biological and chemical data to identify potential drug targets efficiently. They are often used in conjunction with experimental assays and other traditional approaches to enhance target identification in drug development.

VALIDATION OF DRUG TARGET

The process of target validation involves the demonstration of the functional role of the potential target in the disease phenotype. It is an essential step as it ensures that the chosen biological target is suitable for the therapeutic intervention. Figure 2 shows key steps or considerations to be taken for validating a target[35,36].

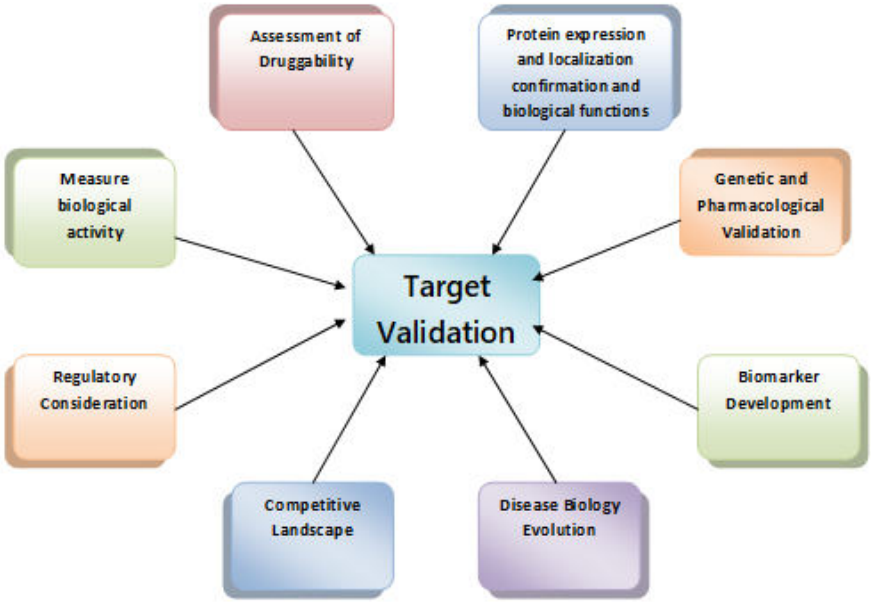


Figure 2: Key Considerations for Validating a Target

COMPOUND DISCOVERY AND TESTING

Scientists search for or design compounds (small molecules, antibodies, etc.) that can interact with the target and potentially treat the disease. These compounds are then tested in lab settings (in vitro) to assess their safety, efficacy, and mechanisms of action. The promising compounds are tested in animals (usually mice or rats) to further evaluate their safety and efficacy.

INVESTIGATIONAL NEW DRUG (IND) APPLICATION

Investigational New Drug (IND) application is a crucial step in the drug development process. It's a regulatory submission made to the regulatory bodies to initiate clinical trials of a new drug or biologic in humans. Every country has its own regulatory body. In certain nations, a single agency handles all aspects of drug regulation, including the approval of new drugs, granting manufacturing licenses, and inspecting manufacturing facilities. In the United States, for example, the FDA handles all aspects of drug regulation. Nonetheless, in certain nations, like India, not all duties are carried out by a single regulatory body; instead, state and centralized authorities share this accountability. In India IND application CT-04 is submitted to the Central Drugs Standard Control Organisation (CDSCO) via the SUGAM portal together with all necessary supporting documentation and the applicable government fee[37,38]. Before submitting an IND application, extensive preclinical research is conducted to gather data on the safety and efficacy of the investigational drug. This includes laboratory and animal studies to assess its potential risks and benefits. The IND application is a comprehensive document that includes detailed information about the drug and the proposed clinical trials. The IND application is a crucial milestone in drug development, as it allows researchers to move from preclinical studies to human trials. It also provides a framework for ongoing communication and collaboration between the drug developer and the regulatory agency to ensure the safety of trial participants and the integrity of the drug development process. It's worth noting that the specific requirements for an IND application may vary by country, as different regulatory agencies have their own processes and criteria for approval.

CLINICAL DEVELOPMENT

Clinical development is a critical phase in the drug development process where a potential new drug undergoes rigorous testing in human subjects through a series of clinical trials. These trials aim to assess the drug's safety, efficacy, and optimal dosing regimens, among other factors. Successful clinical development requires collaboration between pharmaceutical companies, clinical investigators, regulatory agencies, and other stakeholders. It is a resource-intensive and time-consuming process, with many drugs failing to progress beyond certain phases due to safety concerns or lack of efficacy. However, the successful completion of clinical development is a significant milestone in bringing a new drug to market and improving patient care[39-42]. There are three stages in the clinical process.

1. **Phase I - Safety and Dosing**: Phase I trials are the first step in testing a new drug in humans. They usually involve a small number of healthy volunteers or patients. The primary goal is to determine the drug's safety profile, including its side effects, and to establish the appropriate dosage range. These trials are often conducted in specialized research clinics. Safety and dosing assessments are crucial aspects of clinical development in drug development. (Figure 3)
2. **Phase II - Efficacy and Side Effects**: Phase II trials enroll a larger group of patients who have the condition the drug is intended to treat. These trials aim to evaluate the drug's effectiveness against the disease or condition, assess the optimal dose, and gather additional safety data. (Figure 3)
3. **Phase III - Confirmatory Efficacy**: Phase III trials are large-scale studies that involve a more extensive patient population. The primary objective is to confirm the drug's efficacy, safety, and side effect profile in a diverse patient group. These trials are often randomized and controlled and provide the pivotal data required for regulatory approval. (Figure 3)

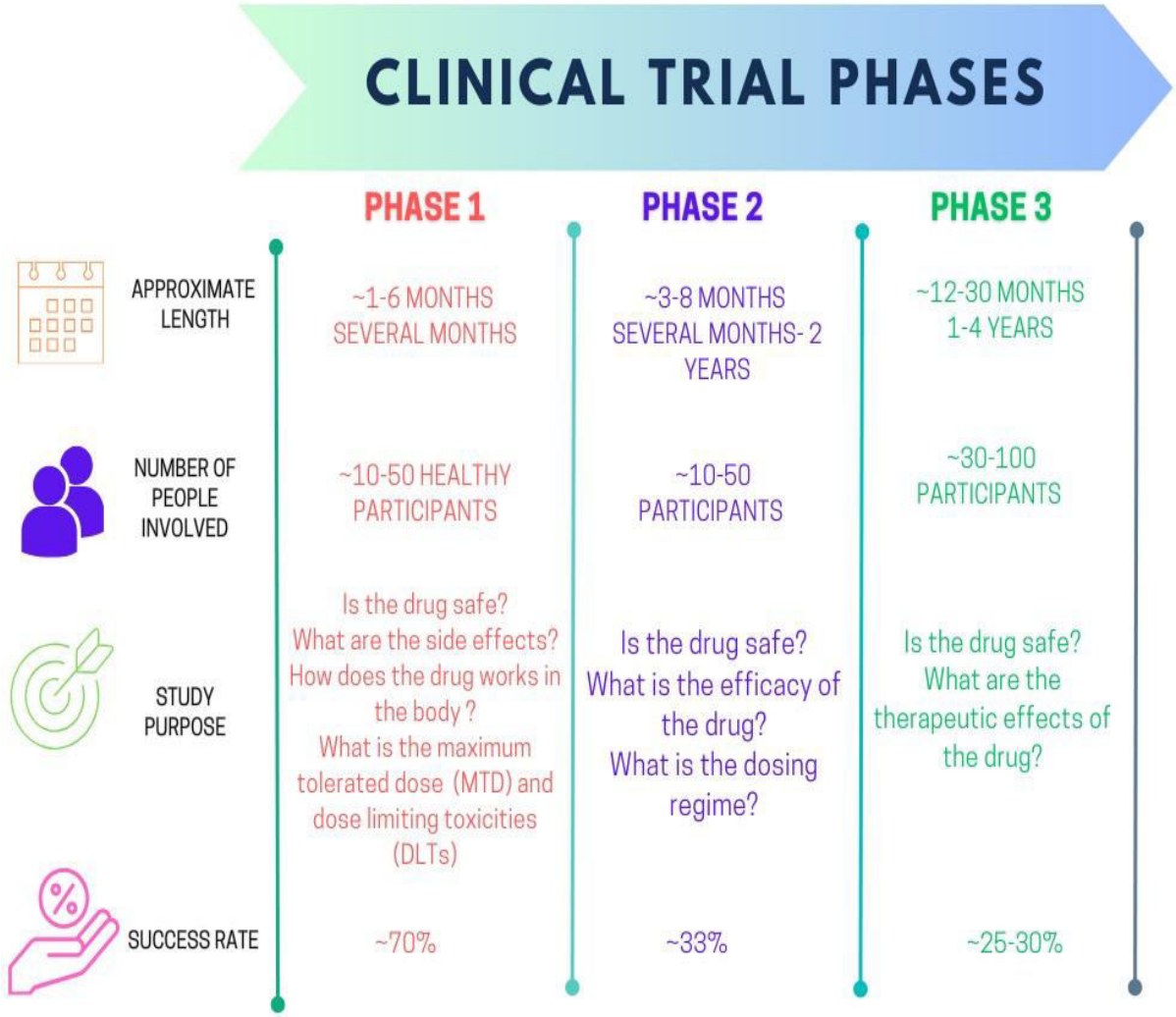


Figure 3: Process of Drug movement through Clinical Trials

NEW DRUG APPLICATION (NDA) SUBMISSION

The New Drug Application (NDA) submission is a crucial step in the drug development process. It represents the formal request to regulatory agencies, such as the U.S. Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA) in Europe, to review and approve a new pharmaceutical product for marketing and use. In India, the process for submitting a New Drug Application (NDA) is regulated by the Central Drugs Standard Control Organization (CDSCO), which is the national regulatory authority responsible for approving and regulating pharmaceuticals.

The NDA submission process in India is somewhat similar to that in other countries, but it has its own specific requirements and procedures. Before submitting an NDA in India, the pharmaceutical company or sponsor compiles all the necessary data, documents, and information related to the drug. This typically includes data from preclinical studies, clinical trials, chemistry, manufacturing, and quality control. The NDA submission must follow a specific format and content requirements, as outlined in Schedule Y of the Drugs and Cosmetics Rules. The Common Technical Document (CTD) is set of stipulations developed by International Council of Harmonization (ICH) to standardize applications to register new therapeutics. CTD is a mandatory format for dossiers in USA and Japan but it is optional in India. Depending on the type of application and the size of the applicant, user fees may apply. The NDA submission process in India can be complex and rigorous, but successful approval allows a new drug to be marketed and made available to patients in the country.

DRUG REGULATORY REVIEW

Pharmaceutical regulations or drug regulations is the combination of administrative, legal and technical measures that governments take to ensure safety, efficacy and quality of approved drugs as well as the relevance and accuracy of product information. The effective development, production, import, export,

distribution of drugs is regulated by strong national regulatory agencies which ensure drugs meet prescribed standards and thus protect and promote public health[43]. To achieve this, regulatory agencies oversee various aspects of drug development, licensing, registration, production, labeling, storage, marketing, distribution, pricing, import and post marketing studies of drugs. Such agencies work diligently to enforce regulations and issue guidelines to ensure that the drugs are safe and effective for use by individuals. World Health Organization (WHO), International Conference on Harmonization (ICH), World Trade Organization (WTO), World Intellectual Property Organization (WIPO) and Pan American Health Organization (PAHO) are some of the International Regulatory Agencies and Organizations[44]. In some countries like USA, single body FDA regulates the drugs, however in India, this responsibility is shouldered by Centralized and State authorities. The important drug regulatory bodies in India along with their role are mentioned in table 4.

Table 4: Various Drug Regulatory Bodies in India[45]

S. No.	Regulatory Body	Role of Regulatory Body
1.	Drugs Controller General of India (DCGI)	It approves drug licenses for import or manufacture.
2.	Central Drugs Standard Control Organization (CDSCO)	It lays regulatory measures, amendments to Acts and Rules. It regulates the standard of drugs.
3.	State drug licensing authorities	Its role is to regulate the production, sales and marketing of drugs, granting license to drug testing laboratories in state
5.	National Pharmaceutical Pricing Authority (NPPA)	It controls prices of controlled bulk drugs and medical devices, monitor availability of drugs and identify shortage if any.
6.	Indian Council of Medicinal Research (ICMR)	It formulates, coordinate and promote biomedical intramural and extramural research.
6.	Department of Pharmaceuticals (DOP)	It plays crucial role in discovering, developing market safe, efficient and cost effective medicines for patients.
7.	Review Committee on Genetic Manipulation (RCGM)	It monitors the safety and protection of all ongoing research activities from genetically engineered organisms.
8.	Genetic Engineering Appraisal Committee (GEAC)	It plays critical role in regulating the use, production, storage, import of hazardous microbes and genetically modified organisms and cells in India.

REVIEW OF REGULATORY DOCUMENTS

CDSCO reviews submitted documents for accuracy and relevance. A parallel review may be conducted by DCGI-registered ethical committee. CDSCO evaluates a new drug approved outside India in 90 days and 30 days to evaluate drug discovered and synthesized in India. During review process, additional information/clarification may be sought from sponsors. If application is complete, it is passed to subject expert committee (SEC) for further technical review and recommendations. Comments made by SEC are sent to sponsors and need be responded within 4 weeks of receipt. After SEC reviews and sponsors responses, DCGI makes final decision. If satisfied, CDSCO issue approval letter for three years. A new drug is marketed in India after obtaining official communication from the CDSCO.

APPROVAL PROCESS AND POST MARKET SURVEILLANCE

Approval Process: The regulatory bodies review the NDA which leads to three possible actions to be sent to the sponsor: Approved: means drug is approved. Approvable: means drug can be approved after correcting label changes. Not Approvable: Reasons of non approval and the list of deficiencies is mentioned[46]. Figure 4 shows the process of drug approval process in India

In India, Both the Central and State levels of the drug regulation system are in operation. At the national level, Central Drugs Standards Control Organisation (CDSCO) is delegated primary responsibility of approving new drugs. The Drug and Cosmetic Act 1940 and its Rules 1945, 122A, 122B, 122D and further appendix I, IA and VI of Schedule Y govern the import, manufacturing, distribution, and sale of cosmetics and drugs[47-49]. Schedule Y contains the criteria and requirements for clinical trials, Section 2.4a of schedule Y of The Drug and Cosmetic Act 1940 refers to essentiality of conducting clinical trials of new drugs in India with the highest standards of quality, safety and ethics[50]. According to Section 2.4b of schedule Y of The Drug and Cosmetic Act 1940, applicant need to submit available data of drugs discovered in other countries and licensing authorities may require repeating all studies or allow proceeding to phase III clinical trials. As per Section 2.8 of schedule Y of The Drug and Cosmetic Act 1940, licensing authority may require pharmacokinetic studies to show data generated in Indian population is equal to data generated abroad and then require him to proceed to phase III trials[51].

The Drug and Cosmetic Act 1940 was amended in 2005 to bring it in line with internationally accepted practice. The modifications include defining Phase I-IV studies and creating explicit duties for

investigators and sponsors. In 2006, clinical studies were further classified into two types. Clinical trials can be done in other markets with competent and mature regulatory systems in category A, but not in the category B. Category A clinical trials (authorized in the United States, the United Kingdom, Switzerland, Australia, Canada, Germany, South Africa, Japan, and the European Union) are qualified for fast tracking in India and are expected to be approved within eight weeks. Clinical studies in category B are scrutinized more closely and approved in 16 to 18 weeks[52]. The DCGI is responsible for managing new drug approval, import, clinical trials, licenses of new drugs etc[53]. There is provision in rule 122A of Drug and Cosmetic Act 1940 and Rules 1945 that in interest of public health, DCGI may waive some trials and grant permission for import of new drugs based on trials done in other countries. Similarly as per another provision in Rule 122 A, clinical trials can be waived for new approved drugs if they are used in other countries for several years. Some of the important rules of Drug and Cosmetic Act are listed in table 5

Table 5: Rules of Drug and Cosmetic Act in India

S.No.	Rules	Description
1	122A	Application for permission to import new drugs
2	122B	Application for approval to manufacture new drugs
3	122D	Permission to import or manufacture FDC
4	122DA	Permissioin to conduct clinical trials for new /investigational new drug
5	122DAA	Clinical Trial Definitions
6	122E	New drugs Definitions include unapproved drugs, modified or new claims, dosage forms, combination of two or more drugs

DCGI must receive an application to perform clinical trials in India, as well as data from chemistry, manufacturing, control, and animal investigations. The trial protocol, investigator's brochures, and informed consent paperwork should all be dated. The application (form 44) is submitted to ethical committee (EC) and clinical trials begin only after approval of DCGI (the licensing authority) and EC[51]. After the trials, new drug registration is applied on form 44 along with comprehensive information on safety, efficacy and marketing status in other countries. Information on Animal pharmacology and toxicology, testing protocols, prescription samples, product monograph, clinical protocol, investigator information labels and cartons is also required. Application is reviewed in 12-18 months. The NDA approval allows company to distribute and market the product, which enters phase 4 for exploration of new uses and long term effects[54]. In India, the process of new drug approval (Figure 4) is complex and should meet essential necessities along with NDA to FDA.

POST MARKET SURVEILLANCE

It is an important part of science of pharmacovigilance (PV) that detects Adverse Drug reactions (ADRs) of a drug, after its introduction to the market[55]. WHO defines ADRs as any injury or harm as the response of any drug which leads to unintended, unwanted, noxious, undesirable reactions to the patient given to them for any surgery, diagnosis, curing of disease or for any modification of physiological functions in the body. The premarketing testing of drugs cannot provide knowledge about efficacy and safety of drugs as it is performed on fewer number and types of patients as compared to patients finally prescribed the drug[56]. Post Market Surveillance has important role to discover undesirable effects and drug exposures over the time. In post marketing surveillance study, the information like: - case report, cohort studies, case control studies, prescription event monitoring and drug-drug / food interactions etc is collected. Figure 5 shows the flow of information among PV centres and the global monitoring organizations by using PV analytical tools for ADRs analysis.

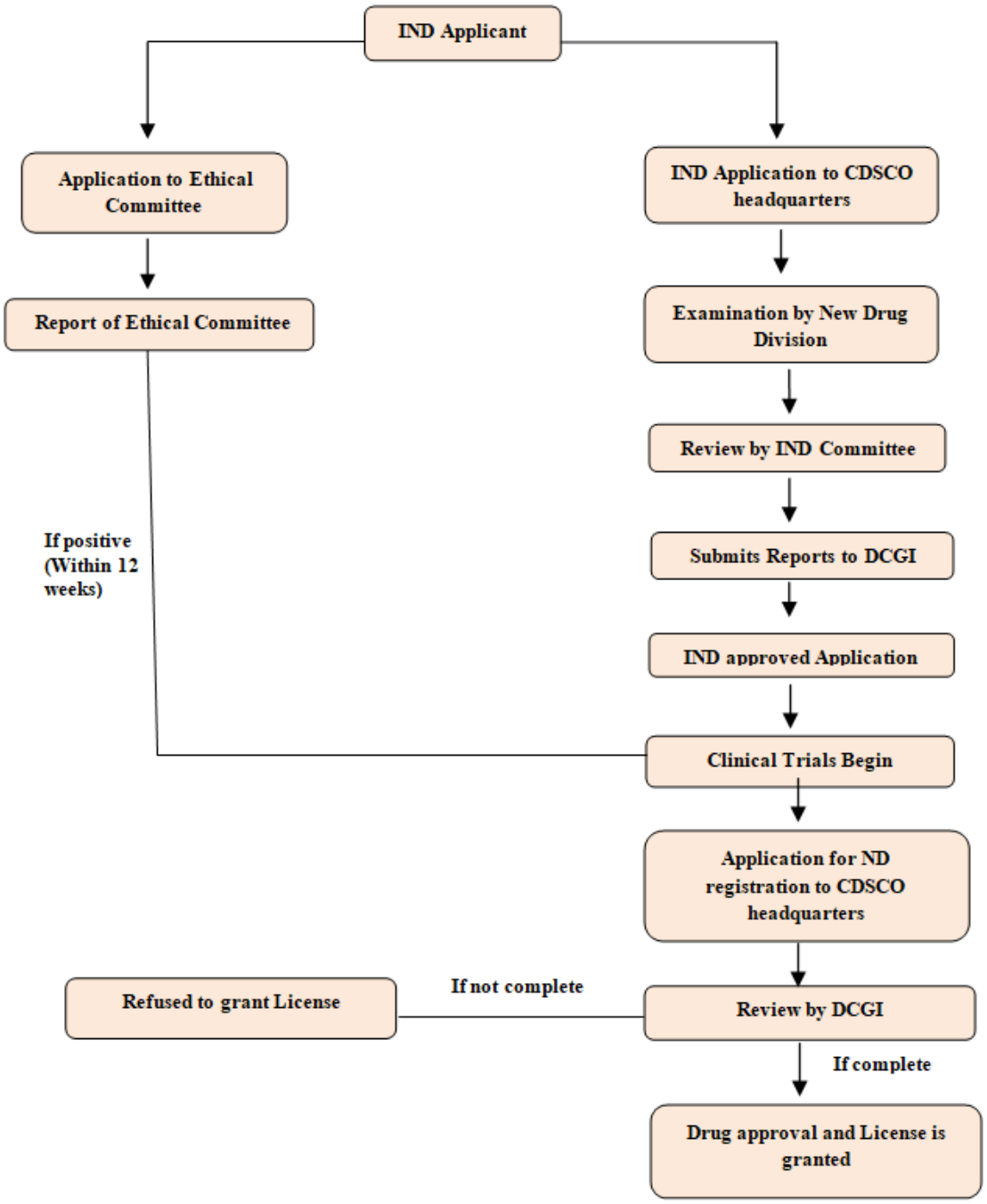


Figure 4: Flowchart showing drug approval process in India.

PHARMACOVIGILANCE AND ADR MONITORING IN INDIA

In 1986, a 12- regional centre ADR monitoring system was proposed for India to cover a population of 50 million in each centre. In 1997, India collaborated with World Health Organisation (WHO-ADR) Programme based in Uppsala, Sweden. Three ADR monitoring centers, one at National pharmaovigilance centre located at AIIMS, New Delhi and the other two at KEM Hospital (Mumbai) and JLN hospital, Aligarh were identified. The chief role assigned to these centres was to monitor ADRs and report to drug regulatory authority of India, but these could not function due to lack of funding from government. Later in 2005, World Bank funded and WHO sponsored National Pharmacovigilance program (NPP) were launched in India, which was supervised by Central Drugs Standard Control Organisation (CDSCO), New Delhi. Government launched the National Pharmacovigilance Advisory Committee (NPAC) to monitor the performance of various zonal, regional, and peripheral centres and functions as "Review Committee" for this program. North East and South west zonal centres were established respectively in Mumbai and New Delhi, to compile ADRs information from all over India and convene it to Committee and Uppsala Monitoring centre (UMC) in Sweden[57]. Two regional centres

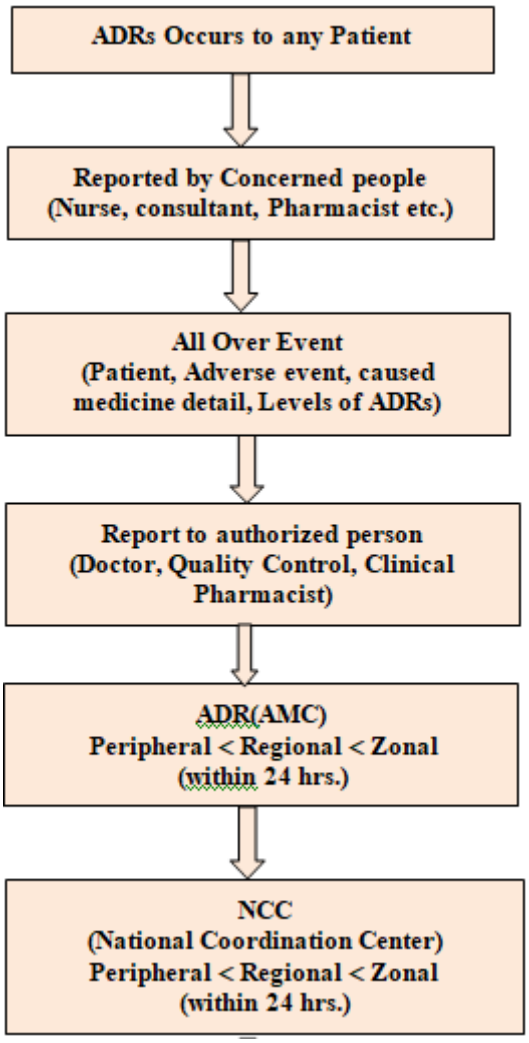
were to report to New Delhi centre and three regional centres to report to Mumbai centre. Several peripheral centres were established which would report to regional centres. Currently there are 24 peripheral centres. Figure 4 shows the procedure of ADR reporting using PV analytical tools[58].

PHARMACOVIGILANCE PROGRAMME OF INDIA (PvPI)

PvPI was launched by Ministry of Health and family welfare (MoHFW), Govt. of India in 2010 at AIIMS, New Delhi as National Coordinating centre (NCC). The program was then transferred to Indian Pharmacopoeia Commission (IPC) as NCC in April, 2011[59]. IPC-PvPI became the NCC for Matereiovigilance Programme of India (MvPI) from July 2015. From July 2017, IPC, NCC-PvPI became a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes & Regulatory services. The functions of various ADR monitoring centres are listed in Table 6.

Table 6: Functions of ADR monitoring centres

ADRs Monitoring Centres (Peripheral, Regional, Zonal)	NCC-PvPI	Zonal/Subzonal CDSCO Offices	CDSCO, HQ, New Delhi
Monitoring and reporting ADRs	• Prepare SOPs, guidance documents and training manuals. • Data Compilation, cross check completeness, Casualty assessment etc. as per SOPs. • Organize Training workshops • Publish Medicines safety newsletter	It lends administrative support to ADR monitoring centres	• On the base of NCC-PvPI recommendations, it takes proper regulatory decision and actions. • Propagate medicine safety related decisions to stakeholders.



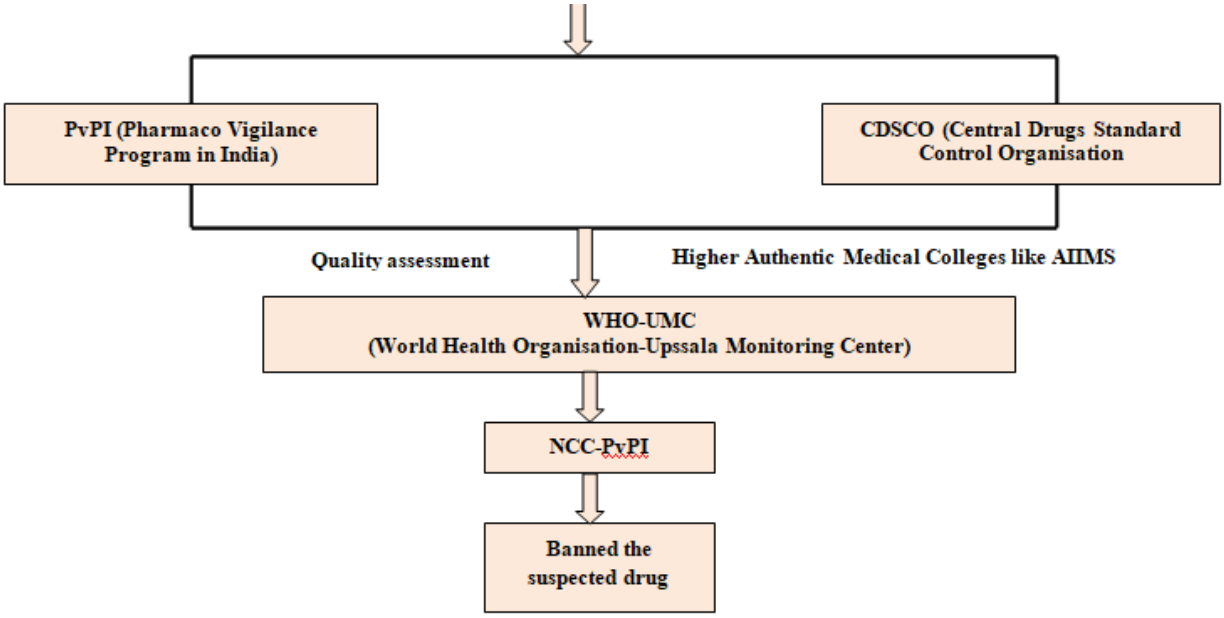


Figure 5: Flow of information among PV centres and the global monitoring organizations by using PV analytical tools for ADRs analysis.

The Month wise ADRs reported to NCC-PVPI for year 2023 are shown in Figure 6. Pharmaceutical companies, healthcare professionals notify the regulatory authorities about ADRs on a form labeled as Individual case study report (ICSR). The Individual case safety reports (ICSRs) in India show continuous rise from 2011 to 2018.[60]

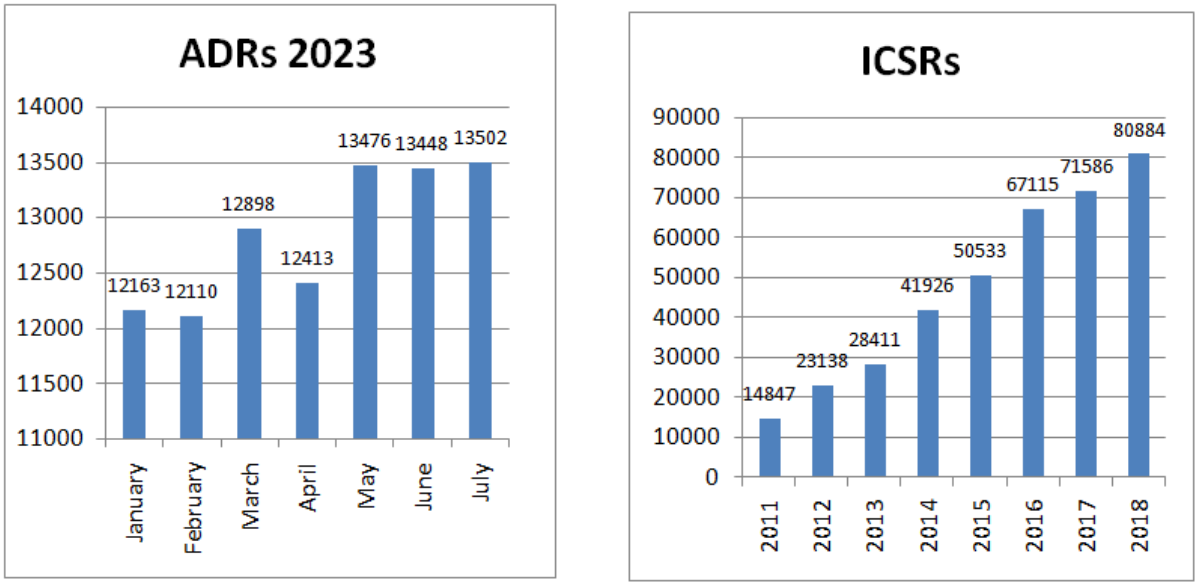


Figure 6: Monthwise ADRs reported in 2023 and ICSRs in India from 2011-18

After proper checking of ICSRs, the AMCs report ADR to NCC through web based tool Vigiflow (WHO-UMC software). Vigibase is entrusted with maintaining worldwide ICSRs data storage[61]. The contribution of India to WHO global Individual case safety reports (ICSRs) database is 3%. UMC releases results of documentation assessment for ICSRs to national centres, which include completeness score range from 0 to 1 on an ICSR. The WHO-UMC completeness score for Indian ICSR is 0.94 out of 1.0.

PHARMACOVIGILANCE (PV) ANALYTICAL TOOLS

The PV implementation requires the use of specific tools (Figure 7) that will help to communicate with the prescribers and end-users.

1. **Vigibase:** It is an essential tool and the largest database of ADRs maintained by WHO and contains 21 million reports of ADRs from over 130 countries. It collects and analyze reports of suspected ADRs and the Pharmacovigilance professionals utilize Vigibase to find safety trends and potential risks associated with particular

vaccine and drug. Besides, Vigibase is used to generate safety report, including periodic safety update reports (PSURs) and risk management plans (RMPs) required by regulatory authorities. VigiAccess was launched in 2015 by WHO to provide public access to information in VigiBase[62].

2. **VigiFlow:** It is software developed by UMC and is used for processing of individual case safety reports (ICSRs) received from sources like patients, doctors, regulatory authorities etc. It processes ICSRs by ensuring consistency in data entry, validation and coding of ADRs using international terminology such as MeDRA. It supports electronic data interchange (EDI) protocols such as E2B (R3) which enables exchange of ICSRs[63]
3. **VigiLyze:** It is an application software to monitor ADRs and other safety concerns of pharmaceutical products. It uses advanced algorithms to analyze data from clinical trials, post market surveillance and social media. It enables health care professionals and drug manufacturers to take necessary actions to protect patients. It includes updating product labelling, changing prescribing protocols or even withdrawing drug from market if required[64,65].

Figure 7: PV tools to detect, process and monitor the ADRs.

LIFE CYCLE MANAGEMENT

Life Cycle Management (LCM) involves various strategies aimed at extending patent term of drug, maximizing revenue and gaining competitive edge over other drugs in a crowded market[66]. It also benefits the patients by providing them with improved treatments and access to existing drugs for longer period. Product life cycle management (PLM) involves studying various aspects such as workflow, information sharing, market analysis, information management, product stages, new inventions and innovations, sophisticated technology, patient requirements, cost concepts, and market growth rate. The stages of PLM consist of design, reliability/validity assessment, model development, sample production, manufacturing, and final product release. In the design phase, the actual design or development of the product takes place. This is followed by a reliability and validity assessment, which checks for reliable performance and analyzes potential failure modes. Next, a prototype of the model is developed to test the functionality of the product in various aspects. Sample production is then conducted to gauge customer response and manufacturing is carried out at larger scale. Finally, the product is released in the market, marking the end of PLM process[67]. The three stages of pharmaceutical product life cycle broadly include: Development, commercialization and generic competition. The Pharmaceutical companies employ different strategies to maximize product's value and retain market dominance before patent expiry. **FDA recommended following strategies for successful pharmaceutical development:**

- Pharma companied need to collect comprehensive and accurate patient insights from all relevant stakeholders
- To design clinical trials, pharma companies need to explore what matters to the patients.
- Pharma companies to gather, store and analyze clinical outcome assessment to get patient centric drug development.

Strategies for successful commercialization of drug:

- Product life cycle management involves four main steps, including packaging and labeling, inventory management& transportation, product distribution, product tracking and tracing.
- Monitor post launch success that requires tweaking and optimization.
- To avoid generic competition which can do market share loss of pharma companies, following strategies can be deployed.
- Practice of improving drugs (ever greening)in order to extend their patent term
- The drugs exclusively for adults are expanded usage to children (pediatric exclusivity) which delay patent expiry for six months.

Besides it other strategies for LCM of drug are reported in Table 7 [68]

OTHER CHANGES IN THE LIFE CYCLE OF A MEDICINE

Medicines are protected by patents when first marketed, preventing other companies from making and selling similar products. When patent term ends, other pharma companies can create generic versions. New medicines are usually authorized as POMs (Prescription only medicines). For first few years, health care workers supervise the safety of drugs. The status of medicine changes and are called Over-The counter (OTC) medicine which require a new license. OTC medicines can be bought without a prescription from pharmacies or supermarkets.

Table 7: Strategies for LCM of Drug

S.No.	Strategies		Description
1.	**Regulatory strategies**	**Indication Expansion**	It involves identifying new indications for drug and seeking regulatory approval to expand drug's label. It will widen drug's market, enhance its sale and extend patent term.
		Reformulation	It involves developing new improved drug formulations of existing formulations by improving dosage, administration or delivery systems.
		Combination Therapies	To extend effectiveness of drug and extend its patent term, this strategy involves combining a drug with other drug from same or different company.
2.	**Marketing strategies**	**Pricing strategies**	Through a competitive pricing strategy, one way to manage drug life is to decrease price in direct competition with generic drugs, the other way is pharma companies focus on those new market segments that can enable companies to uphold or even raise their prices.
		Product Differentiation	This market strategy involve differentiation methods like fresh modes of delivery such as patches, liquid, tablets and revised packaging etc.
		Promotion	In this strategy, quality differences between generic and branded product are promoted that reduces competition from generic products. In addition, branded products have larger resource base and are able to provide free samples to hospitals which is not afforded by generic companies, thus it blocks or minimize the generic drug usage and extend life cycle of a product.
		Switch to OTC	The marketing status of drug from prescription is changed to over the counter (OTC) i.e. non prescription, this can increase drug utilization for same indication with same strength, dosage etc. and thus extend life of a drug.
		Branded generics	When product patent expires, the drug life is extended by is selling it under brand name by pharmaceutical companies reducing the price of branded product as compared to generic product**.**
	Legal strategies	**Patenting strategies**	Drug manufacturers extend drug life cycle by filing multiple patents on one drug and covering all elements of a drug, filing patents on isomers, metabolites, prodrugs, new drug formulations and fixed dose combinations. The strategy protects drug from biosimilar competitors.
		Generic settlements	Branded companies have the option between granting a license to use their names or be motivated to withdraw their patent claims.

CONCLUSIONS AND FUTURE PROSPECTIVES

The drug development process requires collaboration among scientists, clinicians, regulatory bodies, and pharmaceutical companies, with the ultimate goal of improving patient outcomes and advancing medical science. However, success is never guaranteed, and many potential drugs do not progress beyond early stages. Nonetheless, drug development remains a vital cornerstone of modern medicine, offering hope for innovative treatments and cures for various diseases and conditions.

With an eye toward the future, the drug development landscape is expected to experience additional changes. Thanks to advancements in data analytics and genomics, personalized medicine may now provide patients individualized treatments that are best suited to them (Topol, 2019). With gene treatments and monoclonal antibodies providing new approaches to disease care, biotechnology is still very important (Baum, 2020).

The dynamic regulatory environment, marked by programs like adaptive licensing, aims to provide access to novel treatments more quickly while upholding strict safety regulations (Eichler et al., 2012). With an emphasis on both effectiveness and patient benefit, these advancements will surely influence how drugs are developed in the future.

In conclusion, the process of developing new drugs remains at the forefront of medical progress, advancing the boundaries of what is possible in healthcare. We can look forward to a future where novel and cutting-edge treatments keep emerging,

providing hope and better outcomes for patients worldwide, with continued research and collaboration.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation**.**

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REFERENCES

1. Deore A, Dhumane J, Wagh R, Sonawane R. The Stages of Drug Discovery and Development Process. Asian J Pharma Res Dev. 2019;7(6):62–7. DOI:https://doi.org/10.22270/ajprd.v7i6.616.
2. DiMasi JA, Feldman L, Seckler A, Wilson A. Trends in risks associated with new drug development: success rates for investigational drugs. Clin Pharmacol Ther 2010;87:272–7. https://doi.org/10.1038/clpt.2009.295
3. (a) Dickson M, Gagnon JP. Key factors in the rising cost of new drug discovery and development. Nature reviews Drug discovery. 2004 May;3(5):417-29. https://doi.org/10.1038/nrd1382. (b) Singh N, Vayer P, Tanwar S, Poyet JL, Tsaioun K, Villoutreix BO. Drug discovery and development: introduction to the general public and patient groups. Frontiers in Drug Discovery. 2023 May 24;3:1201419. doi: 10.3389/fddsv.2023.1201419. (c) Eichler HG, Oye K, Baird LG, Abadie E, Brown J, Drum CL, Ferguson J, Garner S, Honig P, Hukkelhoven M, Lim JC. Adaptive licensing: taking the next step in the evolution of drug approval. Clinical Pharmacology & Therapeutics. 2012 Mar;91(3):426-37. https://doi.org/10.1038/clpt.2011.345. (d) Duarte Y, Márquez-Miranda V, Miossec MJ, González-Nilo F. Integration of target discovery, drug discovery and drug delivery: a review on computational strategies. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2019 Jul;11(4):e1554. https://doi.org/10.1002/wnan.1554.
4. Bowes J, Brown AJ, Hamon J, Jarolimek W, Sridhar A, Waldron G, Whitebread S. Reducing safety-related drug attrition: the use of in vitro pharmacological profiling. Nature reviews Drug discovery. 2012 Dec;11(12):909-22. https://doi.org/10.1038/nrd3845.
5. Anastassiadis T, Deacon SW, Devarajan K, Ma H, Peterson JR. Comprehensive assay of kinase catalytic activity reveals features of kinase inhibitor selectivity. Nature biotechnology. 2011 Nov;29(11):1039-45. https://doi.org/10.1038/nbt.2017
6. Terstappen, G.C., et al., Target deconvolution strategies in drug discovery. Nature Reviews Drug Discovery, 2007. 6(11): p. 891-903. https://doi.org/10.1038/nrd2410
7. Lindsay MA. Target discovery. Nature Reviews Drug Discovery. 2003 Oct 1;2(10):831-8. https://doi.org/10.1038/nrd1202
8. Maguire JJ, Kuc RE, Davenport AP. (2012) Radioligand binding assays and their analysis.In: Davenport, A. (eds) Receptor Binding Techniques. Methods in Molecular Biology, vol 897. Humana Press, Totowa, NJ. https://doi.org/10.1007/978-1-61779-909-9_3. Print ISBN978-1-61779-908-2 Online ISBN978-1-61779-909-9
9. Lea WA, Simeonov A. Fluorescence polarization assays in small molecule screening. Expert opinion on drug discovery. 2011 Jan 1;6(1):17-32. https://doi.org/10.1517/17460441.2011.537322
10. Pollack SJ. Surface Plasmon Resonance for Identifying and Characterising Small Molecule Ligands. Biophysical Techniques in Drug Discovery. 2017 Nov 14;61:170.
11. Ward WH, Holdgate GA. 7 Isothermal Titration Calorimetry in Drug Discovery. Progress in medicinal chemistry. 2001 Jan 1;38:309-76. https://doi.org/10.1016/S0079-6468(08)70097-3
12. Strelow J, Dewe W, Iversen PW, et al. Mechanism of Action Assays for Enzymes. 2012 May 1 [Updated 2012 Oct 1]. In: Markossian S, Grossman A, Brimacombe K, et al., editors. Assay Guidance Manual [Internet]. Bethesda (MD): Eli Lilly & Company and the National Center for Advancing Translational Sciences; 2004-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK92001/
13. Holdgate GA, Meek TD, Grimley RL. Mechanistic enzymology in drug discovery: a fresh perspective. Nature reviews Drug discovery. 2018 Feb;17(2):115-32. https://doi.org/10.1038/nrd.2017.219
14. Larsson P, Engqvist H, Biermann J, Werner Rönnerman E, Forssell-Aronsson E, Kovács A, Karlsson P, Helou K, Parris TZ. Optimization of cell viability assays to improve replicability and reproducibility of cancer drug sensitivity screens. Scientific reports. 2020 Apr 2;10(1):5798.https://doi.org/10.1038/s41598-020-62848-5
15. Chiba T, Tsuchiya T, Mori R, Shimokawa I. Protein reporter bioassay systems for the phenotypic screening of candidate drugs: a mouse platform for anti-aging drug screening. Sensors. 2012 Feb 7;12(2):1648-56. https://doi.org/10.3390/s120201648
16. Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. British journal of pharmacology. 2011 Mar;162(6):1239-49. doi: 10.1111/j.1476-5381.2010.01127.x. PMID: 21091654; PMCID: PMC3058157.
17. (a) Lin JS, Lai EM. Protein–protein interactions: co-immunoprecipitation. In: Journet, L., Cascales, E. (eds) Bacterial Protein Secretion Systems. Methods in Molecular Biology, vol 1615. Humana Press, New York, NY. https://doi.org/10.1007/978-1-4939-7033-9_17. Print ISBN978-1-4939-7031-5 Online ISBN978-1-4939-7033-9. (b) Al-Amin A. Molecular Approaches to Explore Drug-Target Interactions [Internet] [PhD dissertation]. [Uppsala]: Acta Universitatis Upsaliensis; 2019. (Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine). Available from: https://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-374329. ISBN 978-91-513-0560-8.
18. Hamdi A, Colas P. Yeast two-hybrid methods and their applications in drug discovery. Trends in pharmacological sciences. 2012 Feb 1;33(2):109-18. https://doi.org/10.1016/j.tips.2011.10.008
19. Kerppola TK. Bimolecular fluorescence complementation (BiFC) analysis as a probe of protein interactions in living cells. Annu Rev Biophys. 2008;37:465-87.

https://doi:10.1146/annurev.biophys.37.032807.125842 . PMID: 18573091; PMCID: PMC2829326.

20. (a) Perwitasari O, Bakre A, Tompkins SM, Tripp RA. siRNA Genome Screening Approaches to Therapeutic Drug Repositioning. Pharmaceuticals (Basel). 2013 Jan 28;6(2):124-60. https://doi:10.3390/ph6020124. PMID: 24275945; PMCID: PMC3816683. (b) Lavery KS, King TH. Antisense and RNAi: powerful tools in drug target discovery and validation. Current opinion in drug discovery & development. 2003 Jul 1;6(4):561-9.
21. (a) Fellmann C, Gowen BG, Lin PC, Doudna JA, Corn JE. Cornerstones of CRISPR-Cas in drug discovery and therapy. Nat Rev Drug Discov. 2017 Feb;16(2):89-100. https://doi:10.1038/nrd.2016.238. Epub 2016 Dec 23. PMID: 28008168; PMCID: PMC5459481. (b) Barrangou R, Birmingham A, Wiemann S, Beijersbergen RL, Hornung V, Smith AV. Advances in CRISPR-Cas9 genome engineering: lessons learned from RNA interference. Nucleic acids research. 2015 Apr 20;43(7):3407-19. https://doi.org/10.1093/nar/gkv226
22. Szymański P, Markowicz M, Mikiciuk-Olasik E. Adaptation of high-throughput screening in drug discovery-toxicological screening tests. Int J Mol Sci. 2012;13(1):427-52. https://doi: 10.3390/ijms13010427. Epub 2011 Dec 29. PMID: 22312262; PMCID: PMC3269696.
23. Dash SN, Patnaik L. Flight for fish in drug discovery: a review of zebrafish-based screening of molecules. Biology Letters. 2023 Aug 2;19(8):20220541.https://doi.org/10.1098/rsbl.2022.0541.
24. Su TT. Drug screening in Drosophila; why, when, and when not? Wiley Interdiscip Rev Dev Biol. 2019 Nov;8(6):e346. doi: 10.1002/wdev.346. Epub 2019 May 5. PMID: 31056843; PMCID: PMC6786905.
25. (a) Yang X, Kui L, Tang M, Li D, Wei K, Chen W, Miao J and Dong Y (2020) High-Throughput Transcriptome Profiling in Drug and Biomarker Discovery. Front. Genet. 11:19. doi: 10.3389/fgene.2020.00019. (b) Chen B, Butte A. Leveraging big data to transform target selection and drug discovery. Clinical Pharmacology & Therapeutics. 2016 Mar;99(3):285-97. https://doi.org/10.1002/cpt.318
26. Priest BT, Swensen AM, McManus OB. Automated electrophysiology in drug discovery. Curr Pharm Des. 2007;13(23):2325-37. doi: 10.2174/138161207781368701. PMID: 17692004.
27. Meissner, F., Geddes-McAlister, J., Mann, M. *et al.* The emerging role of mass spectrometry-based proteomics in drug discovery. *Nat Rev Drug Discov* 21, 637–654 (2022). https://doi.org/10.1038/s41573-022-00409-3
28. (a) Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, Li B, Madabhushi A, Shah P, Spitzer M, Zhao S. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019 Jun;18(6):463-477. https://doi: 10.1038/s41573-019-0024-5. PMID: 30976107; PMCID: PMC6552674. (b) Najm M, Azencott CA, Playe B, Stoven V. Drug target identification with machine learning: How to choose negative examples. International Journal of Molecular Sciences. 2021 May 12;22(10):5118. https://doi.org/10.3390/ijms22105118
29. Feng Y, Wang Q, Wang T. Drug Target Protein-Protein Interaction Networks: A Systematic Perspective. Biomed Res Int. 2017;2017:1289259. https://doi: 10.1155/2017/1289259. Epub 2017 Jun 11. PMID: 28691014; PMCID: PMC5485489.
30. Loscalzo, J. Molecular interaction networks and drug development: Novel approach to drug target identification and drug repositioning. *The FASEB Journal*. 2023; 37:e22660. https://doi: 10.1096/fj.202201683R
31. Joaquin Dopazo, Genomics and transcriptomics in drug discovery, Drug Discovery Today, Volume 19, Issue 2, 2014, Pages 126-132, ISSN 1359-6446, https://doi.org/10.1016/j.drudis.2013.06.003.
32. Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015 Jul 22;20(7):13384-421. https://doi.org/10.3390/molecules200713384
33. Muhammed MT, Esin AY. Pharmacophore modeling in drug discovery: methodology and current status. Journal of the Turkish Chemical Society Section A: Chemistry. 2021 Aug 8;8(3):749-62. https://doi.org/10.18596/jotcsa.927426
34. Alarcon-Barrera JC, Kostidis S, Ondo-Mendez A, Giera M. Recent advances in metabolomics analysis for early drug development. Drug discovery today. 2022 Jun 1;27(6):1763-73. https://doi.org/10.1016/j.drudis.2022.02.018
35. https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/investigational-new-drug-applications-inds-cber-regulated-products
36. Holbein MB. Understanding FDA regulatory requirements for investigational new drug applications for sponsor-investigators. Journal of investigative medicine. 2009 Aug;57(6):688-94. https://doi: 10.2310/JIM.0b013e3181afdb26. PMID: 19602987; PMCID: PMC4435682.
37. https://www.clinskill.com/docs/ind-and-nda-applications-in-india/
38. https://cdscoonline.gov.in/CDSCO/homepage
39. American Society of Clinical Oncology. Finding a Clinical Trial. Cancer.net. https://www.cancer.net/research-and-advocacy/clinical-trials/finding-clinical-trial. Accessed November 15, 2023.
40. National Institutes of Health. NIH Clinical Research Trials and You. https://www.nih.gov/health-information/nih-clinical-research-trials-you. Accessed November 15, 2023.
41. Umscheid CA, Margolis DJ, Grossman CE. Key concepts of clinical trials: a narrative review. Postgrad Med. 2011 Sep;123(5):194-204. doi: 10.3810/pgm.2011.09.2475. PMID: 21904102; PMCID: PMC3272827.
42. Kandi V, Vadakedath S. Clinical Trials and Clinical Research: A Comprehensive Review. Cureus. 2023 Feb 16;15(2):e35077. doi: 10.7759/cureus.35077. PMID: 36938261; PMCID: PMC10023071.
43. Agarwal NB, Karwa M., book chapter, "Pharmaceutical Regulations in India" , Pharmaceutical Medicine and translational clinical research, 2018, 215-231. (Vohora, Divya, editor, Singh, Gursharan, editor). Publisher: London, England: Academic Press
44. Mankar SD, Gholap VD, Zende, TP, Dighe RS. Drug regulatory agencies in India, USA, Europe and Japan-A review. International Journal of Institutional Pharmacy and life sciences. Apr 2014; 4: 288-97

45. DeAngelis C, Drazen JM, Frizelle FA, Haug C, Horton R, Kotzin S, Laine C, Marusic A, Overbeke AJ, Schroeder TV, Sox HC, Van Der Weyden MB. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. The Medical Journal of Australia. Sep 2004; 181 (6): 293-94.
46. CDER Guidance: IND application process (interactive session). A review for OCRA US RAC study. www.fda.gov./cder/regulatory/applications/ind_page_1.htm. Accessed on AUG 25, 2011
47. Honorio S. Phases of drug development; Good practices in clinical research. Available at: www.hstelearning.mit.edu. Accessed on AUG 26, 2011
48. Ravinder RB& Suresh N, Regulatory stages for New Drug Approvals. Available at www.observerindia.com/cms/export/orfonline/modules/occasional paper/attachments/Drug_Discovery_Book_1260179432814.pdf. Accessed on AUG 28, 2011
49. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Varghese Publishing House, 3rd Edition 1987, 856.
50. Kamnoore K, Venkatesh, MP, Balamuralidhara V, Pramod Kumar, TM. Regulatory requirements for conducting clinical trials in India. Research Journal of pharmacy and technology. 2020; 13(3): 1517-1522. Doi: 10.5958/0974-360x.2020.00276.0
51. Gupta NV, Reddy CM, Reddy KP, Kulkarni RA, Shivakumar HG. Process of Approval of new drug in India with emphasis on clinical trials. International Journal of Pharmaceutical Sciences Review and Research. 2012 March-April; 13 (2): 17-23.
52. Singh PM, Pahwa S, Chaudhary S, Sethi VA. New Drug Approval Procedure in Different Countries: A Review. International Journal of ChemTech Research. 2017; 10 (12): 1-21
53. Pendhakar D, Pasmanbhan NA, The Drug Approval process in India, ASCO annual Meeting, 2017.
54. Mulaje SS, Birajdar SM, Patil BR, Bhusnure OG. Procedure for drug approval in different countries: A review. Journal of Drug Delivery & Therapeutics. 2013; 3(2): 233-38.
55. Adhikari J, Bhandare B, Adarsh E, Satyanarayana V. A study to assess knowledge, attitude and practice of adverse drug reaction reporting among physicians in a tertiary care hospital. Journal of evolution of medical and dental Sciences. 2013 Mar 4; 2 (9): 1027-34. doi: 10.14260/jmemds/374
56. Hegde S, Gogtay NJ, Kshirsagar NA. Postmarketing Surveillance: An overview from India. International Journal of Pharmaceutical Medicine. 2005; 19(3): 141-51. doi: 10.2165/00124363-200519030-00002
57. Balasubramanian J, Swathi V, Gopinath C. Post marketing surveillance: A Real-life effectiveness of essential medicines in Indian population. International Journal of current Pharmaceutical Research. 2014; 6 (3): 8-14
58. University Of Delhi, " Pharmacovigilance," Slide Share, 09 May 2018.
59. Duvvuru AK, Languluri R, Basha SA. Pharmacovigilance Programme of India. Innovations in pharmacy, jan 2015; 6 (1): Article 189. doi: 10.24926/iip.v6i1.371
60. www.ipc.gov.in/mandates/pvpi/adr-reporting/8-category-en/420-adrs-reporting-status of amcs.html
61. Ratre M. A review on adverse drug reaction reporting management from an allergic patient to final authority. World Journal of Pharmacy and Pharmaceutical Sciences. 2020; 9(7): 951-62
62. https://www.who-umc.org/vigibase/vigibase
63. https://www.who-umc.org/global pharmacovigilance/vigiflow
64. https://www.who-umc.org/vigibase/vigilyze
65. The Safety of medicines in public health programmes: Pharmacovigilance an essential tool, WHO, 2006; Pp 9.
66. Cespi D, Beach ES, Swarr TE, Passarini F, Vassura I, Dunn PJ, Anastas PT. Life cycle inventory improvement in the pharmaceutical sector: assessment of the sustainability combining PMI and LCA tools. Green Chemistry. 2015; 17: 3390-400. doi: 10.1039/C5GC00424A
67. Kumar A, Krishna SH, Chandrasekhar S, Vssavi M, Venkatrayulu Ch, Ismath A. Pharmaceutical Product Life Cycle Management Strategies in the contemporary scenario. Journal of Pharmaceutical Negative Results. 2023; 14(3): 512-16. doi: 10.47750/pnr.2023.14.03.064
68. Giridharan John IVR, Srinivasan R. Pharmaceutical product life cycle management-A comprehensive review. International Journal of Pharmacy, 2021; 11 (2): 9-12.