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DRUG DISCOVERY AND DEVELOPMENT PROCESS IN INDIA, US, EUROPE AND JAPAN

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ABSTRACT: An overview of the drug discovery and development process in brief helps scientists whose work could be important in deciding the process to properly design their research report for the successful translation of preclinical research to human subjects. The idea for the drug's discovery and development may have come from a variety of sources, including the demands of the market at the time, clinical and scholarly research, the commercial environment, *etc*. In order to control the marketing of drugs, each pharmaceutical industry is required to abide by the laws, rules, and regulations of their respective nation. The majority of newly developed medications on the market today are synthetic. The process of developing new medications is expensive due to the significant expenses linked to research and development as well as clinical trials. Information regarding drugs, the development process, and regulating bodies in Europe, Japan, the USA, and India are provided in this article.

INTRODUCTION: The process by which a research-intensive organization finds a novel chemical or biological material and turns it into a product that is authorized for use by patients is known as drug discovery and development. The completion of this extremely capital- and knowledge-intensive procedure takes, on average, over $2 billion (2021 numbers) and takes 10 to 15 years [1-3]. Researchers frequently find new medications through new discoveries into a disease process that allow them to create a therapy to prevent or prevent the negative effects of the disease [4-6]. Historically, the majority of medicinal treatments were derived from naturally occurring plant parts, such as digitalis from foxglove, quinine from cinchona, and opium from poppies [7-8].

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Most new drugs that are available on the market today are synthetic. The process of creating new pharmaceuticals is costly because of the major costs associated with clinical trials and research & development [9-11]. For every effective medication, research and development costs range from $900 million to $2 billion on average [11]. The cost of the thousands of errors is included in this figure: In the final analysis, just one compound out of every 5,000–10,000 that enter the manufacturing process for research and development is approved [13-16]. These figures defy belief, but a quick review of the R&D process can help explain why so many compounds fail to reach the market and why it requires such a significant amount of time and money to develop one medication that actually helps patients [17-18].

Substantial funding, the sharpest scientific and logical brains, extremely advanced lab and equipment, and complete project management are all necessary for success. It also requires luck and patience [19].

In the end, the drug discovery process provides billions of patients with comfort, hope, and faith [20].

There are three basic areas of drug research and development:

1. Drug discovery Software study (*Ex-vivo*)
2. Drug discovery (*in-vivo*)
3. Drug Development

A. Preclinical trials

B. Clinical trials

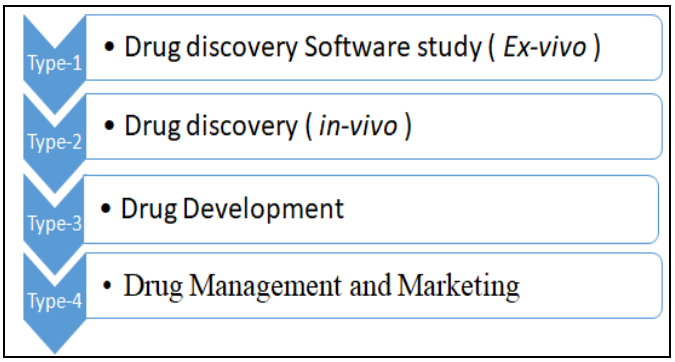

FIG. 1: FLOW CHART OF DRUG DISCOVERY AND DEVELOPMENT

Type 1: Drug Discovery Software Study (*Ex-vivo*): Drug discovery software, which is used to generate novel pharmaceuticals and determine if they will be helpful in treating specific diseases, has an average cost. Medicine discovery software greatly reduces the time-consuming process of developing, testing, and bringing a medicine to market by automating tasks and utilising cutting-edge technologies. The majority of drug discovery solutions include computational, modelling, simulation, screening, and predictive analytics characteristics [21]. These features provide accurate constancy and support with tasks like image analysis and clinical trial results filing. Drug discovery software is used by scientists and researchers to gather market knowledge, benefit from developments in drug design and synthesis, address diseases that are changing and adapting, and preserve and manage data integrity as medications move past the discovery stage.

Type 2: Drug Discovery *(In-vivo)*: Researchers commonly use the following methods to discover novel drugs:

1. New understandings of a disease's pathophysiology that help scientists create treatments to stop or cure the effects of the illness.
2. By taking chemical compounds through a number of experiments in an effort to find possible treatments for diseases [22].
3. Through the use of present therapies that have negative side effects.
4. By using cutting-edge technology that present novel ideas for modifying products to specific diseases.

Many compounds have the potential to become reliable and efficient medical treatments at this point in the process [23].

The Following Are Some Drug Discovery Methods [9, 24, 40]:

Random Screening: Animal behaviour research and other screening experiments are used to assess the biological activity of new chemical entities. These studies are costly, time-consuming, and low-yielding, which may result in the extraction of new drugs that are identical to those already on the market without any additional benefits.

Molecular Manipulation: In this process, biological activity of existing drug analogues is determined through synthesis [41]. This is a more proper method that could result in new compounds with improved potency, more selective action, better absorption, and fewer side effects [42].

Molecular Designing: The most sensible approach to drug development and research. It ends in the creation of materials to carry out particular biological functions. In its most basic form, this might involve the synthesis of a hormone, vitamin, or neurotransmitter precursor that occurs naturally [43]. Levodopa is used for Parkinsonism and dopamine is used for cardiogenic shock.

Drug Metabolites: It is occasionally discovered that a drug's active metabolites have therapeutic benefits over the original compound. For example, paracetamol, a metabolite of phenacetin, functions well as an analgesic without harming the kidneys [44].

SBDD, or Structure-based Drug Design: To create molecules that fit into an active site with high specificity, SBDD uses the target protein's three-dimensional structure. Protein structures are determined by NMR spectroscopy and X-ray crystallography [45].

Fragment-Based Drug Design (FBDD): FBDD involves the identification of compounds that bind to a target by screening small, low molecular weight compounds, or fragments. These pieces can serve as a foundation for the creation of more substantial, effective compounds [46].

Multiple discovery: this term refers to "serendipity or unexpected discovery" and has historically prompted the introduction of numerous treatments. Penicillin is used as an antibacterial agent, and organomercurials are used to treat cardiac oedema.

HTS, or High-throughput Screening: In order to find possible treatment candidates, HTS tests a sizable library of chemical compounds against a particular target or biological assay. Robotics and automation are essential to carrying out these tests on a large scale.

Virtual Screening: Molecules are screened and their potential to bind to a target is predicted using computational techniques. In the initial phases of drug discovery, this is frequently employed. Molecular docking, structure-based drug design, and molecular dynamics simulations are some of the methods used [47].

Computation Drug Design: In contrast to target-based methods, computational techniques such as machine learning and quantitative structure-activity relationship (QSAR) analysis are used to predict the bioavailability of drugs.

Phenotypic screening, on the other hand, entails testing compounds for their effects on entire cells or organisms. This method can be used to find medications with unexpected modes of action [48].

Screening for Natural Products: natural products derived from microbes, plants, and marine organisms have been used as sources of medicinal compounds. High-throughput methods and bioassays are employed to screen natural product libraries [49].

Cell-Based and Biological Assays: These tests assess possible pharmacological compounds' effects on biological systems, frequently with the use of cultured cells or tissues. Cell-based assays can replicate disease processes and offer important insights into the effectiveness of treatment candidates.

Investigations on Pharmacokinetics and Pharmacodynamics (PK/PD): PK/PD studies evaluate a drug's pharmacokinetics how the body absorbs, distributes, metabolises, and excretes it as well as its pharmacodynamics the way it affects the body. Determining the proper dosage and method of administering a medication requires an understanding of these characteristics.

Chemistry in Combinatorial: Using this method, huge libraries of various chemical compounds are synthesised and then simultaneously screened for possible therapeutic candidates.

Discovering Biomarkers: Particular biological indicators known as biomarkers are useful for tracking the effectiveness of treatments, making diagnoses, and forecasting disease outcomes. Drug discovery activities can be directed by identifying pertinent biomarkers.

Proteomics and Genomics: Potential therapeutic targets and biomarkers have been found thanks to developments in proteomics and genomics. Drug discovery involves the use of whole-genome sequencing and analysis of gene expression patterns.

Interference with RNA (RNAi): Researchers can study the function of particular genes and their potential as therapeutic targets by using RNA interference (RNAi) to selectively silence or "knock down" those genes.

Drug Repurposing: This strategy, also referred to as "drug repositioning," entails giving already-approved medications new, therapeutic applications. It can drastically cut down on the expense and duration of drug development.

Collaborative and Open Innovation: Collaborative efforts between academia, pharmaceutical companies, and government agencies can accelerate drug discovery by sharing

resources, data and expertise. Many drug discovery projects combine multiple approaches to increase the chances of success in identifying and developing new pharmaceuticals.

Type 3: Drug Development: Over the past 40 years, the complexity of drug development has multiplied, requiring the preclinical stage of the process, an investigational new drug (IND) application, and extensive clinical testing before the FDA will approve a drug for sale [50]. Before being approved, new drug applications (NDAs) and biologics license applications (BLAs) are typically subjected to thorough review [51]. Following approval, drug performance is then resubmitted to regulatory bodies for post-marketing research [52]. Development accounts for about two-thirds of the total R&D costs [53]. The cost per project is very much greater in the development phase, and increases sharply as the project moves into the later phases of clinical development [54, 55].

FIG. 2: DRUG DEVELOPMENT AND PHASES [56]

Preclinical Trials:

Formulation Development in Preclinical Phase: Formulation development determines how best to get a medication ready for preclinical use before it is intended for clinical use in humans [57]. Examinations are made of variables like tasting, consistency of the formula, frequency and mode of administration, and solubility. This considers the location of the illness or issue, such as the tumor cells or sinuses [58].

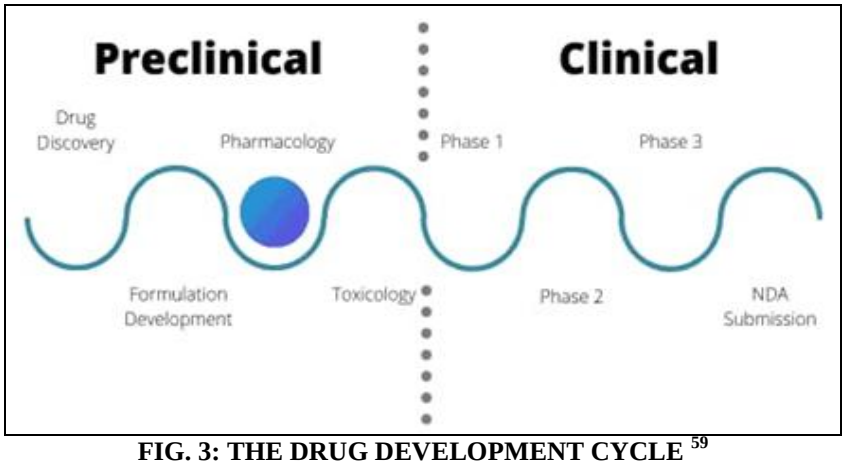

FIG. 3: THE DRUG DEVELOPMENT CYCLE [59]

Pharmacology: The pharmacology stage assesses the safety of a drug as well as its ADME – Absorption; Distribution; Metabolism; and Excretion. ADME is the backbone of pharmacology [60].

ADME: Absorption concerns the bioavailability of the drug once administered. Before most drugs can achieve their goal, the bloodstream carries them away. The bioavailability of the drug measures the fraction of an administered drug dose that reaches the target system, while also measuring the uptake in the target cells and organs [61]. Once the body has absorbed a drug, the latter distributes from one part of the body to another. Metabolism studies the

metabolites produced by the drug's breakdown. It then evaluates whether they are active or harmful, and the breakdown's location in the body. Finally, excretion looks at how the drugs and the metabolites produced exit the body. While ADME is not a regulatory requirement for a first-time, in man (FTIM) study, having conducted it helps improve the quality of the safety information and gives further information to pharmacology and toxicology studies.

Safety: The safety assessment of a drug monitors both pharmacodynamics (PD) and pharmacokinetic (PK) interactions. PD interactions are where the drug administered can affect the actions of another specified drug without affecting its concentration, such as warfarin and antibiotics used in tandem. PK interactions are where the drug administered can affect the actions of another specified drug by affecting its concentration or that of its metabolites, such as the relationship between alcohol and paracetamol.

Safety plays a huge part in the preclinical stage of pharmaceutical product development: researchers must test any drugs vying for Investigational New Drug (IND) status extensively before allowing human testing. Researchers can use computer modelling and simulations to an extent, however, they still require animal models to assess safety. This is because they will assess the pharmacodynamics of the drug on a number of the major body systems such as:

1. The cardiovascular and respiratory systems
2. Renal functionality and intestinal transit

Toxicology in the Preclinical Phase: Since, researchers need to conduct Investigational New Drug (IND) tests in animal models, they must conduct studies in two species [62]. This part of the testing is highly regulated. Researchers must use one species that is non-rodent and their use of primates as an animal model is heavily restricted [63].

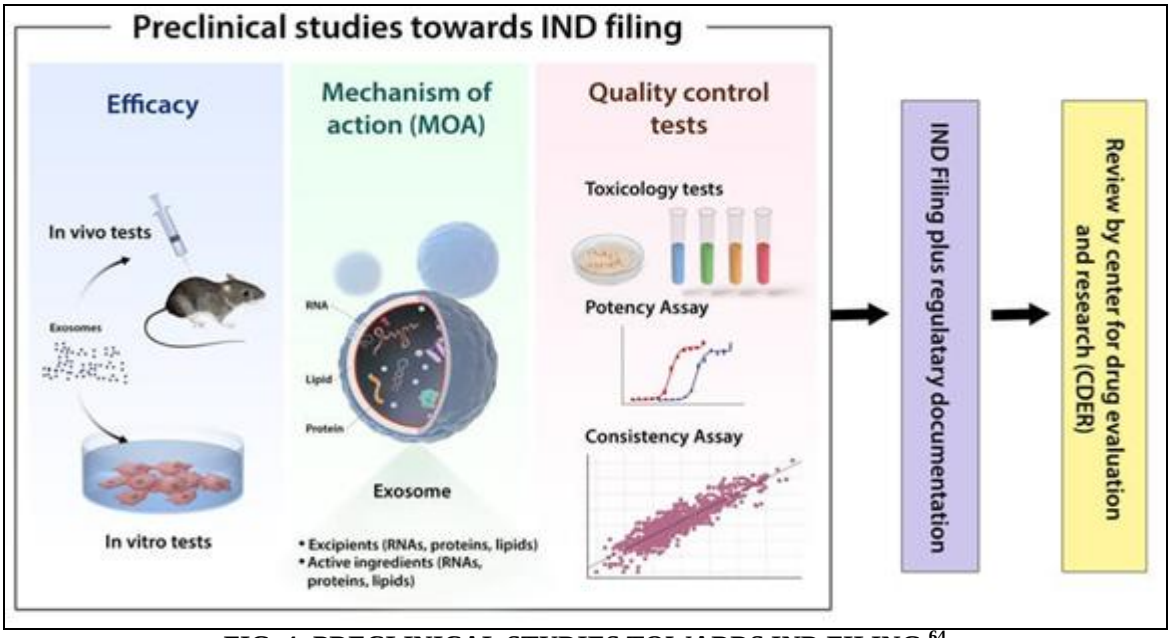

FIG. 4: PRECLINICAL STUDIES TOWARDS IND FILING [64]

Clinical Trials: A clinical trial is a research study conducted on human volunteers to assess whether a new intervention is safe and effective for a specific condition.

The intervention tested can either be a new drug, a device, a procedure, or even changes to a participant's behavior (such as dieting) [65]. It is normally tested against a current standard treatment, a placebo, or no intervention [66].

Phases of Clinicaltrials:

Phase 1 Trial: Verify the safety of a novel treatment on humans. Physicians also determine how best to administer the medication.

A Phase I trial's Objectives are to:

1. Determine the safety of a new treatment.
2. Determine the optimal delivery method for the new medication, such as intravenous or oral.

3. Look for indications that the cancer is responding to the new medication.

Small groups of 20 to 80 volunteer typically participate in phase I trials. Cohorts are the term for these groups [67]. A dose of the novel medication is given to the first cohort. Physicians may take urine or blood samples from their patients to assess their drug levels [68].

A new cohort is given a higher dosage of the same medication if the first cohort experiences no serious side effects. With every new cohort, the dosage is increased until the physicians determine the ideal dosage for upcoming testing. Doctors test each patient to see if they are responding to treatment with each increase in dosage. The treatment will proceed to be examined in a Phase II trial if the physicians determine that it is safe. Many of MD Anderson's Phase I clinical trials are provided by the Clinical Centre for Targeted Therapy. If you'd like more information about this centre, ask your doctor.

Phase II Trials: See if a novel treatment is effective for a particular kind of cancer. In a Phase II trial, fewer than 100 volunteer typically enrol. Physicians continue to monitor side effects closely, even though the primary objective is to determine whether the treatment is effective. In a Phase III trial, physicians may continue to study the novel treatment if it proves effective.

Phase III Trials: Examine whether a novel treatment outperforms the standard one. 1000 to 3000 volunteer typically participate in phase III trials. Thousands or even hundreds of thousands of patients nationwide may participate in phase III trials. In a Phase III clinical trial, patients are randomly assigned to one of the following groups:

Control Group: The control group is the one that standard treatment.

Study Group: the group receiving the novel treatment under investigation. Although they cannot say for sure, doctors think the new treatment is at least as good, if not better, than the current standard of care. The FDA examines the clinical trial findings following the Phase III trial to ensure the treatment is both safe and effective for use by the general public.

Phase 4 Trials: Learn more about the long-term adverse effects. More than one year volunteer typically participate in phase I trials [69]. Physicians investigate FDA-approved treatments in Phase IV trials. Phase IV trials aim to further investigate a new treatment's side effects [70].

FIG. 5: PHASES OF CLINICAL TRIALS [71]

Drug Approval Process: Research in chemistry, molecular biology, biochemistry, preformulation and formulation development, process development and manufacturing, quality control, preclinical and clinical studies, and other areas is heavily involved in the process of developing a new drug. It is the duty of drug regulatory bodies throughout the world to assess whether research findings support a new drug product's quality control, safety, and efficacy in serving the public health. Every nation has a regulatory body that is in charge of issuing guidelines to control the marketing of pharmaceuticals and enforcing laws and regulations [72]. The regulatory requirements for approving new

drugs vary amongst nations. It is currently nearly impossible to find a single regulatory approach that is applicable to multiple countries for INDs, NDAs, or marketing authorization applications (MAAs). As a result, it is essential to understand the legal prerequisites for each nation's drug approval procedure.

There are two stages in the new drug approval process: the IND stage is the first, and the NDA and marketing authorization stages are the second. First, non-clinical testing on the medication is finished to guarantee its effectiveness and safety. The application for conducting clinical trials must be submitted to the appropriate national authority as the next step. The following step involves conducting clinical trials in four phases, namely phase 1 through phase 4 studies. These studies are conducted to ensure drug safety and efficacy as well as to optimise dosage for human use. Then, the application for the drug's marketing is approved by the appropriate authorities.

Drug Approval Process in India: The Indian parliament established the Drug and Cosmetic Act 1940 and Rules 1945 to control the import, production, distribution, and sale of pharmaceuticals and cosmetics [73]. It was decided to create the Drugs Controller General (DCGI) office and the Central Drugs Standard Control Organization (CDSCO). The Indian government modified the 1945 Drug and Cosmetics Rules by adding Schedule Y in 1988. The rules and guidelines for clinical trials are outlined in Schedule Y, which was updated in 2005 to conform to internationally recognized standards. A company in India must apply for authorization from the licensing authority (DCGI) by filing Form 44 and providing the information specified in Schedule Y of the Drugs and Cosmetics Act 1940 and Rules 1945 in order to manufacture or import a new drug. It must perform clinical trials in compliance with the requirements outlined in Schedule Y and submit the results of such trials in the format required in order to demonstrate its efficacy and safety in the Indian population [74, 75].

Rule: According to Section 122A of the Drug and Cosmetics Act, clinical trials may not be required for novel medications that have received approval and have been in use for a number of years in other nations. Schedule Y of the Drugs and Cosmetics Act 1940 and Rules 1945 states in Section 2.4 (a) that all phases of clinical trials must be completed for drug compounds found in India. According to Schedule 2.4(b) of the Drugs and Cosmetics Act 1940 and Rules 1945, if a drug substance is found in a nation other than India, the applicant must submit the data that is available from those nations. The licensing authority may then mandate that the applicant repeat all of the studies or allow the applicant to move forward with Phase III clinical trials.

1. Generic name

2. Patent status

3. Brief description of physico-chemical/biological

4. Technical information

A. Stability

B. Specifications

C. Manufacturing process

D. Worldwide regulatory status

E. Animal pharmacology and toxicity studies

5. Published clinical trial reports

6. Proposed protocol and pro forma

7. Trial duration

8. During master file

9. Undertaking to Report Serious or Life-threatening Adverse Drug Reactions.

The state of the medication in other nations determines whether local clinical trials are required in India. Phase III trials are usually necessary if the medicine has already received approval in another country. In India, phase I trials are not permitted unless outside data sources are consulted. DCGI gives the go-ahead to carry out Phase I studies in India if the medication has a unique bearing on an Indian health issue, such as tuberculosis or malaria. Studies on bioavailability and bio equivalency (BABE) are to be carried out in accordance with BABE criteria. In addition to safety and effectiveness data, detailed information about the drug's marketing status in other nations is also needed. It is also necessary to give information on

the prescription, samples, testing procedures, product monographs, and labelling. In India, approval of a clinical trial typically takes three months. The Clinical Trials Registry of India (CTRI) is a database that contains information about clinical trials, including their subjects' names [76]. The 1945 Drugs and Cosmetics Rules stipulate the following guidelines to be adhered to:

Rule 122 - A: Application for permission to import new drug.

Rule 122- B: application for approval to manufacture new drug other than the drugs specified under Schedule C and C (1).

Rule 122 - D: Permission to import or manufacture fixed dose combination.

Rule 122 - DA: Application for permission to conduct clinical trials for New Drug/Investigational New Drug.

Rule 122 - DAB: Compensation in the case of injury or death during the clinical trials.

Stages of Approval:

1. Submission of Clinical Trial application for evaluating safety and efficacy.
2. Requirements for permission of new drugs approval.
3. Post approval changes in biological products: quality, safety and efficacy documents.
4. Preparation of the quality information for drug submission for new drug approval.

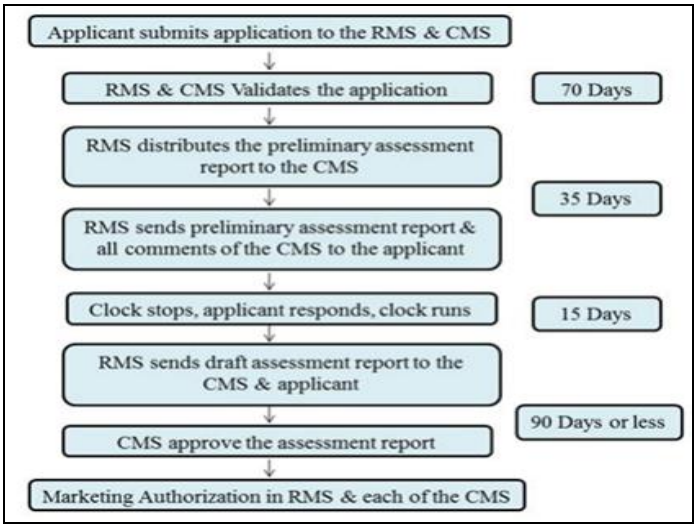

FIG. 6: FLOW CHART OF DECENTRALIZED PROCEDURE [77]

Drug Approval Process in India:

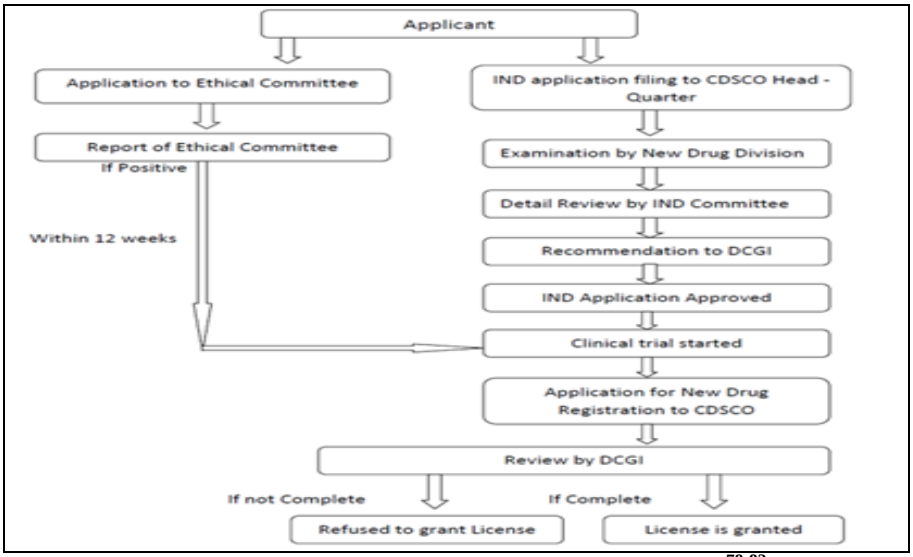

FIG. 7: DRUG APPROVAL PROCESS IN INDIA [78-82]

Type 4: Drug Management and Marketing: Phase IV studies are undertaken after marketing has begun and evaluate new indications, new doses or formulations, long-term safety or cost-effectiveness [83, 84].

Market Approval & Launch (The Drug Registration Process): If stages I through III yield favorable results, a new drug application (NDA) is submitted for market approval. It may take several months to prepare the application materials, and it will then take another six to ten months for the authorities to process the application.

Market Launch: The candidate, or drug as it is now called, is prepared for distribution to consumers if the appropriate regulatory agencies accept an application. The procedure of negotiating prices might vary significantly between nations.

Phase IV Studies - Monitoring Marketing and Safety: Regulation bodies may mandate phase IV follow-up studies following a drug's approval for the market. Data from clinical practice, or actual care providers used by patients, is gathered in order to carry out this [85].

Increasing pharmacovigilance is the goal [86]. Phase IV studies assess the drug's potential for interactions with other drugs and carry out additional safety testing [87]. When it comes to medications intended to treat uncommon illnesses, phase IV trials may be important because phase I–III studies often involve a small number of patients [88].

Supplemental Applications: Developers must file a supplemental application if they wish to make any significant changes from the original NDA [89]. Generally, any changes in formulation, labeling, or dosage strength must be approved by FDA before they can be made.

Drug Advertising: No advertisement, no matter how subtle or overt, can make incorrect or misleading representations about a product. They have to be accurate when it comes to a drug's effectiveness, adverse effects, and prescribing details. These commercials can be seen in newspapers, periodicals, and medical journals as well as on the Internet, radio, television, and other social media platforms.

Generic Drugs: Once new medications are authorized for sale, their patents are secured. This implies that the sponsor only is authorized to promote the medication. Like brand-name medications, generic medications must have the following qualities:

- ✓ Dosage form
- ✓ Strength
- ✓ Safety
- ✓ Quality
- ✓ Performance characteristics
- ✓ Intended use

Reporting Problems: The FDA offers a number of programs that let producers, medical professionals, and patients report issues related to products that are approved.

- MedWatch is a platform for reporting issues with pharmaceuticals and equipment used in medicine as well as for learning about updated safety data. You can sign up to receive frequent safety alerts from MedWatch.
- The Medical Product Safety Network (MedSun) keeps a watch on medical products' efficacy and safety. The FDA releases the MedSun newsletter once a month [90].

Drug Approval Process in United States: The United States has the world's most stringent standards for approving new drugs. Drug approval standards in the United States are considered to be the most demanding in the world [91–93].

Investigational New Drug (IND) Application: If the drug was determined to be safe based on preclinical trial reports, an application would be submitted to the FDA to begin human clinical trials. The organization or company referred to as a Sponsor is in charge of submitting the IND application [25]. It is possible to schedule a pre-IND meeting with the FDA to go over a variety of topics, including the planned protocol for carrying out the clinical trial, the chemistry, manufacturing, and control of the investigational drug, and the design of animal research, which is necessary to

support the clinical studies [94]. A meeting of this kind will assist the Sponsor in planning the animal research, collecting information, and creating the clinical protocol in accordance with FDA recommendations. This is an application that is submitted to the FDA in order to initiate human clinical trials in the event that the results of preclinical trials indicate that the drug is safe. The organisation or company that is referred to as a Sponsor is in charge of submitting the IND application.

It is possible to schedule a pre-IND meeting with the FDA to talk about the following topics:

- ❖ The design of animal research, which is required to lend support to the clinical studies
- ❖ The intended protocol for conducting the clinical Trial
- ❖ The chemistry, manufacturing, and control of the investigational drug

A gathering like this can help the Sponsor in assemble data, plan animal studies, and create the clinical procedure using advice from the FDA.

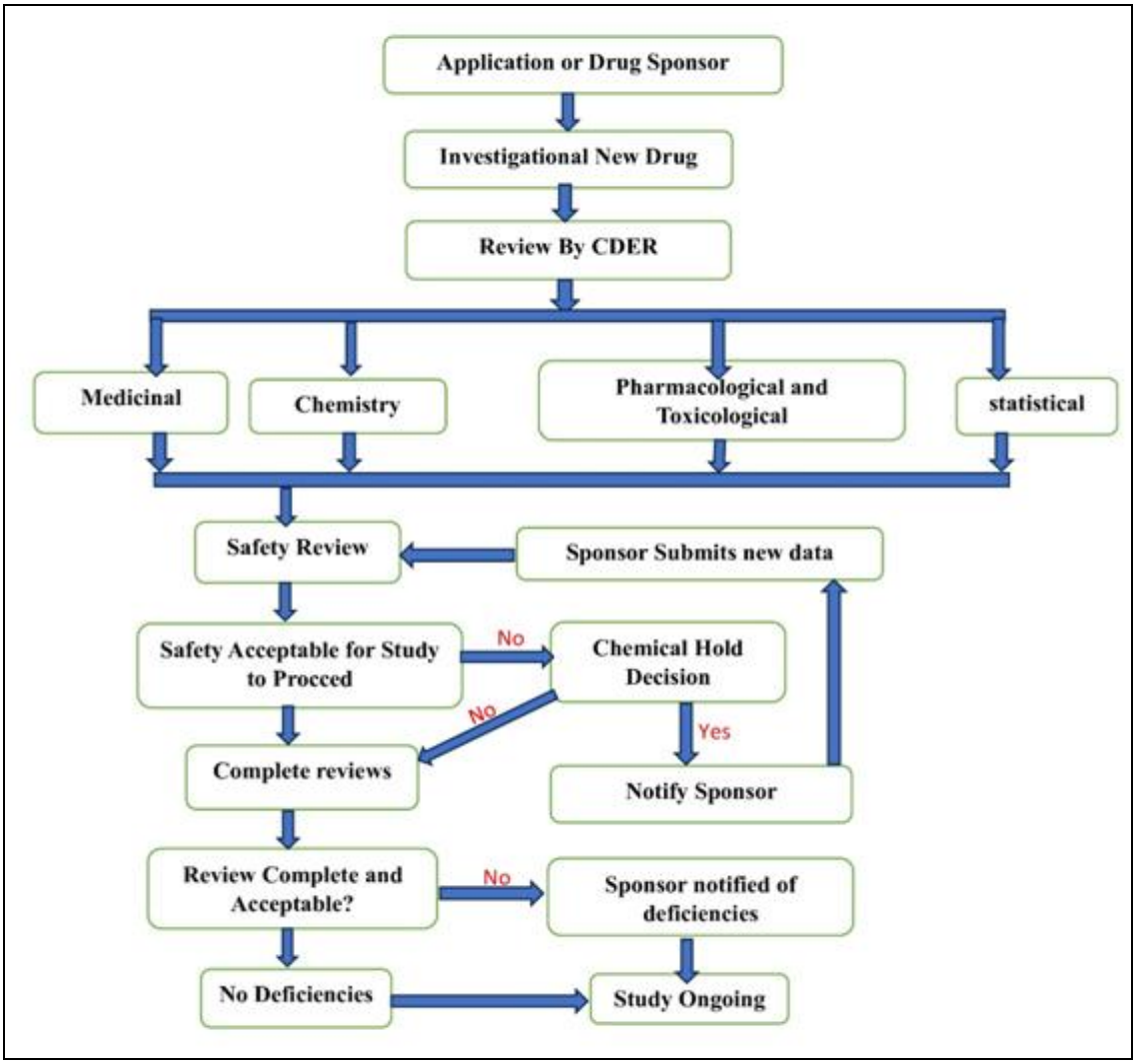

FIG. 8: INVESTIGATIONAL NEW DRUG APPLICATION (IND)

New Drug Application (NDA): A manufacturer submits a New Drug Application (NDA), which is essentially a request to manufacture and sell a new drug in the United States, if clinical studies show that the drug is reasonably safe, effective, and doesn't put patients at unreasonable risk [95, 96].

Once clinical trials verify that a novel medication is reasonably safe, effective, and won't put patients at undue risk, the maker submits a New Drug Application (NDA), which is a formal request to produce and market the medication within the US.

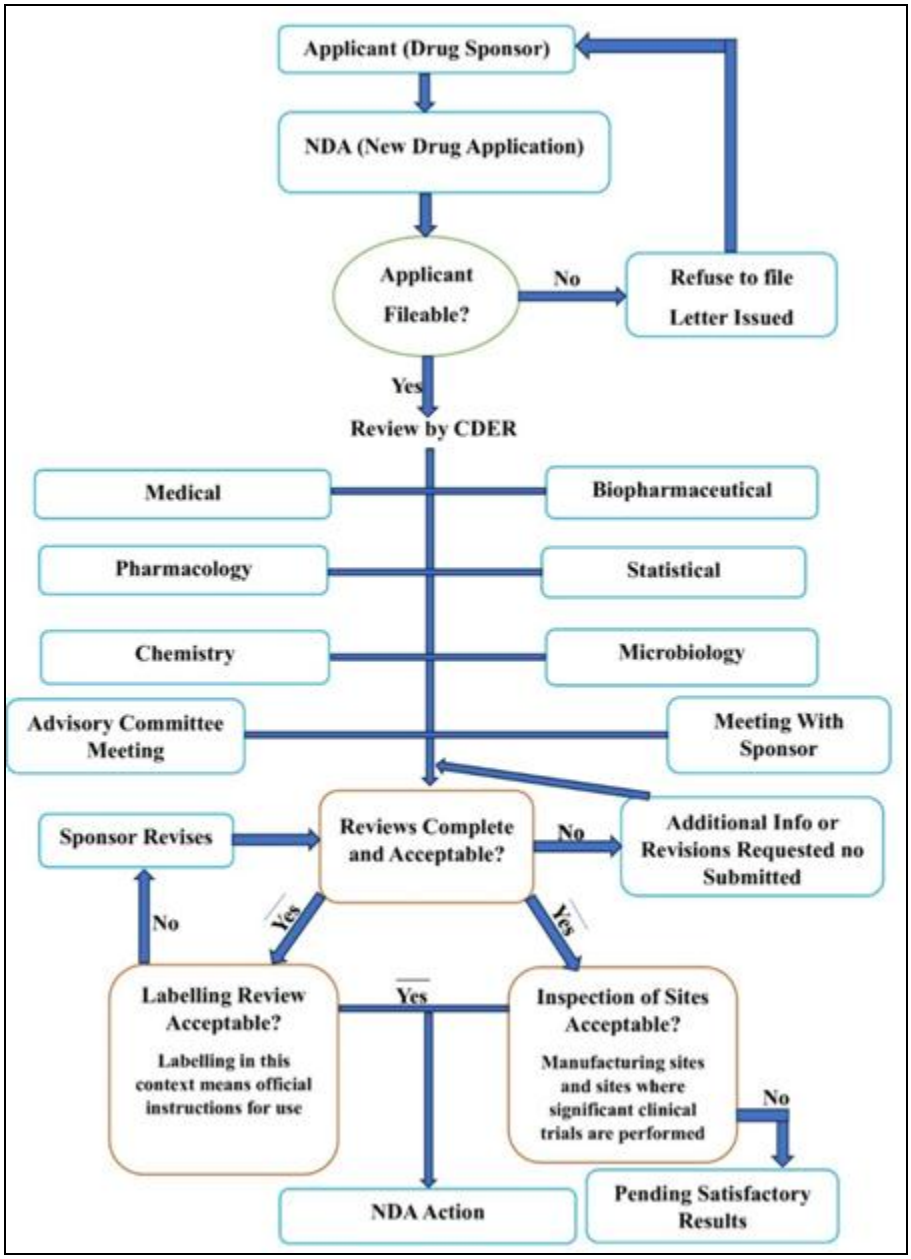

FIG. 9: NDA (NEW DRUG APPLICATION) CHART

Abbreviated New Drug Application (ANDA): This is an application to approve generic medications. The clinical trials conducted for the original, name-brand product do not have to be replicated by the sponsor. Rather, producers of generic drugs need to prove that their product is identical to and bioequivalent to a previously authorised brand-name product. For clinical trial testing involving humans Studies in Phase 1 (usually involving 20–80 people) and Phase 2 (usually involving a few dozen to approximately 300 people). Phase 3 studies (usually involving a few hundred to roughly three thousand participants). The FDA and drug sponsors often meet during the pre-NDA period, which comes right before a new drug application (NDA) is filed. The official process by which the FDA evaluates a drug for approval for marketing is the submission of an NDA 8. The FDA has sixty days from the date of receipt of an NDA to determine whether to file it for review 9. An FDA review team is tasked with assessing the sponsor's safety and efficacy studies if the FDA files the NDA. Information included on a drug's professional label which provides instructions on how to use the medication is reviewed by the FDA. As part of the approval process, the FDA inspects the manufacturing facilities for the drug. FDA reviewers will approve the application or find it either “approvable” or “not approvable”

It's an application made for approval of Generic Drugs. The sponsor is not required to reproduce the clinical studies that were done for the original, brand name product. Instead, generic drug manufacturers must demonstrate that their product is the same as, and bioequivalent to, a previously approved brand name product.

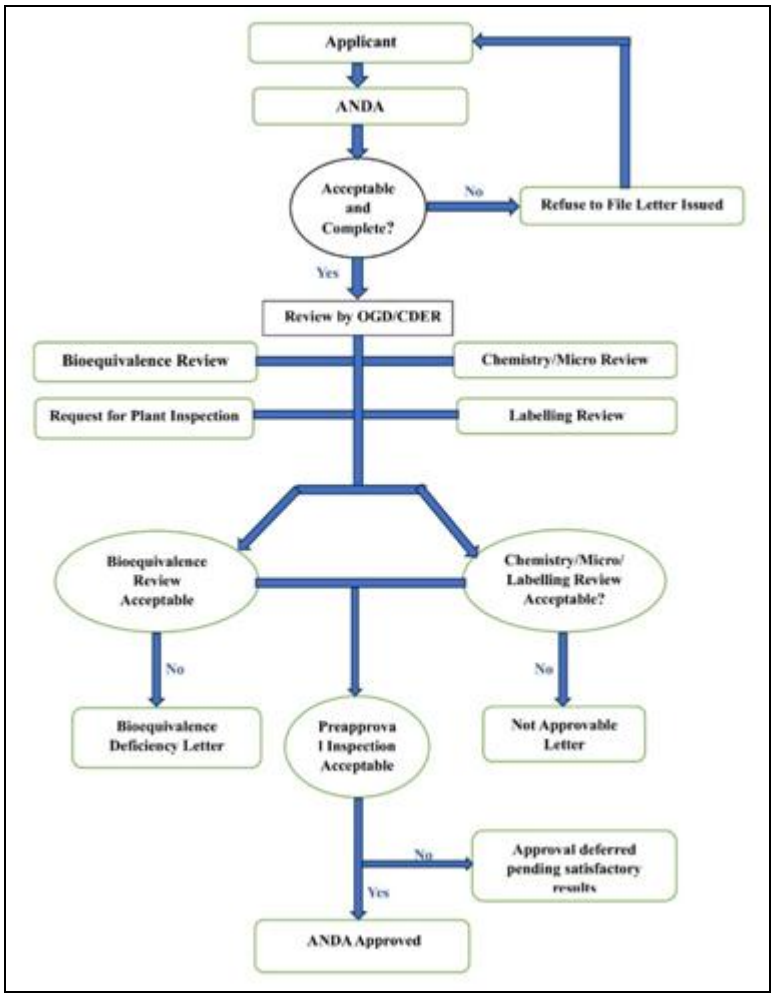

FIG. 10: GENERIC DRUG (ANDA) REVIEW PROCESS

Drug Approval Processs in Europe:

National Authorization Procedure: Every EU nation has its own protocols for approving a new drug's application for marketing. To learn more about the approval procedure, a sponsor can visit the website of the regulatory body in each nation where it wants to get marketing approval. By employing the decentralised or mutual recognition process, a sponsor can also simultaneously request approval from multiple EU nations.

1. The Nationalized procedure is one which allows applicants to obtain a marketing authorization in one-member state only.
2. In order to obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State.
3. New active substances which are not mandatory under Centralized procedure can obtain marketing authorization under this procedure.
4. Timeline for this procedure is 210 Days.

Decentralized Procedure: Sponsors may submit under the decentralised procedure for products that are not covered by the European Medicines Agency's (EMA) centralised procedures. Through this procedure, a sponsor can submit applications for concurrent authorization in multiple EU member states for goods that are not yet authorised in any EU member state. The process of mutual recognition [97]. A product is first authorised by one EU member state in line with that nation's national procedures before being recognised by other EU

members states under the mutual recognition procedure. Later, additional marketing authorizations may be requested from other EU nations that consent to recognise the first nation's decision rather than carrying out their own review. By using this process, businesses can simultaneously apply for authorization for products that haven't been approved in multiple EU countries. Approved in every nation within the EU and basically do not fit under the purview of the centralised process' necessary medication list. According to the evaluation report, which is produced by the RMS and any feedback received Marketing authorization must be granted by the CMS. Awarded in line with the judgement made in this decentralised system by the RMS & CMS protocol.

- Generally used for those products that has not yet received any authorisation in an EU country
- Time: 210 days.

Centralized Procedure: The European Medicines Agency is in charge of overseeing drug approvals in Europe. With its headquarters located in London, England, the EMA is a decentralised entity within the EU. It is in charge of conducting the scientific review of applications for permission to sell pharmaceuticals in Europe (through the centralised procedure). The Committee for Medicinal Products for Human Use (CHMP) reviews marketing applications for pharmaceuticals intended for human use. The following requirements must be satisfied for products to be eligible for review under the centralised procedure.

1. Biologic drugs developed by recombinant technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, and hybridoma and monoclonal antibody methods medicinal products containing new active substances for the following indications: AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune diseases and other immunedys functions, and viral diseases.

2. Orphan medicinal products other new active substances may, at the request of the applicant, be accepted for consideration under the centralized procedure when it can be shown that the product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a community authorization is in the best interests of patients at the Community level.

The centralized procedure is one which allows applicants to obtain a marketing authorization that is valid throughout the EU.

Results in a single authorization valid in EU, Norway, Iceland and Liechtenstein.

- Application evaluated by an assigned Rapporteur.
- Timeline: EMA opinion issued within 210 days, and submitted to European Commission for final approval.

Centralized Process is Compulsory for:

- Those medicines which are derived from any biotechnology processes, such as genetic engineering.
- Those medicines which are intended for the treatment of Cancer, HIV/AIDS, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions.
- Medicines officially designated 'Orphan medicines' (medicines used for rare diseases).

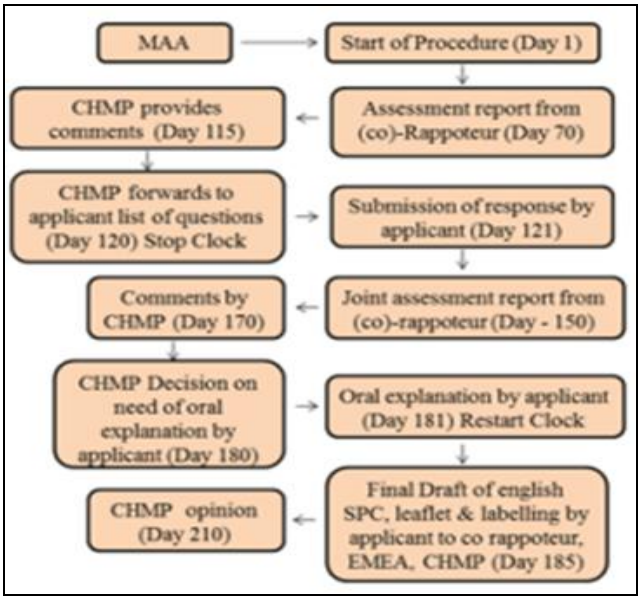

FIG. 11: FLOW CHART OF CENTRALIZED PROCEDURE [98]

Mutual Recognition Procedure: Through the Mutual Recognition process, candidates can get a marketing authorization in the other Concerned Member States (CMS) less than the member state of reference (RMS), where the medication has prior approval.

- Applicant submits identical dossier to all EU member states in which they want marketing authorization, including required information.
- As soon as one Member State decides to evaluate the medicinal product (at which point it becomes the "RMS"), it notifies this decision to other Member States (which then become the "CMS"), to whom applications have also been submitted.
- RMS issues a report to other states on its own findings.
- Generic industry is the major user of this type of drug approval procedure.
- This process may consume a time period of 390 days [98].

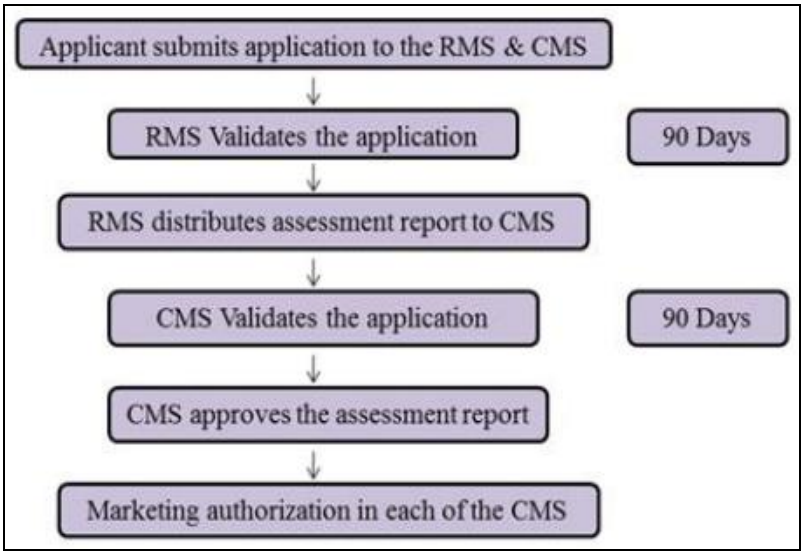

FIG. 12: FLOW CHART OF MUTUAL RECOGNITION PROCEDURE [98]

Pre-submission Process: A sponsor is required to notify the EMA of their intention to submit, along with the month of submission, at least seven months in advance of submitting a marketing authorization application (MAA). This pre-submission consists of several documents, one of which is a statement from the sponsor explaining why the application should be submitted through the centralized procedure. After reviewing the pre-submission, the EMA will decide whether to accept the MAA and will let the sponsor know.

Selection of Rapporteur/co-rapporteur: Within the EU, the rapporteur is a regulatory body with national jurisdiction. The CHMP members designate the rapporteur (reviewer) and co-rapsporteur (if necessary). The rapporteur is chosen using objective standards in order to guarantee impartial scientific advice and optimal utilization of the EMA's expertise. Completing the scientific evaluation and preparing an assessment report for the CHMP are the responsibilities of the rapporteur. If a co-rapporteur is engaged, the CHMP may choose to have the co-rapporteur either create an independent assessment report or offer a critique of the rapporteur's report. The appointment of a rapporteur or co-rapporteur is typically started during the CHMP meeting after a letter indicating the intention to submit is received. The sponsor is notified of the rapporteur/co-rapporteur once the EMA has deemed a submission admissible.

The Drug Approval Process in Japan: Beyond language barriers Japan's drug licensing process is simpler and less complicated than in some other nations. Apart from regulatory aspects, the PMDA provides sponsors with advisory services to help them understand the requirements and complicated procedures of medication approval [99]. This is a good development, as many manufacturers decide to register and market their medications in Japan.

One of the biggest markets in the world for pharmaceuticals is Japan. A study projects that the Japanese pharmaceutical market would grow between 2022 and 2027 at a CAGR of 1.06%. The gross domestic product (GDP) of Japan is estimated to be $5 trillion. Including over-the-counter drugs, the market value is estimated by the Ministry of Health, Labour and Welfare (MHLW) to be at $95 billion.

Numerous study papers indicate that the nation's market for pharmaceuticals and medical equipment will keep expanding. Experts claim that this happens because of the aging population that is happening so quickly and the necessity for new drugs to treat related illnesses. Approximately 35% of Japan's prescription drug imports come from the US, and this need grows daily.

Regulatory authority for drug approval in Japan:

In Japan, the two main regulatory bodies that examine and approve medications and medical equipment are

- Pharmaceuticals and Medical Devices Agency (PMDA), and
- Ministry of Health, Labour, and Welfare (MHLW).

Pharmaceuticals and Medical Devices Agency (PMDA) services:

PMDA provides the following services in drug regulatory:

- ✓ Consultation
- ✓ Pharmaceutical affairs consultation on R&D strategy
- ✓ Clinical trial consultation
- ✓ Regulatory review
- ✓ Pre-market review
- ✓ Re-examination
- ✓ Re-evaluation
- ✓ Use-results evaluation
- ✓ GLP/GCP/GPSP compliance assessments
- ✓ GMP/QMS/GCTP inspections
- ✓ Standards development
- ✓ Safety measures
- ✓ Relief services for adverse health events

Who can Apply for Drug Approval: Medical products can be registered, imported, and marketed in the Japanese market by a competent local entity that possesses a Marketing Authorization Holder (MAH) or a Designated Marketing Authorization Holder (DMAH).

How can a foreign manufacturer market drugs in Japan?

The following requirements must be met by foreign producers in order for their medications and medical equipment to be approved for sale:

Foreign Manufacturer Accreditation (FMA):

- A foreign manufacturer is a single foreign business that plans to produce pharmaceuticals, quasi-pharmaceuticals, cosmetics, or medical equipment and then import them into Japan.
- To market their goods in Japan, foreign producers must first receive a Foreign Manufacturer Accreditation (FMA) from the Ministry of Health, Labour, and Welfare.

Foreign Restrictive Approval:

- It is conceivable for international pharmaceutical producers to submit a straight application for market approval under their own names.
- In addition to other mandatory processes, foreign producers must conduct clinical trials to prove the efficacy, safety, and quality of the medications they are sending to Japan.

The Investigational New Drug (IND) approval process in Japan:

- Because the Japanese regulatory body uses the Common Technical Document (CTD) format for drug applications, applicants must prepare their IND applications and supporting documentation using the CTD format.

- The applicant may arrange a pre-IND consultation with PMDA prior to submitting an application, since these meetings aid in guaranteeing a faultless and efficient IND application procedure.
- While follow-up IND consultations might only take 14 days, initial consultations might take up to 30 days. The PMDA assesses the preclinical data, clinical study protocols, and other relevant documentation after the applicant's application.
- The applicant is required to promptly answer any questions posed by the PMDA during the evaluation. The Institutional Review Board (IRB) must be consulted for approval after the PMDA has finished its review.

Investigational New Drug (IND) Approval Process Flow:

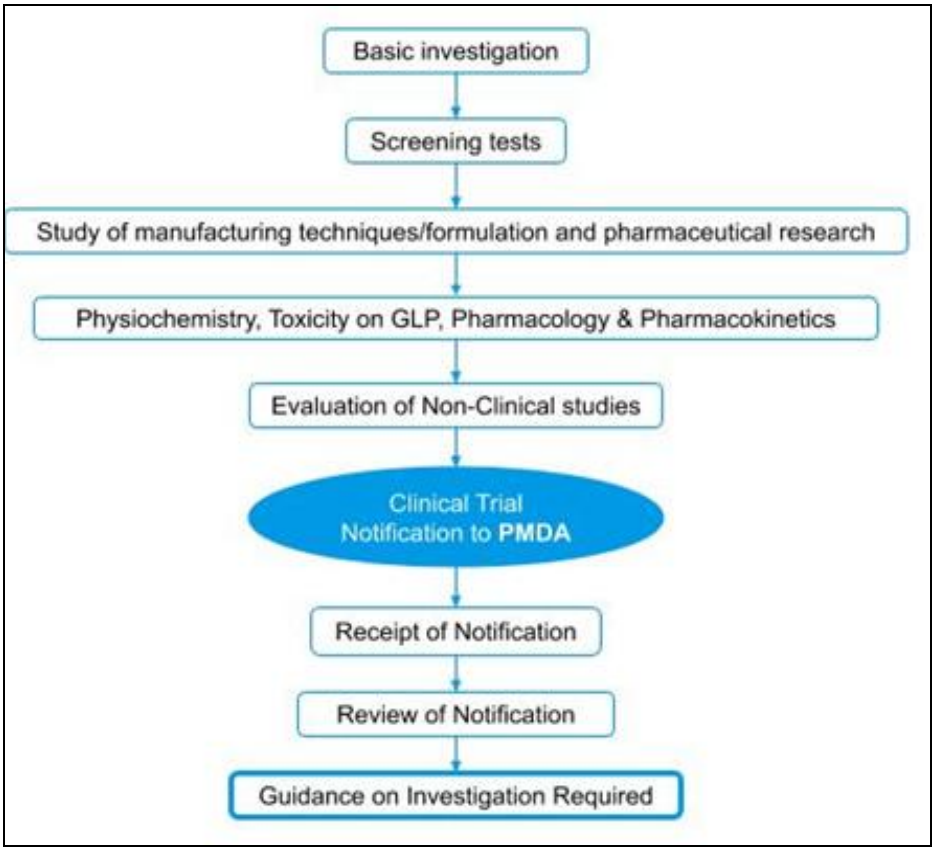

FIG. 13: INVESTIGATIONAL NEW DRUG (IND) APPROVAL PROCESS FLOW [100]

New Drug Application (NDA) approval process in Japan: The PMDA receives the applicant's New Drug Application (NDA) paperwork in order to approve them for sale.

After reviewing the application, the PMDA may decide to set up a face-to-face meeting with the applicant if they think it is required.

The applicant must discuss and respond to the PMDA's questions during the meeting, and the PMDA reviewer will create a review report following the in-person meeting. The PMDA arranges an Expert Discussion if the review reveals any important problems. It entails a conversation about the suggested critical issue between the external expert and the PMDA reviewer. Following evaluation, the specialists provide the findings and GMP conformance inquiry reports to the Ministry of Health and Labor Welfare (MHLW). The MHLW, the Ministry of Health and Labor Welfare, may approve the new drug application (NDA) after consulting with the Pharmaceutical Affairs and Food Sanitation Council (PAFSC).

The approval certificate is issued by the MHLW's Evaluation and Licensing Division upon approval. The PMDA provides the certification of approval for the medications that the bureau has examined.

Regulatory Process flow for New Drug Application (NDA) Approval:

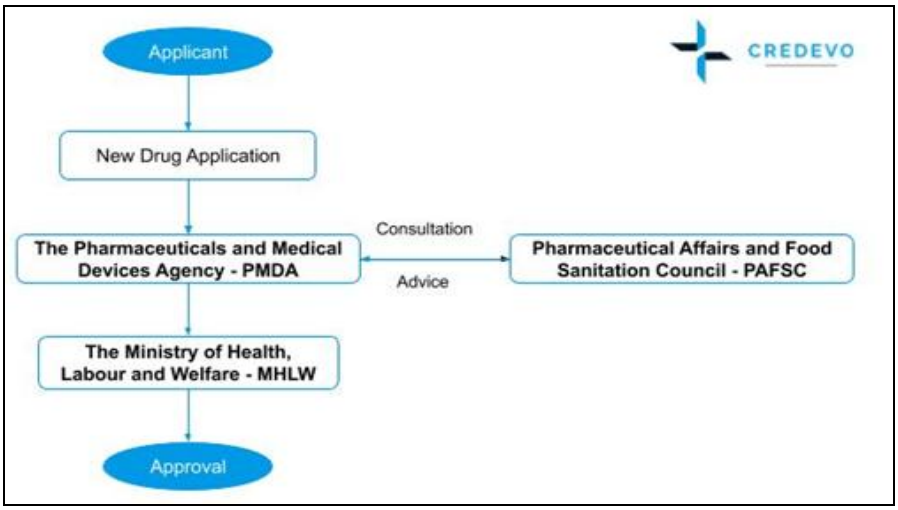

FIG. 14: REGULATORY PROCESS FLOW FOR NEW DRUG APPLICATION (NDA) APPROVAL [100]

Complete Overview of the Approval Process in Japan:

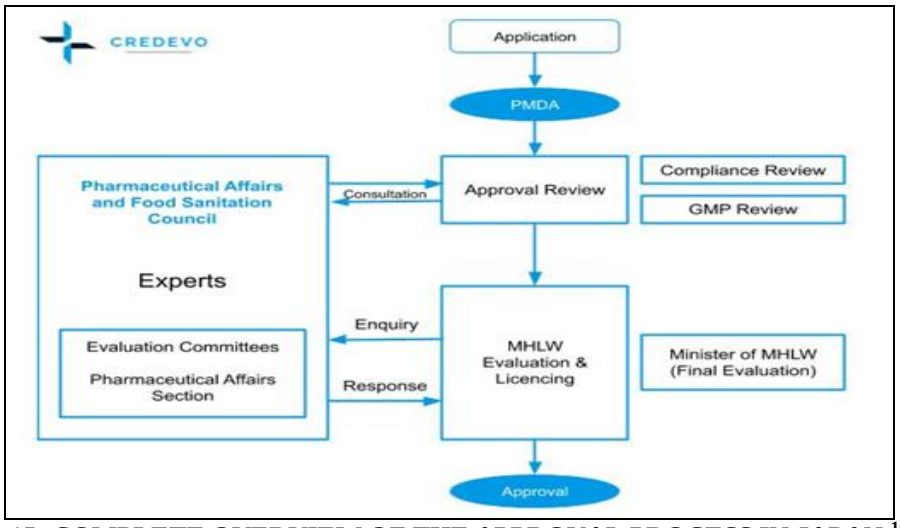

FIG. 15: COMPLETE OVERVIEW OF THE APPROVAL PROCESS IN JAPAN [100-105]

CONCLUSION: Scientists whose work may be crucial in determining the method to appropriately design their research report for the effective translation of preclinical research to human subjects can benefit from a brief summary of the drug discovery and development process.

The needs of the market at the time, academic and clinical research, the business world, *etc*., could have all contributed to the idea for the drug's discovery and development. Each country's laws, rules, and regulations pertaining to the pharmaceutical sector must be followed in order to regulate the marketing of medications. This article contains information about medications, their development, and the regulatory agencies in Europe, Japan, the USA, and India.

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REFERANCES:

1. Smith GC and OíDonnel JT: The Process of New Drug Discovery and Development, Eds., 2nd edition, Informa6+ Healthcare, New York 2006.

2. Stegemann S, Moreton C, Svanbäck S, Box K, Motte G and Paudel A: Trends in oral small-molecule drug discovery and product development based on product launches before and after the Rule of Five. Drug Discovery Today 2023; 28(2): 103344.
3. Garcia Jimenez D, Poongavanam V and Kihlberg J: Macrocycles in drug discovery─ learning from the past for the future. J of Medicinal Chemistry 2023; 66(8): 5377-96.
4. Ashwini T, Reema Narayan, Padmaja A. Shenoy and Usha Y. Nayak: Computational modeling for the design and development of nano-based drug delivery systems. Journal of Molecular Liquids 368(A) 2022. 120596. https://doi.org/10.1016/j.molliq.2022.120596.
5. Berdigaliyev N and Aljofan M: An overview of drug discovery and development. Future Medicinal Chemistry 2020; 12(10): 939-47. https://doi.org/10.4155/fmc-2019-0307.
6. Zhang C, Chen G, Tang G, Xu X, Feng Z, Lu Y, Chan YT, Wu J, Chen Y, Xu L and Ren Q: Multi-component chinese medicine formulas for drug discovery: state of the art and future perspectives. Acta Materia Medica 2023; 2(1): 106-25.
7. Joshi V, Avasare N and Bhangale R: Nanobots in the medical field: A comprehensive review. InAIP Conference Proceedings 2024; 2985: 1. AIP Publishing.
8. Nitulescu GM: Techniques and Strategies in Drug Design and Discovery. International Journal of Molecular Sciences 2024; 25(3): 1364. https://doi.org/10.3390/ijms25031364
9. Friedman LM, Furberg CD and Demets DL: Fundamentals of clinical trials. 4th ed. New York: Springer Science and Business Media LLC 2010.
10. Cox PB and Gupta R: Contemporary computational applications and tools in drug discovery. ACS Medicinal Chemistry Letters 2022; 13(7): 1016-29.
11. Young RJ, Flitsch SL, Grigalunas M, Leeson PD, Quinn RJ, Turner NJ and Waldmann H: The time and place for nature in drug discovery. Jacs Au 2022; 2(11): 2400-16.
12. Mak KK, Wong YH and Pichika MR: Artificial intelligence in drug discovery and development. Drug Discovery and Evaluation: Safety and Pharmacokinetic Assays 2023; 1-38.
13. Mercurio FA, Vincenzi M and Leone M: Hunting for novel routes in anticancer drug discovery: Peptides against Sam-Sam interactions. International Journal of Molecular Sciences 2022; 23(18): 10397.
14. Duboc C and Flitsch SL: Drug Discovery and Development. JACS Au 2024; 4(2): 276-8.
15. Avram S, Bologa CG, Holmes J, Bocci G, Wilson TB, Nguyen DT, Curpan R, Halip L, Bora A, Yang JJ and Knockel J: Drug Central 2021 supports drug discovery and repositioning. Nucleic Acids Research 2021; 49(D1): D1160-9.
16. Berdigaliyev N and Aljofan M: An overview of drug discovery and development. Future Medicinal Chemistry 2020; 12(10): 939-47.
17. Moffat J, Vincent F, Lee J, Eder J and Prunotto M: Opportunities and hallenges in phenotypic drug discovery: an industry perspective. Nature Reviews Drug Discovery 2017; 16(8): 531-543.
18. Vincent F, Nueda A, Lee J, Schenone M, Prunotto M and Mercola M: Phenotypic drug discovery: recent successes, lessons learned and new directions. Nature Reviews Drug Discovery 2022; 21(12): 899-914.
19. DiMasi JA, Hansen RW and Grabowski HG: The price of innovation: new estimates of drug development costs. Journal of Health Economics 2003; 151-185.
20. Gashaw I, Ellinghaus P, Sommer A and Asadullah K: What makes a good drug target. Drug Discovery Today 2012; 17: S24-S30.
21. Zhang Y, Liu C, Liu M, Liu T, Lin H, Huang CB and Ning L: Attention is all you need: utilizing attention in AI-enabled drug discovery. Briefings in bioinformatics 2024; 25(1): bbad467.
22. O'Connor EC, Kambara K and Bertrand D: Advancements in the use of xenopus oocytes for modelling neurological disease for novel drug discovery. Expert Opinion on Drug Discovery 2024; 19(2): 173-87.
23. Hasselgren C and Oprea TI: Artificial intelligence for drug discovery: Are we there yet?. Annual Review of Pharmacology and Toxicology 2024; 64: 527-50.
24. Pharma Central, Materials and Knowledge Platform. Drug Discovery and Development: a step by step guide. PharmaCentral | Materials and Knowledge Platform. 2021. Available from: https://pharmacentral.com/learning-hub/technical-guides/drug-discovery-and-development-a-step-by-step-guide/
25. Available from: https://googleweblight.com/i?u=https://www.nature.com/subjects/drugdiscovery &grqid=DEji1MmA&hl=en-IN
26. Rick NG, Drugs from discovery to approval. 2nd ed., John Wiley & Sons, Inc., (Hoboken, New Jersey). p.201-210.
27. Vogel HG: Drug Discovery and Evaluation 2nd edition. Springer, USA, 2002.
28. Pharmacology-I, Essential of pharmacotherapeutics, By F. S. K. Barar S. chand publication, 1stedition 1985; 56-612.
29. Available from:https://googleweblight.com/i?u=https://www.slideshare.net/mobile/rahul_pharma/drug discovery-and-development-10698574&grqid=dRB10k76&hl=en-IN
30. Shayne CG: Introduction: drug Discovery in the 21st Century. Drug Discovery Handbook, Wiley Press, 2005; 1-10.
31. IRA R Berry, Robert P Martin, Editors, The Pharmaceutical Regulatory Process. 2nd ed., Informa Healthcare. p.45,46.
32. Faqi AS: A comprehensive guide to toxicology in preclinical drug development. Waltham, MA: Elsevier; 2013.
33. Karara AH, Edeki T and McLeod J: PhRMA survey on the conduct of first-in-human clinical trials under exploratory investigational new drug applications. Journal of Clinical Pharmacology 2010; 50: 380– 391.
34. Fitzpatrick S: The clinical trial protocol. Buckinghamshire: Institute of Clinical Research 2005.
35. Kinders and Robert: Phase 0 Clinical Trials in Cancer Drug Development: From FDA.
36. DiMasi J: Risks in New Drug Development: Approval success Rates for Investigational Drugs. Clinical Pharmacology & Therapeutics 2001; 297-307.
37. Friedhoff L: New Drugs: An Insider's Guide to the FDA's New Drug Approval Process for Scientists, Investors and Patients. New York, NY: PSPG Publishing 2009.
38. FDA (2003). New Drug Approval Reports. http://www.fda.gov/cder/rdmt/default.htm.
39. FDA, The FDA and the Drug Development Process: How the FDA insures that drugs are safe and effective, FDA Fact sheet, 2002.
40. Adams CP and Brantner VV: New Drug Development: Estimating entry from human clinical trials. Bureau of Economics Federal Trade Commission. 2003.
41. Kiriiri GK, Njogu PM & Mwangi AN: Exploring different approaches to improve the success of drug discovery and

development projects: a review. Futur J Pharm Sci 2020; 6(27): https://doi.org/10.1186/s43094-020-00047-9

42. Marshall S, Madabushi R, Manolis E, Krudys K, Staab A, Dykstra K and Visser SA: Model-informed drug discovery and development: current industry good practice and regulatory expectations and future perspectives. CPT: Pharmacometrics & Systems Pharmacology 2019; 8(2): 87-96.
43. Bradshaw EL, Spilker ME, Zang R, Bansal L, He H, Jones RD, Le K, Penney M, Schuck E, Topp B and Tsai A: Applications of quantitative systems pharmacology in model-informed drug discovery: perspective on impact and opportunities. CPT: Pharmacometrics & Systems Pharmacology 2019; 8(11): 777-91.
44. Chen W, Liu X, Zhang S and Chen S: Artificial intelligence for drug discovery: Resources, methods, and applications. Molecular Therapy-Nucleic Acids 2023; 31: 691-702.
45. Sobh EA, Dahab MA, Elkaeed EB, Alsfouk AA, Ibrahim IM, Metwaly AM and Eissa IH: Computer aided drug discovery (CADD) of a thieno [2, 3-d] pyrimidine derivative as a new EGFR inhibitor targeting the ribose pocket. Journal of Biomolecular Structure and Dynamics 2024; 42(5): 2369-91.
46. Nag S, Baidya AT, Mandal A, Mathew AT, Das B, Devi B and Kumar R: Deep learning tools for advancing drug discovery and development. 3 Biotech 2022; 12(5): 110.
47. Singh V, Mambwe D, Korkor CM and Chibale K: Innovation Experiences from Africa-Led Drug Discovery at the Holistic Drug Discovery and Development (H3D) Centre. ACS Medicinal Chemistry Letters 2022; 13(8): 1221-30.
48. Ferreira LL, de Moraes J and Andricopulo AD: Approaches to advance drug discovery for neglected tropical diseases. Drug Discovery Today 2022; 27(8): 2278-87.
49. Cheung E, Xia Y, Caporini MA and Gilmore JL: Tools shaping drug discovery and development. Biophysics Reviews 2022; 3(3).
50. Jens M. Kelm, Madhu Lal-Nag, Gurusingham Sitta Sittampalam and Marc Ferrer: Translational in vitro research: integrating 3D drug discovery and development processes into the drug development pipeline. Drug Discovery Today 2019; 24(1): 26-30. https://doi.org/10.1016/j.drudis.2018.07.007.
51. Jimonet P, Druart C, Blanquet-Diot S, Boucinha L, Kourula S, Le Vacon F, Maubant S, Rabot S, Van de Wiele T, Schuren F and Thomas V: Gut Microbiome Integration in Drug Discovery and Development of Small Molecules. Drug Metabolism and Disposition 2024; 52(4): 274-87.
52. Hopkins MM, Kraft A, Martin PA, Nightingale P and Mahdi S: Is the Biotechnology Revolution a Myth? Elsevier eBooks [Internet]. 2007. p. 591–613. Available from: https://www.sciencedirect.com/topics/nursing-and-health-professions/drug-development
53. Deore AB, Dhumane JR, Wagh R & Sonawane R: The Stages of Drug Discovery and Development Process. Asian Journal of Pharmaceutical Research and Development 2019; 7(6): 62–67. https://doi.org/10.22270/ajprd.v7i6.616
54. Available from: https://www.fiosgenomics.com/drug-development-process-preclinical-phase/
55. Bender A and Cortes-Ciriano I: Artificial intelligence in drug discovery: what is realistic, what are illusions? Part 2: a discussion of chemical and biological data. Drug Discovery Today 2021; 26(4): 1040-52.
56. Process of new drug development | Our R&D | SEIKAGAKU CORPORATION. Available from: https://www.seikagaku.co.jp/en/development/flow.html
57. Krishnaswami S, Austin D, Della Pasqua O, Gastonguay MR, Gobburu J, Van der Graaf PH, Ouellet D, Tannenbaum S and Visser SA: MID3: mission impossible or model-informed drug discovery and development? Point-counterpoint discussions on key challenges. Clinical Pharmacology and Therapeutics 2020; 107(4): 762.
58. Vijayan RS, Kihlberg J, Cross JB and Poongavanam V: Enhancing preclinical drug discovery with artificial intelligence. Drug discovery today 2022; 27(4):967-84.
59. Available from: https://www.fiosgenomics.com/bioinformatics-and-the-pharmaceutical-industry/
60. Sharma R, Kaur G, Bansal P, Chawla V and Gupta V: Bioinformatics paradigms in drug discovery and drug development. Current Topics in Medicinal Chemistry 2023; 23(7): 579-88.
61. Qureshi R, Irfan M, Gondal TM, Khan S, Wu J, Hadi MU, Heymach J, Le X, Yan H and Alam T: AI in drug discovery and its clinical relevance. Heliyon 2023.
62. Łapińska N , Pacławski A , Szlęk J and Mendyk A. Serotonin AI: Serotonergic System Focused, Artificial Intelligence-Based Application for Drug Discovery. Journal of Chemical Information and Modeling 2024.
63. Gene Vision. Clinical trials - Gene Vision. Gene Vision. 2020. Available from: https://gene.vision/knowledge-base/clinical-trials/#clinical_trial
64. Reiner AT, Witwer KW, Van Balkom BWM, De Beer J, Brodie C, Corteling RL, Gabrielsson S, Gimona M, Ibrahim AG, De Kleijn D, Lai CP, Lötvall J, Del Portillo HA, Reischl IG, Riazifar M, Salomon C, Tahara H, Toh WS, Wauben MHM, Yang VK, Yang Y, Yeo RWY, Yin H, Giebel B, Rohde E and Lim SK: Concise Review: developing best-practice models for the therapeutic use of extracellular vesicles. Stem Cells Translational Medicine. 2017; 6(8): 1730–1739. Available from: https://doi.org/10.1002/sctm.17-0055
65. Galluppi GR, Brar S, Caro L, Chen Y, Frey N, Grimm HP, Rudd DJ, Li CC, Magee M, Mukherjee A and Nagao L: Industrial Perspective on the Benefits Realized From the FDA's Model-Informed Drug Development Paired Meeting Pilot Program. Clinical Pharmacology and Therapeutics 2021; 110(5): 1172.
66. Phases of clinical trials. MD Anderson Cancer Center. Available from: https://www.mdanderson.org/patients-family/diagnosis-treatment/clinical-trials/phases-of-clinical-trials.html
67. Bordukova M, Makarov N, Rodriguez-Esteban R, Schmich F and Menden MP: Generative artificial intelligence empowers digital twins in drug discovery and clinical trials. Expert Opinion on Drug Discovery 2024; 19(1): 33-42.
68. Polasek TM and Rostami-Hodjegan A: Virtual twins: understanding the data required for model-informed precision dosing. Clinical Pharmacology and Therapeutics 2020; 107(4): 742-5.
69. Madabushi R, Benjamin JM, Grewal R, Pacanowski MA, Strauss DG, Wang Y, Zhu H and Zineh I: The US Food and Drug Administration's model-informed drug development paired meeting pilot program: early experience and impact. Clinical Pharmacology & Therapeutics 2019; 106(1): 74-8.
70. https://med.uc.edu/depart/psychiatry/research/clinical-research/crm/trial-phases-1-2-3-defined

71. Available from: https://images.app.goo.gl/RmWekEzAwCLxsdg99
72. Boike L, Henning NJ and Nomura DK: Advances in covalent drug discovery. Nature Reviews Drug Discovery 2022; 21(12): 881-98.
73. Surur AS, Fekadu A, Makonnen E and Hailu A: Challenges and opportunities for drug discovery in developing countries: the example of cutaneous leishmaniasis. ACS Medicinal Chemistry Letters 2020; 11(11): 2058-62.
74. Gupta NV, Reddy CM, Reddy KP, Kulkarni RA and Shivakumar: Process of Approval of New Drug in India with Emphasis on Clinical trials 2012; 13: 17-23
75. European Union drug approval: Overview of new European Medicines Evaluation Agency and approval process. U.S. GAO. Available from: https://www.gao.gov/products/HEHS-96-71
76. Available from: http://www.cdsco.nic.in/writereaddata/Guidance%20documents.pdf
77. Pharmaceutical Regulatory Affairs: Open Access, Regulatory Requirements and Drug Approval Process in India, Europe and US, Pharmaceut Reg Affairs 2018, 7:2.
78. Clinical Trial & Global Clinical Trial. [cited 2014 January].Available from: http://cdsco.nic.in/clinical_trial.htm.
79. The New Drug Approval Process.[cited 2014 January].Available from: http://www.fda.gov/cder/handbook.
80. CDER Guidance: IND application process (interactive session).[cited 2014 January].Available from: www.fda.gov/cder/regulatory/applications/ind_ page_1.htm.
81. Guidance for industry on preparation of common technical document for import/ manufacture and marketing approval of new drugs for human use. (NEW DRUG APPLICATION–NDA). .[cited 2014 January].Available from: http://cdsco.nic.in/CTD_Guidance%20- Final.pdf.
82. A review on drug approval process for us, europe and India, International Journal of Drug Regulatory Affairs 2014; 2(1): 1- 11, ISSN: 2321 – 6794.
83. Rick NG: Drugs from discovery to approval. 2nd ed., John Wiley & Sons, Inc., (Hoboken, New Jersey). p.201.
84. Walker PA, Ryder S and Lavado A: The evolution of strategies to minimize the risk of human drug-induced liver injury (DILI) in drug discovery and development. Arch Toxicol 2020; (94): 2559–2585. https://doi.org/10.1007/s00204-020-02763-w
85. Subbaiah MA, Rautio J and Meanwell NA: Prodrugs as empowering tools in drug discovery and development: recent strategic applications of drug delivery solutions to mitigate challenges associated with lead compounds and drug candidates. Chemical Society Reviews 2024.
86. Madabushi R, Seo P, Zhao L, Tegenge M and Zhu H: Role of model-informed drug development approaches in the lifecycle of drug development and regulatory decision-making. Pharmaceutical Research 2022; 39(8): 1669-80.
87. Singh N, Vayer P, Tanwar S, Poyet JL, Tsaioun K and Villoutreix BO: Drug discovery and development: introduction to the general public and patient groups. Frontiers in Drug Discovery 2023; 3: 1201419.
88. Available from:https://www.pharmacologyeducation.org/clinical-pharmacology/drug-development-and-marketing.
89. Mak KK, Wong YH and Pichika MR: Artificial intelligence in drug discovery and development. Drug Discovery and Evaluation: Safety and Pharmacokinetic Assays 2023; 1-38.
90. Available from: https://www.biostock.se/en/2023/01/drug-development-the-four-phases/
91. Office of the Commissioner. Step 5: FDA Post-Market drug safety monitoring [Internet]. U.S. Food And Drug Administration. 2018. Available from: https://www.fda.gov/patients/drug-development-process/step-5-fda-post-market-drug-safety-monitoring
92. Rick NG: Drugs from discovery to approval. 2nd ed., John Wiley & Sons, Inc., (Hoboken, New Jersey). p.202.
93. IRA R Berry, Robert P Martin, Editors, the Pharmaceutical Regulatory Process. 2nd ed., Informa Healthcare 45.
94. Surur AS, Fekadu A, Makonnen E and Hailu A: Challenges and opportunities for drug discovery in developing countries: the example of cutaneous leishmaniasis. ACS Medicinal Chemistry Letters 2020; 11(11): 2058-62.
95. Rick NG: Drugs from discovery to approval. 2nd ed., John Wiley & Sons, Inc.,(Hoboken, New Jersey). 205-7.
96. Rick NG, Drugs from discovery to approval. 2nd ed., John Wiley & Sons, Inc., (Hoboken, New Jersey) 208-10.
97. Yingngam B: New drug discovery. In Multidisciplinary Applications of Natural Science for Drug Discovery and Integrative Medicine 2023; 134-184. IGI Global.
98. Available from: https://www.researchgate.net/publication/261635461
99. Surur AS, Fekadu A, Makonnen E and Hailu A: Challenges and opportunities for drug discovery in developing countries: the example of cutaneous leishmaniasis. ACS Medicinal Chemistry Letters 2020; 11(11): 2058-62.
100. Expert T: The drug approval process in Japan. Credevo Articles. 2022. Available from: https://credevo.com/articles/2020/04/15/the-drug-approval-process-in-japan/
101. Available from: https://www.thepharmaletter.com/article/japan-pharma-market-review
102. Dabney J, Dabney J. How are drugs priced in Japan? [Internet]. Market Realist. 2016. Available from: https://marketrealist.com/2016/04/drugs-priced-japan/
103. Pharmaceuticals and Medical Devices Agency. Available from: https://www.pmda.go.jp/english/about-pmda/0004.html
104. Available from: http://www.jpma.or.jp/english/parj/pdf/2018.pdf
105. Available from:http://www.nifds.go.kr/brd/m_95/down.do?brd_id=board_mfds_411&seq=21651&data_tp=A&file_seq=1

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