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Review Article

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Regulatory requirements for the New Drug approval process in different Countries

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Abstract

Currently, different nations must adhere to various regulatory standards in order to get a new drug's marketing authorization application (MAA) approved. The US Food and Drug Administration (USFDA), the European Medicines Agency (EMA), the Central Drug Standard Control Organization (CDSCO), the Therapeutic Goods Administration (TGA) in Australia, the State Food and Drug Administration (SFDA) in China, and the Therapeutic Products Directorate (TPD) in Canada were all studied for this production's regulatory requirements and drug approval process.

Keywords: Drug Regulatory affairs, NDA, USFDA, EMA, CDSCO, New Drug Approval Process, FDA, Marketing authorization applications (MAA)

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1. Introduction

The profession of regulatory affairs (RA) serves as the point of contact between the pharmaceutical sector and drug regulatory agencies around the globe. It mostly entails the registration of pharmaceutical products in the relevant nations prior to their marketing. (1) The pharmaceutical industry is well-organized, and systematic, and adheres to worldwide regulatory requirements to produce medical equipment, traditional herbal items, cosmetics, and chemical and biological medications for human and veterinary consumption. (2)

In recent years, there have been difficulties with the government's price regulation, patent licensing requirements, and medicine approval procedures in India.(3) Regulating bodies is essential in giving access to medicines and tracking their costs because the prohibitive cost of drugs restricts access to health care globally. Each country has its own regulatory framework in place to ensure that its population receives high-quality, priced healthcare. The Drug Controller General of India (DCGI) is the primary regulatory body in India. It is a part of the Central Drugs Standard Control Organization (CDSCO).(4) New medications and clinical trials must be approved in India by the office of the Drug Controller General. The European Medicines Agency (EMA) was established in the European Union (EU) in 1995. London is home to the EMA, a decentralized EU body. Drugs created by pharmaceutical companies for use in the EU must undergo scientific evaluation, oversight, and safety monitoring by the EMA. One of the first federal regulatory organizations, the Food and Drug Administration (FDA) of the United States (US), was established in 1906.(5)

It is practically impossible to find a single regulatory method for marketing authorization applications (MAA) that is relevant to different nations. The regulatory requirements for MAA in each country must therefore be understood.

An application for authorization to market a novel drug is known as a new drug application (NDA), which is made to the appropriate regulatory authority. A sponsor must provide preclinical and clinical test results, a description of the manufacturing processes, and other information to request this permission. Different Clinical Trial Phases:

- Mice, rats, rabbits, and monkeys were used in the preclinical investigation
- Phase I Human Pharmacology Trial: Assessment of Safety and Tolerance

- Phase II exploratory trials assess the effectiveness and short-term adverse effects,
- while Phase III confirmatory trials assess therapeutic benefits.
- The post-marketing trial, or Phase IV, refers to research conducted following drug approval.(6)

NDA is subjected to a technological screening after being received by the agency. This assessment makes sure that there is enough data and information in each section to support "filing" the application. Following the review of an NDA, the sponsor may get one of three actions:

Not Approval—in this letter, list any shortcomings and explain why. Changes that could be approved, along with a potential commitment to conduct post-approval studies.

Approval—It states that the medication has received approval.

If the activity taken is either approved or disapproved, the regulatory body gives the applicant the chance to meet with the agency and go over the shortcomings. The governing body gives the applicant the chance to meet with the agency and go through the shortcomings if the activity taken is either approved or not approved.(7)

The process for drug clearance in several nations, including India, the United States, Australia, China, Canada, and European nations, is the focus of the review article.

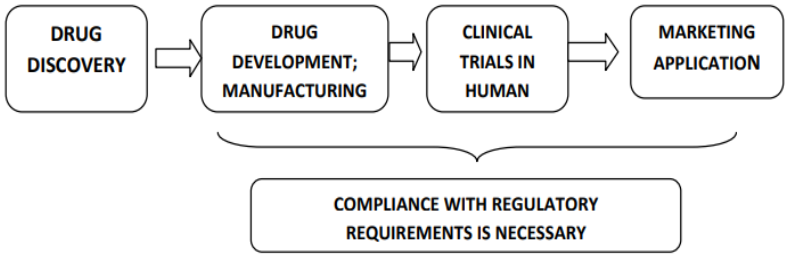

Figure 1. Drug development phase

2. Drug approval in the United States

The original Food and Drug Act was approved by Congress and signed by President Theodore Roosevelt the same year that the United States Pharmacopoeia was formed. Interstate trade in misbranded and tainted foods, beverages, and medicines is forbidden by the Food and Drugs Act. But the sulfanilamide catastrophe in 1937 led to the introduction of the Federal Food, Medicine, and Cosmetic Act and other regulations, including the need that a drug must demonstrate its safety before going on sale. The Kefauver- Harris Amendment Act, which mandates that makers must demonstrate a drug's efficacy and safety, was passed in 1962. Drugs, biologics, gadgets, and food are all regulated by separate FDA centers.(7)

The world's strictest rules for licensing new medications may be found in the United States. Many people believe that the United States has the strictest requirements in the world for drug approval.

A novel medicine's sponsor's plans for human testing in clinical trials are described in an investigational new drug application (IND). Studies in phases 1 and 2 (usually involving 20 to 80 persons) (typically involve a few dozen to about 300 people). third-phase research (typically involving several hundred to about 3,000 people).

Pre-NDA meetings, which take place just before a new drug application (NDA) is submitted, typically involve the FDA and drug sponsors. Before deciding whether to grant a drug's marketing clearance, the FDA must obtain an NDA.

New Drug Application

NDA is an application submitted to the FDA for permission to market a new drug. To obtain this permission a sponsor submits preclinical and clinical test data to NDA for analyzing the drug information, description of manufacturing procedures.

After NDA received by the agency, it undergoes a technical screening. This evaluation ensures that sufficient data and information have been submitted in each area to justify “filing” the application that is FDA formal review. At the conclusion of FDA review of an NDA, there are 3 possible actions that can send to sponsor:

Not approvable- In this letter list of deficiencies and explain the reason.

Approvable - It means that the drug can be approved but minor deficiencies that can be corrected like-labeling changes and possible request commitment to do post-approval studies.

Approval- It state that the drug is approved.

If the action taken is either an approvable or a not approvable, then FDA provides applicant with an opportunity to meet with agency and discuss the deficiencies.

2.1. The Evolution of US Drug Law and Regulations (8-12):

Establish requirements for drug strength and purity, the United States Pharmacopoeia (USP) was founded in

1820. Significant turning points in US drug law development include:

Food and Drugs Act (1906): It mandates that the purity and strength of the medications must meet recognized standards.

Federal Food, Drug, and Cosmetic Act (1938): After the sulfanilamide tragedy, legislation was passed requiring drugs to be shown to be safe before going on sale.

Kefauver-Harris Amendment (1962): The thalidomide tragedy led to its passage. Manufacturers are required to substantiate the effectiveness and safety of their products. Reports of unfavourable effects should be sent to FDA by all companies.

Orphan drug Act (1973): This allows tax deductions for drug companies to develop orphan drugs.

Generic drug enforcement Act (1992): It deals with convictions related to ANDA approvals.

FDA Modernization Act (1997): Regarding the assessment of user fees, their collection, and the expedited approval procedures, it makes some amendments to the Federal Food, Drug, and Cosmetic Act.

2.2. Investigational New Drug (IND) Application (13):

Prior to human testing, the FDA received an application. Information on chemistry, manufacturing and controls, pharmacology, and toxicology, as well as any prior human experience, is fully described. The complete process of INDA has been illustrated in Figure 1.

a) Types of IND

An Investigator IND: It is offered by a physician who initiates the inquiry, manages its execution, and is personally responsible for the administration or dispensing of the investigational substance. An unapproved drug or an approved product could be the subject of a research IND that a doctor submits to suggest investigating it for a new use or in a new group of patients.

Emergency Use IND: As a result, the FDA can approve the use of an investigational medicine in situations where there isn't enough time to submit an IND.

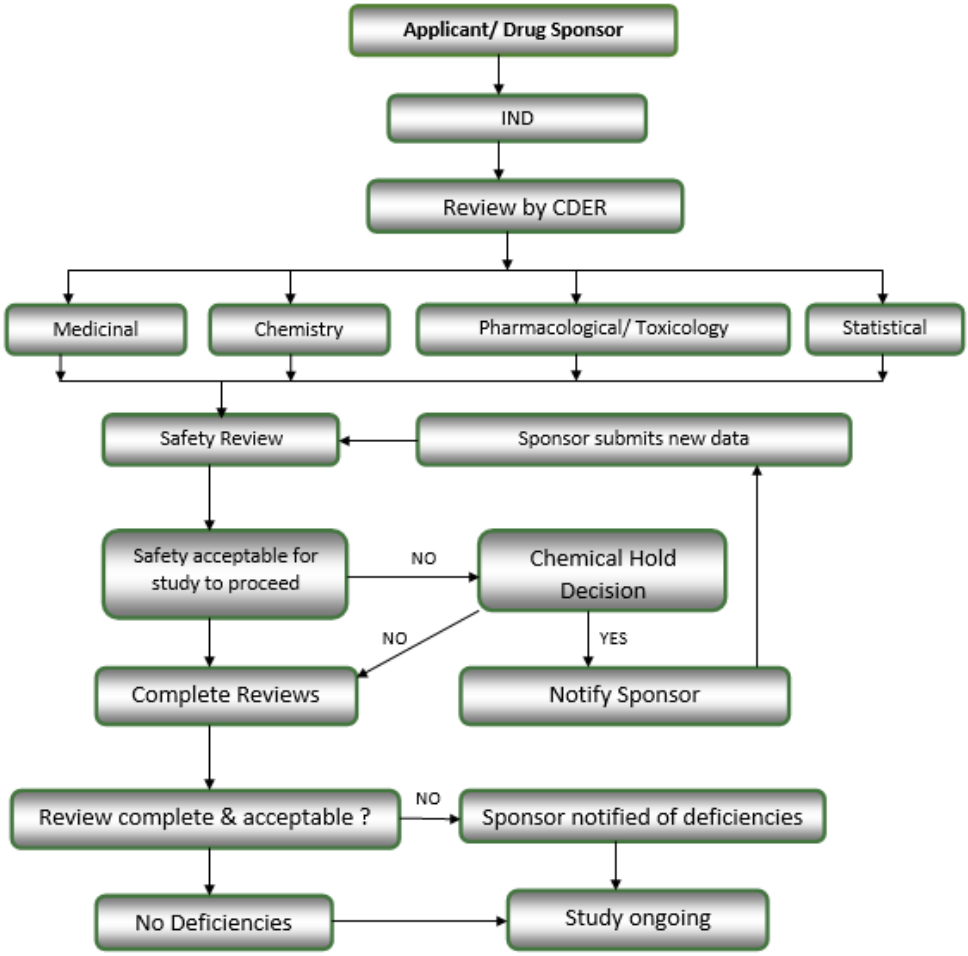

Figure 2. Investigational New Drug Application

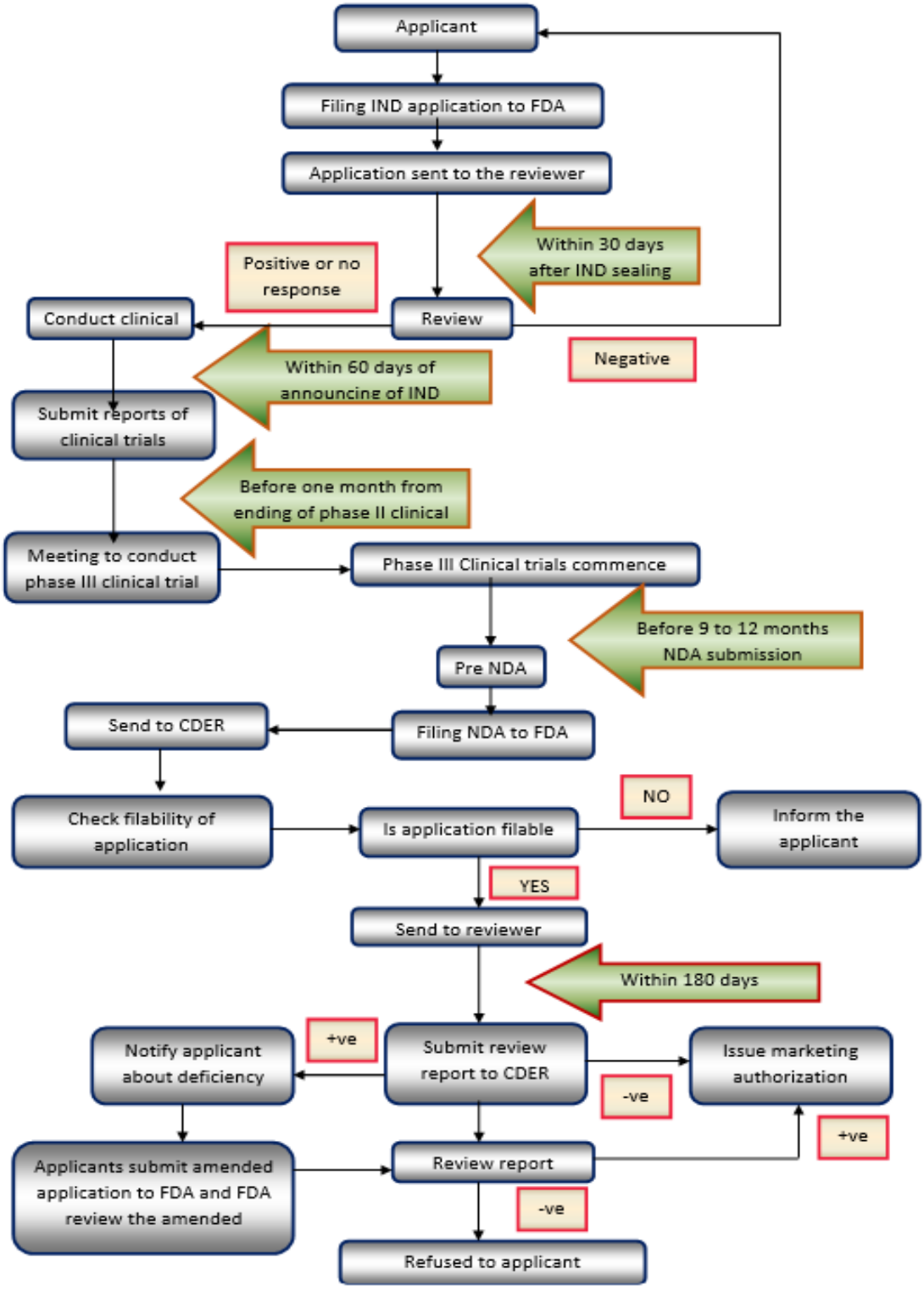

Figure 3. New Drug Approval in US (NDA)

Treatment IND: It is submitted for investigational treatments that have shown promise in clinical trials for serious or immediately life-threatening illnesses while the FDA review is ongoing, and the final clinical work is being done.

The two IND categories are commercial and research (non-commercial) types. The IND application must contain information in three broad areas:

(1) Animal Pharmacology and Toxicology Studies

(2) Manufacturing Information and

(3) Clinical Protocols and Investigator Information.

The sponsor is required to hold off on starting any clinical studies for 30 calendar days after submitting the IND. Ensure that research subjects won't be exposed to unreasonably high risk, FDA has the chance to assess the IND during this time.

b) IND Content and Format *(13):*

In Section 312 of the 21 Code of Federal Regulations (CFR), the standards for the IND application's format and substance are stated. An

"Investigational New Drug Application" should be submitted in the following formats by either a sponsor (commercial entity) or an investigator who wants to carry out a clinical study:

- Form FDA 1571
- Table of contents
- Introductory statement and investigational plan
- Investigator's brochure
- Protocols
- Chemistry, manufacturing, and control (CMC) information
- Pharmacology and toxicology information
- Previous human experience
- Additional information.

2.3. New Drug Application (NDA)

A new drug application (NDA), which is the formal request to manufacture and market the drug in the United States, is filed by the manufacturer if clinical trials show that the drug is generally safe, and effective, and won't put patients at undue risk.(14-16)

To obtain authorization for the commercialization of a new drug in the USA, a New Drug Application is submitted. An NDA includes details from the IND as well as the findings of clinical trials demonstrating efficacy and safety. After the FDA receives an NDA, the review procedure must begin within 60 days.

NDA Contents and Format The application is in two copies and is:

(a) Archival copy

(b) Review copy.

a) Archival Copy

It contains copies of tabulations and clinical study case report forms, and it also acts as a reference source for FDA reviewers to locate material not present in the review copy.

The following components are included:

- Application form FDA 356
- Index
- Summary
- Technical sections: further typed to-
- Chemistry, manufacturing, and controls section
- Non-clinical pharmacology and toxicology section
- Human pharmacokinetics and bioavailability section
- Microbiology section
- Clinical data section
- Statistical section
- Paediatric use section
- Samples and Labelling
- Case report form

b) Review Copy

Each technical section is separately bound in each folder. Each technical section should contain:

- Index
- Copy of FDA Form 356 h
- Copy of cover letter
- Letters of authorization
- Copy of application summary.

The FDA may meet with the sponsor at least twice, once at the conclusion of Phase 2 clinical trials and once prior to the submission of an NDA, or "pre-NDA meeting." The review panel will evaluate the findings of the investigation and decisions regarding the application. The process of NDA has been illustrated in Figure 2.

2.4. Abbreviated New Drug Application (ANDA)

Incredible New Drug Application (SNDA) All substantial alterations to the conditions outlined in the applications must receive approval after NDA or ANDA approval by filing a supplementary NDA or ANDA. Such modifications, such as those to packaging or ingredients, must receive CDER approval. Because they need fewer resources to examine than original-use approvals of medications falling under this category, new-uses approvals are a better form of innovation.

3. Drug approval in Europe

Medical items in the European Union (EU) were initially authorized for marketing at the National level. A single national examination for pharmaceutical and medical products seeking marketing clearance in EU nations became possible with the introduction of the mutual recognition mechanism in 1938. The main objective of this process was to establish a uniform standard for product review among national regulatory agencies. By directive 87/22, a concentration procedure for high-tech or biologically derived products was established in 1987. Under this procedure, in addition to the regular national regulatory review, the Committee for Proprietary Medicinal Products (CPMP) is responsible for conducting a product assessment.(6)

Furthermore, the concertation system was replaced with a centralized procedure in 1993 by council regulation (EEC) 2309/93, through which the EU's CPMP assessed and approved the wide-scale marketing of all high-tech and biologically derived products. Clinical trial and marketing authorization are the two stages of the medication approval procedure in European nations. To perform the clinical trial within the EU, a clinical trial application (CTA) is submitted to the state's competent authorities.(6)

The member state's relevant authority assesses the application. Only after approval is the clinical trials conducted. Comparable to what is outlined in the FDA drug approval procedure, clinical trials have similar goals and phases. The procedure for authorizing clinical trials in the EU is shown in Figure 2. A marketing authorization application (MAA) containing all animal and human data, their analysis, as well as

pharmacokinetics, manufacturing, and suggested labelling, is submitted following the completion of all three phases of a clinical study.(6) The following regulatory processes are available to the corporation in the EU member states:

Before a medicine is authorized to be marketed in the European Union, two regulatory steps must be completed, which are like the US regulations. Clinical trial application and marketing authorization application are these two steps.

It is a proposal submitted for generic drug approval. The original, brand-name product's clinical tests did not have to be repeated by the sponsor. Instead, generic medication makers must show that their product is identical to and bioequivalent to a brand-name product that has already received approval. Figure 4 provides an illustration of the ANDA method.(14-16)

Clinical Trial Applications are approved at the member state level in the European Union, which has twenty-eight member states (as of July 2013); Marketing Authorization Applications are approved at both the member state and centralized levels.

3.1. Centralized procedure

- By using the unified process, applicants can get marketing permission that is good for the entire EU.
- Ends with a single authorization that is valid in Norway, Iceland, the EU, and Liechtenstein.
- A designated Rapporteur evaluates the application.
- Timeline: Within 210 days, the EMA published its conclusion and submitted it to the European Commission for final approval. The complete process has been illustrated in Figure 3.

A centralized process is compulsory for:

- Drugs produced using any biotechnological procedures, such as genetic engineering.
- Drugs used to treat conditions like cancer, HIV/AIDS, diabetes, neurological illnesses, autoimmune diseases, and other immune system problems.
- Drugs formally recognized as "Orphan medications" (medicines used for rare diseases).(17)

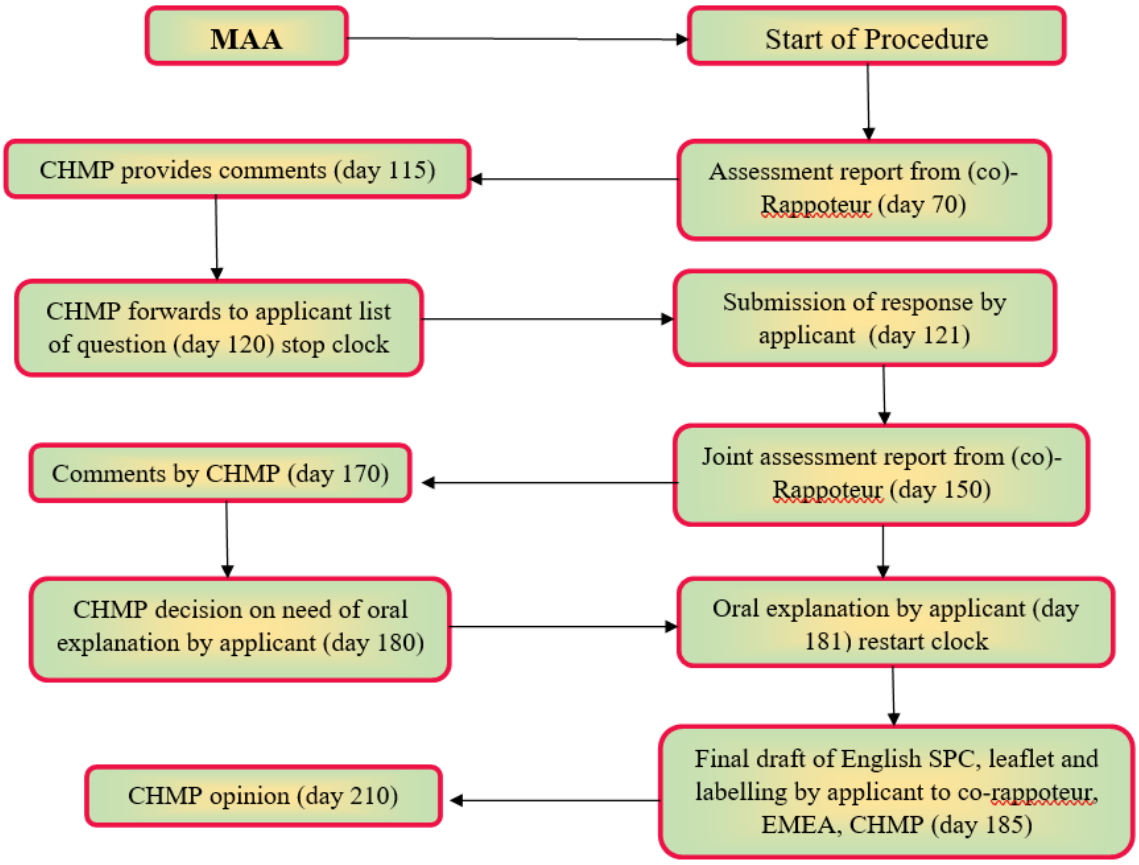

Figure 4. Centralized Procedure for New Drug Application in Europe

3.2. Mutual Recognition Procedure

The Mutual Recognition procedure enables applicants to get marketing authorization in member states (Concerned Member State) as opposed to the member state (Reference Member State) where the medicine has already received approval.(18)

- When a Member State agrees to review the medical product (at which point it becomes

the "RMS"), it tells other Member States (which then become the "CMS") to which applications have already been submitted.

- RMS makes its own results public in a report to other states.

Most of this type of drug approval procedure users are in the generic industry, and the procedure itself may take 390 days. The process has been illustrated in Figure 5.

3.3. Decentralized Procedure

The centralized approach is not required to get marketing authorizations across multiple member states; instead, the decentralized procedure should be used. Where marketing authorization is required, an application is filed to the appropriate authorities in each member state. Information on quality, effectiveness, safety, and administrative matters must also be provided, along with a list of all Concerned Member States (CMSs) and a reference member state (RMS). The CMSs and the RMS validate the application within a 14-day window after preparing a draft assessment report on the drug. Within 120 days, the RMS drafts the labelling, packaging leaflet, and summary of the product's features. 90 days can pass before this report is authorized. (6)

However, CMS(s) will notify other CMS, RMS, and the applicant if a medicinal product is thought to represent a substantial risk to the public's health, and a decision will be made in this matter within 30 days. All member states agree on the course of action within 60 days of the notification of the points of disagreement. Following a member-state agreement, the RMS documents the agreement and notifies the applicant. If the member states are unable to agree, the CHMP steps in and makes a final determination while taking the applicant's written or oral arguments into consideration.(6) The decentralized EU marketing authorization process is depicted in Figure 4.

Based on the assessment report which is prepared by the RMS & any comments made by the CMS, marketing authorization should be granted in accordance with the decision taken by the RMS & CMS in this decentralized procedure.(18)

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

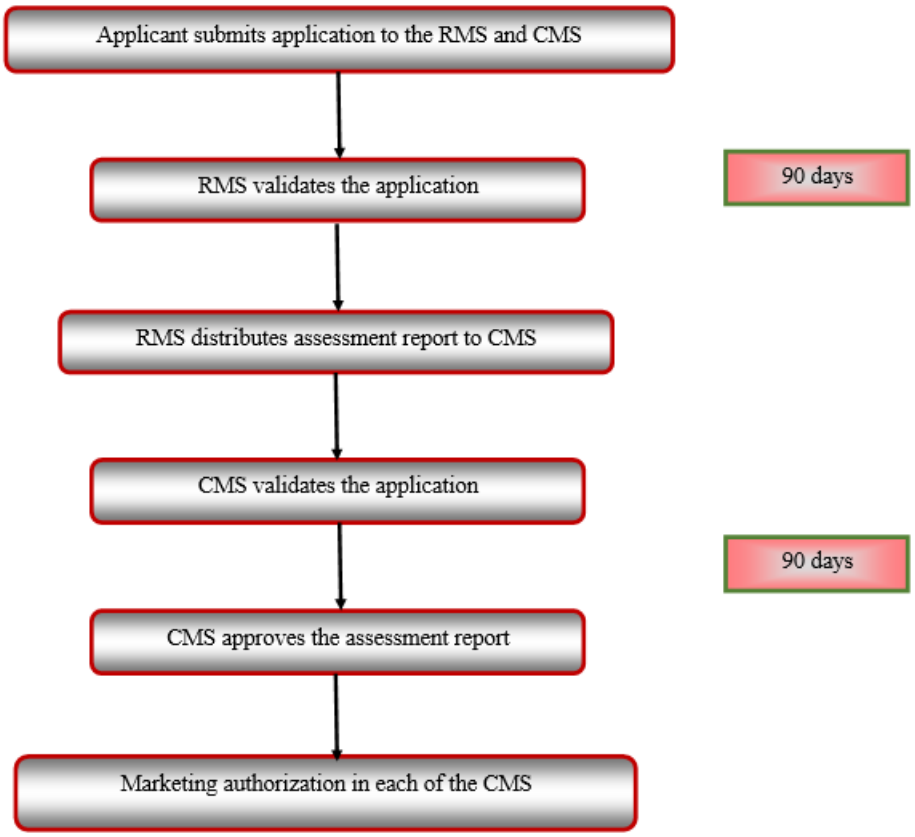

Figure 5. Mutual Recognition Procedure for Europe

3.4. National Procedure

Every country in Europe has its own governing body. A national process is a set of rules that each country has individually adopted. Even small companies can afford the costs. It reduces the expense of translation into English or other regional languages. It establishes a foundation for mutual recognition. Procedure Through the national procedure, biotechnological procedures cannot be registered. It is

required for the same to use centralized filing through EMA. A marketing permit is issued when the sponsor's application, presented in accordance with national regulations to the national competent authority, has been reviewed.(19) The national procedure of authorization is limited to medicinal products which are not to be authorized in more than one member state.(20)

These products cannot be registered through this program: Orphans Medical Products, All Biotechnology Based Products, Specific Aids and Cancer Medicines, Specific Antiviral Medicines, Specific Medicines for Neurodegenerative Disorders including Diabetes, and Specific Medicines for Auto Immune Diseases/dysfunctions.(7)

4. Drug Approval Procedure in India

The Drugs and Cosmetics Act 1940 and Rules 1945 were passed to regulate the import, manufacture, distribution, and sale of drugs and cosmetics. The drug approval procedure is controlled in India by the Central Drugs Standard Control Organization (CDSCO). CDSCO is headed by the Drugs Controller General of India (DCGI).(21) DCGI works under the Ministry of Health (MOH) and is in New Delhi.

The Drug and Cosmetics Rules of 1945 received Schedule Y from the Indian government in 1988. The rules and specifications for clinical trials are contained in Schedule Y, which was further reviewed in 2005 to bring it into compliance with accepted international practice. To produce or import a novel drug in India, a company must submit Form 44 together with the information required under Schedule Y of the Drugs and Cosmetics Act 1940 and Rules 1945 in order to request approval from the licensing body (DCGI). Conduct clinical trials in compliance with the specifications listed in Schedule Y in order to show their efficacy and safety in the Indian population and submit the report of such clinical trials in the designated format.(22)

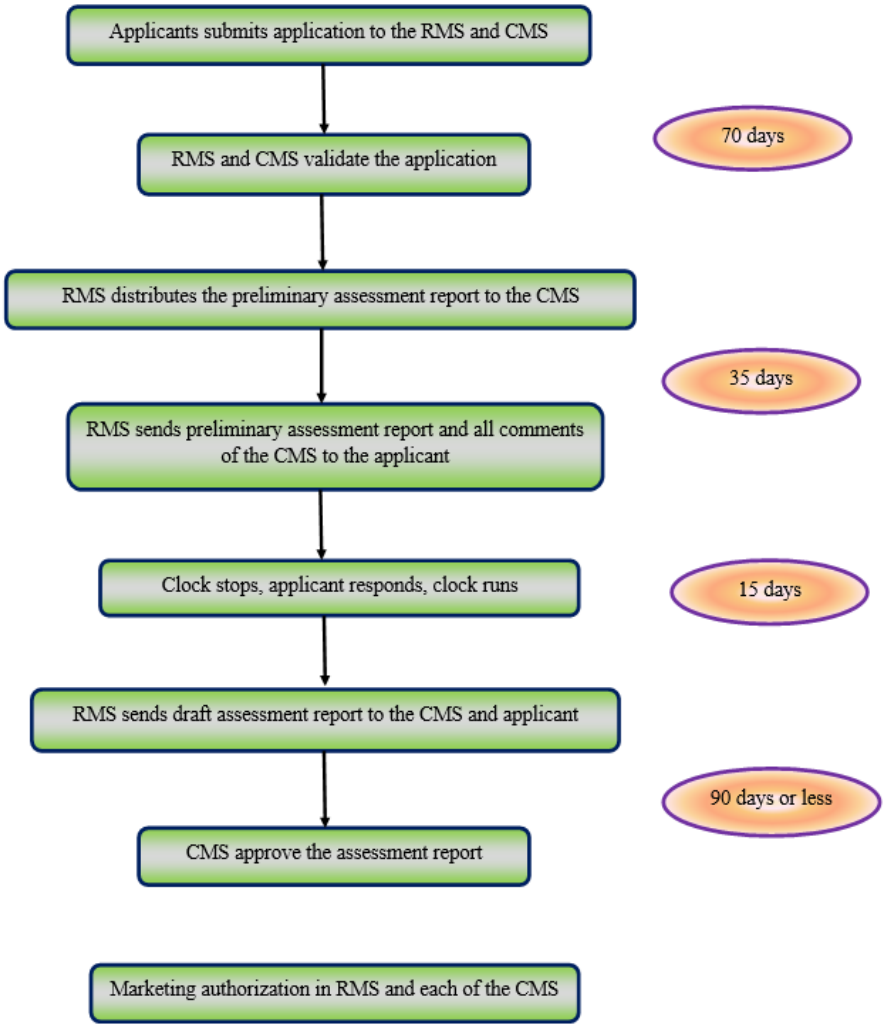

Figure 6. Decentralized Procedure for Europe

4.1. Rule

For an investigational new drug, the sponsor needs to provide detailed information to the DCGI about:

- Generic name
- Patent status
- Brief description of Physio-chemical /biological
- Technical information

- Stability
- Specifications
- Manufacturing process
- Worldwide regulatory status
- Animal pharmacology and toxicity studies
- Published clinical trial reports
- Proposed protocol and pro forma
- Trial duration
- During the expert file
- Undertaking to Report Serious or Life-threatening Adverse Drug Reactions.

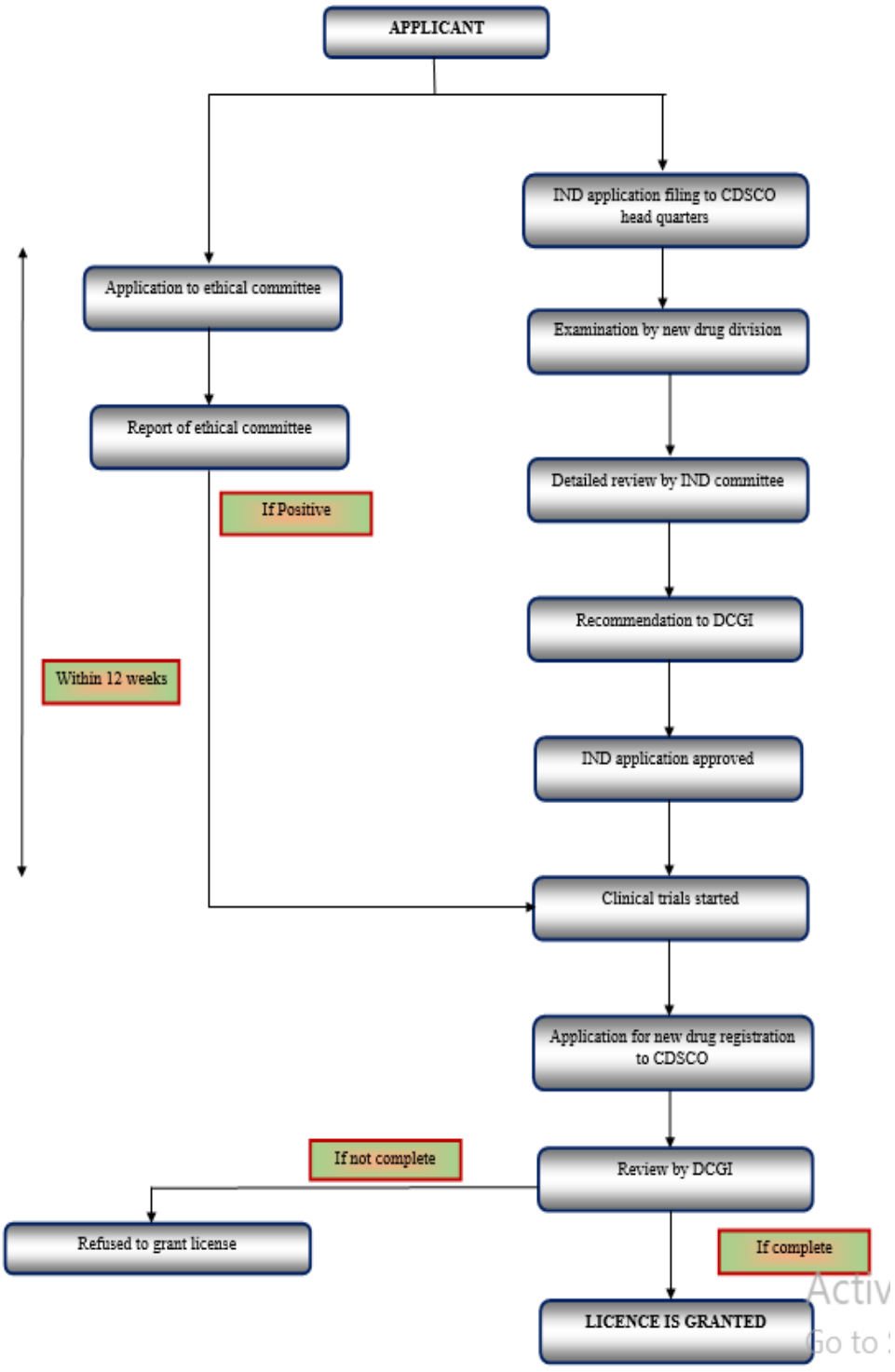

Figure 7. New Drug Approval in India

The requirement for regional clinical trials in India depends on the drug's standing in other nations. In general, Phase III trials are necessary if the medicine has already received approval in other nations.(23)

India does not permit phase I trials unless data from other nations is provided. If medicine has a unique connection to an Indian health issue, such as malaria or tuberculosis, DCGI will approve its use in Phase 1 trials in India.(24,25)

Studies involving bioavailability and bioequivalence (BABE) are to be carried out in accordance with BABE regulations. In addition to the details about

safety and efficacy, thorough information must also be provided regarding the drug's status as a marketing product in other nations. Additional information that must be provided includes product monographs, labels, samples, and testing techniques.(26)

Clinical study approval in India typically takes three months. The Clinical Studies Registry of India (CTRI) is the place where clinical trials can be registered, with information about the trials and the participants.(27)

The rules to be followed under The Drugs and Cosmetics Rules 1945 are:(26)

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

Rule 122- B: application for approval to manufacture new drugs other than the drugs specified under Schedule C and C1.

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 clinical trials.

The Drugs and Cosmetics Act has been amended to clarify the roles of sponsors and investigators and to define what constitutes a Phase I–IV trial. In 2006, there were two additional categories created for clinical trials. Clinical trials that fall into one category (category A) can be carried out in other markets with capable and developed regulatory systems, but those that don't fall into category A fall into category B instead.

Clinical trials under category A, which have received approval from the United States, Great Britain, Switzerland, Australia, Canada, Germany, South Africa, Japan, and the European Union, are eligible for fast-tracking in India and are most likely to be accepted within eight weeks. The approval of category B clinical trials takes 16 to 18 weeks and is subject to further examination. The complete process of NDA in India has been illustrated in Figure 6.

The DCGI shall receive an application for the conduct of clinical trials in India along with the data of chemistry, manufacturing, control, and animal research. Documents pertaining to informed consent, investigator's brochures, and the trial protocol date should all be provided. The ethical committee must get a copy of the application, and clinical trials are only carried out with DCGI and ethical committee approval.

Phase I clinical studies are carried out to control the maximum tolerated dose in humans and adverse effects in healthy human volunteers. In Phase II trials, 10–12 patients at each dose level are used to determine the therapeutic applications and effective dose ranges. To verify efficacy and safety claims, confirmatory trials (Phase III) are carried out to gather data on the drug's efficacy and safety in roughly 100 patients (in 3–4 centres). If the new therapeutic ingredient is not already marketed in another nation, phase III studies should be carried out on at least 500 patients spread over 10–15 centres.(28,29)

Phase IV studies, where potential new uses or populations, long-term impacts, etc. are investigated, are those that take place after the NDA approval when an organization can distribute and promote the product.

For the United States, the European Union, Canada, Japan, and other nations, the Common Technical Document (CTD) guideline has been developed through the International Conference on Harmonization (ICH) process.

Most countries have adopted the CTD format. Hence, CDSCO has also decided to adopt the CTD format for technical requirements for the registration of pharmaceutical products for human use.

4.2. Stages of approval

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

The procedure for approving drugs varies depending on the nation. In certain nations, the FDA is the only organization in charge of drug regulation and oversees all regulatory tasks, including the approval of new pharmaceuticals, granting manufacturing licenses, and inspecting manufacturing facilities. However, in certain nations, such as India, not all regulatory activities are carried out by a single regulatory entity; instead, centralized and state bodies share this role. Some nations, like the USA, have two review processes: a regular review process and an accelerated review process, while others, like India, only have one. The format for the demonstration of the dossier submitted for drug approval is likewise different.(6,30,31) In some countries like in USA, EU, Canada, and Japan, it is mandatory that the dossier should be represented in eCTD format only.

5. Drug Approval Procedure in Australia

The Federal Government's Therapeutic Goods Administration oversees the control of pharmaceuticals and medical equipment. The Australian Register of Therapeutic Goods lists prescription drugs and over-the-counter medications that adhere to Australian criteria for quality, safety, and efficacy. Drugs may be listed or registered. After a rigorous assessment, registered products are given an AUST R number and labelled. A nationwide system of controls relating to the quality, safety, efficacy, and prompt availability of therapeutic goods used in Australia, whether produced in Australia or elsewhere, or exported from Australia, is one of the goals of the Therapeutic Goods Act 1989, which is administered by the TGA.(32) Fees for

inspections, assessments, and yearly registrations cover all costs associated with these operations. U.S.T.R. goods registered medications include:

- the majority of prescribed drugs
- Despite not being required by law to be prescribed, some products, like vaccines, call for thorough analysis.
- Almost all conventional over-the-counter medications

A relatively small number of complementary medicines there, where the TGA has been satisfied that specific claims of efficacy in the treatment or prevention of a condition are backed by appropriate evidence.

5.1. Prescription medicines

Since it was founded in 1963, the Australian system for the pre-registration evaluation of new active substances, as well as things like new administration methods and the expansion of authorized uses (or "indications") of already marketed drugs, has changed. Most currently marketed prescription drugs have been assessed using this technique. Today, an application for the registration of a new active substance must be accompanied by extensive documentation regarding the substance's synthesis, the process used to make the dosage forms, animal studies on its pharmacology and toxicology, and human clinical trials proving the product's efficacy and safety in the intended use.

Additionally, verification of compliance with Good Manufacturing Practices by the manufacturer is required. In Australia, registration is perpetual. Until there are grounds for cancellation, or the sponsor stops marketing, a product remains registered. Long before there was an evaluation procedure in place, Australia received a tiny number of active drugs, including aspirin. Unless a safety concern or suggested change in use is raised, their registration is not reviewed. Many of the prescription drugs used in Australia are repackaged versions of the original substance, typically made by different companies. These generic goods must adhere to the same manufacturing laws and quality requirements.

However, rather than a comprehensive demonstration of efficacy and safety, simply proof that the formulation is bioequivalent to the innovator medicine is needed. 1 Although bench top testing of the product's dissolution may be sufficient for some items, bioequivalence investigations typically entail a comparative evaluation of the product in human volunteers. To back up the claims of modified-release formulations, a similar study on human volunteers is necessary.

5.2. Over-the-counter medicines

Nowadays, almost all the active chemicals in over-the-counter medications start out on the market as components of prescription drugs. It typically takes at least two years of prescription drug use for an active ingredient to determine whether it is appropriate for use in a non-prescription therapy. Not all active ingredients are transferable from over the counter to prescription use. Because the registration of the over-the-counter product can draw on the accumulated experience as a prescription product, there is typically less fresh information to support efficacy and safety.

The TGA evaluates new over-the-counter products for quality, effectiveness, and safety. The regulations for items like quality and manufacturing conditions are remarkably similar to those for prescription medications. These Products categorized as listed products & considered low risk by the TGA (AUST L). The list of medications is almost completely made up of complementary treatments. These consist of herbal remedies, the majority of vitamin and mineral supplements, and other dietary additions, conventional medications like Ayurvedic and conventional Chinese medicines, and aromatherapy oils. To control products that by their very nature looked to pose little chance of having negative consequences, this category of listed products was established in 1991. T R products must comply with similar manufacturing specifications, including certification of Good Manufacturing Practice, but they are not examined before being included in the ARTG. The Therapeutic Goods Regulations of 1990's standards serve as the main safeguard for assuring the safety of these items. AUST L drugs must:

- Not be covered by national rules that restrict access to numerous drugs, come from endangered animals, or include substances that are restricted from import (Standard for the Uniform Scheduling of Drugs and Poisons)
- Conform to lists of permitted ingredients (minerals, vitamins, declared listable substances).
- There may be additional constraints, such as dose caps, detailed label warnings, and restrictions on plant parts or preparation techniques. Some herbs are prohibited.
- The initial approach to regulation of AUST L products did not require evidence to support manufacturers' claims, provided the products were not for the treatment of serious illnesses.

In April 1999, a rule requiring sponsors of AUST L items to have proof of their claims was introduced in response to worries that numerous, occasionally impossible claims were being made about products. If a problem or complaint arises at any point during the life of a product, the TGA may request and assess this evidence. The TGA may remove the product from the listing if the proof is insufficient. The compliance with the listing requirements is thoroughly evaluated for a random sample of about 20% of new listings. An expert committee advised in 2003 that sponsors of AUST L medications produce summaries of the evidence they have to substantiate the effectiveness of their offerings and that the TGA conducts a random examination of this data. 3 Registration (AUST R

status) can be requested when there is evidence that an AUST L drug is effective in treating a serious condition.

5.3. Exemptions

Currently, the TGA does not have the authority to regulate medicines that are prescribed or extemporaneously made for a specific person (apart from gene therapy). This exemption is being used by some pharmacies and clinics to distribute medications produced there to a sizable number of patients. There are times when statements are made about special qualities, such as "slow-release product." The TGA does not review or control such items. Individual prescriptions of medication from practitioners of traditional Chinese medicine and homeopathy are also exempt from these restrictions. The necessity for inclusion in the ARTG is also waived in the case of some other medications. Homeopathic remedies are arguably the most significant. Homeopathic somatropin and homeopathic melatonin have both been marketed because of this exemption from TGA oversight.(32) NDA-New Drug Application, DSEB-Drug Safety, and Evaluation Branch, TGA-Therapeutic Goods Administration, ADEC-Australian Drug Evaluation Committee.

6. Drug Approval Procedure in China

The Chinese Ministry of Health planned drug regulation in 1963 for the administration of new medications. The New Drug Management Regulations were released in 1979 by China's State Pharmaceutical Administration and the Ministry of Health (no need to conduct systematic scientific experiments on new drugs). The first complete Drug Administrative Law was drafted in 1985 with the intention of safeguarding public health and fostering economic advancements in the pharmaceutical industry. Two new provisions for the approval of novel drugs and new biological products were added to this statute in 1999. Enough preclinical data are included in the approval process of New Drug Applications (NDA) to verify the safety of the drug and support the start of clinical studies. (33)

The Drug Administrative Law empower the State Food and Drug Administration (SFDA) to approve the sale of new medications. The clinical study application and the new drug application are additional components of the process for registering novel drugs. Just after receiving the medication registration application, the Provincial Drug Administration Authorities (PDAAs) should set up the official review of supplied materials, including on-site inspection and sampling. The formal review's purpose is to ensure that all necessary materials have been provided and that the supplied documents' content and format adhere to the specifications. The PDAAs forward the eligible applications to the SFDA for additional evaluation after a formal review. The applicant should submit the import drug registration application directly to SFDA.

The Department of Drug Registration of the SFDA thoroughly examines the accuracy of the information submitted, files the approved applications, and sends all the approved applications' materials to the SFDA-affiliated center for Drug Evaluation (CDE). Sending the review report to SFDA, CDE decides if the safety and efficacy data provided for a new medicine are sufficient for manufacturing and marketing authorization. SFDA Determines whether the drug registration application may be authorized, issues the certificate of drug approval and drug approval number to the qualified applicant, carefully considers the recommendations, and review the findings of CDE. Figures 10 and 11 show, respectively, China's procedures for approving clinical trials and new drugs.(33,34)

7. Drug Approval Procedure in Canada

The Therapeutic Products Directorate (TPD) of Health Canada oversees the regulation of pharmaceuticals (both prescription and over the counter) and medical equipment intended for human use. The Biologics and Genetic Therapies Directorate (BGTD) at Health Canada oversees overseeing the regulation of biologics, including xenografts, viral and bacterial vaccines, cells, tissues, and blood and blood products. The regulatory frameworks for drug goods in Canada and the US are remarkably similar. The Therapeutic Products Directorate, a division of Health Canada that oversees the country's pharmaceutical industry, is the FDA's equivalent in Canada at the federal level. The Therapeutic Products Directorate must approve any drug products before they may be sold in Canada. Like the U.S., where states control pharmacies, pharmacies in Canada are governed by the provinces.(4)

The pharmaceutical market in Canada is the eighth largest in the world by sales, making up around 2% of the global market. After China, the US, and Spain, Canada has the fourth-fastest expanding pharmaceutical industry, and it has demonstrated a consistent development pattern. Required new drug submissions contain information on clinical trials as well as manufacture, packing, labelling, usage guidelines, and adverse effects. These drugs must not have been sold in Canada for long enough or in sufficient quantities to show their safety and effectiveness. An administrative screening process is an initial step when submitting an NDS to TPD to make sure all relevant components are included and in the proper format. This is not a study of the information. The goal is to complete the screening procedure within 45 days of receipt of thins. The file is then directed toward the appropriate Bureau responsible for reviewing drugs in each therapeutic area. TPD currently has a 300-day performance guideline to complete a standard NDS review, and 180 days to complete a priority NDS. (4)

8. Discussion

The two primary steps in the drug approval procedure were the requests for a clinical trial and marketing authorization for the drug from the regulatory body. In some ways, the procedures used by different nations to approve new drugs are similar, while in other ways they differ. In most countries, the

sponsor first applies for a clinical trial, and only after the regulatory authority has given it permission, does the applicant conduct the clinical studies and then apply to the regulatory authority for a drug's marketing authorization. Although the quality, safety, and effectiveness of drugs are all subject to regulatory authorities' evaluation, the time, cost, and review procedure for clinical studies and marketing license applications vary across all jurisdictions. The International Conference on Harmonization (ICH) has made significant strides toward harmonization by recommending a unified interpretation and application of technical criteria. The Common Technical Document (CTD) guideline has been created for the United States, European Union, Canada, Japan, and other nations through the International Conference on Harmonization (ICH) process. India thus keeps track of the same. The requirement for duplicating work done during the development of new pharmaceuticals will eventually be lessened because of this step, as a result, worldwide medication approval procedure harmonization by ICH or WHO get started. USFDA and CDSCO are the respective regulatory authorities for the USA and India, whilst EMEA, CHMP, and the National Health Agency are the corresponding regulatory bodies for Europe. Comparing Europe to the US and INDIA, several different regulatory processes exist. The approval period, which ranges from 12 to 18 months, is the same across all nations. When compared to EUROPE and INDIA, the cost of approving a new medicine is high in the US.

Table 1. Principle difference between US, Europe, and India

Requirements	US	EU	INDIA
Agency	One Agency **USFDA**	Multiple Agencies • **EMEA** • **CHMP** • **National Health Agencies**	One Agency **DCGI**
Registration Process	One registration process	Multiple registration process • Centralized(European community) • Decentralized (at least 2 member states) • Mutual recognition (at least 2 member states) • National (1 member state)	One registration process
TSE/BSE data study	Not Required	Required	Required
Braille code	Braille code is not required on labelling	Braille code is required for labelling	Braille code is not required on labelling
Post approval changes	Post-approved changes in the approved drug: • Minor • Moderate • Major	Post variation in the approved drug: • Type IA • Type IB • Type II	Post-approval changes: • Major • Moderate

Table 2. Administrative Requirements

Requirements	US	EU	INDIA
Application	ANDA/NDA	MAA	MAA
Department classification	Required	Not required	Not required
Number of Copies	3	1	1
Approval Timeline	18 months	12 months	12 – 18 months
Fees	Under $2 million – NDA application $1,520 million – ANDA application	National fee (including hybrid application): £103,059 Decentralized procedure where UK is CMS: £99,507	50,000 INR
Presentation	eCTD and Paper	eCTD	Paper

Table 3. Manufacturing and Control Requirements

Requirements	US	EUROPE	INDIA
Number of Batches	1	3	1
Packaging	A Minimum of 1,00,000 Units	Required	Required
Process Validation	Not required at the time of submission	Required	Required

Batch Size	1 Pilot scale or a minimum of 1 lakh units whichever is higher	2 Pilot scale + 1 Lab batch or a minimum of 1 lakh units whichever is higher	Pilot Scale Batch

Table 4. Finished Product Control System

Requirements	US	EUROPE	INDIA
Justification	ICH Q6A	ICH Q6A	ICH Q6A
Assay	90 – 100 %	95 – 105 %	90 – 110 %
Disintegration	Not required	Required	Required
Colour Identification	Not Required	Required	Required
Water Content	Required	Not required	Required

Table 5. Stability Requirements

Requirements	US	EUROPE	INDIA
Number of Batches	3 Pilot Batch or 2 Pilot Batch & 1 Small scale	2 Pilot Scale (If API stable) 3 Primary Batches (If API unstable)	2 Pilot Scale/Production scale (If API stable) 3 Primary Batches (If API unstable)
Condition: Long-term stability, Accelerated stability	Long-term: 25°C/65%RH Accelerated: 40°C/75%RH (0,3,6 months) Intermediate: 30°C/65%RH	Long-term: 25°C/65%RH Accelerated: 40°C/75%RH (0,3,6 months) Intermediate: 30°C/65%RH	Long-term: 30°C/70%RH Accelerated: 40°C/75%RH (0,3,6 months)
Minimum time period for submission	6 months accelerate & 6 months long term	6 months accelerate & 6 months long term	6 months accelerate & 6 months long term
Container orientation	Inverted & Upright	Do not address	Inverted & Upright
Clause	21 CFR part 210 & 211	Volume 4 EU Guidelines for medicinal products	ICH Q1F
QP Certification	Not required	Required	Required

Table 6. Bioequivalence Requirement

Requirements	US	EUROPE	INDIA
CRO (Audits)	Audited by FDA	Audited by MHRA	CDSCO
Reserve Sample	5 times the sample required for analysis	No such requirement	-
Fasted / Fed	Must be as per OGD recommendation	No such requirement	As CDSCO recommendation
Retention of samples	5 years from date of filing the application	No such requirement	3 years from date of filing the application
BE study for generic drugs	Against US RLD in any country. To refer 'BE recommendation' in FDA site for guidance	Against EU reference product (ERP) in any country	Against US/EU/Australia RLD in any country except Thailand, where BE to be done locally against local reference product.

9. Conclusion

The drug approval process comprises two steps:

- Application to conduct clinical trials
- Application to the regulatory authority for marketing authorization of the drug.

The United States of America (USA) and the European Union (EU) are widely acknowledged as the two most promising markets for pharmaceutical products in the world. Accordingly, this article concentrated on the pharmaceutical laws of the US and EU, as well as our own nation, India, and a few other nations like China, Canada, and Australia. In contrast to the Committee for Medicinal Products for Human Use (CHMP) in the European Union, the Therapeutic Goods Administration (TGA) in Australia, the State Food and Drug Administration (SFDA) in China, and the Therapeutic Products Directorate (TPD) in Canada, the Centre for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration serves as the primary watchdog for drugs in the United States. In different countries, the drug approval procedure has similarities in the information to be submitted about safety, efficacy, and quality aspects of the drug but there are differences regarding the time period of reviewing an application, registration fee to be paid by the sponsor, and formats of various applications. The usage of different approaches in applications among different countries made it difficult to review them, thus delaying approvals. With the globalization of the pharmaceutical industry, there was a need to harmonize the recommendations and regulatory requirements for the development of new drugs in various countries. For harmonization, ICH has initiated a generic format, called CTD which eliminates unnecessary delays in the approval of new drugs globally.

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Conflict of Interest

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