Available online on 15 Jun, 2025 at https://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

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Review Article **Open Access**

Development and Registration of Drug Product across the various Regulatory Authorities (India, US, Europe, Australia, Japan)

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Abstract

The process of obtaining regulatory approval for pharmaceuticals constitutes a critical and methodical framework aimed at validating the safety and effectiveness of innovative therapies. Although the essential stages of drug discovery, development, pre-clinical research, clinical trials, and approval remain consistent, regulatory bodies in various jurisdictions follow distinct criteria in their assessment and endorsement of pharmaceuticals. The evaluation of the safety and efficacy of chemical compounds identified during the drug discovery process is conducted through pre-clinical trials carried out in laboratory settings and utilizing animal models. Clinical research is conducted in three main phases to assess the drug's safety, effectiveness, and recommended dosage in humans. Drug clearance in India is managed by CDSCO, that closely complies to worldwide regulations while also taking into account extra factors particular for the Indian market, including affordability and availability. The FDA (Food and Drug Administration) is in the position of approving pharmaceuticals in the US including requires a New Drug Application (NDA) and extensive clinical trial data. In a similar spirit, the EMA in Europe emphasises safety for patients and scientific proof when examining applications. A comparable method is employed with Japan's PMDA, with careful assessment of the cultural and legal idiosyncrasies. Comparable information is additionally demanded by Australia's TGA, and these focusses on public safety and wellness findings.

Conclusion:

The regulatory approval process for pharmaceuticals is a rigorous global framework ensuring safety and efficacy. While the core stages-discovery, development, pre-clinical, and clinical trials are consistent, regional bodies such as India's CDSCO, the US FDA, Europe's EMA, Japan's PMDA, and Australia's TGA have unique criteria tailored to their local markets and priorities, such as affordability, cultural considerations, and public health focus.

Keywords: Drug Discovery, Product development, pre-clinical study, clinical Trials, Drug approval procedure, ADME, CDSCO, FDA, EMA, PMDA, TGA

Article Info: Received 21 Apr 2025; Review Completed 27 May 2024; Accepted 30 May 2025

Cite this article as:
Pal J, Manna A, Ahmed S, Chandra A, Ray J. Development of the Registration process for the Drug Products across the various Regulatory Authorities (India, US, Europe, Australia, Japan). Int. J. Drug Reg. Affairs [Internet]. 2025 Jun 15 [cited 2025 Jun 15]; 13(2):25-42. Available from:
http://ijdra.com/index.php/journal/article/view/755

DOI: https://doi.org/10.22270/ijdra.v13i2.755
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1. Introduction

The discovery process of drug starts when an ailment or disease or an indication exists for which there are no satisfactory treatment approach available. The initiation of the project is driven by the inability to meet the clinical needs. Often carried out in academic contexts, preliminary studies yield data to support the hypothesis of the activation or regulation of a protein or pathway having a therapeutically beneficial effect on a clinical condition. This operation leads to the selection of a target that may require additional confirmation prior to continuing with the lead discovery stage. (1) The process of turning a drug candidate into a molecule (finished result of the discovery phase) into a product that has received commercial authorisation by the respective regulatory bodies is known as drug development.

Efficiency in medication development is critical to commercial success for two reasons:

About two-thirds of total R&D expenses are for development. Throughout the development stage project costs are much higher and costs will escalate markedly when a project progresses to the later stages of clinical development. For the management, a top priority is keeping these expenses in check. It is a high-cost approach that allows for the waste of significant amounts of money.

1.1 Drug development aims to –

a) create a marketable pharmaceutical

b) get regulatory approval for its usage in certain indications as soon as possible. (2–4)

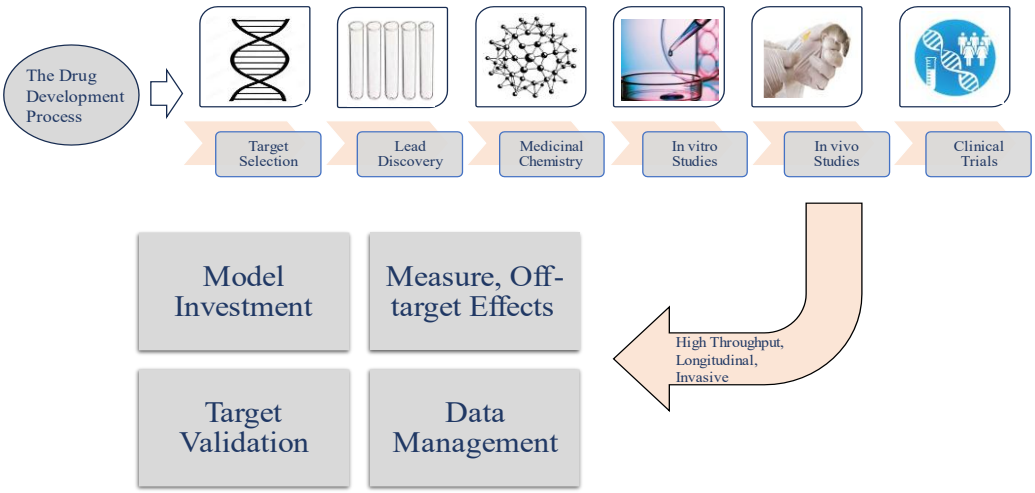

Figure 1. Drug development process

Figure 2. Pre-clinical development phase

2. Processes of Drug Discovery

a) Random Screening – In a process known as "blind hitting," novel chemical entities—whether synthetic or natural—are put through a series of pharmacological screening tests intended to investigate various forms of biological activity.

b) Serendipity – This is observed when A new therapeutic purpose for an existing medication is found, or a new way to treat its side effects is found. (5,6)

2.1 Rational Drug Designing:

a) Target-centred approach: The target-centred approach in drug design, as described in figure 2a, focuses primarily on understanding and manipulating the target—usually a protein or receptor—that is involved in a disease process.

b) Compound-centred approach: The compound-centred approach in drug design focuses on the properties, characteristics, and behaviour of the drug molecules themselves, with the goal of optimizing their interactions with the target protein or receptor as shown in Figure 2b. (7–9)

3. Pre-clinical studies

3.1 Preclinical Studies: Laboratory and Animal Trials: Preclinical studies represent a vital bridge across the drug discovery continuum. They are situated at the interface between laboratory-based experimental investigations and subsequent clinical trials Most of these works follow standards laid down in a formal operating code known as "Good Laboratory Practices" assuring reliability and reproducibility of laboratory data and minimizes human errors. (10–12)

3.2 Pharmacokinetics and Pharmacodynamics

Pharmacokinetics: Pharmacokinetics typically refers to the study of Absorption, Distribution, Metabolism, and Excretion (ADME) of a pharmaceutical compound in an organism, these studies also further establish its relative bioavailability besides getting information about its absorption, metabolism and excretion studies. The half-life of drug elimination is also calculated from the pharmacokinetic data discussed in figure 4. (13–16)

Pharmacodynamics: Pharmacodynamics elaborates the effect of drugs on physiological processes and defines their mechanism of action. This emphasizes the interaction of drugs with specific receptors or biological targets leading to desirable therapeutic effects or adverse side effects. (17–19)

These have received worldwide acceptance via its enormous successful outcomes throughout its several phases. Implementing standardized guidelines universally enhances data credibility and secures approval from regulatory bodies worldwide. (4,7,20,21)

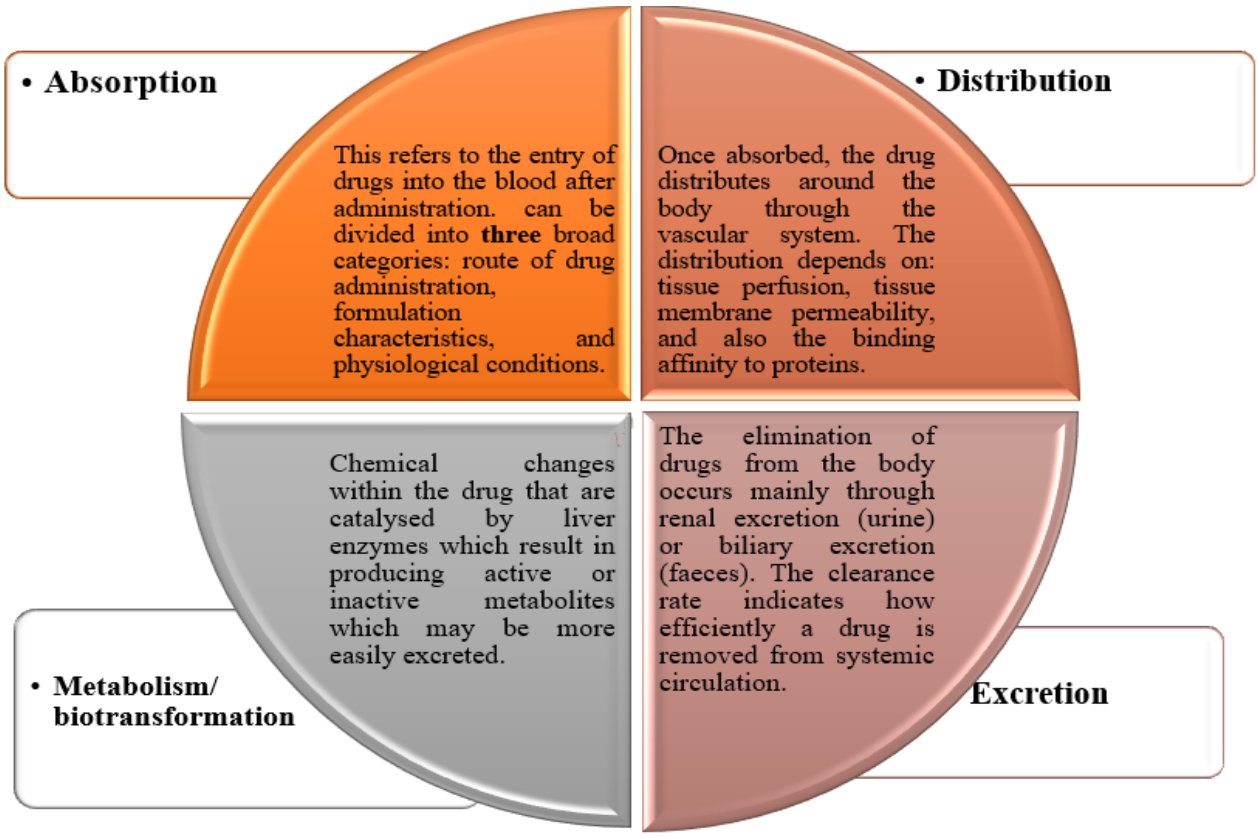

Figure 3. Phases of Pharmacokinetics

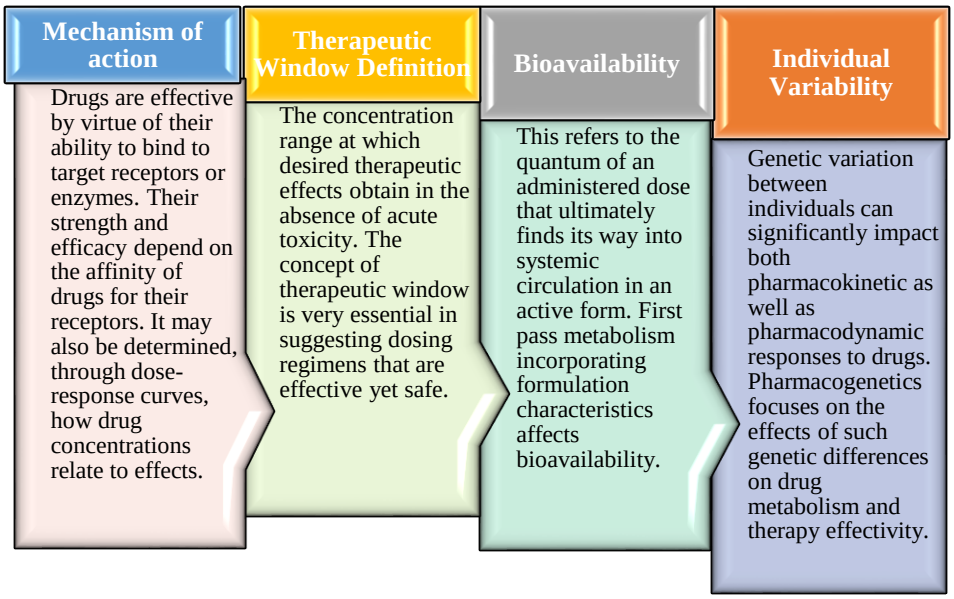

Figure 4. Phases of Pharmacodynamics

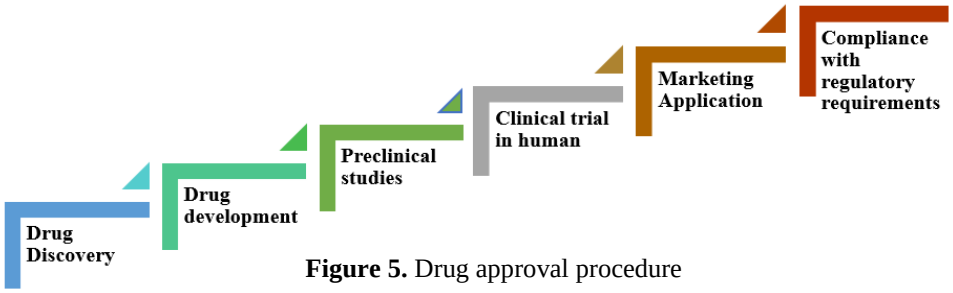

Figure 5. Drug approval procedure

4. Clinical trials

For many years, clinical trials have been used to determine the safety, quality and effectiveness of a drug.

a) Clinical trial and its phases: A clinical trial is any systematic investigation of a novel medication in human patients to gather information on pharmacokinetics, pharmacodynamics, and adverse events in order to assess the medication's safety and effectiveness. (18,22–25)

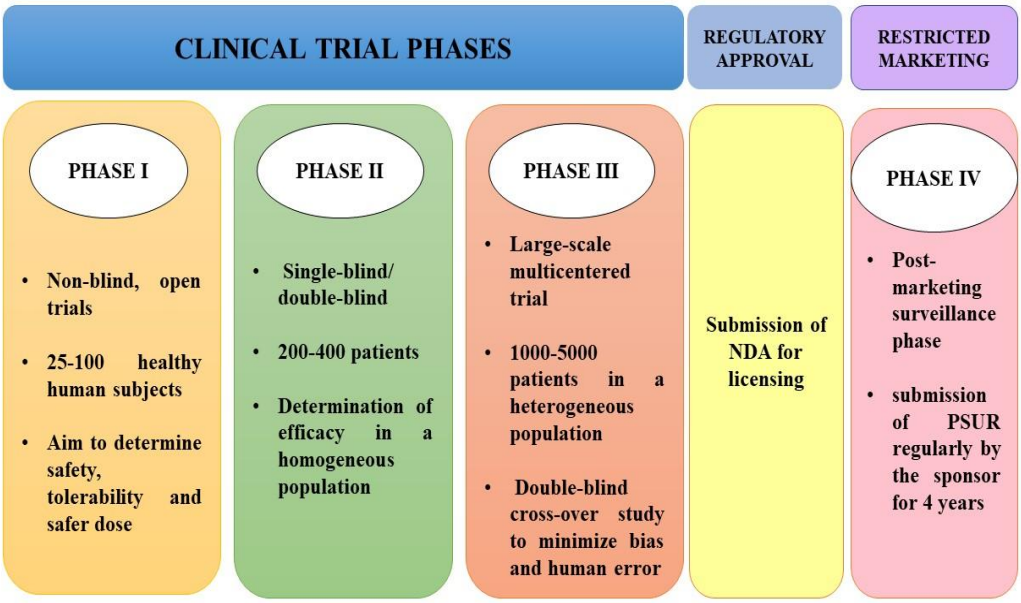

Figure 6. Clinical Trial Phases

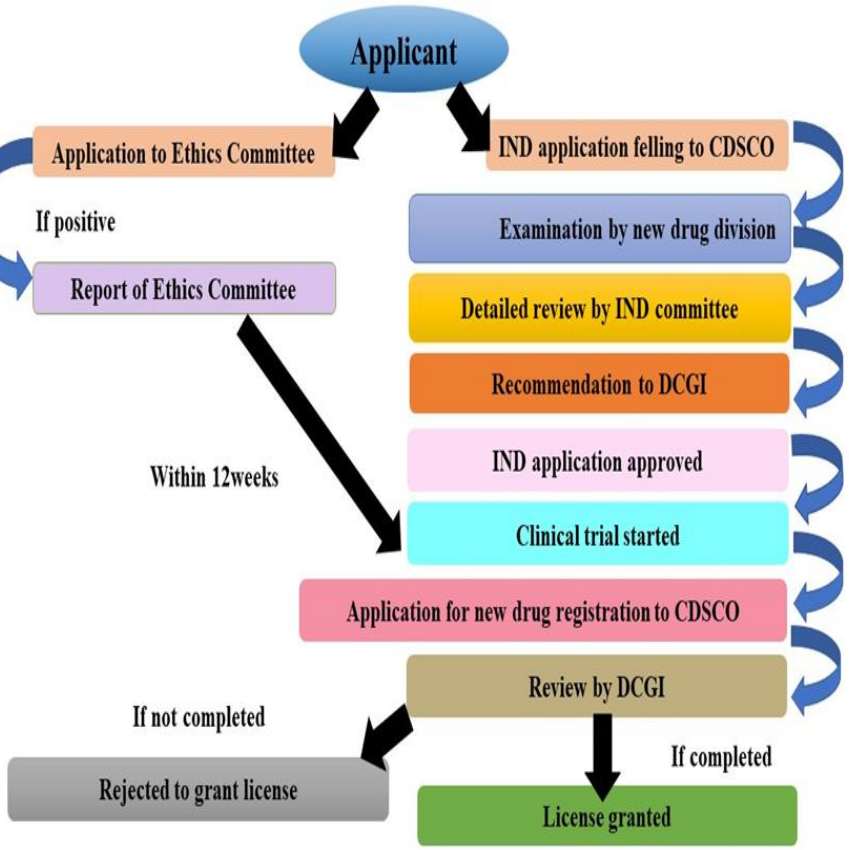

Figure 7. Drug approval process of India

5. Regulatory Approval Process for Drugs Across:

5.1. India

In India, a corporation is required to submit Form 44 and detailed specifications in Schedule Y of the Drugs and Cosmetics Act, 1940, to the Drug Controller General of India (DCGI) to acquire a licence for the manufacturing or importation of a new medication. (26,27)

a) The application for approval of a new drug is forwarded to CDSCO (overseen by DCGI) coupled with information on chemistry, manufacturing, control (CMC), and animal research data.
b) An Ethical committee also receives one copy.
c) Analysis and assessment of the novel medication.
d) IND committee evaluation and DCGI reports
e) DCGI makes decisions based on the reports of the ethical and IND committees.
f) DCGI has approved INDA and granted authorization for clinical trial research.
g) A clinical trial with three phases was completed.
h) Submitting an NDA for clinical and nonclinical data (CTD) registration
i) DCGI and CDSCO reviewed and assessed the data.
j) A license for market authorization is given if it is complete; if not, the company receives deficiency letter.
k) Form 44 and a fifty-thousand-rupee fee are required for registration.

5.2 USA

a) NDA (NEW DRUG APPLICATION):

a) **NDA Submission**: Drug sponsors formally submit a New Drug Application (NDA) to the FDA for marketing clearance in the US. FDA reviews it within 60 days to decide whether to accept it.

b) **PDUFA Timelines**: The Prescription Drug User Fee Act (PDUFA) requires CDER to review 90% of standard NDAs within 10 months and priority drugs within 6 months.

c) **Approval Rates**: FDA approves about 20 drugs annually that begin clinical trials, as per the Tufts Centre for Drug Development.

d) **Key Engagement Phases**: Major interactions occur in the pre-NDA phase and post-Phase 2 trials, where sponsors and FDA plan Phase 3 large-scale studies.

e) **Pre-NDA Conference**: Focuses on FDA's expectations for the application and trial design. (28–30)

b) Abbreviated New Drug Application (ANDA)

a) **Purpose of ANDA**: Used for generic drugs mimicking approved treatments; does not require nonclinical or clinical trial reports,

b) except for in vivo bioavailability studies if deemed necessary by the FDA.

c) **Approval Criteria**: Generics must demonstrate bioequivalence to branded drugs under the Drug Price Competition and Patent Term Restoration Act of 1984.

d) **Bioequivalence Guidance (1992)**: The FDA's Office of Generic Drugs published guidelines for statistical analyses in bioequivalence studies using a standard two-treatment crossover design.

e) **ANDA Reports**: Must include key clinical data, adverse reactions, and protocol deviations.

f) **Recent Draft Guidance**: FDA introduced a draft for public comments on bioequivalence evaluations using population and individual approaches, intended to replace the 1992 guidelines. (3,31–35)

5.3 Europe

The European Commission, the EMA, and the 30 EEA countries (a total of 27 EU Member States, plus Iceland, Liechtenstein, and Norway) comprise the network of about 50 regulatory bodies that make up the European pharmaceuticals regulatory system. This framework is what makes the EU regulatory structure unique. (35) The European framework offers different means of acquiring such a license.(36,37)

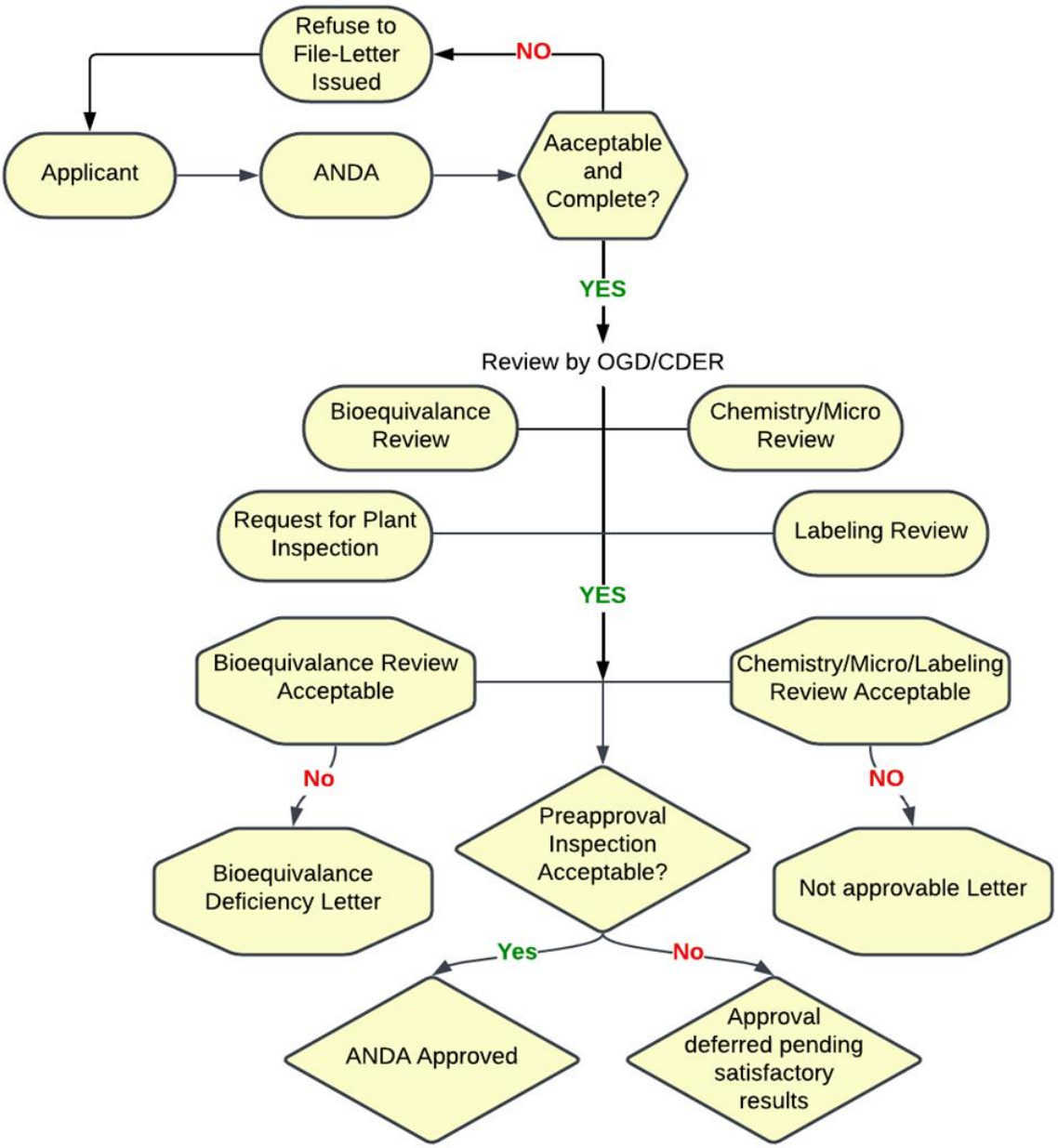

Figure 8. Abbreviated New Drug Application Process of United States

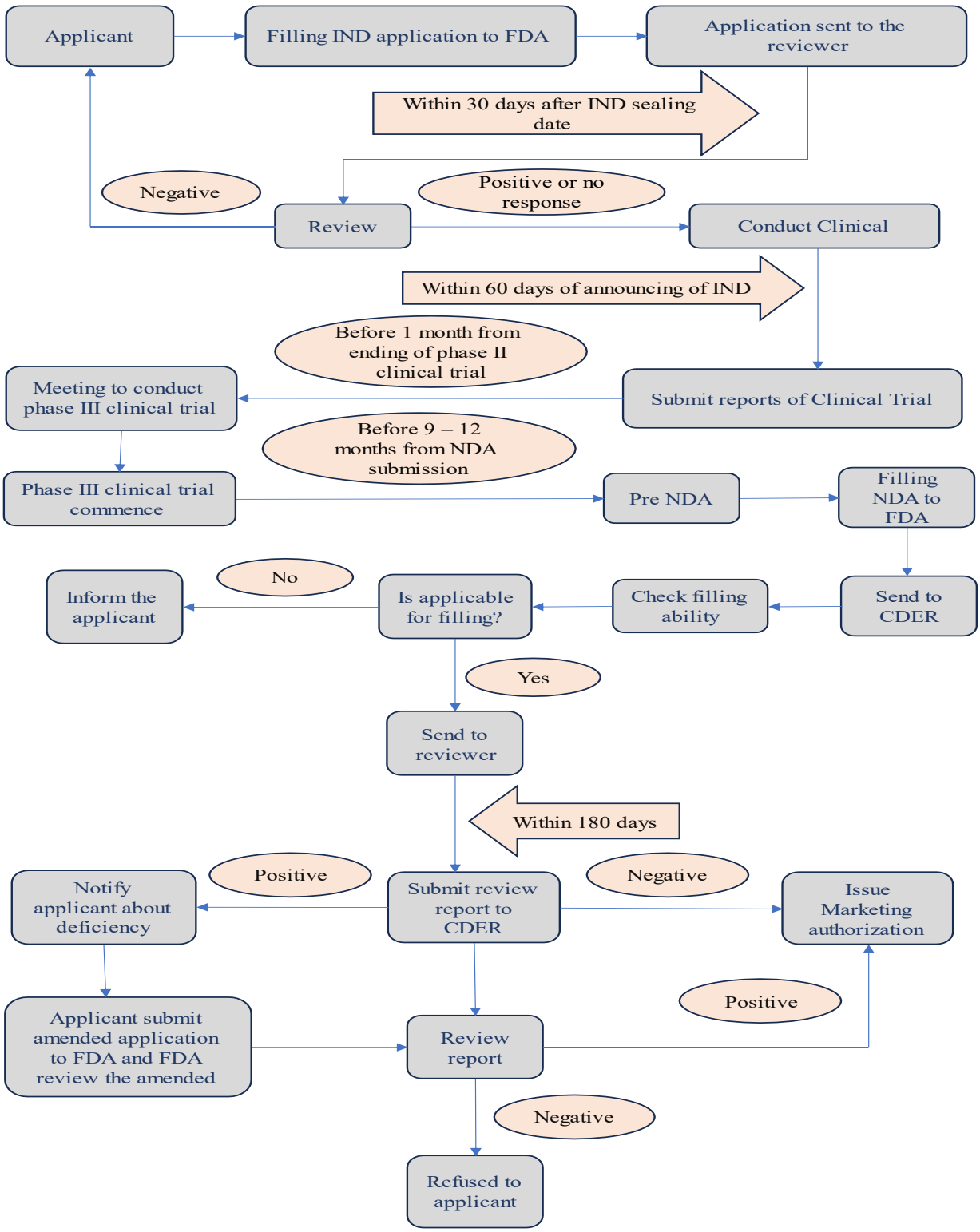

Figure 9. New Drug approval process of US

a) The Centralised Procedure (1995)

The centralised procedure is essential for three kinds of products:

- Pharmaceuticals created using any biotechnological techniques;
- New active components having a therapeutic indication towards the medical management of viral infections, cancer, neurological disorders, diabetes, a condition autoimmune disease, along with other immunological malfunctions; and
- Pharmaceuticals classified as orphan medicinal products. (36)

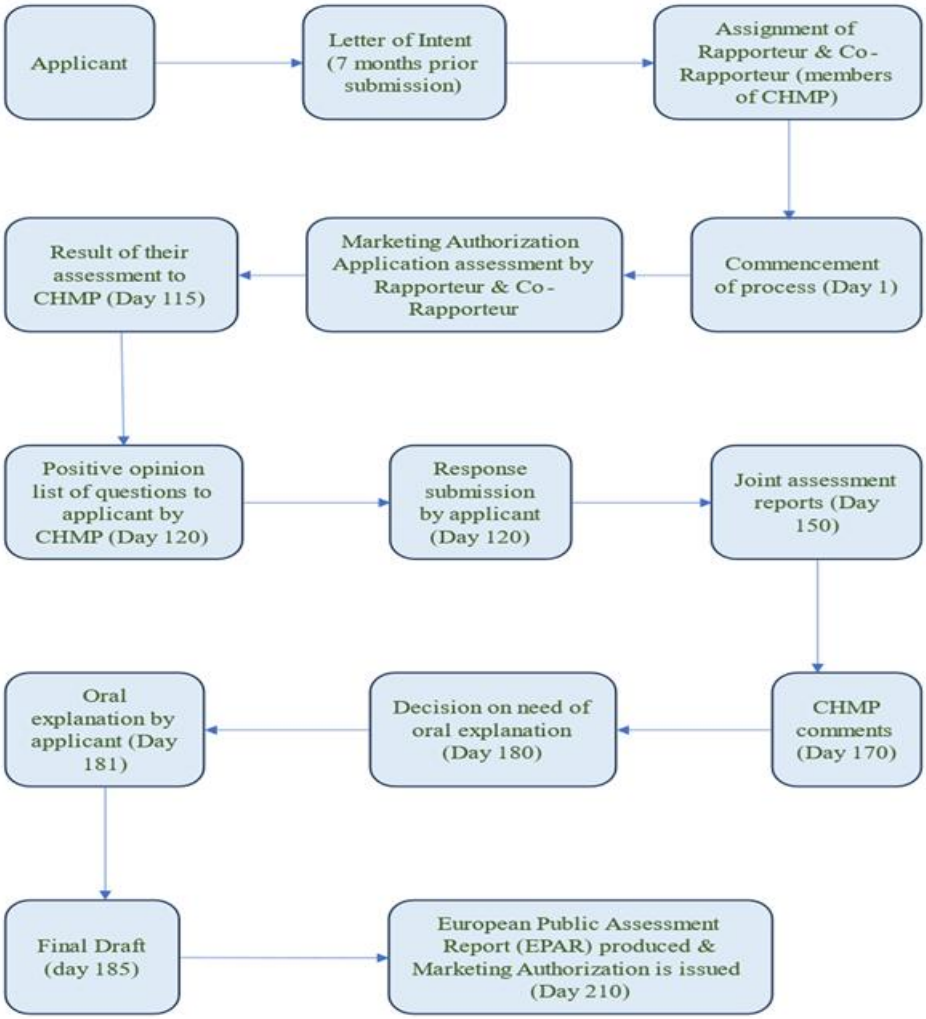

Figure 10. Centralized procedure for EU Marketing Authorization

b) The Mutual Recognition Process (1995)

- **Reciprocal Licensing (1995)**: Allows businesses to seek recognition of a drug licensed in one EU Member State in other EU states.
- **Scientific Opinion Sharing**: Member nations rely on each other's scientific evaluations.
- **Initial Approval**: The drug must first obtain national permission from a single EU Member State, designated as the Reference Member State (RMS).
- **Mutual Recognition Procedure (MRP)**: In the second stage, the applicant requests recognition in additional EU Member States, called Concerned Member States (CMS). (36)

c) The Decentralised Procedure (2005)

For the Decentralised Procedure, the applicant will simultaneously contact each of the chosen member states. This will be accomplished by the applicant designating a RMS to assess the MAA and confer with one of the chosen member states regarding the results. MRP or DCP applicants choose whichever EU member states to apply for authorisation from. (38,39)

d) National Procedure:

- **National Procedure**: Businesses can apply for marketing authorization for medicines intended for sale in one EU member state via the national procedure, reviewed by the respective national regulatory body.
- **Unified Standards**: All EU pharmaceuticals adhere to the same norms and standards, irrespective of authorization method.
- **Role of NCAs**: National Competent Authorities (NCAs) oversee veterinary and human drug regulations in EU member states.

e) HMA Collaboration:

Heads of Medicines Agencies (HMA) ensure smooth operation of the European medicines regulation network by working closely with EMA and the European Commission. (39–45)

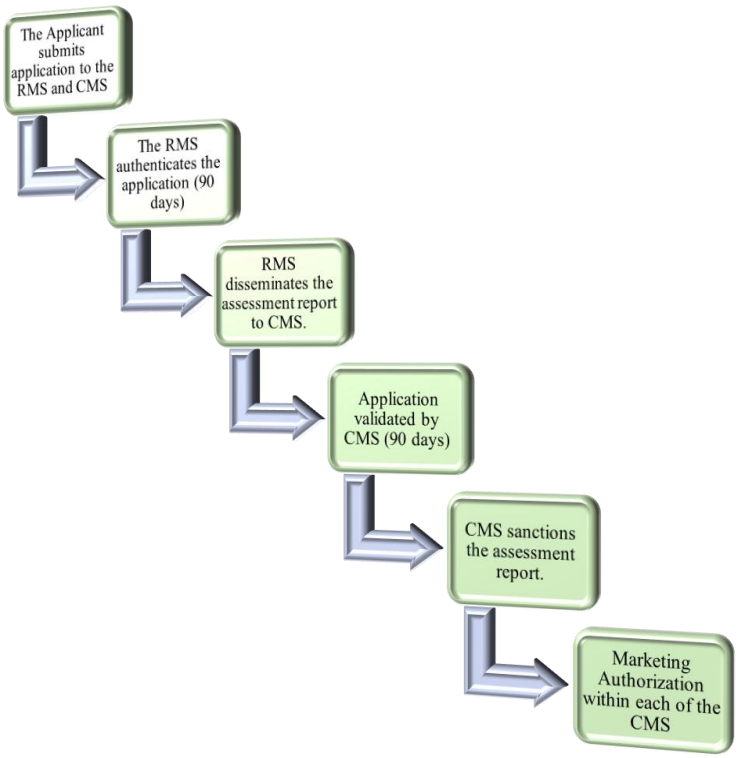

Figure 11. Mutual Recognition Mechanism for Drug Acceptance in EU

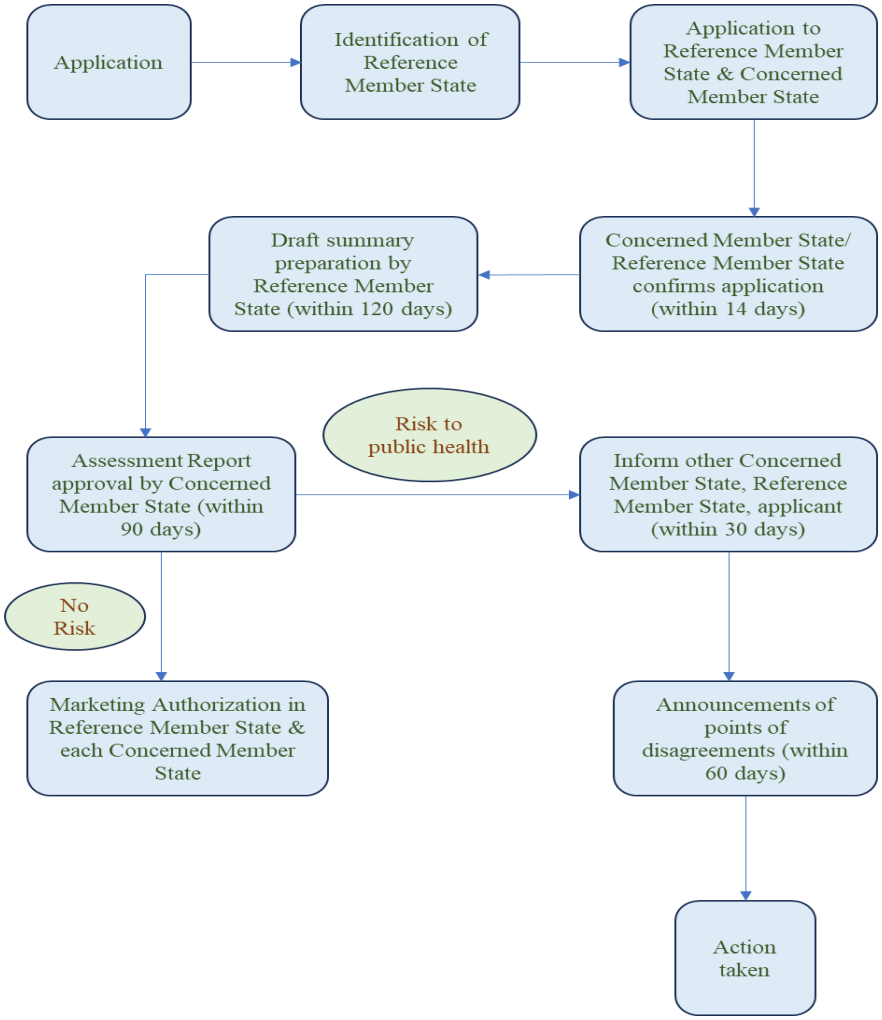

Figure 12. EU's Decentralised Procedure for Marketing Authorisation

5.4 Australia

Applications for prescription drugs must be substantiated by nonclinical, clinical, and/or bioequivalence data (category 1 and category 2) to be eligible to be approved with the TGA. In addition to defining the essential regulatory requirements, report describes this process.(46) Application must be structured according to with the CTD standards while adhering to the regulations provided within the Australian Regulatory Regulations for Prescribed Medicines (ARGPM). However, before authorisation can be provided, the advertiser might be requested for additional information or clarification if inadequacies are detected. (47–51)

a) Approval process (Stages of approval):

Pre-submission stage:

- Complete the Pre-submission Preparation Format (PPF) with high-quality clinical and non-clinical evidence.
- Receive a TGA Preparation statement with goal dates and timelines.
- Submit required documents, including PPF, Module 2 data, certificate, costs, and modifications. (46,52,53)

Submission phase:

- Submit the application in eCTD format within seven months of receiving the planning letter.
- Notification letter advises acceptance or denial of the application based on compliance with TGA regulations.

Initial assessment:

- Evaluators review dossier information; Milestone 3 letter concludes the first round.
- Generic applications require 3 months; other applications need 4 months for review. Complex cases may involve guidance from ADEC. (27,54)

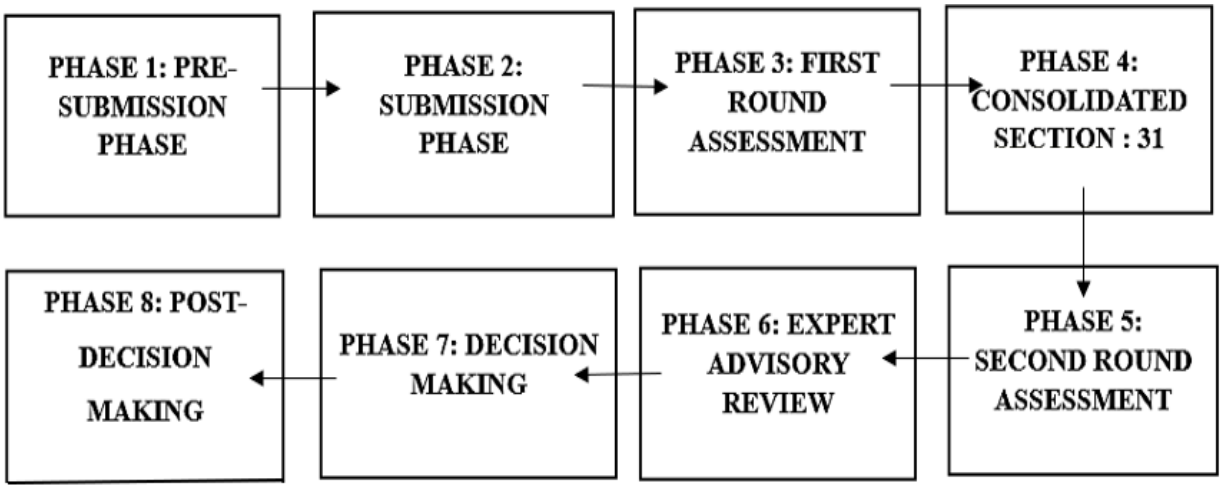

Figure 13. Drug approval Phases

Second round evaluation:

- Respond to S31 requests within 30–60 days using CTD format for documents.
- Assessment resumes only after receiving S31 response. (52)

Professional advisory review:

- ACPM reviews the delegate's proposal; applicants submit pre-ACPM responses before meetings.
- ACPM guidance published in the Australian Public Assessment Report (AusPAR).

Decision phase:

- TGA Representative decides approval or rejection; outcome notified within 28 days.
- ACPM advice shared; selection phase concludes six weeks after ACPM meeting. (47)

Post-decision phase:

- The administrative and regulatory tasks are finished at this stage.
- Administrative tasks completed; ARTG entry uploaded post-certification.

Promotional activities initiated, converting the preliminary ARTG document into the Register of Registration

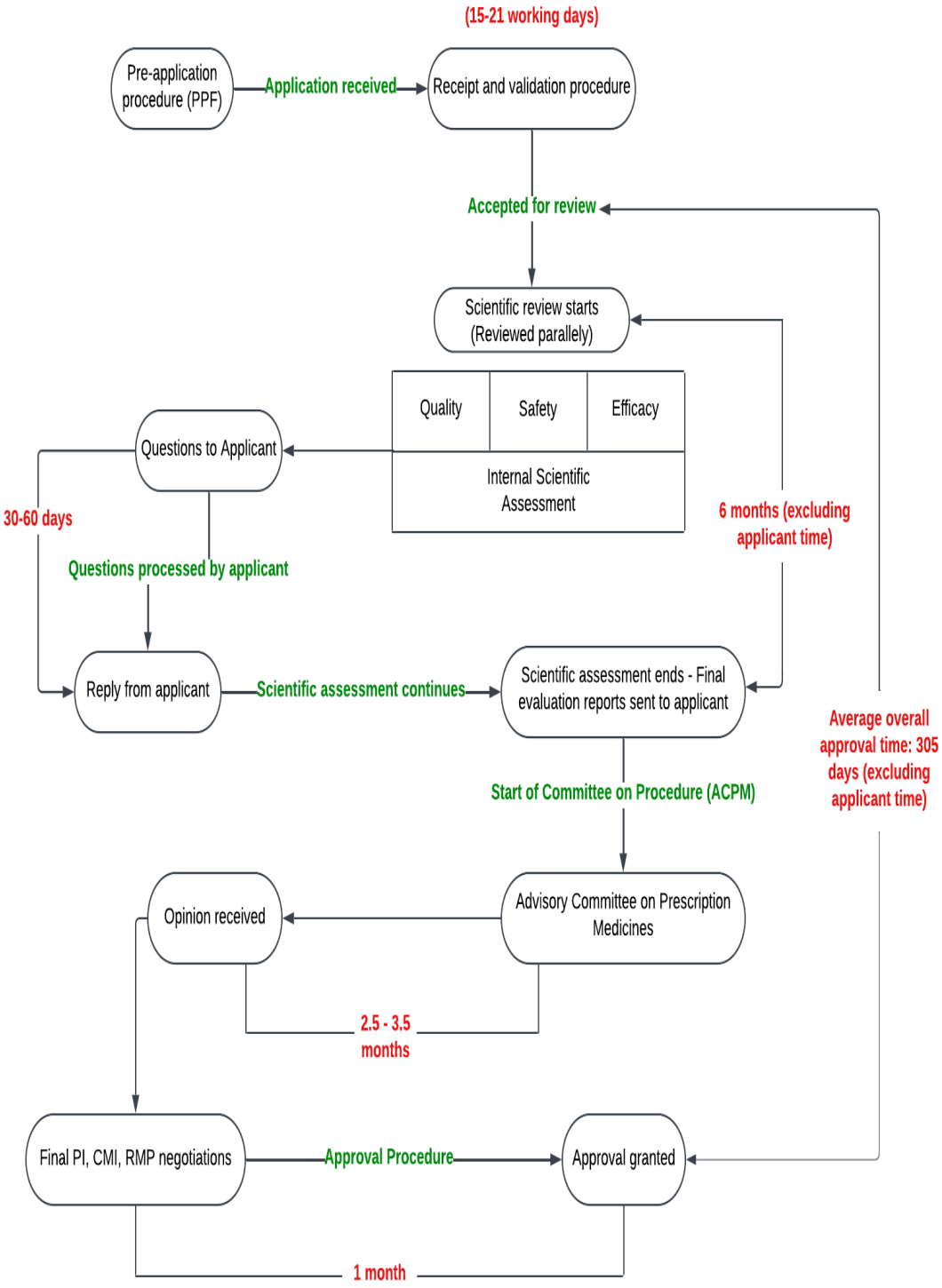

Figure 14. Drug approval process of Australia

5.5 Japan

The Pharmaceuticals and Medical Devices Agency (PMDA) under MHLW certifies medications in Japan. Organizations submit an INDA to the PMDA for new drug production/import. The application undergoes IRB review before research begins. In post-research, data adhering to CTD standards is included in a Marketing Authorization Application (MAA). (55–59)

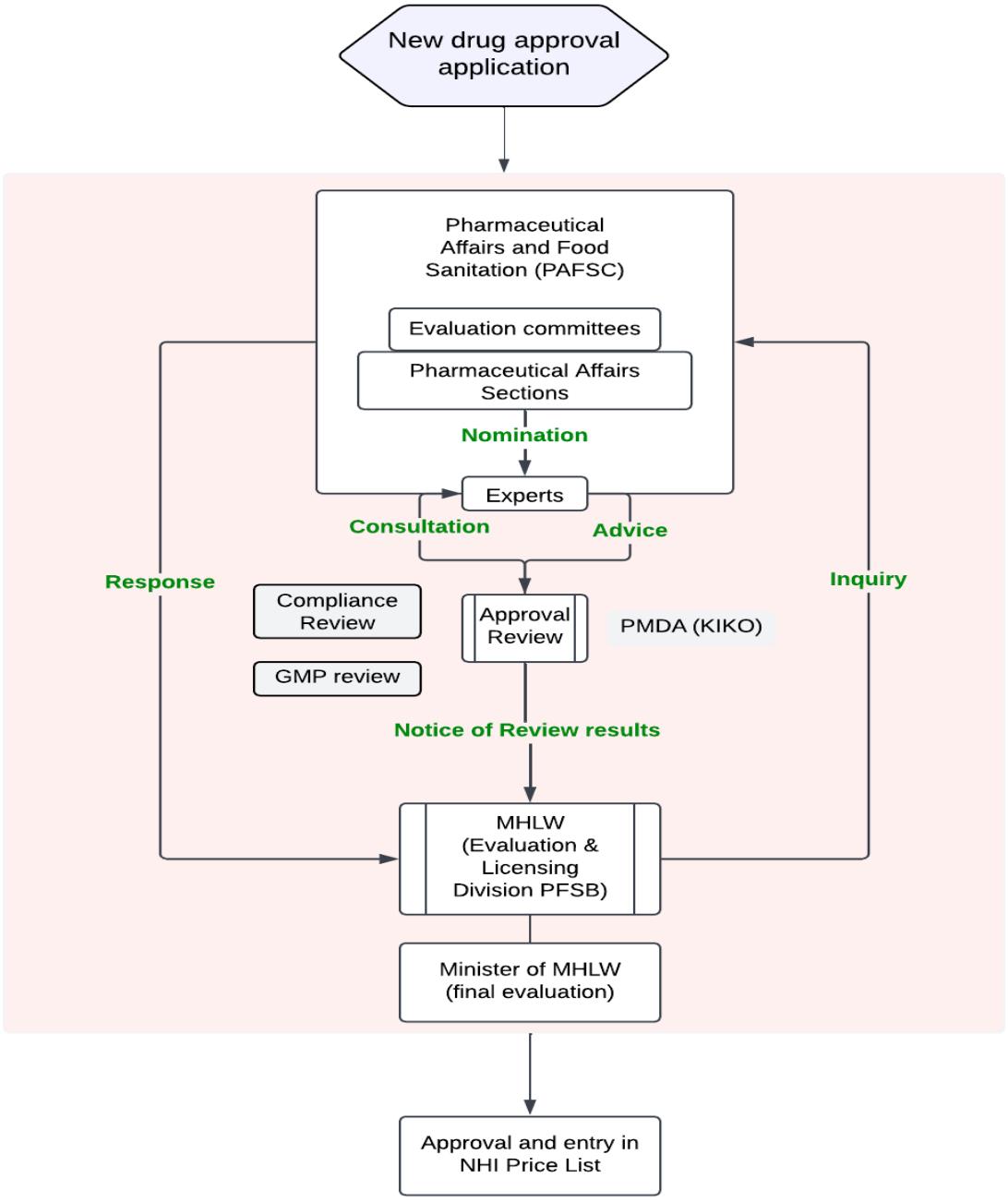

Figure 15. Drug approval process of Japan

a) PROCESS OF APPROVAL:

- **INDA FILING:** An INDA must be submitted to the MHLW to register a new drug in Japan.
- **PMDA ASSESSMENT:** PMDA evaluates the application and prepares a report for IRB review. Research starts once IRB clearance is issued.
- **MASTER FILE REGISTRATION:** Applicant submits a Master File ensuring data aligns with CTD standards. (58,59)
- **REVIEW PROCESS:** Reviewers and external experts discuss application-related issues, led by the review director.
- **FINAL EVALUATION:** Results and evaluation report are submitted to MHLW, which consults the Pharmaceutical Affairs and Food Sanitation Council.
- **APPROVAL:** If all standards are met, the novel medication is authorized for circulation. (59)

Table 1. Parameters for Drugs Approval across various Regulatory Authorities:

Feature	India	USA	Europe	Australia	Japan
Regulatory Body	Central Drugs Standard Control Organization (CDSCO)	Food and Drug Administration (FDA)	European Medicines Agency (EMA)	Therapeutic Goods Administration (TGA)	Pharmaceuticals and Medical Devices Agency (PMDA)
Agencies for Drug Regulation	▪ Central Drug Standard Control Organization (CDSCO) ▪ Government of India Directory of Health and Family Welfare ▪ Indian Council of Medical Research (ICMR) ▪ Ministry of Health and Family Welfare	▪ Centres for Disease Control and Prevention ▪ Department of Health and Human Services (DHHS) ▪ Fed World - US Government Information ▪ The Food and Drug Administration (FDA) ▪ National Centre for Complementary and Alternative Medicine (NCCAM) ▪ National Institutes of Health (NIH) ▪ National Library of Medicine ▪ National Science Foundation ▪ Office of Disease Prevention	▪ EU Legislation – EudraLex ▪ European Directorate for the Quality of Medicines and Healthcare (EDQM) ▪ European Medicines Agency (EMEA) ▪ Heads of Medicines Agencies (HMA)	▪ Australia's Department of Health and Aged Care ▪ Therapeutic Goods Administration (TGA)	▪ Ministry of Health and Labour Welfare (MHLW) ▪ Pharmaceuticals and Medical Devices Agency (PMDA) ▪ Pharmaceutical and Food Safety Bureau (PFSB)
Registration Process	One registration process	One registration process	▪ Multiple registration process ▪ Centralised (European community) ▪ Decentralised (at least 2 member states) ▪ Mutual recognition (at least 2 member states) ▪ National (1 member state)	One registration process With 8 phases.	One registration process.
Application Type	New Drug Application (NDA)	New Drug Application (NDA)	Marketing Authorization Application (MAA)	Registration Application	Marketing Authorization Application (MAA)

Feature	India	USA	Europe	Australia	Japan
Data Submission Type	Master File with Form 44	eCTD and Paper	eCTD	eCTD	eCTD
Clinical Trials	Required for all new drugs	Required for all new drugs	Required for all new drugs	Required for most new drugs	Required for most new drugs
Review Process	Multi-stage review involving scientific committees and expert panels	Rigorous scientific review by FDA experts	Scientific review by EMA committees and national competent authorities	Scientific review by TGA experts	Scientific review by PMDA experts
Approval Time Frame	Varies depending on the complexity of the drug and the completeness of the application	Can vary significantly, but generally takes several months to years	Can vary depending on the complexity of the drug and the review process	Generally, takes several months to years	Generally, takes several months to years
Post Approval Changes	▪ Post approval changes: ▪ Major ▪ Moderate	▪ Post approval changes in the approved drug: ▪ Minor ▪ Moderate ▪ Major	▪ Post variation in the approved drug: ▪ Type IA ▪ Type IB ▪ Type II	The Therapeutic Goods Administration (TGA) is responsible for a number of crucial tasks that guarantee the continued efficacy, safety, and market compliance of therapeutic products.	Modifications may be made to the drug's formulation, manufacturing location, production processes, or usage instructions.
Post-marketing Surveillance	Ongoing monitoring of drug safety and efficacy after approval	Ongoing monitoring of drug safety and efficacy after approval through the FDA Adverse Event Reporting System (FAERS)	Ongoing monitoring of drug safety and efficacy after approval through the Eudra-Vigilance system	Ongoing monitoring of drug safety and efficacy after approval through the Australian Adverse Drug Reactions Database (ADRAC)	Ongoing monitoring of drug safety and efficacy after approval through the Japan Adverse Drug Event Reporting System (JADER)

6. Discussion

The two main steps in the process of authorising a drug were submitting to the regulatory body for marketing authorisation to commercialise the medication and requesting permission to conduct clinical research. The new medicine approval procedures in various nations differ in several aspects, but they also have significant similarities. The sponsoring organisation typically submits the required documentation to conduct a clinical investigation before requesting drug marketing authorisation from the appropriate regulatory body. The scientific investigation is only carried out with the regulatory body's approval. Although there are differences in the length of time, expense, and review process for clinical studies and marketing permission submissions, all countries provide regulatory bodies with information regarding the safety, effectiveness, and purity of pharmaceuticals in the same way. The comparison in the drug approval framework among the 5 countries are laid out in Table 2.

7. Conclusion

The US FDA, EMA (Europe), TGA (Australia), PMDA (Japan), and CDSCO (India) are the five main regulatory agencies whose drug approval procedures have been reviewed in this review. Although every agency takes a different strategy, a number of similarities show up. All place a high priority on patient safety and efficacy, evaluating drugs' safety and effectiveness through rigorous scientific examination that includes pre-clinical and clinical trials. Important distinctions are seen in acceptability standards, regulatory schedules, and the focus on various facets of medication development. Because of their vast resources and significant experience, the FDA and EMA often have stricter regulations and lengthier review periods. Japan and Australia have simplified procedures while emphasising patient access and innovation. India is changing quickly, yet it still has problems with infrastructure development and resource allocation. Reducing redundancy and accelerating worldwide drug development are the goals of harmonisation projects, such as those carried out by the worldwide ICH. Significant geographical variances still exist, though. In conclusion, this analysis has investigated the complicated tapestry of medication approval processes across five main regions — India, USA, Europe, Australia, and Japan – revealing the intricacies and commonalities in their approaches.

Acknowledgement

We extend our profound appreciation to the editors and reviewers for their invaluable time, experience, and constructive critiques offered during the manuscript's review process.

Their astute observations and recommendations have significantly enhanced the quality and clarity of the text. We express our gratitude to Mr. Jaydip Ray, Ms. Ananya Chandra Assistant Professor in the Department of Regulatory Affairs at Guru Nanak Institute of Pharmaceutical Science and Technology, Panihati, Sodepur, Kolkata-700114, for their support and assistance in the writing of this review article. This work is also supported by the Guru Nanak Institute of Pharmaceutical Science and Technology. We recognise the contributions of all persons who have directly or indirectly aided in the creation of this manuscript. I appreciate the chance to submit this review article to the International Journal of Pharmaceutical Sciences and Research. We are appreciative for the consideration given to our work.

Financial Disclosure statement:

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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