WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 6, 786-816. Review Article ISSN 2277– 7105

REGULATORY REQUIREMENTS FOR NEW DRUG APPROVAL IN DIFFERENT COUNTRIES: AN OVERVIEW

Sonal Jain*

Consultant -Senior Medical Writer, Lower Parel, Mumbai-400013, Maharashtra, India.

Article Received on
12 April 2016,

Revised on 03 May 2016,
Accepted on 24 May 2016

DOI: 10.20959/wjpr20166-6407

***Corresponding Author**
Dr. Sonal Jain
Consultant -Senior Medical Writer, Lower Parel, Mumbai-400013, Maharashtra, India.

ABSTRACT

A new drug development process requires extensive research in terms of chemistry, manufacturing, controls, preclinical and clinical trials. It is a huge responsibility of drug reviewers in regulatory agencies across the globe of evaluating the authenticity of research data supporting the safety, effectiveness and quality control of a new drug product to serve the public health. This review emphasizes on the regulatory requirements for attaining MA for new drugs in United States Food & Drug Administration (USFDA), European Medicines Agency (EMA), Japan, China, Australian region and India based on the regulatory guidelines as laid by them. There is focus on Investigational new drug (IND) and New drug application (NDA) as USFDA requirements. In EU, the procedure comprise of four different processes: Centralized Procedure, Decentralized Procedure, National Procedure and, Mutual Recognition Procedure. In India, CDSCO is the primary regulatory authority to get MA for new drugs. Similarly, SDFA, PMDA and TGA are main regulatory authorities in China, Japan and Australia for reviewing efficacy and safety data and thus granting MA for new drugs in these countries.

KEYWORDS: Central Drugs Standards Control Organization(CDSCO), Drug Lag, European Medicines Agency (EMA), European Union(EU), US Food and Drug Administration (USFDA), Marketing Authorization (MA), Pharmaceuticals and Medical Devices Agency (PMDA), State Food and Drug Administration(SDFA), Therapeutic Goods Administration (TGA).

INTRODUCTION

The pharmaceutical industry is considered as one of the extremely regulated industries, with specific laws and legislations as obligated by the government for human health protection.

Therefore it is the responsibility of national governments to establish regulatory authorities with specific and stringent guidelines for quality assurance and drug regulations in the respective territories. This necessitated the inception of International Council on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), a collaborative initiative between the EU, Japan, and the United States with observers from World Health Organization (WHO), European Free Trade Association (EFTA), and Canada.[1]

Drug approval is a very complex process therefore it is necessary to have knowledge of guidelines and standards specific to different countries. Hence, it is imperative to analyze the alterations and commonness between the regulatory requirements and pharmaceutical legislations of different countries of the world. The pharmaceutical market can be categorized into two groups on the basis of the diversity in the regulation region and marketing interest: regulated and emerging markets. The countries with well-structured regulatory requirements constitute the regulated market (United States (US) and the EU are the biggest and the most potential markets for in the world and are categorized under the regulated markets.[2] On the other hand, the emerging market includes countries with "drug-lag" and not so well-defined regulations for drugs. ROW (Rest of the World) market includes all the emerging markets like Rest of the World (Asia Pacific except Japan, ANZ, GCC, LATAM, CEE, CIS): (LATAM: Latin America; CEE – Central East Europe; CIS – Commonwealth of Independent States; ANZ – Australia, New Zealand; GCC -Gulf Co-operation Council; ROW – Rest of World).[3]

Biopharmaceutical Research and Drug Development Process

Stages of Clinical Trials

First Stage - Phase 1-3 clinical trials.[4]

Second Stage- For marketing authorization of drug (phase 4 clinical trials).[4]

Pre-Clinical Studies

The drug development is initiated with non-clinical/ pre-clinical phase of the study which includes animal toxicology studies. Pre-clinical are conducted for testing biologic effects and adverse effects. These studies usually include assessment of drug exposure, primarily parent drug plasma concentration.[4,5] The pre-clinical safety data before initiating a clinical trial comprises: single dose toxicity, repeated dose toxicity, local tolerance, reproduction toxicity, genotoxicity, carcinogenicity, safety pharmacology and pharmacokinetics.[6]

Clinical Trials (Phase 1-3)

Phase 1-3 clinical trials are conducted to assure safety, efficacy and dosage optimization of drug in human being.[4,7,8]

Phase 1[4, 7, 8]

No. of patients

Conducted on 20-100 healthy volunteers or people with the disease/condition.

Duration of Study

Several months.

Parameters tested

Safety and dosage.

Mostly healthy volunteers are participants of Phase 1 studies. However, if a new drug is projected for use in cancer patients the participants are the particular type of cancer.

The primary objective of Phase 1 studies – to determine what the drug's most frequent side effects are often, the side effects associated with increased dosage, its absorption, distribution, and excretion.

Phase 2[4,7,8]

No. of patients: Conducted on several hundred people with the disease/condition.

Duration of Study

Several months to 2 years.

Parameters tested

Efficacy and side effects.

Phase 2 studies emphasize on determining efficacy of the drug in a small population who have a specific disease or condition• However, these studies aren't large enough (involving only a few hundred patients) to highlight efficacy of the drug. On the other hand, Phase 2 studies provide additional safety data. This data can be utilized to develop more refined research methodology for conducting Phase 3 trials.

Phase 3[4, 7, 8]

No. of Patients

Conducted on 300-3,000 volunteers with the disease or condition.

Duration of Study

1- 4 years.

Parameters tested

Efficacy and monitoring of adverse reactions (ARs).

Phase 3 is pivotal trial, usually multi-center, to assess the efficacy and safety of the drug. These trials target drug at different dosages in different populations – usually include several hundred to about 3000 subjects – are often multi-center trials.

Phase 4(Post Marketing studies)[4,7, 8]

No. of Patients

Conducted on several thousand volunteers with the disease/condition.

Parameters tested

Safety and efficacy.

Phase 4 trials are carried out after the drug or device has been approved by Food and Drug Administration (FDA) during the Post-Market Safety Monitoring.

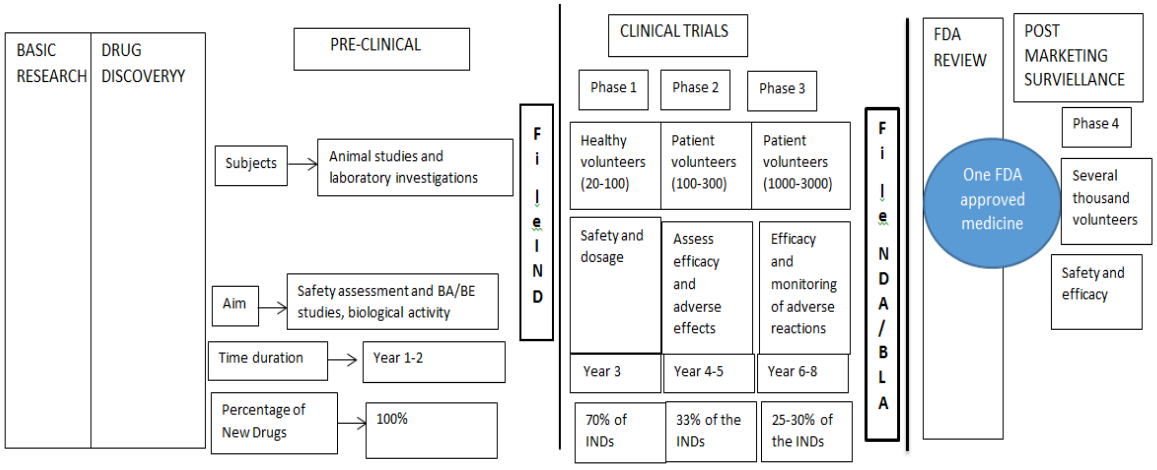

Fig.1: Phases in the Drug Development Process[4,7- 9]

IND: Investigational New Drug; NDA: New drug Application; BLA: Biologic License Application; BA: Bioavailability; BE: Bioequivalence

New Drug Approval Process in Different Countries

New drug development is a complex process requiring enormous research work terms of in chemistry, manufacturing and controls (CMC), preclinical experiments and clinical trials. It is a moral responsibility of regulatory bodies across the globe to specifically evaluate the precision of research data supporting the safety, efficacy and quality control of a new drug product in view of human health protection. In today's scenario every country has its own regulatory authority responsible for implementing the rules and regulations and regulates marketing of drug by applying the procedures enumerated in the regulatory guidelines.[10]

New Drug Approval Process in the United States (USA)

The United States has the world's most rigid regulatory approval process for new drugs.[7,11] Major agencies for drug regulatory approval in US are Centers for Disease Control and Prevention (CDC), Department of Health and Human Services (DHHS), Fed World - US Government Information, The Food and Drug Administration (FDA), National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health (NIH), National Library of Medicine, National Science Foundation and Office of Disease Prevention.[4]

Steps in the Standard Drug Approval Process[12]

There are four FDA steps for a new drug approval for marketing in the US.

- Investigational New Drug (IND) Application.
- Clinical Trials.
- New Drug Application (NDA).
- FDA Review.

1. Investigational New Drug (IND) Application[4,11-13]

The IND is submitted to the FDA to initiate clinical trials in humans post pre-clinical studies (if drug has shown adequate safety profile and toxicity studies). A Sponsor (a firm or institution) generally submits the IND application.

Sponsor/FDA Meetings (Pre-IND)

The sponsor requires proof that the compound is clinically active before the clinical studies on humans can be initiated. The sponsor and the FDA need data indicative of that the drug is adequately safe for initial administration to humans.[13] In view of this a pre - IND meeting can be arranged with the FDA to discuss a number of issues.

- The pre-clinical study design, which is required to lend support to the clinical studies[13]
- An envisioned protocol for conducting the clinical trial[13]
- The chemistry, manufacturing, and control of an investigational drug[13]

Besides data on pre-clinical studies, proposed protocol and CMC for investigational drug, an IND must also include the written approval of an Institutional Review Board (IRB) and "Indication for Use" section. A manufacturer can begin clinical testing, unless FDA objects which is not more than 30 days from FDA to review the IND application.[12]

Though the primary role of the IND is to provide information about the data to proceed for clinical trials, the IND is not an application for marketing approval. It is a request for an exemption from the Federal statute that forbids an unapproved drug from being shipped in interstate commerce. As to pursue for clinical studies a sponsor will undoubtedly require shipping the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement which is attained by filing the IND.[13]

Categories of INDs

1. Commercial INDs

Applications that are submitted primarily by companies with an objective to get marketing approval for a new product.

2. Noncommercial INDs

The major proportions of INDs are filed for noncommercial research. These types of INDs include "Investigator INDs," "Emergency Use INDs," and "Treatment INDs."[13]

- **"Investigator IND"**

Submitted by a physician who both initiates and conducts an investigation, and under whose immediate supervision the investigational drug is administered. The primary purpose to submit these IND is to propose studying an unapproved drug or to conduct research for a new indication in new patient population for an approved drug.[14]

- **"Emergency Use IND"**

These type of INDs are submitted to get an authorization from FDA to use an experimental drug in an emergency situation due to lack of time for submission of an IND in accordance with 21CFR(code of Federal Regulations) (Section. 312.23 or Section. 312.20). Besides,

these INDs are also submitted for patients who don't meet inclusion criteria as described in study protocol or if an approved study protocol does not exist.[14]

- **"Treatment IND"**

Submitted for experimental drugs showing promising results in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.[14]

A flowchart of the IND review process by CDER is illustrated in figure 2.[13]

2. Clinical Trials

The process of clinical trials for new drug approval in US is described above comprising of clinical trial phase 1, 2 and 3 (Fig .1)[4,7- 9]

Defining Safety, Efficacy and Effectiveness[12]

Safety

Safety studies are conducted to define the highest tolerable dose or the optimal dose of a drug required to attain the desired benefit. Safety is generally evaluated by toxicity testing. Studies for safety assessment also identify any potential adverse effects (AEs) that may result from exposure to the drug.

Efficacy

When a drug establishes a health benefit over a placebo or other intervention in an ideal situation, such as a tightly controlled clinical trial.

Effectiveness

Describes the health benefit obtained by a drug in a real-world situation. Effectiveness is often lower than efficacy because of number of factors associated while testing the drug in real-world situation which are not hindrances in a controlled clinical trial like drug interactions, patient's health conditions, sufficient dose or duration of use not prescribed by the physician, non-compliance of required drug intake by the patient and use for an off-label condition that had not been tested.

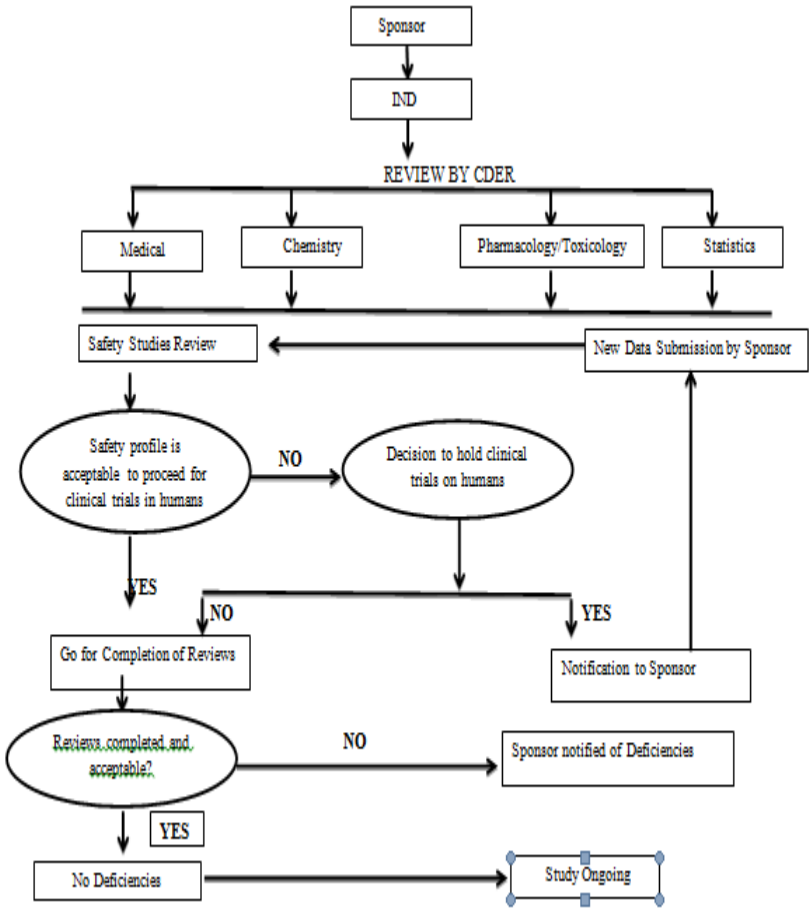

Fig.2: IND review process by CDER[13]

3. New Drug Application(NDA).[4,11-13]

Sponsor/FDA Meetings (Pre-NDA)

Pre-NDA meetings are conducted to discuss the presentation of data (both paper and electronic format) in support of the application by the sponsor which includes.

- A synopsis of clinical studies to be submitted in the NDA[13]
- The proposed format for organizing the submission, including methodology used for presenting the data[13]
- Other requisite information needed[13]

The NDA is submitted post completion of the clinical trials by the sponsor to FDA's Center for Drug Evaluation and Research (CDER). The required information while submitting NDA includes: results of clinical trial results, information about the manufacturing process and facilities (quality control and assurance procedures). Besides, NDA application also includes a detailed product description (chemical and molecular formula, pharmacodynamics, and

pharmacokinetics); the indication (specifying one or more diseases or conditions and the target population), labeling and a proposed Risk Evaluation and Mitigation Strategy (REMS) (if applicable).

The reviewing criteria of FDA are focused on three major aspects: (1) safety and effectiveness of the drug's proposed use and whether the benefits of the drug outweigh the risks. (2) suitability of the proposed labeling (3) sufficiency of manufacturing methods to assure the drug's identify, strength, quality, and identity.[12,13]

After filing of NDA, a meeting may also occur 90 days after the first submission of the application to cover up the issues not discussed in the initial review.[13]

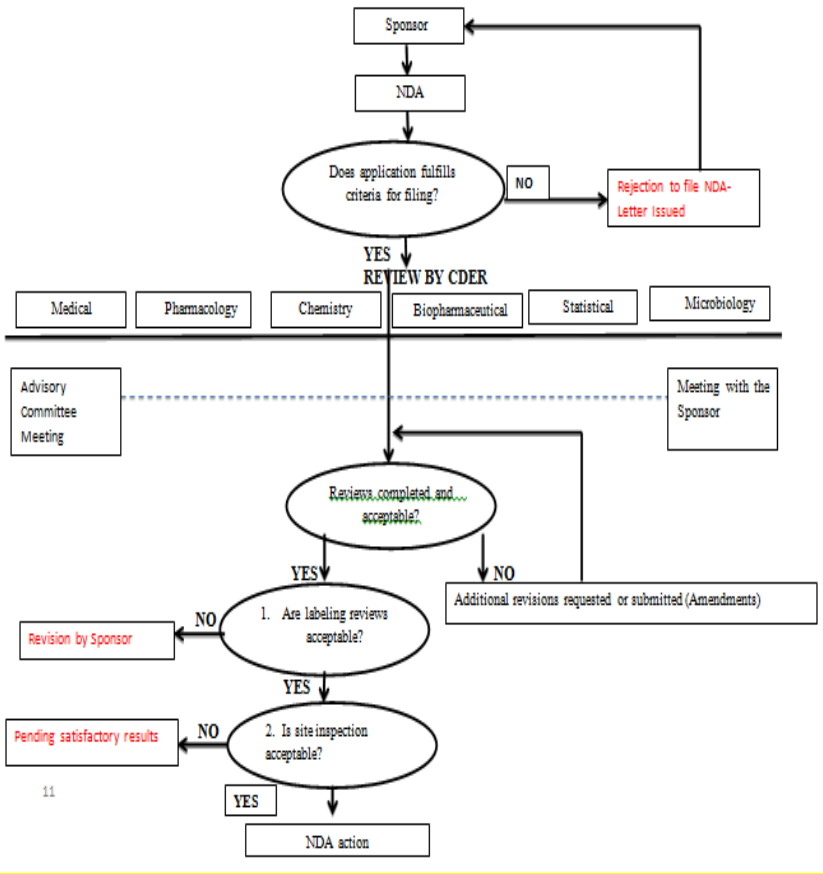

Fig.3: NDA review process by CDER[13]

Special Regulatory Procedures to Expedite the Development and Review Process

To ascertain the availability of drugs those treat serious diseases, particularly when the drug has advantages over existing treatments there is necessity of expedited regulatory approval. The FDA has developed four distinct and successful approaches for rapid availability of these drugs,[12,15]

- Priority Review
- Breakthrough Therapy
- Accelerated Approval
- Fast Track

Accelerated approval

"Accelerated approval" is done when a drug or biologic product that provides a "meaningful therapeutic benefit. Over existing treatments." The rule covers two situations: **1.** "A surrogate endpoint that is reasonably likely to predict clinical benefit." **2.** Addresses drugs whose use FDA considers safe and effective only under set restrictions that could include limited prescribing or dispensing. FDA usually requires post-marketing studies of products for this situation.[12,15]

Fast track

"Fast track" approval can be given under two criteria

1. the product must concern a serious or life-threatening condition; **2.** It should be potentially capable to address an unmet medical need.[12,15]

Priority review

The "Priority Review" process begins only when a sponsor officially submits an NDA. In 1992, under the Prescription Drug User Act (PDUFA), FDA set specific goals for improving the drug review time and created a two-tiered system of review times– Standard Review and Priority Review. A Priority Review is designated when action on an application is taken within 6 months (compared to 10 months under standard review).[12,15]

Breakthrough Therapy

Breakthrough Therapy is designated when a drug is intended to treat a serious condition with favourable preliminary clinical evidences and might demonstrate substantial improvement over existing treatment modalities on a clinically significant endpoint(s). The clinically significant endpoints to get designated for Breakthrough Therapy generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. Preferably, a Breakthrough Therapy designation should be requested no later than the end-of-phase-2 meetings to FDA.[15]

FDA Regulatory Processes for Approved Drugs

FDA's ensures drug's safety and effectiveness even after the drug has demonstrated a drug's safety and effectiveness for a particular set of population and specified conditions and it appears on the market by its post-market regulatory procedures.[12]

FDA postmarket drug safety and effectiveness activities describes nine activities: product integrity, labeling, reporting, surveillance, drug studies, risk management, information dissemination, off-label use, and direct-to- consumer advertising.[12]

1. Product Integrity

A primary concern of FDA is to assure product integrity. The Federal Food and Drug Cosmetic Act (FFDCA) prescribe mandatory requirements which allow FDA to regulate manufacturing facilities, warehouses, and transportation plans. Some of the important requirements include.

- Annual registration of any establishment in any State engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs[12]
- Submission of lists of products like ingredients and labeling[12]
- Inspection of drug lots for packaging and labeling control[12]
- Sampling and testing of in-process materials and drug products.[12]

2. Labeling

Labeling is one of the prime factor in the presentation of drug safety and effectiveness information. FDA can introduce label changes based on information it gathers from mandatory industry reports to its Adverse Events Reporting System (AERS), manufacturer-submitted postmarket studies, and voluntary adverse event information from clinicians and patients. Besides, manufacturer can also ask for label changes if has supporting data from original or published studies in favour of new indication to support a new marketing claim.[12]

3. Reporting

Reporting is done to monitor safety of the drug. It is done by reporting all serious and unexpected adverse reactions to FDA's AERS within 15 days of its acquaintance. Health professionals and patients may report adverse reactions to FDA's MedWatch reporting system at any time which are later added to the AERS database.[12]

4. Surveillance

Sometimes AEs may occur after the use of a drug for some unrelated reasons which necessitates surveillance to assess which ones may indicate a drug problem. Surveillance might lead to change in drug labeling to alert users to a potential problem, or it may require the manufacturer to study the observed relationship between the drug and the adverse event.[12]

5. Drug Studies

FDA can recommend and enquire product sponsors to conduct studies, however, the law permits FDA to demand for drug studies in the post approval period only in limited situations.[12]

- **Postmarket Studies Required upon Drug Approval**

Accelarated approval, animal efficacy and pediatric assessments.[12]

- **Postmarket Studies Required after Drug Approval**

Pediatric assessments and based on new information available to secretary.[12]

6. Risk Management

FDA approach to risk management is an "iterative process" comprising both risk assessment and risk minimization to identify and minimize risk to patients. The Food and Drug Administration Amendments Act of 2007 (FDAAA) designated this risk-management process the Risk Evaluation and Mitigation System (REMS). A REMS plan includes the following components.

1. A Medication guide[12]
2. Healthcare provider information[12]
3. Elements to assure safe use (ETASU)[12]

7. Information Dissemination

A number of communication channels have been sustained by FDA to distribute information on drug safety and effectiveness to clinicians, consumers, pharmacists, and the general public. These include a monthly Drug Safety Newsletter, Drug Safety Communications, FDA Drug Safety Podcasts, FDA Drug Info Rounds, and FDA Drug Information on Twitter.[12]

8. Off-label use

An "off-label" use is defined as a prescription to an individual with different demographic or medical characteristics from FDA's approved labeling and is a recognized medical practice. Prescribing drugs by medical practitioners for indications or situations for which safety and effectiveness has not been demonstrated can create evaluation problems for FDA safety reviewers.

Examples of Off-Label Use

- A drug that was tested in an eight-week trial may be prescribed for long-term use.[12]
- Established at one dose, it may be used at higher or lower doses.[12]
- Tested in adults may be prescribed to children.[12]
- Tested for the treatment of one disease may be prescribed in an attempt to prevent another.[12]

9. Direct-to-Consumer Advertising

The FDA is the main regulatory body for the advertising of prescription drugs. Though the Federal Trade Commission regulates nonprescription drug advertising but the product labeling of the nonprescription drug ads is also regulated by FDA. FDAAA mandates that television and radio ads should reflect the required information on side effects and contraindications in a "clear, noticeable, and unbiased manner."[12]

New Drug Approval Process in Europe

Same as the US approval process, approval processes for new drug in European Union also divided into two regulatory steps. These are: 1. clinical trial application; 2. marketing authorization application (MAA). There are 27 member states in the European Union (as of August 2007). The approval of clinical trial applications is done at the member state level, while MAA's are approved at the member state and centralized levels.[11,16,17] The main regulatory agencies in EU are: EU Legislation - Eudralex, European Directorate for the Quality of Medicines and Healthcare (EDQM), European Medicines Agency (EMEA) and Heads of Medicines Agencies (HMA).[4]

There are four procedures for submitting a MAA in the EU.

- The centralized procedure (CP).[11,16-19]
- The mutual recognition procedure (MRP)[11,16-19]
- The decentralized procedure (DCP)[11,16-19]

- The nationalized procedure (NP)[11,16-19]

1. Centralized procedure

The centralized procedure allows applicants to obtain a marketing authorization (MA) that is valid throughout the EU.

- Leads to a single authorization valid in EU (27 countries) as well as Norway, Iceland and Liechtenstein.[11,16-19]
- Application evaluated by an assigned Rapporteur.[11,16-19]

Timeline

- European Medical Agency (EMA) issues opinion within 210 days, which is submitted to European Commission for final approval.[11,16-19]

  Centralized process is compulsory for:
- Medicines derived from any biotechnology processes like genetic engineering.[11]
- Medicines intended for the treatment of Cancer, HIV/Aids, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions.[11]
- Medicines officially designated 'orphan medicines'-medicines used for rare diseases.[11]

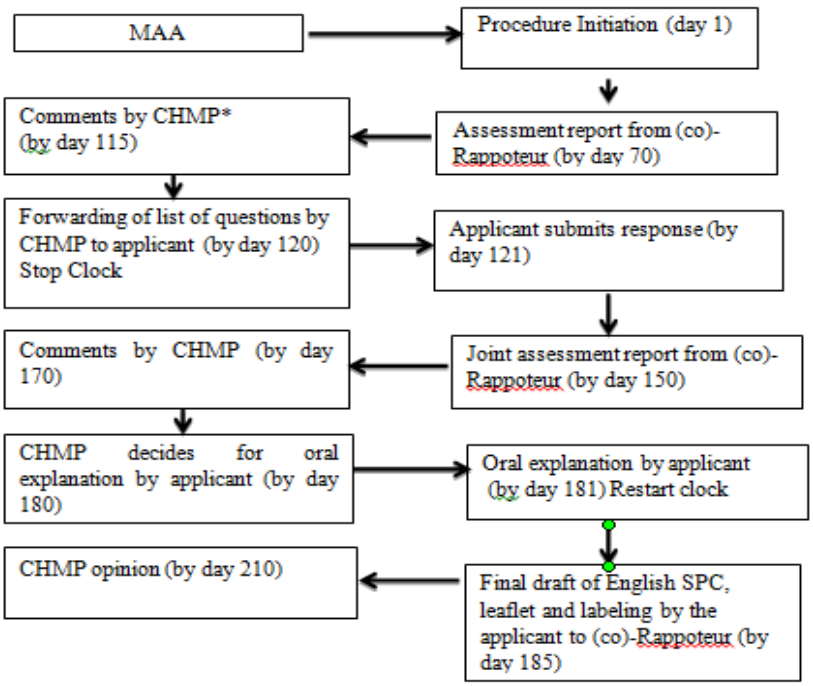

Fig.4: Centralized Procedure [11, 16-19]

*CHMP: Committee for Human Medicinal Products.

2. The Mutual Recognition Procedure (MRP)

The primary goal of this procedure is to get MA in one or several Member States, when the medicinal product has already been authorized by at least one country in the European Community. The procedure is initiated by identical applications for mutual recognition to one Member States. The Member State then decides to evaluate the medicinal product (so referred to as "Reference Member State(RMS)" now), it informs this decision to other Member States (so referred to as "Concerned Member States(CMS)" now), and to whom applications have also been submitted. CMS will then await the RMS decision on the product.[11,16-19]

The timeframe for evaluation procedure by the RMS might take 210 days and thus permitting marketing authorization in that Member State. If a marketing authorization had already been granted by the RMS it shall update the existing assessment report in 90 days. The copies of this report are sent to all Member States post assessment, together with the approved summary of product characteristics (SPC), labeling and package leaflet. The CMS validates the decision of RMS in 90 days together with SPC, labeling and package leaflet as approved by it. National marketing authorizations will be granted within 30 days after acknowledgement of the agreement.[11,16-19]

In case of refusal of the original national authorization by any Member state, due to potential serious risk associated to public health, the issue will be referred to the coordination group. Within 60 days, Member States within the coordination group reach to an agreement. In case of failure of this process, it is submitted to the appropriate EMEA scientific committee (CHMP or CVMP, as appropriate) for settlement.[11,16-19]

- An identical dossier (including required information) must be submitted by the applicant to all EU member states in which it wants authorization.[11,16-19]
- The Member State then decides to evaluate the medicinal product (now referred to as "Reference Member State(RMS)"), it informs this decision to other Member States to whom applications have also been submitted (now referred to as "Concerned Member States(CMS)").[11,16-19]
- RMS issues an evaluation report to other states on its own findings.[11,16-19]
- The MRP process for drug approval is mainly applicable to generic industry.[11,16-19]
- The time required to complete the MRP process is 390days.[11,16-19]

Marketing approval already granted by an EU Member State, now referred to as the Reference Member State (RMS)

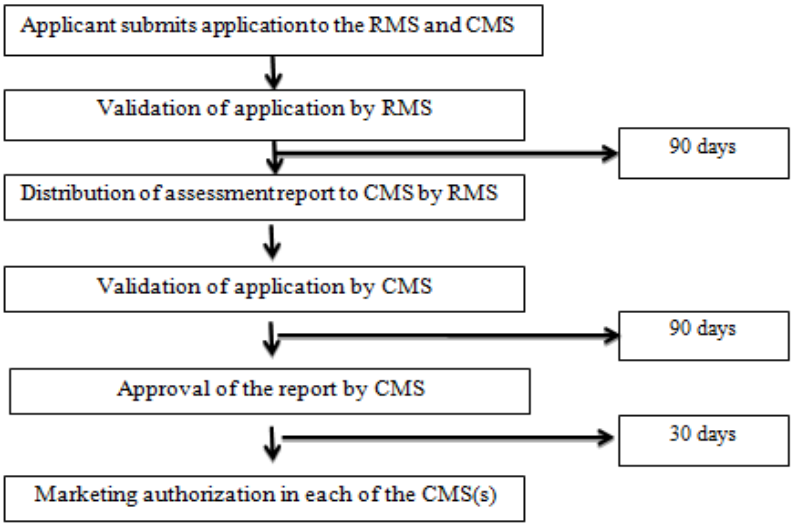

Fig.5: Mutual Recognition Procedure[11,16-19]

3. The Decentralized Procedure (DCP)

The DCP procedure is primarily directed to obtain MA in several Member States, in the situation of no prior MA has been granted in the European Community and essentially for the products that do not fall within the centralized procedure's essential drugs list.

The time required to complete the DCP is 210 days.[11,16-19]

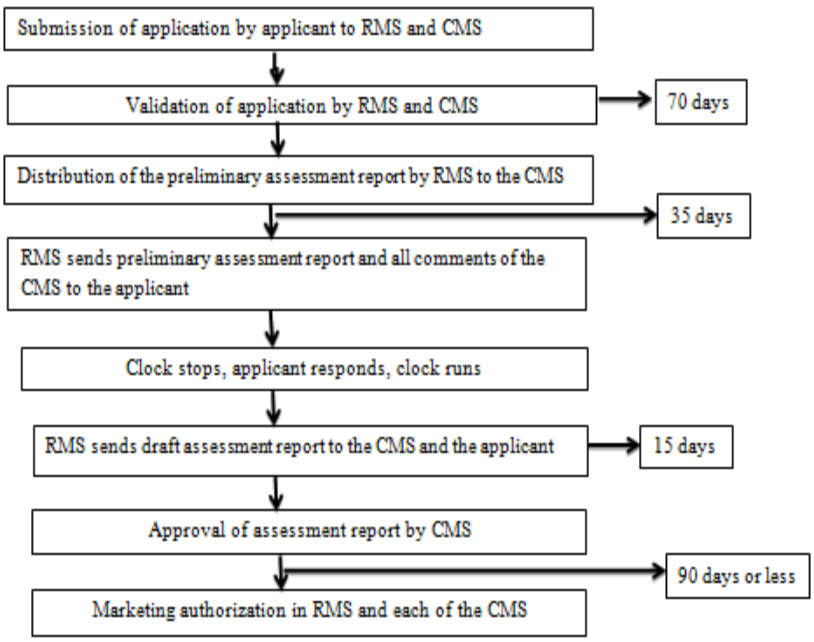

Fig.6: The Decentralized Procedure (DCP)[11,16-19]

4. The Nationalized Procedure(NP)

The NP procedure allows applicant to obtain a MA in one member state only. New active substances which are not under compulsory list of CP procedure can obtain MA under this procedure. The time required to complete the DCP is 210 days[11, 20]

New Drug Approval Process in India

In India a complicated process exists for approval of new drug, which should meet necessary requirements along with NDA to FDA[10,19] In India, permission from the licensing authority, Drug Controller General of India (DCGI) by filing in Form 44 is mandatory when a company wants to manufacture/import a new drug. Besides, submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 is also required. The company is required to conduct clinical trials according to the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format to prove the efficacy and safety of new drug in Indian population.[10,20]

Schedule Y provides the guidelines and requirements for clinical trials for approval of new drug in India. There are established definitions for Phase 1-4 trials together with precise roles for investigators and sponsors. The clinical trials are divided into two categories:

Category A

C These type of clinical trials are approved in the U.S., Britain, Switzerland, Australia, Canada, Germany, South Africa, Japan and EU and are eligible for fast tracking approval in India within 8 weeks.

Category B

These type of clinical trials are under more scrutiny, and approve within 16 to 18 weeks.

An application should be submitted DCGI to conduct clinical trials in India along with the data of chemistry, manufacturing, control (CMC) and animal studies. Besides, other mandatory documents include the date regarding the trial protocol, investigator's brochures, and informed consent documents. A copy of the application must be submitted to the ethical committee and the clinical trials are conducted only after approval of DCGI and ethical committee.

Phase 1 clinical trials

Conducted only on healthy human volunteers to estimate the maximum tolerated dose, adverse reactions, etc.

Phase 2 clinical trials

Conducted on 10-12 patients to determine the therapeutic uses and effective dose ranges at each dose level. **Phase 3 clinical trials (the confirmatory trials):** Conducted to evaluate efficacy and safety of the drug in ~ 100 patients (in 3-4 centers). If the new drug substance is not marketed in any other country, Phase 3 trials should be conducted on a minimum of 500 patients across 10-15 centers.

The new drug registration is applied post completion of clinical trials along with Form 44 and full pre-clinical and clinical testing information. Other required information include: the broad information on the marketing status of the drug in other countries prescription information, product monograph samples and testing protocols, labels, and cartons. The application can be reviewed in a range of about 12-18 months.

Phase 4 trials (post marketing approval)

These trials are conducted post NDA approval when the drug is allowed to be distributed and marketed in which new uses or new populations, long-term effects, etc. are explored.[19, 20]

Changes in the clinical trials according to the exact requirements

1. According to one provision of Rule - 122A of Drugs and Cosmetics Act 1940 and Rules 1945, the licensing authority may waive certain trials, and may permit for import of new drugs based on the supporting data of the trials done in other countries. Similarly, according to another provision in Rule - 122A, the licensing authority may waive clinical trials in the case of those new drugs which are approved and being used for several years in other countries.[10,20]
2. According to Section 2.4 (a) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945, all phases of clinical trials are to be conducted for those drug substances which are discovered in India.[10,20]
3. According to Section 2.4 (b) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945, submission of the data available from other countries is required for those drug substances which are discovered in countries other than India. On the basis of the data

obtained the licensing authority might require repetition of all the studies or permit to proceed from Phase 3 clinical trials[10,20]

4. According to Section 2.8 of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945, the licensing authority permits for Phase 3 clinical trials only after data generated for pharmacokinetic studies (Bioequivalence studies) in Indian population is equal to the data generated in population from other countries.[10,20]

Table 1 shows comparison of Administrative requirements and Bioequivalence requirements for new drug approval in US, Europe and India

S.NO	**REQUIREMENT**	**US FDA**	**EUROPE**	**INDIA**
ADMINISTRATIVE REQUIREMENTS				
1	Application	IND/NDA/ANDA	MAA	IND/MAA
2	Number of copies	3	1	1
3	Approval Timeline	18 months	12 months	12 months
4	Fees	No Fees	10-20 Lakh	Rs 50,000
5	Presentation	e CTD , Paper	e CTD , Paper	Paper
BIOEQUIVALENCE REQUIREMENTS				
1	CRO	Audited by FDA	Audited by Medicines and Healthcare products Regulatory Agency (MHRA)	Audited by CDSCO
2	Reserve Sample	5 times the sample required for analysis	No such requirement	----------
3	Fasted/Fed	As per Office of Generic Drugs (OGD) recommendation	No such requirement	As per CDSCO recommendation
4	Retention of samples	5 years from date of filling the application	No such requirement	3 years from the date of filling the application

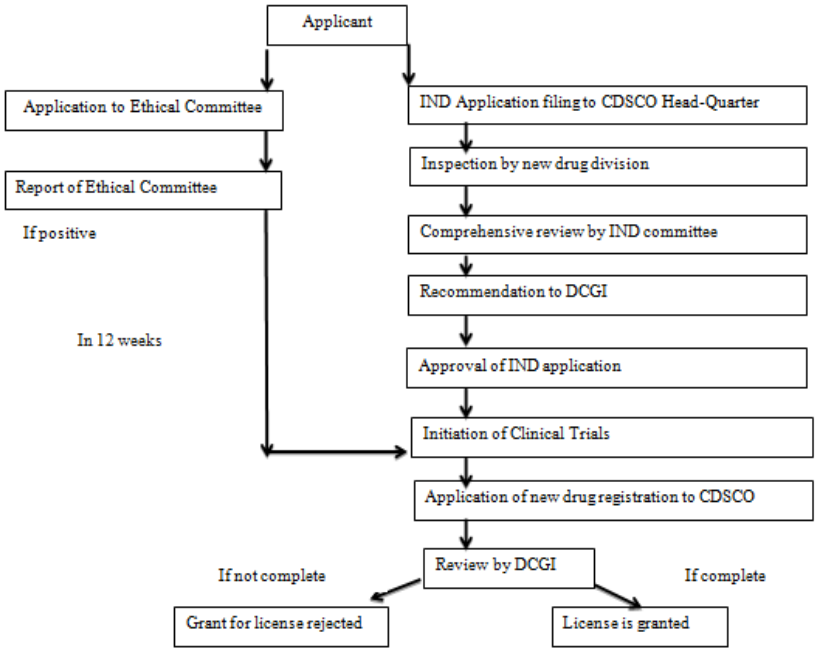

Fig.7: Drug Approval Process in India[10,19,20]

New Drug Approval Process in Japan

1. Japan New Drug Application (J-NDA)

The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) are the primary regulatory agencies for the regulatory affairs related to new drug and devices. The MHLW plays a key role in drug regulation throughout Japan by maintaining stringent price control. The PMDA is responsible from the initiation of preliminary nonclinical phases through the late phases including pivotal clinical trials. It conducts scientific reviews for the MA of new drugs, vaccines, and devices.[21]

J-NDA submission and review/approval processes have same requirements as FDA and/or EMA however; there are some important differences as follows:[22]

- Submission of main results on the Japanese population if Japan is a participant country in global studies or regional studies (like Asian studies) is mandatory. This factor is very imperative as it requires substantial programming support.[22]
- The submission of the CSR (clinical study report) and common technical document (CTD) are main documents requiring programming involvement in Japan, which is similar to FDA and EMA. But, the pooling of AEs from multiple studies may require inclusion of different indications and therefore additional programming support is required as per PMDA's requirements.[22]

- The review time after filing J-NDA is similar to FDA and EMA (12 months for standard filing and 9 months for the "Orphan Drug Designation"). There are two big periods of PMDA questions during review: 1. After **MENDAN** meeting (face to face meeting with PMDA roughly 2-3 months after filing); 2. After GCP (Good Clinical Practice) compliance check conducted by PMDA inspectors but before the Expert Review meeting.[22]

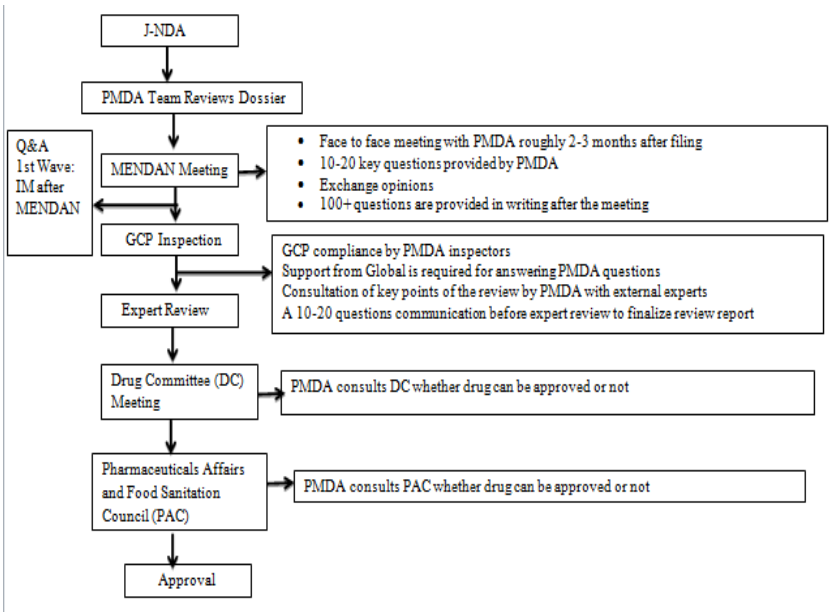

Fig. 8: New Drug Approval Process in Japan[22]

2. The Drug Lag

Even though Japan is the second-largest pharmaceutical market globally and a center for innovative life-science research, there is an appallingly slow approval process for new drugs. A new drug is typically approved in the US or the EU several years in advance of Japan, a condition called the "drug lag." Consequently, the delay of clinical trials leads to launch lags and application lags to regulatory authorities.[21]

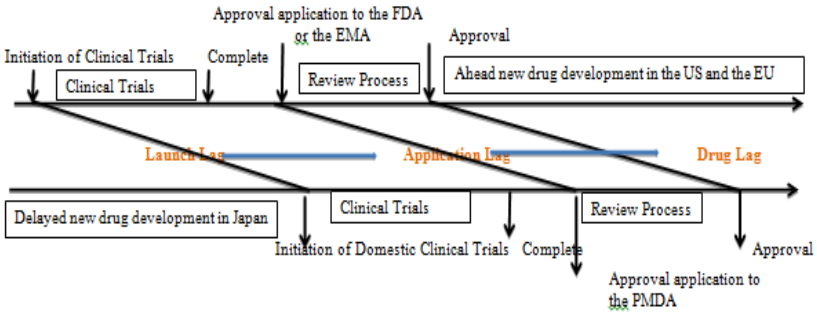

Fig. 9: Typical drug development pattern in Japan[21]

3. Challenges in pharmaceutical drug approval processes in Japan

Pharmaceutical drug development processes in Japan face typical challenges which are divided into below mentioned four topics.

1) Pharmaceutical associated health hazards; 2) Drug lag; 3) Vaccination policies problems and controversies; 4) Clinical study misconduct.[21]
2) To overcome these challenges government has recently implemented some policies given in Table 2.

Table 2 Current challenges related to the benefit-risk assessment for pharmaceuticals in Japan[21]

Challenges	Recently implemented policies by the government
Pharmaceutical associated health hazards	• Increasing staff for safety monitoring at the PMDA • Strengthening of risk communication and management
Drug lag	• Increasing staff for regulatory review at the PMDA • Promotion of global clinical trials • Shortening of time period for regulatory review • Enhanced conditional approval (only for regenerative medicine) • Early availability to unapproved drugs (only in selected hospitals) • Formation of the Japan Agency for Medical Research and Development(Japan AMED)
Vaccination policy	• Increased number of vaccine coverage in the routine immunization program
Clinical study misconduct	• Increased transparency regarding conflict of interest • Stringent regulation and implementation for post-marketing surveillance study including long-term data preservation

New Drug Approval Process in China

The new drug approval process in china is divided into two steps: 1. Approval to initiate clinical trials and conducting bio-efficacy and pivotal clinical trials; 2. Approval for drug registration. The State Food and Drug Administration (SFDA) is the primary regulatory agency for drug approval in China.[23,24]

Step1: Application to initiate clinical trials

For permission to conduct clinical trials; an application dossier is submitted to SDFA and clinical trial permission (CTP) is granted within about 10-12 months after submission. After acknowledgement of application by SFDA (in 30 days); the review is done by Center for Drug Evaluation (CDE) for pharmacology, toxicology, and clinical related data and National Institute for the Control of Pharmaceuticals and Biological Products (NICPBP) for sample examination. It takes 120 days for review by both CDE and NICPBP. The further suggestions by CDE and NICPBP are then notified to SFDA to make decision on approval for clinical trial, which takes mostly 20 -30 days, post of which the final result is delivered to the applicant. The time period to complete clinical trials is 12 to 18 months and it is 3 to 6 months for completion of bioequivalence trials (bio efficacy test). After completion of clinical trials applicant can submit drug approval application.[23,24]

Step 2: Application for drug registration

For drug registration process an application together with the efficacy and safety results from clinical trials is submitted to SFDA and Import drug license (IDL) is granted 12-18 months after submission.[23,24]

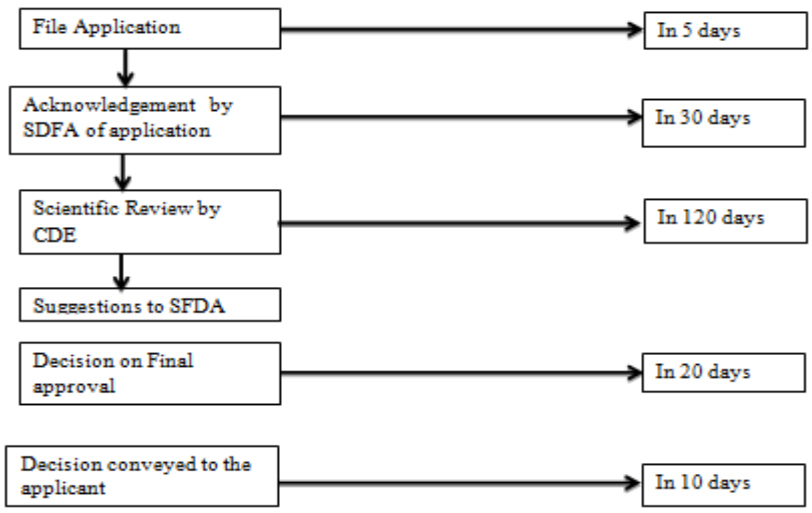

Fig. 10: New Drug Approval Process in China[23,24]

New Drug Approval Process in Australia

The Therapeutic Goods Administration (TGA) is the regulatory agency for medicines, medical devices, blood and tissues in Australia. The information regarding therapeutic goods is contained in a database called Australian Register of Therapeutic Goods (ARTG).[25]

1. Types of Therapeutic Goods

According to the TGA act regulations all type of therapeutic goods are categorized into medicines and devices. Medicines are su-divided into.

i. Prescription medicines (PM)

PM are high-risk medicines containing ingredients described in **Schedule 4**(for supply by a pharmacist only), **Schedule 8**(Substances requiring restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence) or **Schedule 9**(Substances which may be abused or misused, the manufacture, possession, sale or use of which should be prohibited by law excluding when required for medical or scientific research) of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). The Drug Safety Evaluation Board (DSEB) evaluates the most of the PM applications.[4,25]

ii. Non-prescription medicines (NPM) (Over-the-Counter (OTC) Medicines, Complementary medicines).

a. OTC Medicines

An OTC medicine is a therapeutic good described in Part 3 of Schedule 10 of the Therapeutic Goods Act (TGA) and includes non-prescription registered medicines. For Example: mild analgesics, cough/cold preparations, and antifungal creams. The non-prescription Medicines Branch (NPMB) evaluates OTC medicines.[4,25,26] The main advisory committee of TGA for approval and monitoring the activities of safety and efficacy of OTC medicines is Medicines Evaluation Committee (MEC).[25]

b. Complementary medicines

CM are known as 'traditional' or 'alternative' medicines as they mainly consists of one or more designated active ingredients, each of which has a undoubtedly established identity and for traditional use. For Example: vitamins, minerals, herbals, and homoeopathic products. The Office of Complementary Medicines (OCM) evaluates complementary medicines at the TGA.CM are generally obtained from retail outlets such as supermarkets, health food stores and pharmacies and can be used as self-medication.[4,25,26] The main advisory committees of TGA for approval and monitoring the activities of safety and efficacy of complimentary medicines is Complementary Medicines Evaluation Committee (CMEC).[25]

c. Export only medicines

Products containing substances or labels without mandatory warning statements required for listing for supply in Australia which would require registration for domestic supply will be assessed under Section 26 of the Act.[25]

For Example: commercial export of medicines, export of medicines for donation or humanitarian purposes, export of human body fluids/ tissue and export of medical devices. [25]

2. Registration or Listing of Medicines

As per the TGA regulations high risk medicines are mandated to be registered and low risk medicine are mandated to be listed at ARTG for marketing the drug products in Australia. A drug is assigned as AUST R number (registered) or AUST L number (listed medicines) post approval of medicine.[4,25]

AUST R products

TGA evaluate registered medicines for quality, safety and efficacy. Registered medicines include.[4,25,27]

- Nearly all prescription medicines.
- Products not classified in law as demanding a prescription warrant detailed evaluation such as vaccines.
- Almost all OTC medicines; for example: aspirin and paracetamol tablets sold from supermarkets.
- Some CM are registered.

AUST L products

Listed medicines are entirely CM. These include herbal medicines, vitamin and mineral supplements, other nutritional supplements, traditional medicines like ayurvedic medicines and Chinese medicines, and aromatherapy oils.[4,25,27]

Some of the specific requirements for AUST L medicines are.[4,25,27]

- Must not contain prohibited import substances or come from endangered species or be covered by the national regulations which control access to many substances (SUSDP)
- Follow to lists of permitted ingredients (minerals, vitamins, declared listable substances).

- Follow additional requirements such as dose limits, specified label warnings and limits on plant parts or methods of preparation. Some herbs are not permitted.
- The regulation of AUST L products should not require evidence to support manufacturers' claims, provided that the products are not for the treatment of serious illnesses.

3. Drug Approval Procedure for Prescription Medicines

Prescription medicines are classified in to three categories like, Category-1; Category-2 and Category-3 type applications.[25,28]

Category 1 applications[25,28]

- Submitted under sub-regulations 16C (3) (b) and 16D (3) (b) of TGA act.
- Category-1 application includes: new chemical entities, new dosage forms, new strengths and new generic products, extensions of indications and amendments to the Product Information (PI) and significant variations to an existing application.

Category 2 applications[25,28]

- Submitted under sub-regulations 16C (3)(a) and 16D(3)(a) of TGA act.
- Can only be submitted when an application has been previously.
- It is mandatory to submit the evaluation reports as described in sub-regulations 16C (4) and (5) and 16D (4) and (5)). The product should be identical to that registered in the acceptable countries, in terms of formulation, directions for use and indications.

For Category 1 and 2 applications, the processing time comprises **a period for acceptance of the application** (40 days and 20 days for category 1 and 2 respectively) after submission of application and **a period for evaluation** (255 days and 175 days for category 1 and 2 respectively).[25,28]

Category 3 applications[25,28]

Category 3 applications are provided for under Regulations 16F and 16G and include changes to the quality data of medicines already included on the ARTG. Thus, does not render the medicines separate and distinct (so no requirement of separate registration) and do not need to be evidenced by clinical, non-clinical or bioequivalence data. The types of quality changes a Category 3 application may include, but are not limited to.

- Specifications for the active ingredient, finished product or excipients

- Manufacturing method and manufacturing site of the active ingredient and finished product
- The shelf life and storage conditions
- The labeling and packaging, including container type
- A replacement trade name
- Any small changes in formulation.

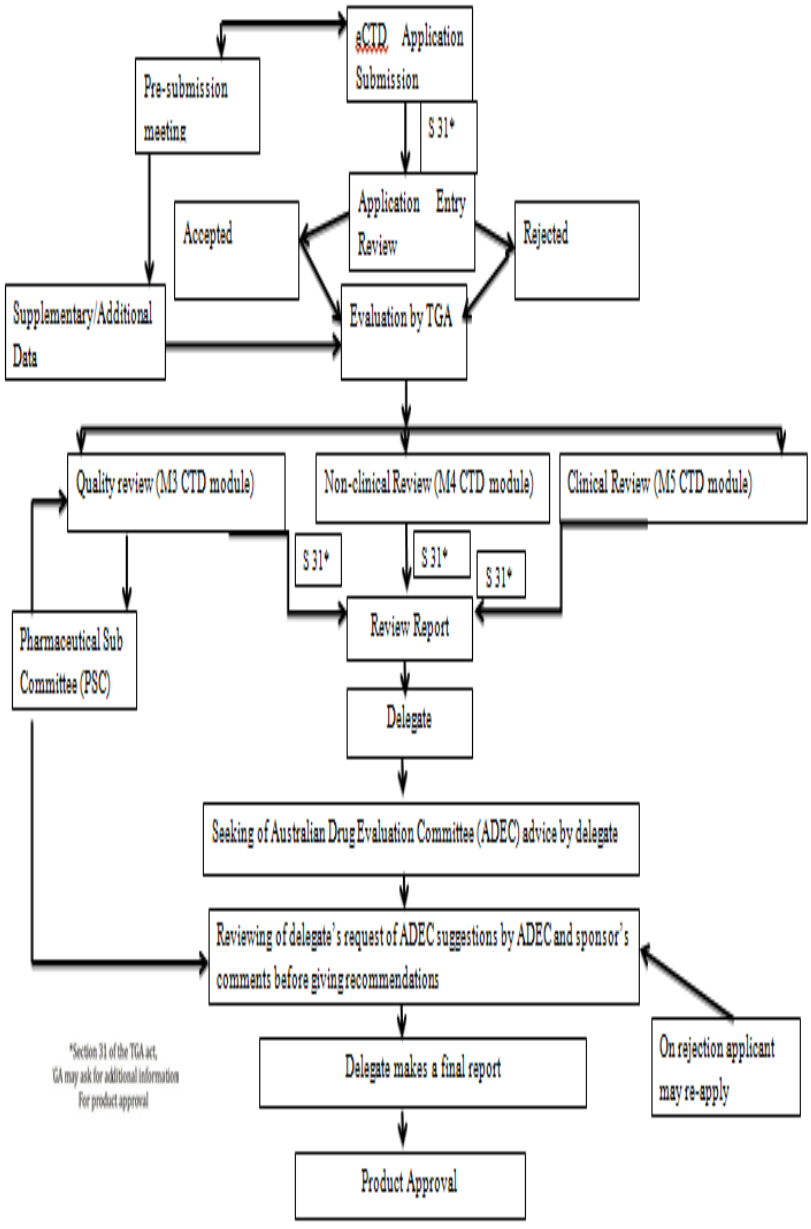

Fig.11: Category-1 and 2 Application Evaluation Procedure for PM in Australia [25]

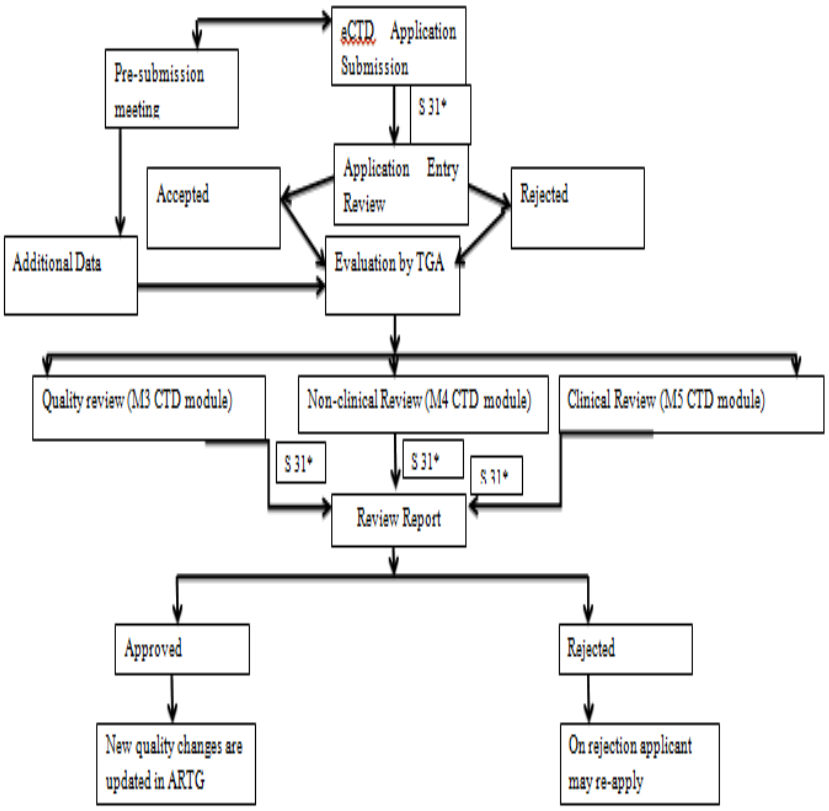

Fig.12: Category 3 Application Evaluation Procedure for PM in Australia[25]

REFERENCES

1. http://www.ich.org/home.html (Accessed on April 16, 2016).
2. www.fda.com (Accessed on April 16, 2016).
3. Badjatya JK. Overview of Drug Registration Requirements for Pharmaceuticals in Emerging Market. Journal of Drug Delivery & Therapeutics, 2013; 3(2): 227-232.
4. Mulaje SS, Birajdar SM, Patil BR and Bhusnure OG. Procedure for Drug Approval in Different Countries: A Review. Journal of Drug Delivery & Therapeutics, 2013; 3(2): 233-238.
5. Brodniewicz T and Grynkiewicz G .Preclinical Drug Development. Acta Poloniae Pharmaceutica -Drug Research, 2010; 67(6): 579-586.
6. Hans-Gerd Pauels. Recommendations for the conduction of preclinical toxicological tests for new drugs and drug compounds. PARA Bioscience Dossier, 2004.
7. http://www.fda.gov/ForPatients/Approvals/Drugs/default.htm (Accessed on April 16, 2016).
8. Biopharmaceutical Research & Development: The Process Behind New Medicines, 2015. http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf

9. Lipsky MS..From Idea to Market: The Drug Approval Process. J Am Board Fam Med., 2001; 14(5).
10. Vishal P, Rahulgiri G, Pratik M, Badjatya JK. A Review on Drug Approval Process for US, Europe and India. International Journal of Drug Regulatory Affairs, 2014; 2(1): 1-11.
11. Nitin Kashyap U, Gupta V and Raghunandan HV. Comparison of Drug Approval Process in United States & Europe. J. Pharm. Sci. & Res., 2013; 5(6): 131–136.
12. Thaul S. How FDA Approves Drugs and Regulates Their Safety and Effectiveness. 2012. CRS Report for Congress. Prepared for Members and Committees of Congress. Congressional Research Service, 1-19.
13. New Drug Development and Review Process. Center for Drug Evaluation and Research (CDER) Handbook. Available at URL: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM198415.pdf (Accessed on April 23, 2016).
14. Investigational New Drug (IND) Application. http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm (Accessed on April 23, 2016).
15. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. http://www.fda.gov/ForPatients/Approvals/Fast/default.htm (Accessed on April 23, 2016)
16. Kohler M. Regulatory pathways in the European Union. mAbs, 2011; 3(3): 241-242. Landes Bioscience.
17. Ghalamkarpour A. Marketing Authorization Procedures in the European Union – Making the Right Choice.Life science/ technical bulletin, SGS life Sciences, 2009; 33.
18. The Mutual Recognition Procedure**. http://ec.europa.eu/health/authorisation-procedures-mutual-recognition_en.htm** (Accessed on May 7, 2016)
19. Chowdary KPR, Ravi Shankar K and Saranya G. A Comparative Study of Drug Approval Process in United States, Europe and India. Wjpr, 2015; 4(7): 419-427.
20. Draft Guidance on Approval of Clinical Trials & New Drugs. 2011. http://www.cdsco.nic.in/writereaddata/Guidance_for_New_Drug_Approval-23.07.2011.pdf (Accessed on May 8, 2016)
21. Tanimoto T. A perspective on the benefit-risk assessment for new and emerging pharmaceuticals in Japan. Drug Design, Development and Therapy, 2015; 9: 1877–1888.

22. Hara R. Japanese submission/approval processes from programming perspective. http://www.lexjansen.com/pharmasug/2015/SS/PharmaSUG-2015-SS02.pdf (Accessed on May 14, 2016).
23. Kumar AN, Dileep KG, Ravindra CK and Suthakaran R. An Overview of Chinese Drug Regulatory System: A Review. International Journal of Drug Regulatory Affairs, 2014; 2(3): 14-18.
24. The procedure for Import Drug SFDA registration.http://www.sfdachina.com/info/80-1.htm (Accessed on May 15, 2016).
25. Anand K, Mallu UR, Kuraku M and Bapatu HR. Pharmaceutical Drug Products Approval Procedure in Australia. The Experiment, 11(3): 690-705.
26. Standards, guidelines & publications (OTC medicines. https://www.tga.gov.au/standards-guidelines-publications-otc-medicines (Accessed on May 15, 2016).
27. McEwen J. What does TGA approval of medicines mean? Aust Prescr, 2004; 27: 156–8.
28. Gupta MM and Bhati VS. Dossier Submission to TGA for Prescription Only Medicines. IJPSR, 2010; 1(1): 1-10.