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Process for review of an application submitted to EMA: A brief review

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Abstract
Present scenario of regulatory world has been divided into two categories i.e., regulated countries and non - regulated countries. All the countries have their own rules and regulation. Here the regulatory bodies work like a bridge between market requirement and manufacturing unit. They ensure the safety and efficacy of the drug product which are available in the market. Once the drug molecule is discovered, non-clinical study of the drug should be conducted to ensure safety and efficacy. The clinical trials areconducted, after an application is submitted to competent authority. When theclinical trials are completed successfully as per approved protocols, the sponsor may apply for marketing authorization and the approval is given after reviewing the application. Even after approval, government monitors safety by post marketing surveillance. This review article describes the process involved in approval of drug to be marketed in European Union (EU) and also the roles of different committees in the approval process.

Keywords: European union, EU, marketing authorization, regulatory approval

1. Introduction

1.1 Regulatory bodies

They are independent governmental bodies established by government in order to set standard in specific field of activity, or operations and then to enforce those standards. Regulatory may or may not function outside direct executive supervision. Main functions of regulatory bodies: a) Regulation and guides, b) Review and assessment, c) Licensing, d) Inspection e) Corrective action and f) Enforcement [1].

Regulatory bodies in Pharma industries

Regulatory agencies and organizations ensure the safety, quality and efficacy of medicines and medical devices. They need to involve in the overall procedure of drug development. Once the drug is discovered, the manufacturer applies for the clinical trial, here the regulatory bodies are responsible for the conductance of clinical and non-clinical trials to ensure its safety and efficacy.

Regulatory authorities act as a guardian that ensures the safety, efficacy and quality of drugs available to the public, to identify the strengths and weaknesses of drug regulation and to propose strategies to improve drug regulation. They also play a vital role to ensure and increase regulatory implementation in non-regulated parts of the world for safety of people residing there. The international regulatory organizations play essential role inall aspects of pharmaceutical regulations related to drug product registration, manufacturing, distribution, price control, marketing, research and development, and intellectual property protection [2].

1.2 Introduction to EU (European Union)

European Union (EU) have set a standard for the marketing and authorization of medicinal products in the world. EU is a giant in the drug regulating markets; it has very stringent requirements for drug development, drug processing, and drug approval. The Medicines Agency (EMA) is a decentralized body of EU which is in charge for the safety and promotion of public health and animal health, through the evaluation and supervision of medicines for human and veterinary use.

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The European Union have decided standard, rules and regulations to be followed for marketing of medicines of human as well as animal use.EU is giant in the world of medicinal market. It has stringent rules and boundaries for new drug product development and its authorization [3]. EU is the regulatory body of Europe which ensures the safety, quality and efficacy of the medicines which are sold in Europe market. They promote the health of the people across the world. The European medicines regulatory system is based on network of around 50 regulatory authorities from 31 EEA (European Economic Area) countries, EC (European commission) and EMA (European Medical Agency).

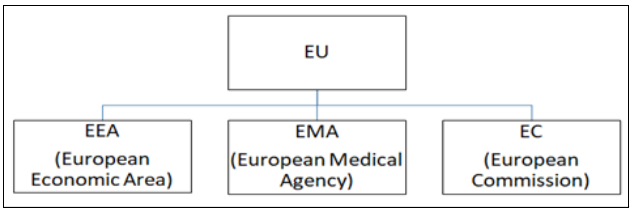

Fig 1: Bodies of EU

EMA and the Member States cooperate and share expertise in the assessment of new medicines and of new safety information. They also rely on each other for exchange of information in the regulation of medicine, for example regarding the reporting of side effects of medicines, the oversight of clinical trials and the conduct of inspections of medicines' manufacturers and compliance with good clinical practice (GCP), good manufacturing practice (GMP), good distribution practice (GDP), and good pharma covigilance practice (GVP). This works because EU legislation requires that each Member State operates to the same rules and requirements regarding the authorization and monitoring of medicines [3] as the European Union (EU) have set a standard for the marketing and authorization of medicinal products in the world. EU is a giant in the drug regulating markets; it has very stringent requirements for drug development, drug processing, and drug approval. The Medicines Agency (EMA) is a decentralized body of EU which is in charge for the safety and promotion of public health and animal health, through the evaluation and supervision of medicines for human and veterinary use.

- **European Economic Area (EEA)**: The EEA was established on 1 January 1994 upon entry into force of the EEA Agreement. The contracting parties are the EU, its member states, and Iceland, Liechtenstein, and Norway. The European Economic Area (EEA) was established via the *Agreement on the European Economic Area*, an international agreement that enables the extension of the European Union's single market to member states of the European Free Trade Association. The EEA links the EU member states and three EFTA states (Iceland, Liechtenstein, and Norway) into an internal market governed by the same basic rules. These rules aim to enable free movement of persons, goods, services, and capital within the European Single Market, including the freedom to choose residence in any country within this area EEA consist of28 EU member State, Norway, Liechtenstein and Iceland [4].

- **European commission (EC)**: The European commission performs a vital role in regulation of medicine in European Union. Once the EMA complete scientific evaluation of application, the EC have to decide either to approve or refuse change or suspends marketing Authorization for medicines that have been submitted viathe centralized procedure. EC is the decision-making committee, they work to ensure the safety and efficacy of the product.

EC may also take actions concerning other aspects of medicine regulation like,

Right of Initiative- it can propose new or amended legislation for the pharmaceutical sector.

Implementation– it can adopt implementing measures as well as oversee the correct application of EU laws on pharmaceuticals

Global outreach– it ensures appropriate collaboration with relevant international partners and promotes the EU regulatory system globally [5].

- **European Medical Agency (EMA):** The EMA is EU regulatory body responsible for the scientific evaluation and supervision of medicines developed by pharmaceutical companies for use in EU. These medicines are of human as well as animal use.

There are seven scientific committees that evaluate medicines at the EMA and six of them are for human medicines and CVMP is responsible for medicines for veterinary use. The agency secretariat supports the work of these committees in a scientific and logistic capacity. Importantly four of these committees have members representing presenting patients which gives them to share expertise in their field of interest [5].

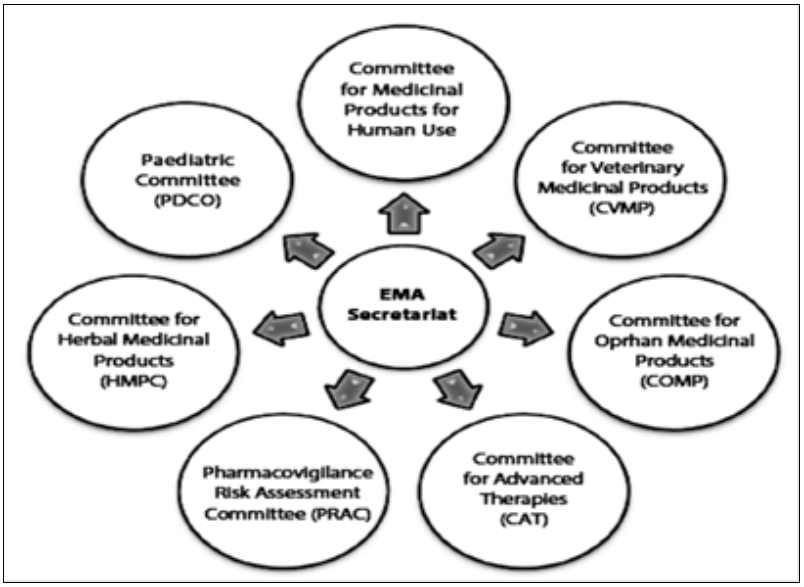

Fig 1: Organization of EMA

2. Drug approval process in EU

There are two regulatory steps to go through before a drug is approved to be marketed in EU. These 2 steps are: Clinical trial application (member state level) and Marketing authorization application (the member state or centralized levels). Qualify person has to certify that investigational medicinal product is manufactured according to GMP.

2.1 Clinical trial application

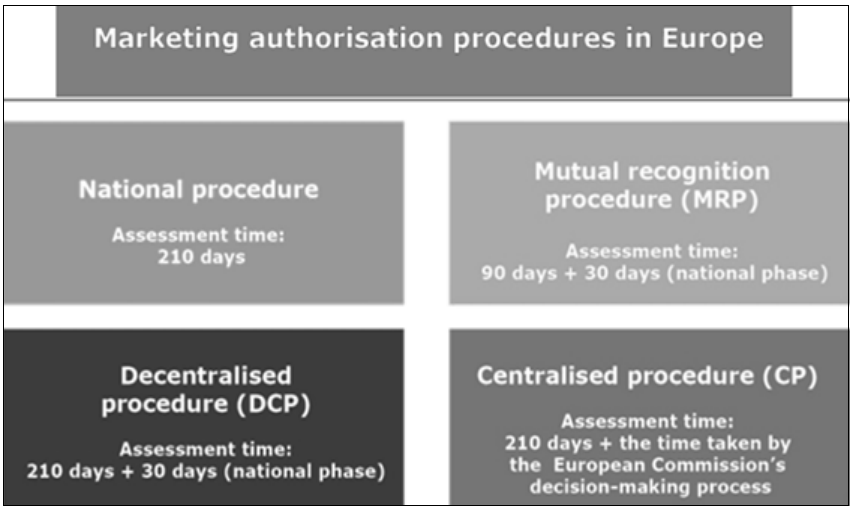

Fig 3: Types of Procedure for Marketing Authorization

The European Medicines Agency (EMA) completes the scientific assessment by taking overview on the clinical trials done by the manufacturing company. Although the authorization of clinical trials occurs at national level, EMA ensure the clinical trials which are performed for the investigational product, are approved in EEA and conducted as per protocols and must complies GCP are applied across the European Economic Area (EEA) in cooperation with the Member States. It also manages a database of clinical trials carried out in the European Union (EU). The regulation of clinical trials aims to ensure that the rights, safety and well-being of trial subjects are protected and the results of clinical trials are credible. Regardless of where they are conducted, all clinical trials included in applications for marketing authorization for human medicines in the EEA must have been carried out in accordance with the requirements set out in Annex 1 of Directive 2001/83/EC. This means that:

- Clinical trials conducted in the EEA have to comply with EU clinical trial legislation (Directive 2001/20/EC);
- Clinical trials conducted outside the EEA have to comply with ethical principles equivalent to those set out in the EEA, including adhering to international good clinical practice and the Declaration of Helsinki
- Clinical trial data is included in clinical-study reports that form a large part of the application dossiers submitted by pharmaceutical companies applying for a marketing authorization via the Agency [6].

Eudra CT: EMA is responsible for the development, maintenance and coordination of the European Union Drug Regulating Authorities Clinical Trials (Eudra CT) database. National competent authorities use Eudra CT to enter clinical trial data from clinical trial sponsors and pediatric investigation plan (PIP) address.

Users may able to view

- The description of phase-II to phase-IV adult clinical trials where the investigator sites are in the EEA.
- The description of any clinical trials in children with investigator sites in the EU and any trials that form part of a PIP including those where the investigator sites are outside the EU [6].

IMPD (Investigational Medicinal Product Dossier): The Investigational Medicinal Product Dossier (IMPD) is one of several pieces of Investigational Medicinal Product (IMP) related data required whenever the performance of a clinical trial is intended in one or more European Union Member States. It is basis for approval of clinical trials by the competent authorities in the EU. The IMPD includes summaries of information related to the quality, manufacture and control of any IMP (including reference product and placebo), and data from non-clinical and clinical studies. The clinical trials directive came in force, harmonizing the laws, relation and administrative provisions of the Member states relating to the implementation of GCP in conduct of clinical trials on medicinal product for human use. The directive introduced a harmonized procedure for the authorization to perform clinical study in any one of the EU member state [7].

2.2 Marketing authorization

In order for a medicinal product to be available on the market, sold and marketed, it needs to have a marketing authorization. The marketing authorization application must provide evidence of the efficacy, safety and quality of the medicine. Once the EMA complete its scientific evaluation of the Marketing Authorization Application (MAA), the EC takes the decision on the basis of assessment by EMA either to approve or change or suspend or reject the application.

National procedure: Used when applying for a marketing authorization in one individual EU member state, Norway or Iceland. The national procedure can only be used if the medicinal product does not already have a marketing authorization in another EU member state, Norway or Iceland. Assessment time: 210 days [8].

Medicines those are mandatory for evaluation at EMA are, rare disease; HIV, cancer, neurodegenerative disease, diabetes; auto-immune disease, viral diseases; all biotech products; gene therapy; monoclonal antibodies.

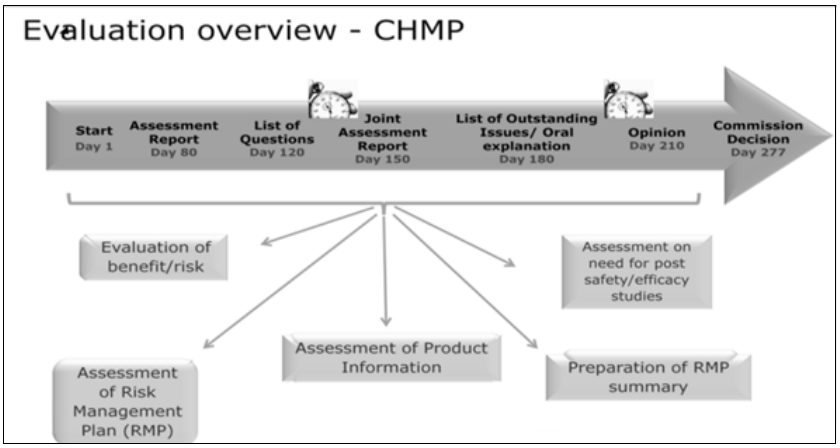

Fig 4: Evaluation Overview

Mutual recognition procedure (MRP): The mutual recognition procedure should be used if the product already has a marketing authorization in another EU -member state, Norway or Iceland. The country in which the national marketing authorization has been granted acts as the reference member state, and the other countries concerned recognize the marketing authorization. Assessment time: 90 days + 30 days (national phase) [8].

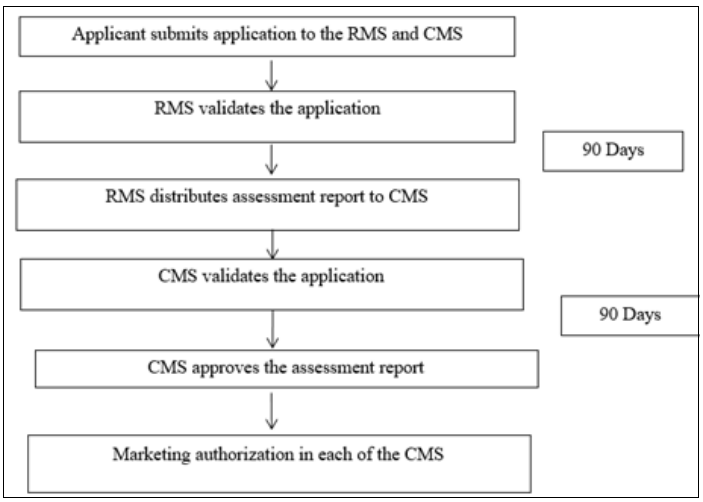

Fig 5: Mutual Recognition Procedure

Decentralized procedure (DCP): The decentralized procedure should be used if the product does not yet have a marketing authorization in any EU country, Norway or Iceland, and if the applicant would like to apply for a marketing authorization in several countries at once [9]. In the decentralized procedure, the applicant asks one-member state to act as the reference member state which evaluates the application and prepares an assessment report. The other member states can comment on the assessment report. At the end of the process, a marketing authorization will be granted in each of the involved member state after completion of the national phase. Assessment time: 210 days + 30 days (national phase) [8].

Centralized procedure (CP): Using this centralized procedure, means applying for a single marketing authorization that covers all EU countries, Norway and Iceland. In the centralized procedure, marketing authorization applications are assessed by the European Medicines Agency (EMA), and the marketing authorization is granted by the European Commission. The centralized Procedure is primarily used for new active substances, and it is mandatory for biopharmaceuticals and other innovative medical products. Assessment time: 210 days + the time taken by the European Commission's decision-making process [8].

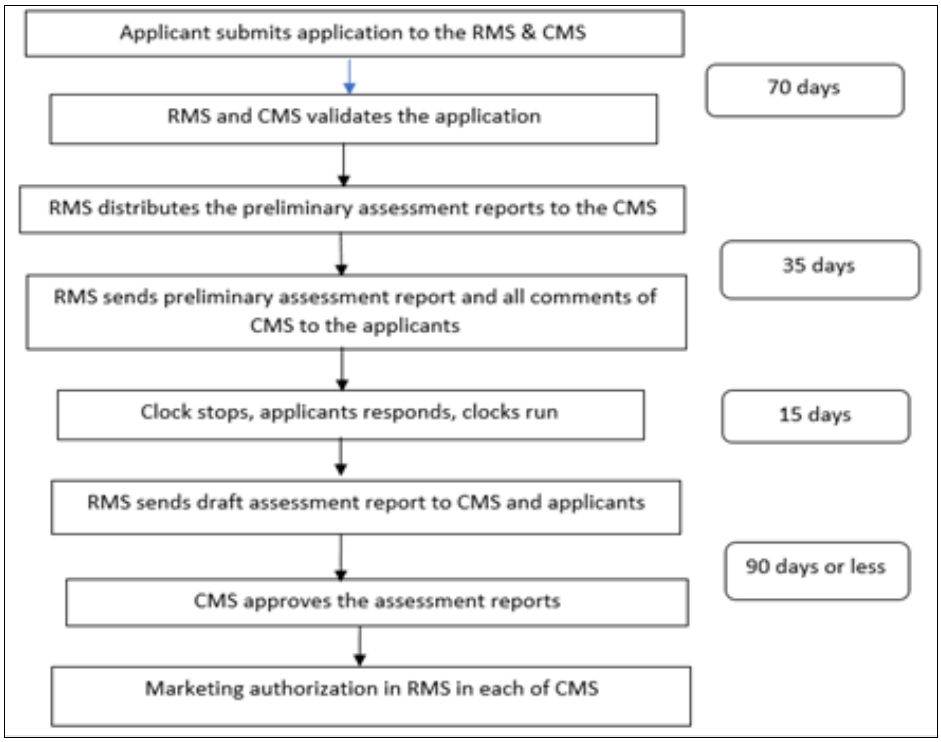

Fig 6: Decentralized Procedure

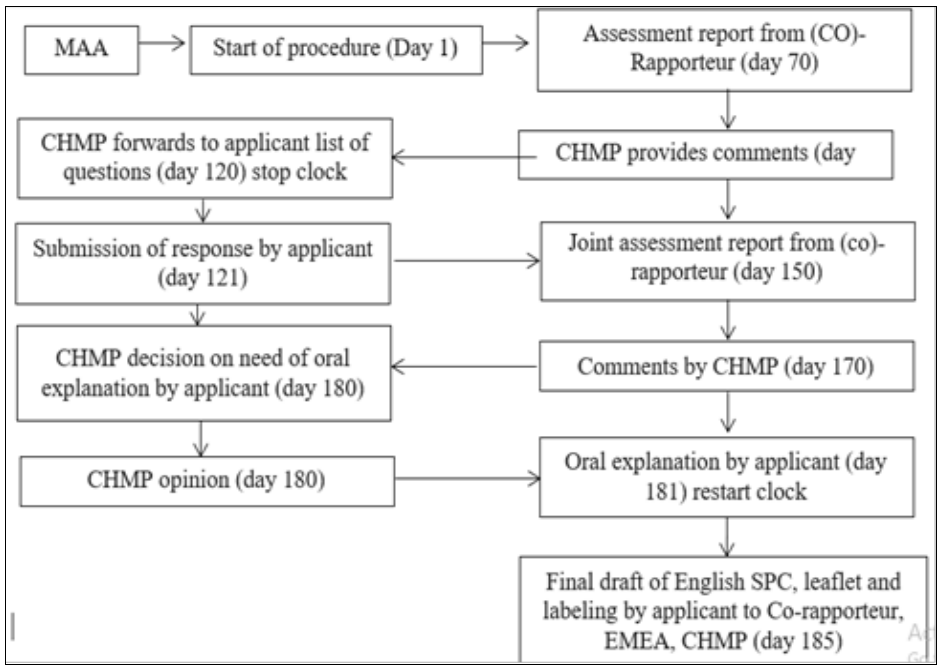

Fig 7: Centralized Procedure

Types of marketing authorization

1. Standard Approval: In this all data of safety and efficacy are provided.

2. Exceptional: applicant gets this kind of approval when they are unable to provide clinical data for safety and efficacy, moreover not expected to submit in near future.

3. Conditional Approval: Medicines for human use areeligible if they are intended for treating, preventing or diagnosing seriously debilitatingor life-threatening diseases. This includes orphan medicines

Its use is also intended for a public health emergency (e.g. a pandemic). For these medicines, less comprehensive pharmaceutical and non-clinical data may also be accepted.[9]

Terms and condition for conditional approval

- The benefit-risk balance of the medicine is positive;
- It is likely that the applicant will be able to provide comprehensive data post-authorization;
- The medicine fulfils an unmet medical need;
- The benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.
- Conditional marketing authorizations has validity of one year, it can be renewed annually

Once a conditional marketing authorization has been granted, the marketing authorization holder must fulfil specific obligations within defined timelines [9].

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