

DRUG PRODUCT REGISTRATION ALONG WITH MAA IN EU**D. G. S. N. Sai Kumar, D. Nagarjuna Reddy*, M. V. Nagabhushanam, Konda Ravi Kumar and Rajesh Akki**

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INTRODUCTION**European Union**

European Union is an union of 28 Member States located primarily in Europe. It has an area of 4,324,782 km² and a population of more than 510 million. EU has developed an internal single market through a standardized system of laws that apply in all Member States. EU policies aims to ensure the free movement of people, goods, services, capital within the internal market enact legislation in justice and home affairs, and maintain common policies on trade, agriculture, fisheries, regional development. Within the Schengen Area, passport controls have been abolished. A monetary union was established in 1999 and came into full force in 2002, and is composed of 19 EU Member States which uses the Euro Currency.^[1-6]

KEY WORDS: European Union, European Medicines Agency, Committee for Medicinal Products, Pediatric Committee.

The EU operates through a hybrid system of supranational and intergovernmental decision making. The seven principal decision making bodies, known as the institutions of the EU are:

- The European Council.
- The Council of the European Union.
- The European Parliament.
- The Court of Justice of the European Union.
- The European Central Bank.
- The European Court of Auditors.

The founding fathers of the EU

- Konrad Adenauer (Germany).
- Joseph Bech (Luxembourg).
- Johan Willem Beyen (Netherlands).
- Winston Churchill (United Kingdom).
- Alcide De Gasperi (Italy).
- Walter Hallstein (Germany).
- Sicco Mansholt (Netherlands).
- Jean Monnet (France).
- Robert Schuman (France).
- Paul Henri Spaak (Belgium).
- Alterio Spinelli (Italy).

Regulatory Agencies in EU**1. EMA (European Medicines Agency)**

The EMA was formed in 1st Jan 1995, under the jurisdiction of European Union (EU). EMA has its Headquarters in London. Its motto is Science, Medicines, Health.

Agency executives

- Guido Rasi, Executive Director.
- Christa Wirthumer-Hoche, Chairperson.

The EMA is an EU^[7-9] agency for the evaluation of medicinal products. Prior to 2004, it was known as the European Agency for the Evaluation of Medicines (EMEA).

The EMA was set up in 1995 with funding from the EU and pharmaceutical industry as well as indirect subsidy from Member States, in an attempt to harmonize the work of existing National medicine Regulatory Bodies. The hope was that this plan would not only reduce the € 350 million annual cost drug companies incurred by having to win separate approvals from each Member State but also that it would eliminate the protectionist tendencies of sovereign states unwilling to approve new drugs that might compete with those already produced by domestic drug companies. The EU is currently the source of about one-third of the new drugs brought onto the world market each year.

Based in London, the EMA was founded after more than seven years of negotiations among EU Governments and replaced the Committee for Proprietary Medicinal products and the Committee for Veterinary Medicinal products, though both of these were reborn as the core scientific advisory committee. After the United Kingdom withdrawal from the European Union referendum it is yet unclear if Agency remains in the UK.

Committees Present In The EMA^[10]

- (a). Committee for Medicinal Products for Human Use (CHMP).
- (b). Pharmacovigilance Risk Assessment Committee (PRAC).
- (c). Committee for Medicinal Products for Veterinary Use (CVMP).
- (d). Committee on Herbal Medicinal Products (HMPC).
- (e). Committee for Orphan Medicinal Products (COMP).
- (f). Committee for Advanced Therapeutics (CAT).
- (g). Pediatric Committee (PDCO).

The work of these committees are supported by working parties of other groups.

In order to register and market a medicinal product, an approval from authority of the respective country is required. No medicinal product can be placed in the market without prior approval from the respected country.

MATERIALS AND METHODS**Registration procedure of drugs in EU**

- Centralized Procedure.
- Decentralized Procedure.
- Mutual Recognition Procedure.
- Nationalized Procedure.

I. Centralized Procedure

Based on Regulation 726/2004. Centralized Procedure allows applicant to obtain a Marketing Authorization that is valid throughout the EU and allow valid through Norway, Lichtenstein, Iceland.

CP is compulsory for drugs used for conditions such as:

- AIDS.
- Cancer.
- Neuro-Degenerative disorder.
- Diabetes Mellitus.
- Orphan medicinal products.
- Biotechnological products.
- Auto-immune disorders.
- Viral disease.

II. Decentralized Procedure (DCP)

Decentralized Procedure is used if the product is not already authorized in any one of the Member States, but does not want Centralized Procedure or the product is not eligible for Centralized Procedure. Here, one of the proposed Member State will be asked by the applicant company to act as Reference Member States (RMS). The RMS does the initial evaluation of the product and issues a draft assessment report. Other Member States known as Concerned Member States (CMS) either agree with RMS's evaluation or they ask further questions.

If all the issues are resolved and the application is successful, each Member State will then issue a

Marketing Authorization for that product permitting it to be marketed in their Country.

Steps involved in DCP

1. Pre-procedural step
 - Scientific / Regulatory advice.
 - Validation.
2. Assessment step – I
 - Includes stop clock.
3. Assessment step – II
4. National step to grant MA
 - Including public assessment report.

III. Mutual Recognition Procedure (MRP)

MRP allows applicant to obtain a MA in the CMS other than the RMS, where the drug is previously approved.

Applicant submits identical dossier to all EU Member States in which they want MA including required information.

As soon as a Member State decides to evaluate the medicinal product (that point it becomes RMS), it notifies this decision to other Member States (which becomes CMS) to whom applications have also been submitted.

RMS issues a report to other states on its own findings.

IV. Nationalized Procedure

Generally, this procedure is no longer used nowadays.

Nationalized Procedure is limited to the initial step of Mutual Recognition Procedure. This procedure is applied if the drug product is intended to be authorized in only one EU Member States. Nationalized Procedure is the starting point for MRP and DCP. In order to obtain a National Marketing Authorization, an application must be submitted to the competent authority of the Member State. If the product is already authorized in any one of the EU/EEA countries, the National Procedure cannot be used.

Legal basis for applications in Europe

The eligibility and the requirements are set in the commission regulation (EC) No 726/2004 and defined in articles 8 and 10 are of the Directive 2001/83/EC.

Types of Applications

1. Full Application
2. Generic Application
3. Hybrid Application
4. Similar Biological Application
5. Well Established Use Application
6. Fixed Combination Application
7. Informed Consent Application.

RESULTS AND DISCUSSION

The EU has one of the most highly regarded regulatory systems in the world. The system comprises of European

parliament, the council of ministers, and the European Commission. EU consists of 28 member states: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom and three countries which are member of European Free Trade Agreement (EFTA) Iceland, Norway, and Liechtenstein. These EFTA members are those countries which were unable to join rest of the 28 member states as common market. These three EFTA member countries along with 28 EU member states, comprises of the European Economic Area (EEA).

Centralized Procedure

- Handled by the EMA and its scientific committees (CHMP) and its rapporteurs.
- CHMP opinion is the basis for European Commission a EU-wide Marketing Authorization.
- Necessary for various Drug products such as Anticancer, Biologics, AIDS, Biotechnology, Vaccines etc.

Decentralized Procedure

- No MS has yet issued an authorization.
- 1 MS leading the assessment.
- Submission to RMS and CMSs.
- Validation (14 Days).
- Assessment I (120 Days).
- Assessment II (90 Days).
- Discussion at CMDh (if necessary).
- National phase.
- Consultations during the assessment.
- Divergent positions resolved by CMDh.
- If not, then by CHMP.

Mutual Recognition Procedure

- National registration in 1 MS
- Act as RMS.
- Updated assessment report.
- Dossier submission to CMSs.
- Validation (14 Days).
- 90 Days assessment.
- Discussion at CDMh (if needed)
- National phase.
- Divergent positions resolved by CMDh.
- If not, then by CHMP.

National Procedure

- Not registered in any of the MS
- National Competent Authority is responsible MA.

CONCLUSION

European Union has different types of registration procedures for different types of drugs following which the drug may be registered in the Entire EU i.e., Centralized Procedure. The drug may be registered in one of the EU member countries and needs registration in other country but is not eligible for Centralized

Procedure then Decentralized procedure is used. Then there is Mutual Recognition Procedure in which the drug is registered in Concerned Member State (CMS) other than the Reference Member State (RMS) where the drug is previously approved. In order to get the drug approved in only one Member Country, there is Nationalized Procedure. EU has different types of procedure and different types of applications which will specify the product and time frame required for the approval of the drug which helps in tracking of life of the respective product. The retaining of the current marketing authorization systems, DCP together with scope of CP provide a great flexibility of the choice between different marketing authorization and also allowed to go for the national application of medicinal product.

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