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R E S E A R C H A R T I C L E

Registration of Drug Products in European Market and their Marketing Authorization Application

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Abstract
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. In keeping with efforts to rationalize and harmonies the regulations of medicinal product, EU established standardize specifications for the medicinal 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.
Keywords: EU, EMA, EMEA, EMU, WHO, MAH, MA

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

European Union: European Union is a 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, passports 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.

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.

Regulatory agencies in EU:

EMA (European Medicines Agency): [7] 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:

Ms. Emer Cooke, Executive Director. Christa Wirthumer-Hoche, Chairperson. 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 existing National medicine Regulatory Bodies. The EU is currently the source of about one-third of the new drugs new drugs brought onto the world market each year.

CMDh (Co-ordination group for Mutual Recognition and Decentralise Procedure-Human):

The CDMh , has been set up in the revised Pharmaceutical Legislation for the examination of any question relating to marketing authorization of a medical product in two or more member states in accordance with the mutual recognition procedure or the decentralized procedure.

HMA (Human Medicines Agency):

The Heads of Human Medicines Agencies is a network of the Heads of the national Competent Authorities whose organizations are responsible for the regulation of Medicinal Products for human and veterinary use in the European Economic Area.

EGA (European Generic Medicine Association):

The EGA was established in 1993. The EGA is the official representative body of the European generic and biosimilar pharmaceutical industry, which is at the forefront of providing high-quality affordable medicines to millions of Europeans and stimulating competitiveness and innovation in the pharmaceutical sector.

2. Methodology

Registration Procedure of Drugs in EU

- Centralized Procedure
- Decentralized Procedure
- Mutual recognition Procedure
- Nationalized Procedure

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.

The process of registration

The applicant must submit an application to the EMA. Applicants meet the EMA to discuss procedural, regulatory and legal issues. Applicant are also obliged to inform the EMA to their intention to submit an application and give a realistic estimate of the month of submission. The scientific evaluation of the application is carried out by the CHMP and a scientific opinion is prepared. The EMA have 210 days to prepare the scientific opinion.

During the process, it becomes apparent that additional information is necessary, the applicant is notified and the clock is stopped. The evaluation of facts is carried out by the rapporteur and co-rapporteur.

The rapporteur and co-rapporteur are elected by the CHMP and they prepare the report in collaboration with the assessors in the National Competent Authorities. The opinion is sent to the European Commission which drafts a decision.

After consulting the Member States through the relevant Standing Committee on which all the Member States sit, the Commission adopts a decision and a Market Authorization is granted. Marketing Authorization granted under Centralized Procedure is valid or the entire community market i.e., the medicinal product may be put on the market in any Member States.

The product information mainly the package leaflet and the Summary of Product Characteristics (SmPC), in al the official languages of the community must be included in the Marketing Authorization. The decision is published on the European Commission Website. The EMA publishes a pubic assessment report of the product.

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. One should use the DCP if he wants to market the medicine in UK and other EU Countries. One state will lead the assessment of the application as RMS. The other Member States are called the CMS.

The committee will reply within 24 hours for booking confirmation ad then will issue a Product License (PL) number and DCP number.

Mutual Recognition Procedure (MRP):

MRP allows applicant to obtain a MA in the CMS other then 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. During validation, the CMS will mark that the application is valid on CTS (Clear to Send) and if not valid and he procedure cannot start.

If f CMS do not mark it (either valid or invalid) on CTS by day-7, the RMS assumes that it is valid, the clock starts and the procedure proceeds. The CMS has 50 days to examine the assessment report prepared by the RMS and give an opinion.

On day 50 the CMS either:

- Recognizes the decision of the RMS and the SmPC approved by it and states that it is ready to grant a MA.
- Considers there are potential serious risks to public health and states that it is not ready to grant a MA.

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. Nationalized Procedure should be finished and a National Marketing Authorization issued within 210 days from the receipt of a valid application includes all the type of requirements for the type of application i.e., all documents has been submitted. The assessment can only start once all the necessary documentation has been received. When a Marketing Authorization is issued nationally, the Authorization is valid only in the Country where it has been issued and can be placed on that Country only.

3. 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). The European Medicines Agency is a decentralized agency of the European Union, located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union and applications for European marketing authorizations for both human and veterinary medicines (centralized procedure).

Under the centralized procedure, companies submit a single marketing- authorization application to the Agency. Once granted by the European Commission, a centralized (or "Community") marketing authorization is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway). The European parliament approves the laws together with the council of ministers. The council of ministers is the voice of Member states and is responsible for enactment of directives.

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 or various Drug products such as Anticancer, Biologics, AIDS, Biotechnology, Vaccines etc.

Decentralized Procedure

- No MS has yet issued an authorization.
- 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.

Marketing authorization applications under the scope of Article 82(1): A marketing authorization for a medicinal product that is different from the previously authorized product cannot be considered as a duplicate. This means that such application could not benefit from any fee reduction that may be applicable for duplicates. a marketing authorisation application for a medicinal product that has already been granted marketing authorisation under the centralised procedure falls under duplicate application, if the applicant is the same that holds that marketing authorization. This will get the advantage of reduction in fees.

Applications outside the scope of Article 82(1):

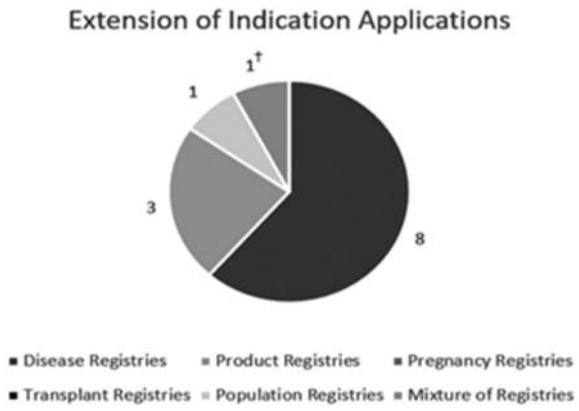
Examples of applications that fall outside the scope of Article 82(1)

- The active substance(s) is not the same.
- The active substance is a different salt that differs significantly in properties regarding safety or efficacy.
- The medicinal product contains different excipients, and these results in significant differences regarding safety or efficacy.
- The manufacturer or manufacturing site is different and this may, as a result of the characteristics of the product (notably in the case of biological products), lead to significant differences regarding safety or efficacy.
- Examples of applications that fall under the scope of Article 82(1)
- The active substance is a different salt that does not differ significantly in properties regarding safety or efficacy.
- The medicinal product contains different excipients but this does not result insignificant differences regarding safety or efficacy.
- Different manufacturer or manufacturing site, unless this leads to significant differences regarding safety or efficacy.
- Differences in the data submitted in connection with the marketing authorization application for a medicinal product with the same composition in active substance(s) and pharmaceutical form provided that the product does not significantly differ regarding safety or efficacy.

Extension Application:

When there is any change regarding quality, safety and efficacy of the product these changes has to be submitted as extension application. There are three main categories of changes to be required submitted as an extension application:

- Changes in the strength, pharmaceutical form and administration route.
- Changes in the veterinary medicinal products to be administered to food-producing animals.
- Changes to the active substance.



CTD followed in EU

The Common Technical Document (CTD) describes the organisation of modules, sections and documents to be used by an Applicant for a Marketing Authorisation for a medicinal product for human use in each of the European Union. The eCTD is

eCTD:

The eCTD is defined as an interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, lifecycle management and archival of the electronic submission.

Since June 2003, applicants have had the option of submitting an eCTD in parallel with the paper submission (CTD), following sign-off by the ICH Steering Committee of the eCTD Specification document at Step 4, and the adoption of this Specification document by the CPMP.

In November 2003, the ICH M2 group revised the specification for the eCTD to eCTD to version 3.2, which remains the current version. In the context of the implementation of the eCTD in the European Union, the Electronic Submission Telematics Implementation Group (TIGes) has developed a specification for the regional module. The Specification has been published in the Notice to Applicants, and the current version is version 2.0.

Background to the Pharmacovigilance legislation:

The development of Pharmacovigilance legislation was based upon the observations that ADRs, noxious and unwanted responses to a medicine caused around 197,000 deaths per year in the EU. In 2005, the EU began to review the European system of safety monitoring such as sponsoring an independent study as well as extensive public consultation through 2006- 2007. Thus, the process resulted in the adoption of new directive and regulation by the European parliament and council of ministers in Dec.2010,bringing about significant changes in the safety monitoring of medicines across the EU.

Company that holds marketing authorization for a medicine has legal obligation to collect data and conduct pharmacovigilance. Data have to be transmitted to the authorities within defined timelines, and any emerging concerns about the benefit-risk balance had to be notified.

The authorities may request further investigations, including formal studies. Regulatory procedures exist from updating product information and implementing other safety measures.

Calculating the Fees:

The basis of calculation of Pharmacovigilance fees for PSURs, Pharmacovigilance referrals and the annual fee in the changeable unit.

The changeable unit a unique combination of the following database derived from information on all medicines authorized in the European Union held by the Agency.

- Name of the medicinal product.
- Marketing authorization holder.
- Member state in which the marketing authorization is valid.
- Active substance.
- Pharmaceutical form.

This is consistent with the obligation of marketing authorization holders referred to in points (b) and (c) of article 57(2) and regulation(EC) No.726/2007 to submit such information to the database referred to in point (1) of the subparagraph of article 57(1) of the regulation.

4. 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.
- In keeping with efforts to rationalize and harmonies the regulations of medicinal product, EU established standardize specifications for the medicinal 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.
- Regulatory requirement for the approval of the medicinal drug was found to be more stringent.
- The European system for registration of Pharmaceutical Products is one of the Regulated Processes. Along with Japan and USA, The EU also obeys ICH.
- The EU market has been one of the fastest growing market along with USA& Japan. Since the past 25 years it has grown vastly.
- The Pharmaceutical industry is responsible for the development, production and marketing of medications.
- The revenue of the world wide Pharmaceutical market is estimated to be 1072 Billion US Dollars. With North America having the highest share of 48.7% followed by EU with 23%. The world pharmaceutical market is estimated to grow to about 1.12 Trillion US Dollars by 2022.
- 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. Regulatory requirement for the approval of the medicinal drug was found to be more stringent.
- The European system for registration of Pharmaceutical Products is one of the Regulated Processes.
- Along with Japan and USA, The EU also obeys ICH.
- The EU is a major player in the world pharmaceutical market. And is one of the most important sources of export to other Regulated and Non-regulated markets.

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