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Review Article

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# Registration of Drug Product dossier application as per EU Guidelines

**Kondepati Bhavya*, Jyothshna Devi Katamreddy, Jayachandra Reddy. P**

*Department of Pharmaceutical Regulatory Affairs, Krishna Teja Pharmacy College, Tirupati, India.*

## ABSTRACT

Due to variations in the regulatory norms of registration dossier in different countries, there is a strong need for harmonization by ICH for approval of drugs. Generic drugs in EU are approved under the Marketing Authorization Application. Bioavailability and Bioequivalence study data is critical in the generic drug approval process. Moreover, there are several approaches to assess BA/BE, each regulatory authority has put forth its own regulations/guidances for conducting BA/BE studies. Medicinal products are highly regulated in the European Union (EU) and are subject to a separate, complicated system of approvals that governs how, when, where, and in what form such products will be allowed to be sold within the borders of EU. The present marketing authorization procedures applicable to European Economic Area included 27 EU member states and the three EEA European Free Trade Association states (Iceland, Liechtenstein and Norway). Marketing Authorization Application is applied based on National procedure, mutual recognition procedure, centralized and decentralized procedure. Hence procedure for Registration of Drug Products was discussed in detail in this current review.

**Keywords:** International council of harmonization (ICH); European Medicines Agency (EMA); European Union (EU); European Economic Area (EEA) country.

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Corresponding author Tel.: +91-8919178446;

E-mail address: kondepatibhavya@gmail.com (Kondepati Bhavya).

## 1. Introduction

The European Medicines Agency (EMA) is a European Union agency for the evaluation of medicinal products. Prior to 2004, it was known as the European Agency for the Evaluation of Medicinal Products. 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 committees. After the United Kingdom withdrawal from the European Union referendum it is yet unclear if the agency remains in UK (1).

The rules governing medicinal products in the European Union contains a list of regulatory guidelines related to procedural and regulatory requirements such as renewal procedures, dossier requirements for Type IA/IB variation notifications, summary of product characteristics, package information and classification for the supply, readability of the label and package leaflet requirements (1). Medicinal products are highly regulated in the European Union (EU) and are subject to a separate, complicated system of approvals that governs how, when, where, and in what form such products will be allowed to be sold within the borders of the EU (3).

Notice to Applicants has been prepared by the European Commission, in consultation with the competent authorities of the Member States and the European Medicines Agency and interested parties in order to fulfill the Commission's obligations with respect to article 6 of Regulation (EC) No. 726/2004, and with respect to the Annex I to Directive 2001/83/EC as amended (3). To each Module a list of relevant CHMP /ICH-guidelines is annexed, which have to be taken into consideration when preparing an EU Marketing authorization dossier. These will be updated at regular intervals.

CTD is an internationally agreed format for the preparation of applications to be submitted to regulatory authorities in the three ICH regions of Europe, USA and Japan. It is intended to save time and resources and to facilitate regulatory review and communication. The new EU-CTD-presentation will be applicable for all types of

marketing authorization applications irrespective of the procedure (CP, MRP, DCP or national) and of type of application (stand alone, generics etc.). The CTD-format will be applicable for new chemical entities, radiopharmaceuticals, vaccines, herbals. To determine the applicability of this format for a particular type of product, applicants should consult with the appropriate regulatory authorities (4).

**2. Scientific committees**

The European Medicines Agency (EMA) has seven scientific committees that carry out its scientific assessments (5).

- Committee for Medicinal Products for Human Use (CHMP)
- Pharmacovigilance Risk Assessment Committee (PRAC)
- Committee for Medicinal Products for Veterinary Use (CVMP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)
- Committee for Advanced Therapies (CAT)
- Paediatric Committee (PDCO)

***Committee for Medicinal Products for Human Use* (5)**

The **Committee for Medicinal Products for Human Use (CHMP)** is responsible for preparing the Agency's opinions on medicines for human use, in accordance with Regulation (EC) No 726/2004.

The CHMP plays a vital role in the marketing procedures for medicines in the European Union:

- In the 'centralised' or 'community' procedure, the CHMP is responsible for conducting the initial assessment of medicines for which an EU-wide marketing authorisation is sought. The CHMP is also responsible for several post-authorisation and maintenance activities, including the assessment of any modifications or extensions ('variations') to an existing marketing authorisation.
- In the 'mutual-recognition' and 'decentralised' procedures, the CHMP arbitrates in cases where there is a disagreement between Member States concerning the marketing authorisation of a particular medicine ('arbitration procedure'). The CHMP also acts in referral cases, initiated when there are concerns relating to the protection of public health ('Community referral procedure').

***Pharmacovigilance Risk Assessment Committee* (6)**

The Pharmacovigilance Risk Assessment Committee **(**PRAC**)** is responsible for assessing all aspects of the risk management of medicines for human use. This includes the detection, assessment, minimisation and communication relating to the risk of adverse reactions, while taking the therapeutic effect of the medicine into account.

***Committee for Medicinal Products for Veterinary Use***

The Committee for Medicinal Products for Veterinary Use (CVMP) is responsible for preparing the Agency's opinions on all questions concerning veterinary medicines, in accordance with Regulation (EC) No 726/2004. The CVMP plays a vital role in the marketing procedures for medicines in the European Union

- In the 'centralized' or 'Community' procedure, the CVMP is responsible for conducting the initial assessment of veterinary medicines for which an EU-wide marketing authorization is sought. The CVMP is also responsible for several post-authorisation and maintenance activities, including the assessment of any modifications or extensions ('variations') to an existing marketing authorization.
- In the 'mutual-recognition' and 'decentralized' procedures, the CVMP arbitrates in cases where there is a disagreement between Member States concerning the marketing authorization of a particular veterinary medicine ('arbitration procedure'). The CVMP also acts in referral cases, initiated when there are concerns relating to the protection of public health or where other Community interests are at stake ('Community referral procedure').

***Committee for Orphan Medicinal Products* (7)**

The Committee for Orphan Medicinal Products (COMP) is responsible for reviewing applications from persons or companies seeking 'orphan medicinal product designation' for products they intend to develop for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect not more than 5 in 10,000 persons in the European Union. The COMP is also responsible for advising the European Commission on the establishment and development of a policy on orphan medicinal products in the EU, and assists the Commission in drawing up detailed guidelines and liaising internationally on matters relating to orphan medicinal products.

***Committee on Herbal Medicinal Products* (8)**

The **Committee on Herbal Medicinal Products (HMPC)** was established in September 2004, replacing the CPMP Working Party on Herbal Medicinal Products. The Committee was established in accordance with Regulation (EC) No 726/2004 and Directive 2004/24/EC, which introduced a simplified registration procedure for traditional herbal medicinal products in EU Member States.

The HMPC's activities aim at assisting the harmonization of procedures and provisions concerning herbal medicinal products laid down in EU Member States, and further integrating herbal medicinal products in the European regulatory framework.

***Committee for Advanced Therapies* (9)**

The Committee for Advanced Therapies (CAT) was established in accordance with Regulation (EC) No 1394/2007 on advanced-therapy medicinal products (ATMPs). It is a multidisciplinary committee, gathering

together some of the best available experts in Europe to assess the quality, safety and efficacy of ATMPs, and to follow scientific developments in the field.

Other responsibilities of the CAT include:

- Participating in Agency procedures for the certification of quality and non-clinical data for small and medium-sized enterprises developing advanced-therapy medicinal products
- Participating in Agency procedures for the provision of scientific recommendations on the classification of advanced-therapy medicinal products in accordance with Article 17 of Regulation (EC) No 1394/2007
- Contributing to the Agency's provision of scientific advice, following relevant procedures established between the CAT and the Scientific Advice Working Party (SAWP)
- Involvement in any procedure regarding the provision of advice for undertakings on the conduct of efficacy follow-up, pharmaco-vigilance and risk-management systems of ATMPs
- Advising, at the request of the CHMP, on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in ATMPs

***Pediatric Committee's*** (10)

The **Pediatric Committee's** (PDCO's) main role is to assess the content of pediatric investigation plans (PIPs) and adopt opinions on them. This includes the assessment of applications for a full or partial waiver and assessment of applications for deferrals.

The Committee's other roles include:

- Assessing data generated in accordance with agreed PIPs
- Adopting opinions on the quality, safety or efficacy of a medicine for use in the Advising Member States on the content and format of data to be collected for surveys on the uses of medicines in children
- Providing advice on questions on pediatric medicines, at the request of the Agency's Executive Director or the European Commission
- Establishing and regularly updating an inventory of pediatric medicine needs
- Advising the agency and the European commission on the communication of arrangements available for conducting research into pediatric medicines
- The PDCO is not responsible for marketing-authorization applications for medicines for use in children. This remains within the remit of the CHMP.

***Composition of EMA committees (11)***

The EMA committees contain members nominated by the medicines regulatory authorities of the European Union (EU) **Member States** (the 'national competent authorities')

- National competent authorities (human)
- National competent authorities (veterinary)

The European Medicines Agency works closely with the 27 European Union Member States as well as the European Economic Area countries (Norway, Iceland and Liechtenstein)as given in Table 1 (11).

**Table 1** European Union Member States (11-12)

| S.NO. | COUNTRY | ISO COUNTRY CODE | AGENCY | ACRONYM |
|---|---|---|---|---|
| 1 | Austria | AT | European Union Telematics controlled terms | AGES |
| 2 | Belgium | BE | Federal agency for Medicines and Health Products | FAMHP |
| 3 | Bulgaria | BG | Bulgarian Drug Agency | BDA |
| 4 | Croatia | HR | Agency for Medicinal products and Medical Devices of Croatia | ALMP |
| 5 | Cyprus | CY | Ministry of Health Pharmaceutical services | MOH |
| 6 | Czech republic | CZ | State Institute for Drug control | SUKL |
| 7 | Denmark | DK | Danish Health and Medicines agency | DKMA |
| 8 | Estonia | EE | The French National agency for Medicines and Health products Safety | ANSM |
| 9 | Finland | FI | Finnish medicines agency | FIMEA |
| 10 | France | FR | | |

**3. Marketing Authorization in EU**

The European Union, consisting of 27 Member States, has continuously worked on improving and streamlining drug review and marketing authorization processes (13).

Medicinal products are highly regulated in the European Union (EU) and are subject to a separate, complicated system of approvals that governs how, when, where, and in what form such products will be allowed to be sold within the borders of the EEA. The regulation of medicinal products is governed in the EU/EEA by Directive 2001/83/EC (the "Directive"). Also known as the Consolidated Directive, it brings many years of separate legislation together into one, detailed document (14).

## 4. Procedures and applications for Marketing authorisation of Medicinal products

In general there are 4 types of marketing authorization for the drug product to enter into European Union drug market (15). They are as follows

***Initial Marketing Authorisation***

4.1. Centralised procedure

4.2. Mutual recognition procedure

4.3. National procedure

4.4. Decenralised procedure

The choice of which procedure to follow depends on the number of countries in which the medicine is going to be marketed and the type of medicine concerned (16).

**Table 2** Legal Types of MAs in the EU/EEA (Type of Application) - Directive 2001/83 (17)

| Full dossier has to contain the complete data | set – CTD Module 1-5 | Article 8 |
|---|---|---|
| Generic | Pure generic application. | Article 10 (1) |
| Generic, additional data | Article 10 (3) | Article 10 (3) |
| Biosimilar | Generic Biotech products | Article 10 (4) |
| Bibliographic application,<br>WEU (Well Established Use) | Non-clinical & Clinical Data replaced by<br>– literature<br>- 10 years systematic and documented use of the substance as a medicinal product in the EU | Article 10a |
| Combination of known Constituents | pre-clinical data and clinical data<br>for the combination | Article 10b |
| Informed consent | Innovator's generic product.<br>(Duplicate dossier) | Article 10c |

***4.1.Centralised procedure***

European drug approvals are overseen by the European Medicines Agency. It is responsible for the scientific evaluation of applications for authorization to market medicinal products in Europe (via the centralized procedure). As per centralised procedure laid down in Regulation724/2004 and Directive 2004/27/EC, applications are made directly to the EMA and led to a grant of European marketing authorization by the EU Commission within 7 months (210 days) (18).

***Mandatory for the Centralised Procedure***

i) Biotechnological medicinal products

ii) Orphan medicinal products

iii) New active substances for which the therapeutic indication is the treatment of

a) Diabetes

b) Cancer

c) Acquired immune deficiency syndrome (HIV)

d) Neurodegenerative disorder (Alzheimer )

e) Auto-immune diseases and other immune dysfunctions

b) Viral diseases

***Optional for the Centralised Procedure***

i) New active substances

ii) Innovative medicinal products

iii) In the interests of patients at Community level

- Pandemic
- Generic medicinal products of nationally authorized reference medicinal products
- OTC medicinal products

iv) Generic medicinal products of reference medicinal products authorized by the CP

***Pre-submission meetings***

At least seven months before submission, applicants should notify the EMA of their intention to submit an application. In that notification applicants should include:

i) A draft summary of product characteristics

ii) A justification of the product's eligibility for evaluation under CP

iii) An indication on the number of strengths / pharmaceutical forms / pack sizes (if already known)

iv) All documents will be presented to all CHMP members

v) Following discussion at CHMP, the EMA will then inform the applicant whether the product is eligible for evaluation via the centralised procedure

***Selection of Rapporteur /Co-Rapporteur***

For any scientific evaluation a Rapporteur, and if relevant a Co-Rapporteur shall be appointed.

i) The role of the Rapporteur is to perform the scientific evaluation and to prepare an assessment report to the CHMP.

ii) Where appropriate, the Rapporteur can be supported by a Co-Rapporteur as agreed by the CHMP.

***Submission of the application***

The date and time of delivery of the dossier to the EMA should be arranged between the applicant and the EMA.

i) The EMA will inform future applicants well in advance of the scheduled CHMP meetings in order to identify optimal submission dates.

ii) The applicant is aware that the original indicated submission date cannot be met he should inform the EMA, Rapporteur and Co-Rapporteur immediately, since a delayed submission can have consequences for already planned activities of the assessment teams of the Rapporteurs and Co-Rapporteurs.

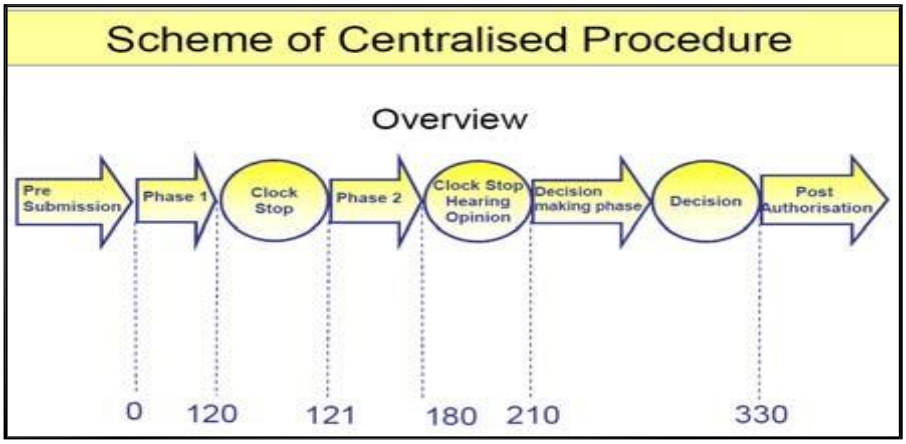


**Figure 1.** Overview of Centralised procedures (18)

***Assessment of the application/dossier***

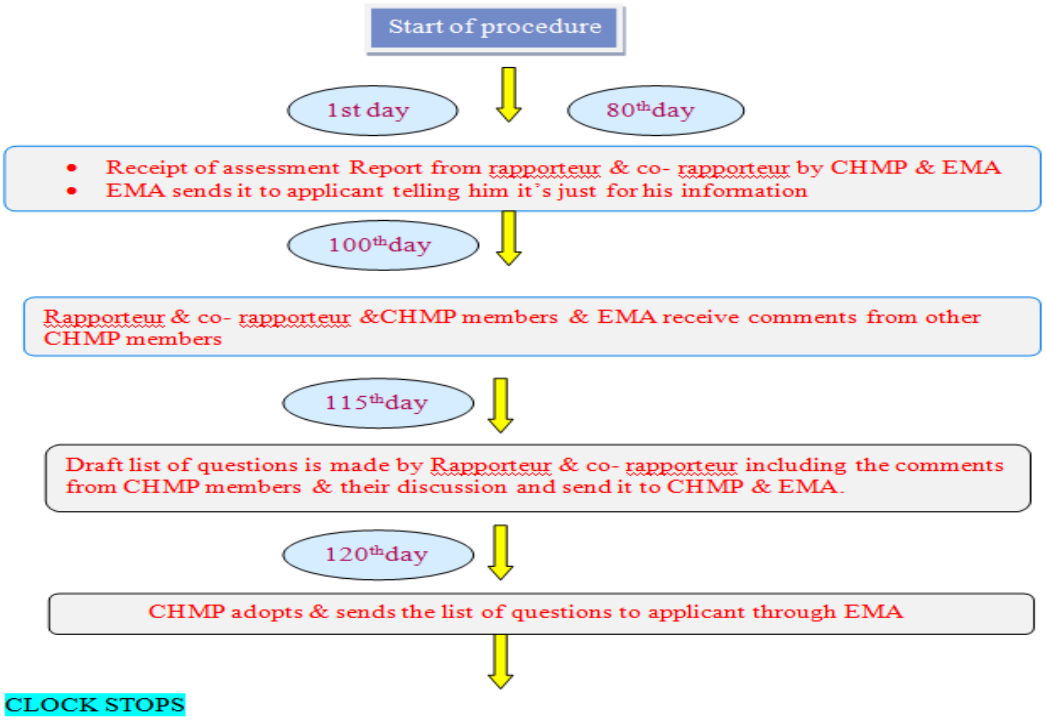


**Figure 1A.** Step 1- Flowchart of Centralized Procedure (18)

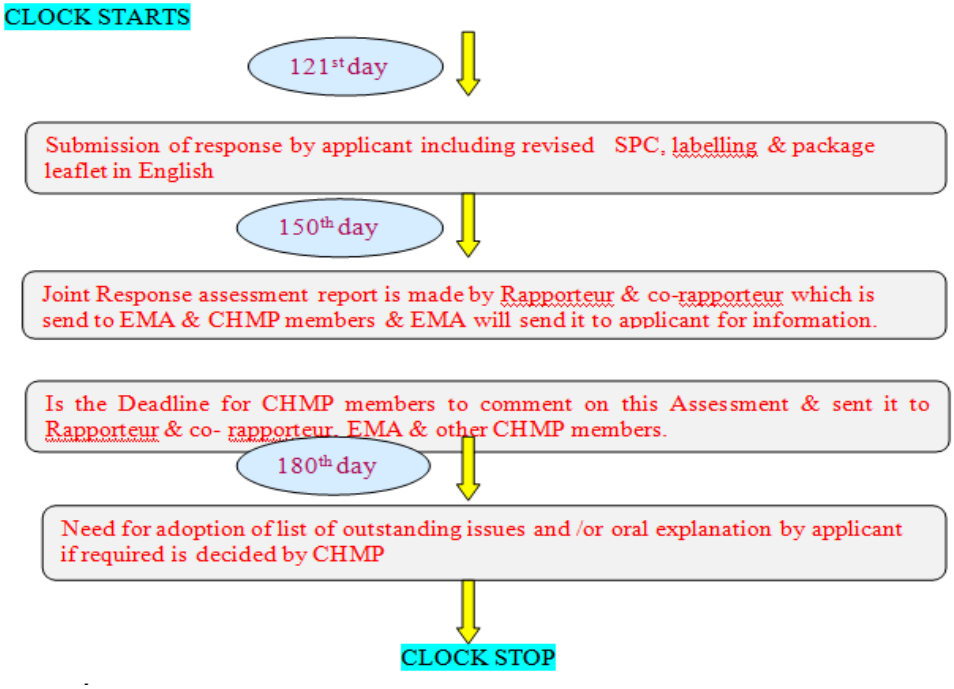


**Figure 1B.** Step 2 - Flowchart of Centralized Procedure (18)

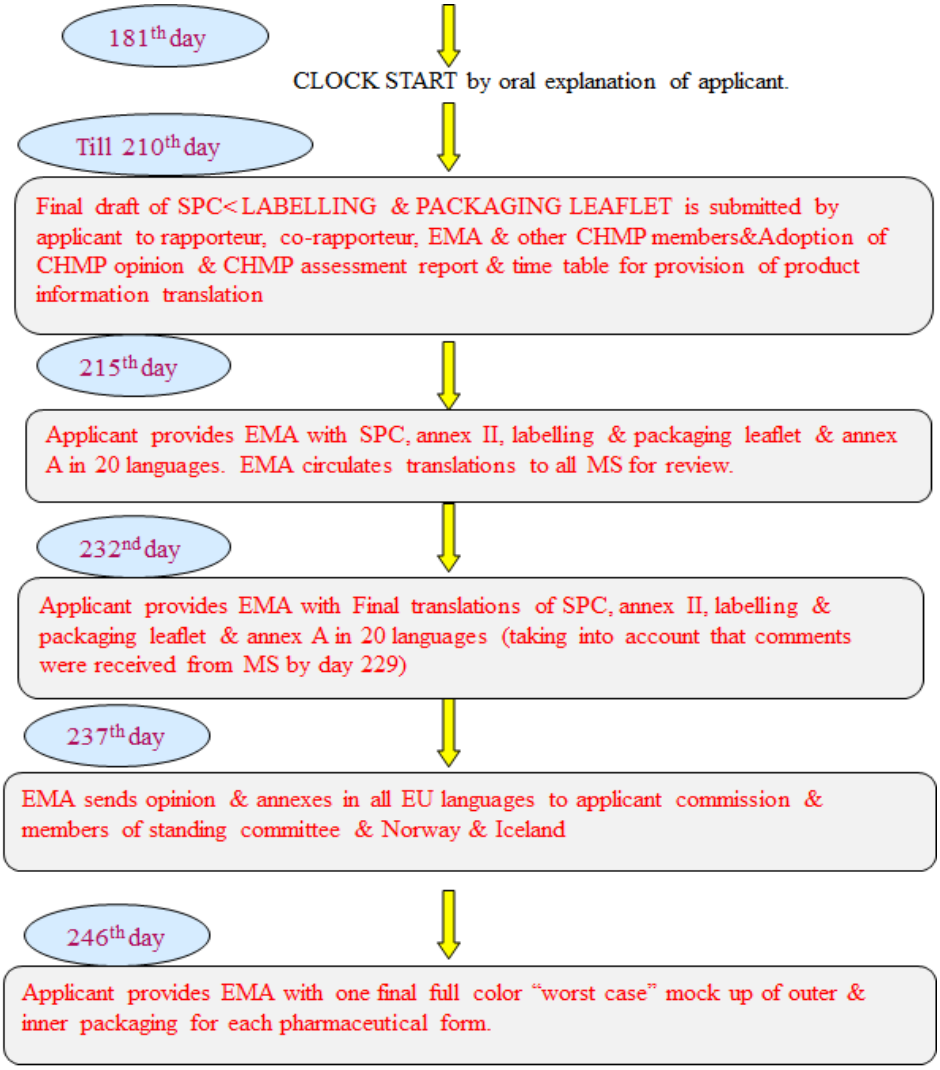


**Figure 1C.** Step 3 - Flowchart of Centralized Procedure (18)

### *4.2.Mutual recognition procedure*

The Regulation for the mutual recognition procedure is laid down in Directive 2001/83/EC. The mutual recognition procedure is mandatory for all medicinal products to be marketed in a Member State other than they were first authorised, since 1 January 1998. The mutual recognition procedure is used in order to obtain marketing authorisations in several Member States where the medicinal product in question has received a marketing authorization in any of the Member State at the time of application (19).

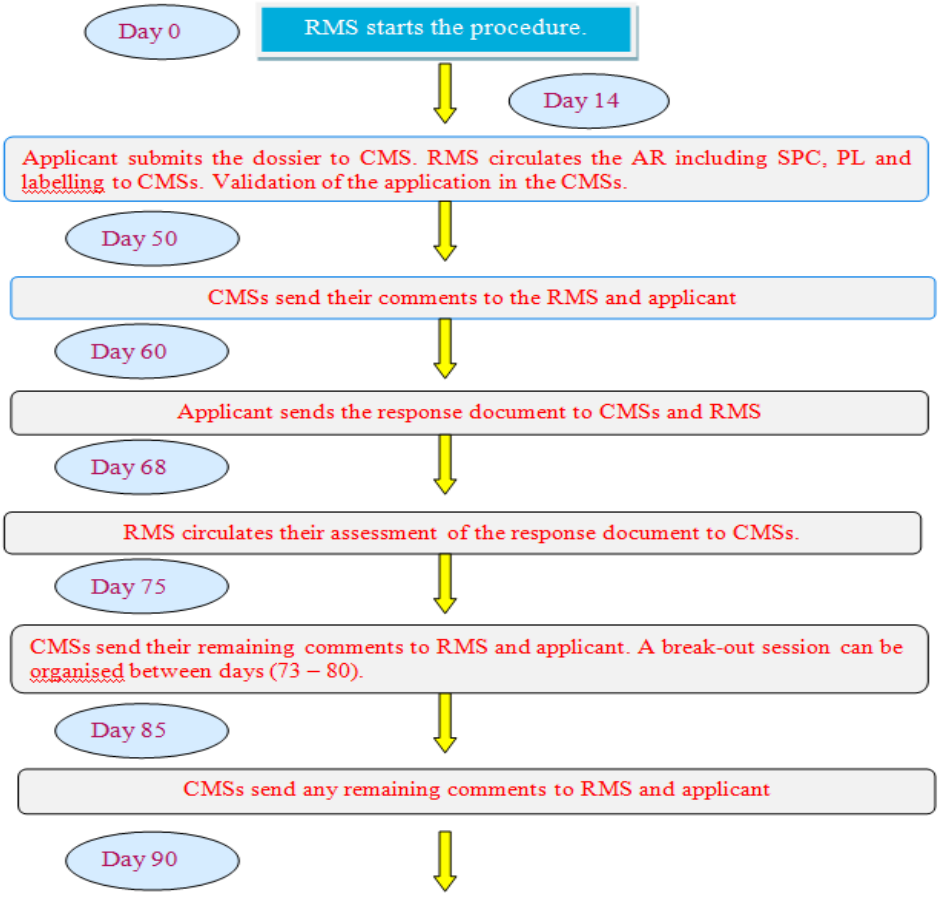


**Figure 2A.** Step 1- Flowchart of Mutual Recognition Procedure (19)

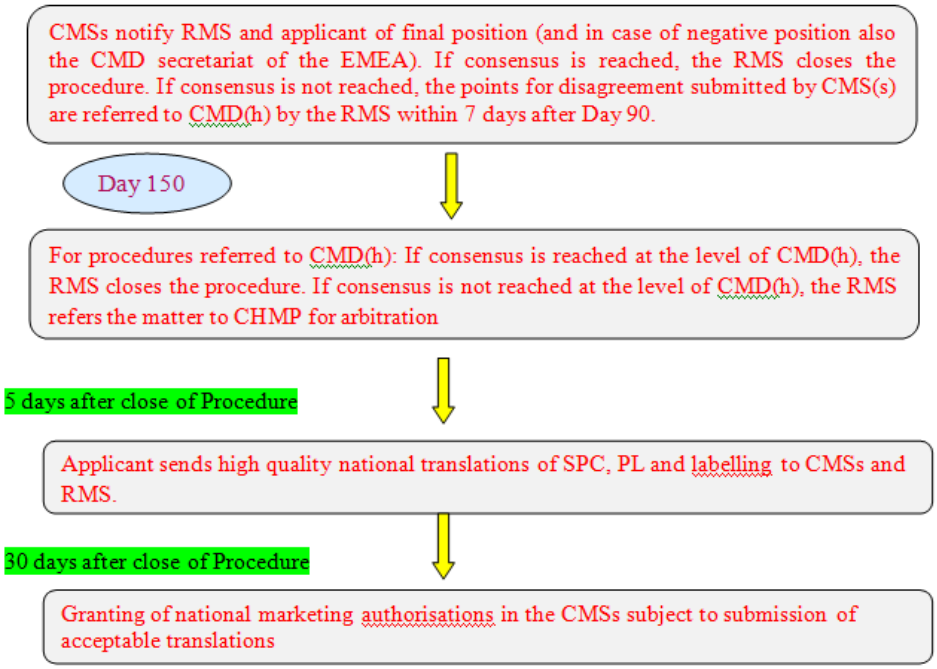


**Figure 2B.** Step 2-Flowchart of Mutual Recognition Procedure (19)

### *4.3.National procedure*

- Until 1998, the pharmaceutical industry could apply only for a national approval.
- The product could then only be sold in that particular EU country.
- In order to obtain an approval the product must be submitted with an SPC (Summary of Products Characteristics) which is the basis for the marketing of the product.
- In order to obtain a national marketing authorisation, an application is submitted to the competent authority of the Member State (20).

If an applicant wishes to obtain a license in one Member State an application must be made to the national Competent Authority which then issues a national license. With the exception of products granted a marketing authorization under the centralized procedure, all products are granted marketing authorizations on a country-by-country basis by the competent authorities in each member state. Such marketing authorizations permit the holder to market the product the member state concerned, subject to any restrictions or requirements that accompany the authorization. A marketing authorisation (MA) is valid for five years and after the first renewal, the MA is valid for an unlimited period. Even now products intended for national use in only one Member State is submitted by the national procedure.

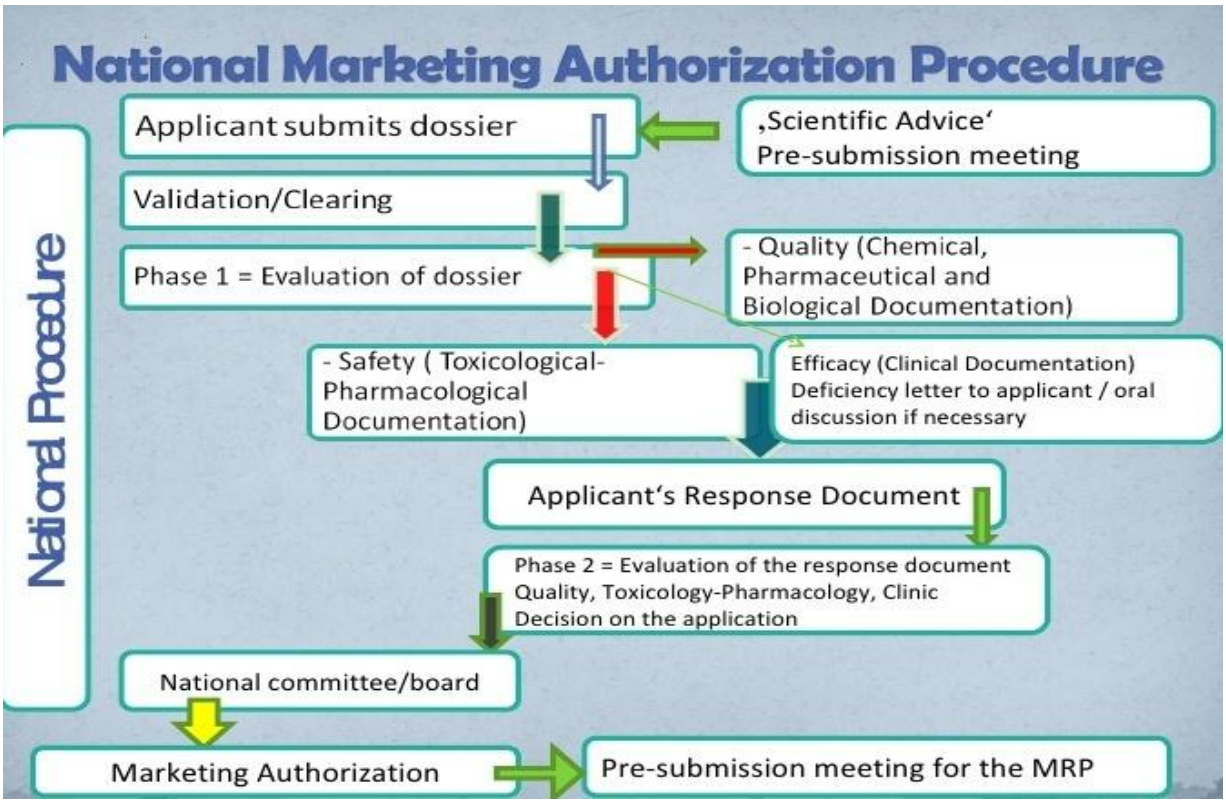


**Figure 3.** National Marketing authorisation procedure (20)

### *4.4.Decentralised procedure*

The decentralised procedure has been created with the review of the legislation and added to the mutual recognition procedure for registration of a product in more than one MS. This procedure is intended for medicinal products which do not have to be admitted by the centralised procedure and which have not• yet been granted a MA in a MS (21).

- Art. 28 para. 3 of Dir. 2001/83/EC
- Only possible, if no authorisation has already been granted
- Most significant difference with MRP = consultation between MS's before 1st MA issued

## 5. Drug registration process in EU

Drug registration is a system that subjects all pharmaceutical products to pre-marketing evaluation, marketing authorization, and post-marketing review to ensure that they conform to required standards of quality, safety, and efficacy established by national authorities. The outcome of the drug registration process is the issuance or the denial of a pharmaceutical product marketing authorization or licence (22).

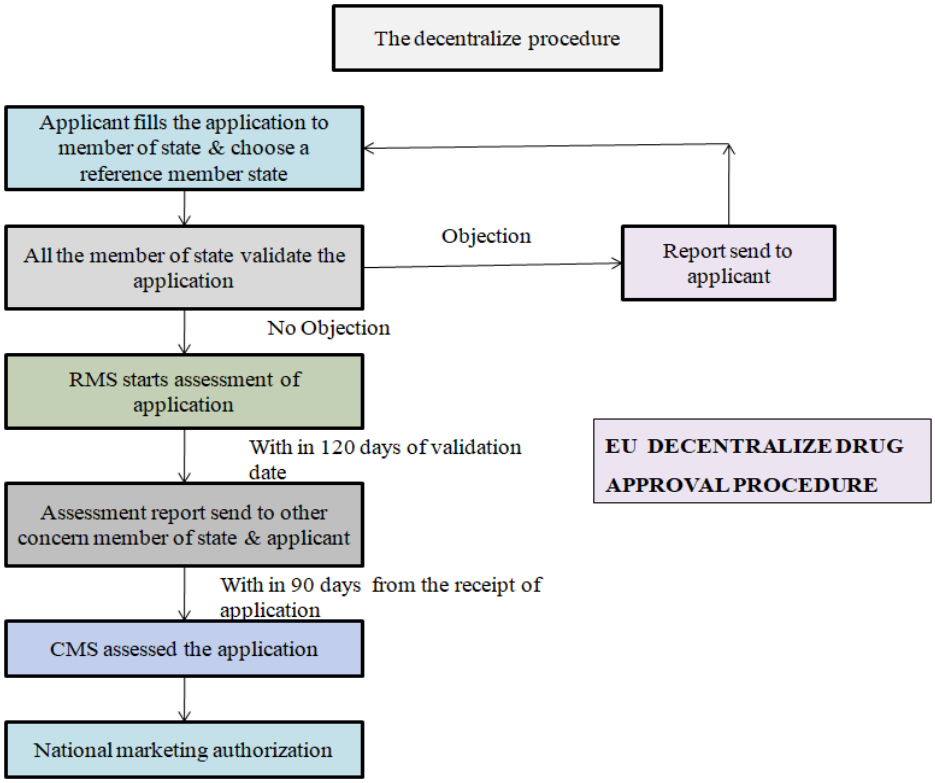


**Figure 4.** Decenralised Procedure (21)

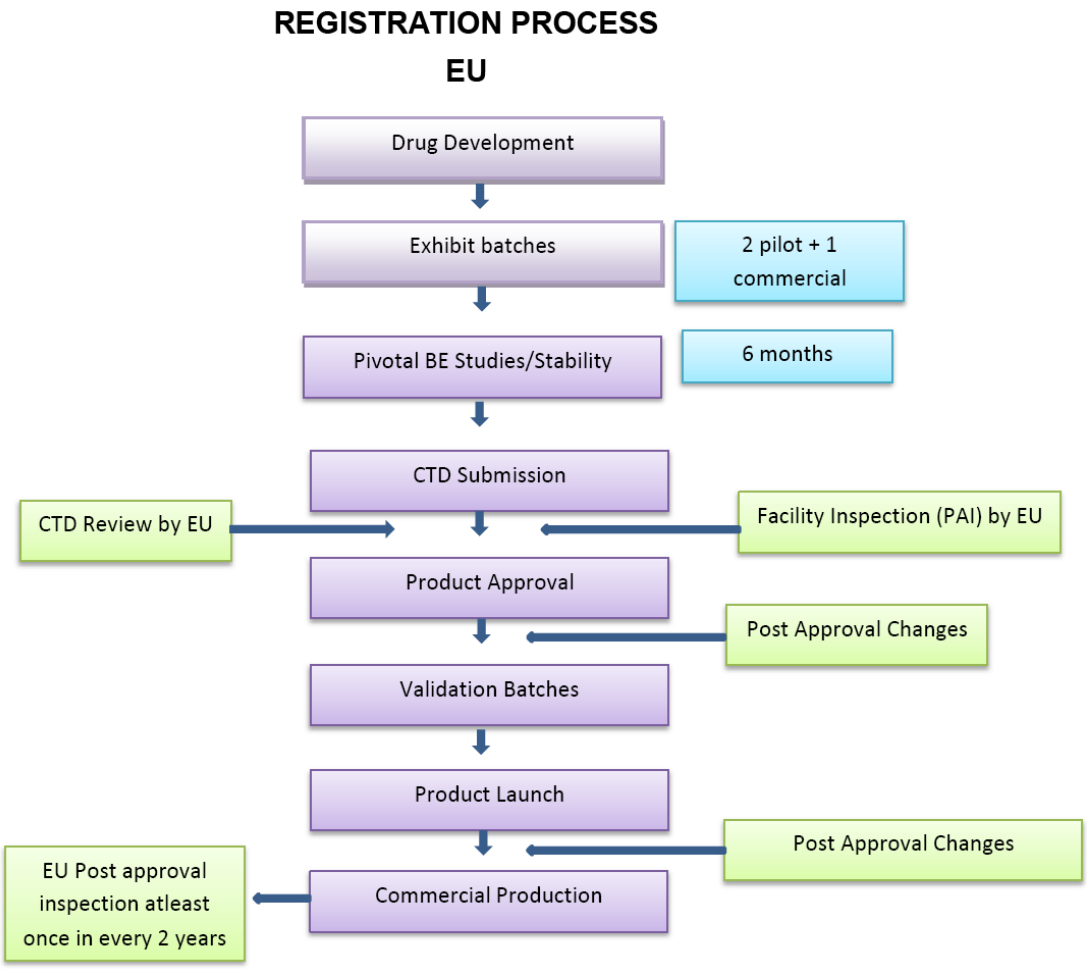


**Figure 5.** Drug registration process in EU (22)

***Compilation of European Commission and Agency guidelines***

However, only adopted guidelines (for medicinal product) the following rationale has been applied for the individual sections.

- **Quality:** As far as possible, the structure of the CTD has been followed. The structure has been adapted where a different method of consolidation was considered as in the case of guidelines which apply to both the active substance and to the finished product (which, in the CTD format, are independent headings).
- **Non-clinical:** The CTD structure has been followed.
- **Clinical efficacy and safety:** Generally, the CTD structure has been followed. In addition, guidelines have been organised into therapeutic groups.
- **ICH:** This section includes guidelines that are harmonised through the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use(ICH). The CTD structure has been followed.
- **Multidisciplinary:** This section contains guidelines that apply to more than one specific area or have been prepared through the collaboration of several working parties (23).

## 6. Conclusion

From the above presented information it is recognizable that each national authority has specific requirements that are not easy to be found. Harmonization of EU requirements at national level is strongly needed and member states should reduce their additional requirements. This leads to speed up the evaluation time for granting national approvals. Hence we conclude that, the above discussed procedures would help the company regulatory authorities in filing the registration of drug products in European Union.

## Acknowledgments

We would like to express our gratitude to Ms. Pavithra E for her continuous support in writing this article.

## Conflict of interest

The authors declare that there are no conflicts of interest.

## Abbreviations

- ICH (International Council for Hormonisation)
- EU (European Union)
- BA/BE (Bioavailability / Bioequivalance)
- EMA (European medicines agency)
- CP (Centralized Procedure)
- DCP (Decentralized Procedure)
- MRP (Mutual Recognition Procedure)
- CHMP (Committee for Medicinal Products for Human Use)
- PRAC (Pharmacovigilance Risk Assessment Committee)
- CVMP (Committee for Medicinal Products for Veterinary Use)
- COMP (Committee for Orphan Medicinal Products)
- HMPC (Committee on Herbal Medicinal Products)
- CAT (Committee for Advanced Therapies)
- PDCO (Paediatric Committee)
- CTD (Common technical document)

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