Review Article

MARKETING AUTHORIZATION OF HUMAN MEDICINAL PRODUCTS TO EUROPEAN UNION/EUROPEAN ECONOMIC AREA

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ABSTRACT

A firm or company intended to market their drug products within the European Economic Area should initially get the marketing authorization from a competent authority of a Member State of European Union (EU) or European Economic Area (EEA country) or when an authorisation has been granted in accordance with Regulation (EC) No 726/2004 for the entire Community (a Community authorisation). The European Economic Area unites the 27 EU member states and the three EEA European Free Trade Association (EFTA) states (Iceland, Liechtenstein and Norway). EEA constitutes total 30 countries, with 26 different languages and 14 types of currencies existing in the region. The total population is about 500 millions. Procedures for application for a marketing authorisation of medicinal product viz. Centralised procedure, National procedure, Mutual recognition procedure and Decentralised procedure, were explained in detail in this article.

Keywords: European Economic Area, Medicinal product, Marketing authorization, Authorization procedures.

1. INTRODUCTION

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.

The presented marketing authorisation procedures applicable to European Economic Area (EEA country), which included 27 EU member states and the three EEA European Free Trade Association (EFTA) states (Iceland, Liechtenstein and Norway). Hence, European Economic Area constitutes total 30 countries (figure 1).

The regulation of medicinal products is governed in the EU/EEA by Directive 2001/83/EC relating to medicinal products (the "Directive"). Also known as the Consolidated Directive, it brings many years of separate legislation together into one, detailed document[1].

A firm or company intended to market their drug products within the European Economic Area should initially get the marketing authorization from a competent authority of a Member State of European Union (EU) or European Economic Area (EEA country) or when an authorisation has been granted in accordance with Regulation (EC) No 726/2004 for the entire Community (a Community authorisation). Before understanding the authorization process of EU one must be aware of the following terminologies:

The European Economic Area: (EEA) The European Economic Area unites the 27 EU member states and the three EEA European Free Trade Association (EFTA) states (Iceland, Liechtenstein and Norway). The details of the member states of European Economic Area are presented in figure 1 and table 1.

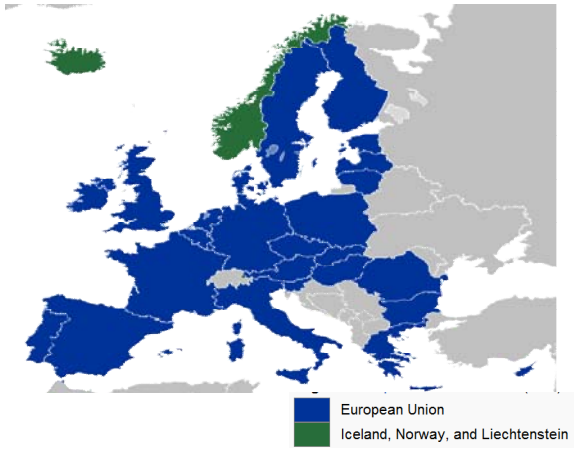

Figure 1: European economic area

European Union: (EU) European Union consists of 27 EU member states (figure 2).

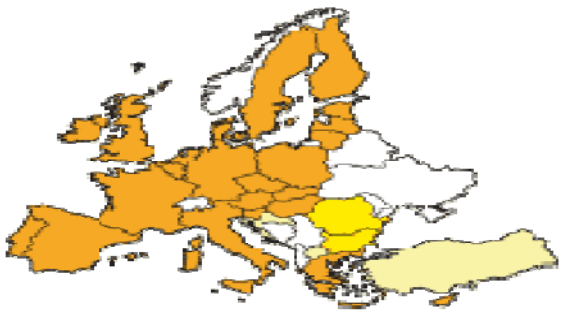

Figure 2: European Union

Member States: Germany, France, Italy, the Netherlands, Belgium, Luxembourg, Denmark, Ireland, United Kingdom, Greece, Spain, Portugal, Austria, Finland, Sweden, Czech Republic, Cyprus, Estonia, Latvia, Lithuania, Hungary, Malta, Poland, Slovenia and Slovakia. [25 by 2004]

New Member States: Bulgaria and Romania. [27] [1 January 2007]

European Medicines Agency

The European Medicines Agency (EMA) is a decentralised body of the European Union with headquarters in London.

Six scientific committees, composed of members of all EU and EEA-EFTA states, conduct the main scientific work of the Agency:

CHMP: Committee for Medicinal Products for Human Use (CHMP),

CVMP: Committee for Medicinal Products for Veterinary Use (CVMP),

COMP: Committee for Orphan Medicinal Products (COMP),

HMPC: Committee on Herbal Medicinal Products (HMPC),

PDCO: Paediatric Committee (PDCO) and the

CAT: Committee for Advanced Therapies (CAT).

Marketing Authorisation: A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorisation has been issued by the competent authority of a Member State (or EEA country) for its own territory (national authorisation) or when an authorisation has been granted in accordance with Regulation (EC) No 726/2004 for the entire Community (a Community authorisation). The marketing authorisation holder must be established within the EEA.[2]

Details of Regulatory Bodies of Member State for European Economic Area (EEA) are presented in table 2.

Table 1: Details of Member States of European Economic Area (EEA)[3]

S. No	Country Name	Country code	Language	Currency	Population	Country Flag
1	Austria	AT	German	Euro	8.3 M	
2	Belgium	BE	French, Dutch and German	Euro	10.7 M	
3	Bulgaria	BG	Bulgarian	Lev	7.6 M	
4	Cyprus	CY	Greek and English	Euro	0.8 M	
5	Czech Republic	CZ	Czech	Czech Koruna	10.3 M	
6	Germany	DE	German	Euro	82.5 M	
7	Denmark	DK	Danish	Danish Krone	5.4 M	
8	Estonia	EE	Estonian	Estonian kroon	1.4 M	
9	Greece	EL	Greek	Euro	11.2 M	
10	Spain	ES	Spanish	Euro	45.3 M	
11	Finland, Suomi	FI	Finnish & Swedish	Euro	5.3 M	
12	France	FR	French	Euro	63.7 M	
13	Hungary	HU	Hungarian	Forint	10.1 M	
14	Ireland	IE	English & Irish	Euro	4.0 M	
15	Iceland	IS	Icelandic	Icelandic Krona	0.3 M	
16	Italy	IT	Italian	Euro	57.3 M	
17	Liechtenstein	LI	German	Swiss Franc	0.04 M	
18	Lithuania	LT	Lithuanian	Litas	3.4 M	
19	Luxemburg	LU	Luxembourgish, French & German	Euro	0.5 M	
20	Latvia	LV	Latvian	Lats	2.3 M	
21	Malta	MT	Maltese & English	Euro	0.4 M	
22	Netherlands	NL	Dutch	Euro	16.4 M	
23	Norway	NO	Norwegian	Norwegian Krone	4.8 M	
24	Poland	PL	Polish	Zloty	38.1 M	
25	Portugal	PT	Portuguese	Euro	10.4 M	
26	Romania	RO	Romanian	Leu	21.5 M	
27	Sweden	SE	Swedish	Swedish Krona	9.2 M	
28	Slovenia	SI	Slovenian	Euro	2.0 M	
29	Slovakia	SK	Slovak	Euro	5.4 M	
30	United Kingdom	UK	English	Pound sterling	60.4 M	

Table 2: Details of Regulatory Bodies of Member States for European Economic Area (EEA)

Country Name	Regulatory Agency Name	Website
Austria	Austrian Agency for Health and Food Safety (AGES)	www.ages.at
Belgium	Federal Agency for Medicines and Health Products	http://www.fagg-afmps.be/en/
Bulgaria	Bulgarian Drug Agency	http://www.bda.bg/index.php?lang=en
Cyprus	Ministry of Health	www.pio.gov.cy
Czech Republic	State Institute for Drug Control	www.sukl.cz
Germany	Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)	http://www.bfarm.de/de/index.php
Denmark	The Danish Medicines Agency	http://www.dkma.dk/1024/visUKLSForside.asp?artikelID=728
Estonia	State Agency of Medicines	www.sam.ee
Greece	National Organisation for Medicines	www.eof.gr
Spain	Agencia española del medicamento	http://www.aemps.es/en/home.htm
Finland, Suomi	Finnish Medicines Agency	http://www.nam.fi/
France	Agence Française de Sécurité Sanitaire des Produits de Santé	http://www.afssaps.fr/
Hungary	National Institute of Pharmacy	http://www.ogyi.hu/main_page/
Ireland	Irish Medicines Board	www.imb.ie
Iceland	Icelandic Medicines Agency	http://www.imca.is/
Italy	Italian Medicines Agency	http://www.agenziafarmaco.it/en
Liechtenstein	Liechtensteinische Landesverwaltung	http://www.llv.li/
Lithuania	State Medicines Control Agency	http://www.vvkt.lt/index.php?3327723903
Luxemburg	Ministère de la Santé	www.etat.lu/MS
Latvia	State agency of Medicines	http://www.zva.gov.lv/index.php?setlang=en&large=
Malta	Medicines Authority	http://medicinesauthority.gov.mt/
Netherlands	The Medicines Evaluation Board (MEB)	http://www.cbg-meb.nl/CBG/en/
Norway	Norwegian Medicines Agency	http://www.legemiddelverket.no/
Poland	Office for Medicinal Products	http://www.urpl.gov.pl/english/index.htm
Portugal	INFARMED – National Authority of Medicines and Health Products	http://www.infarmed.pt/portal/page/portal/INFARMED
Romania	National Medicines Agency	http://www.anm.ro/en/home.html
Sweden	Medical Products Agency	http://www.lakemedelsverket.se/english/
Slovenia	Agency for Medicinal Products	http://www.jazmp.si/index.php?id=56
Slovakia	State Institute for Drug Control	http://www.sukl.sk/en
United Kingdom	Medicines and Healthcare products Regulatory Agency	www.mhra.gov.uk

2. GLANCE OF EUROPEAN ECONOMIC AREA

EEA constitutes total 30 countries, with 26 different languages and 14 types of currencies existing in the region. The total population is about 500 millions.

EEA Languages

Table 1, shown different languages were existing in the European Economic Area. Among all the languages most commonly used language is English, German and French. In the below figure 3 we can find the other most commonly used languages in the European Union.

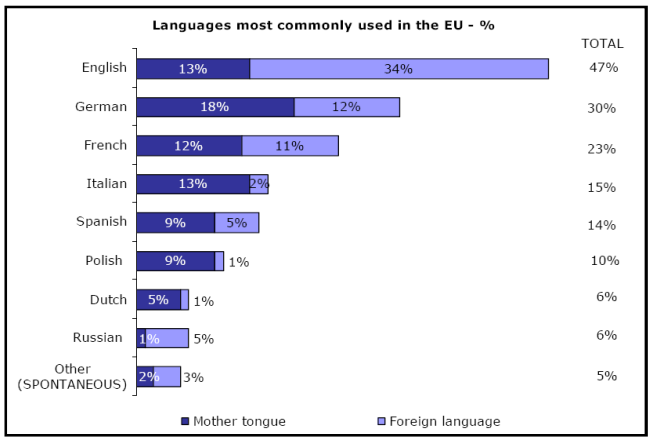

Figure 3: Most commonly used languages in EU.

EEA Population

The total population of EEA is about 500 millions. Below in table 3 illustrated the top 5 highest populated and also lowest populated countries of EEA region. These top 5 highest populated countries population constitutes 60% of total population of EEA. Considering the total population of EEA it stood above the USA population (Around 310 M).

Table 3: EEA Population summary

Ranking order	Country Name	Population
Highest Populated countries		
1	Germany	82.5 M
2	France	63.7 M
3	United Kingdom	60.4 M
4	Italy	57.3 M
5	Spain	45.3 M
Lowest Populated countries		
1	Liechtenstein	0.04 M
2	Iceland	0.3 M
3	Malta	0.4 M
4	Luxemburg	0.5 M
5	Cyprus	0.8 M

3. EUROPEAN LEGAL FRAMEWORK FOR LICENSING OF MEDICINAL PRODUCT[4]

The legal framework of the EU licensing consists of three major columns: Regulations, Directives and Guidelines. The Rules Governing Medicinal Products in the European Union are issued by the EU Commission and can be downloaded from http://eudrams1.is.eudra.org/F2/ eudralex/download. For human medicinal products, including all biological and biotech products, the relevant volumes are:

Volume 1 Pharmaceutical legislation (Summary of all current Regulations and Directives)

Volume 2 Notice to Applicants

Volume 2A Procedures for marketing authorization

Volume 2B Presentation and content of the application dossier

Volume 2C Regulatory guidelines

Volume 3 Guidelines medicinal products for human use

Volume 4 Good Manufacturing Practice (GMP) with in particular

Annex 01 Manufacture of sterile medicinal products

Annex 02 Manufacture of biological medicinal products for human use

Annex 13 Manufacture of investigational medicinal products

Annex 14 Manufacture of products derived from human blood or human plasma

Annex 15 Qualification and Validation

Annex 16 Certification by a Qualified Person and batch release

Annex 18 GMP for active pharmaceutical ingredients (ICH Q7A)

Volume 9 Pharmacovigilance

3.1 Regulations

Regulations are directly effective as supranational law and they are addressing the citizens of the EU Member States.

3.2 Directives

Directives are addressing the Member States and they have to be implemented in national law by the legislation of the Member States.

3.3 Guidelines

Guidelines issued by the CHMP, the European Pharmacopoeia and ICH are not legally binding but where an applicant chooses not to be compliant with a guideline, that decision must be explained and justified. Guidelines are addressing scientific staff of authorities and companies. All guidelines, points to consider or recommendations issued under the roof of the EMA can be found on the EMA web page www.ema.europa.eu.

4. TYPES OF MARKETING AUTHORIZATION APPLICATIONS

Legal types of marketing authorizations are provided Table 4.

Table 4: Legal Types of MAs in the EU/EEA (Type of Application) - Dir 2001/83

Class	Details	Legal Type
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, WEU (Well Established Use)	- Non-clinical & Clinical Data replaced by – literature - 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 for the combination	Article 10b
Informed consent	Innovator's generic product. (Duplicate dossier)	Article 10c

5. MARKETING AUTHORISATION PROCEDURES[5-9]

Procedures for application for a marketing authorisation

- Centralised procedure
- National procedure
- Mutual recognition procedure
- Decentralised procedure

5.1. Centralised Procedure (CP)

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).

In order to obtain a Community Authorization, an application is made to the EMA – The European Medicines Agency. The application is scientifically evaluated by the Committee for Medicinal Products for Human Use (CHMP). A MA granted under the CP is valid for the entire EU/EEA market.

The **centralised procedure** laid down in Regulation **724/2004** and Directive 2004/27/EC. Applications are made directly to the EMA and lead to a grant of a European marketing authorization by the EU Commission within **7 months** after application (210 days). One Member State is assigned Rapporteur for an application and takes the lead in the evaluation process of the CHMP. The decision of the Commission is binding on all EU Member States. The product may be marketed in all Member States with one common Summary of Product Characteristics (SPC).[4]

Mandatory for the Centralised Procedure

• Biotechnological medicinal products,

• Orphan medicinal products

• New active substances for which the therapeutic indication is the treatment of

– Diabetes

– Cancer

– Acquired immune deficiency syndrome (HIV)

– Neurodegenerative disorder (Alzheimer …)

– Auto-immune diseases and other immune dysfunctions

– Viral diseases

Optional for the Centralised Procedure

• New active substances

• Innovative medicinal products

• in the interests of patients at Community level

– *Pandemic*

– *Generic medicinal products of nationally authorized reference medicinal products*

– *OTC medicinal products*

• Generic medicinal products of reference medicinal products authorised by the CP

Products authorised pursuant to the centralised procedure are granted marketing authorisations that cover all EU Member States and the EEA. A further distinguishing feature of this route includes the requirement for the marketing holder to secure also a single EU-wide trademark for the product. However, the convenience of the centralised procedure is also accompanied by fees that are significantly higher than the national procedure. The flow of centralised procedure was illustrated in figure 4 & 5.

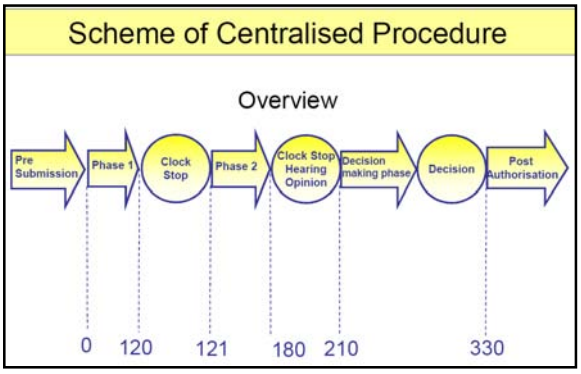

Figure 4: Scheme of Centralised procedure

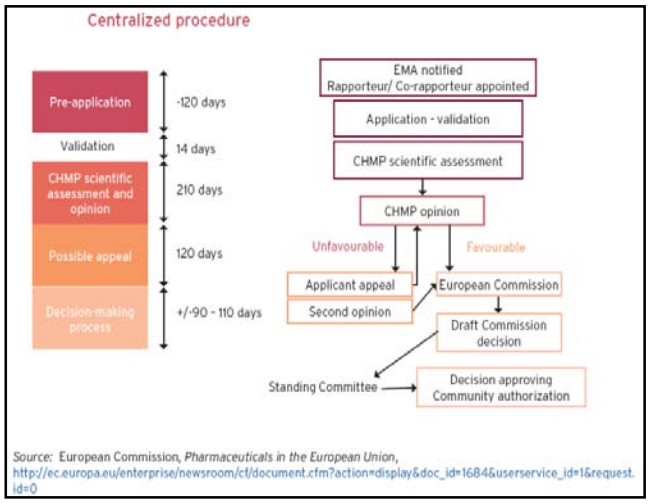

Figure 5: Centralised application procedure

5.2. National Procedure (NP)

If an applicant wishes to obtain a license in one Member State (MS) an application must be made to the national Competent Authority (CA) which then issues a national license.

With the exception of products granted a marketing authorisation under the centralised procedure as set out above, all products are granted marketing authorisations on a country-by-country basis by the competent authorities in each Member State. Such marketing authorisations permit the holder to market the product in question in the Member State concerned, subject to any restrictions or requirements that accompany the authorisation.

5.3. Mutual Recognition Procedure (MRP)

The **mutual recognition procedure (MRP)** laid down in Council Directive 2004/27/EC. Pre-requisite to enter in this procedure is a marketing authorization in one of the EU Member States (reference Member State, RMS). To obtain such initial national marketing authorisation may take 6 to 9 months. An application for mutual recognition may be addressed to any number of Member States (Concerned Member States, CMS). The RMS compiles an assessment report within 90 days and sends this report to all CMS who have 90 days to recognize the decision of the RMS by granting a marketing authorization with an identical SPC. Concerned Member States have additional 30 days for granting the national licenses. The total MR procedure takes **9 months** for the first national Marketing Authorisation **plus 7 months** for the mutual recognition part. [4]

For products to be registered in more than one Member State (MS) and which do not qualify for the Centralised Procedure (CP) applicants must use either the Decentralised Procedure (DP) or the Mutual Recognition Procedure (MRP). The MRP is to be used if the aim is to register in more than one Member State and the medicinal product in question has already received a Marketing Authorisation (MA) in any MS at the time of application.

The MRP is based on the idea that a national license approved in one EU Member State (Reference Member State – RMS) should be mutually recognised in other EU countries (Concerned Member States – CMS). This is based on the assumption that the evaluation criteria in the EU member states are sufficiently harmonised and are of the same standard. At the end of a MRP national licenses are issued in the CMSs involved in the procedure.

Medicines legislation also foresees the possibility that most pharmaceutical companies will wish to market their products in more than one EU country, and provides two mechanisms to applicants that avoid the need to submit full marketing authorisation applications in each country.

The mutual recognition procedure, enables pharmaceutical companies who already hold a marketing authorisation in one EU Member State to ask additional Member States to recognize the marketing authorisation that has already been granted. The procedure involves the preparation of an assessment report by the original Member State that is forwarded to the additional Member States for its consideration. Assuming the other Member States agree with the report, a marketing authorisation will then be issued for the product in the Member States concerned.

However, the Mutual Recognition procedure often sees disagreements between Member States that can hold up the procedure and lead to delays. For such occasions, there is a detailed disputes procedure that must be followed. Flow of MRP is illustrated in figure 6 & 7.

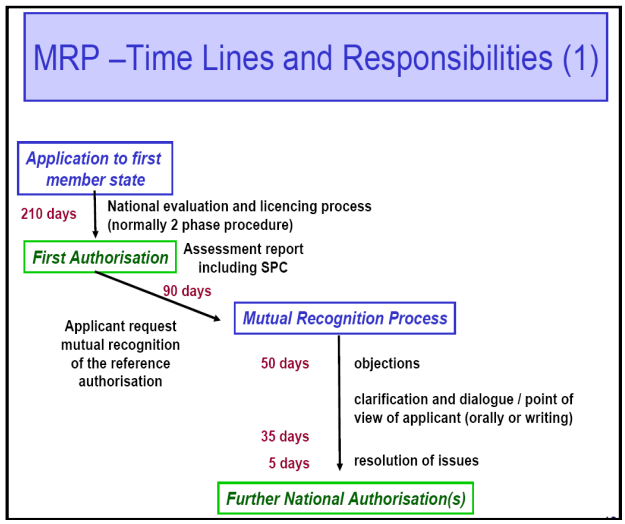

Figure 6: Scheme of Mutual recognition procedure

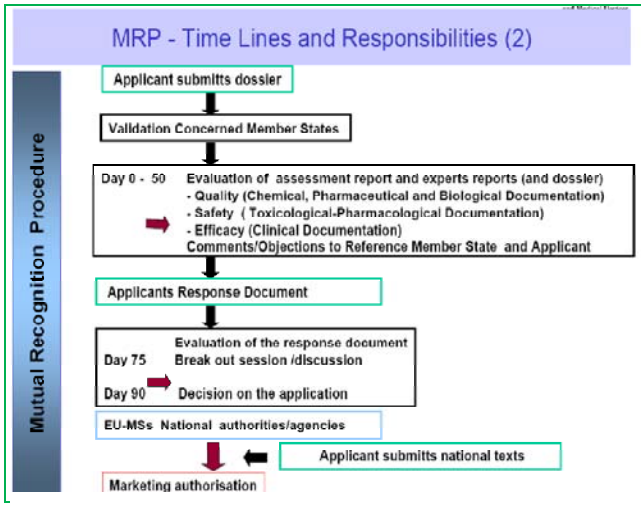

Figure 7: Mutual recognition Application procedure

5.4. Decentralised procedure (DCP)

The **decentralised procedure** (DCP) as laid down in Directive 2004/27/EC, Article 28, paragraph 3 applies where a medicinal product has not received the Marketing authorisation in one Member State. [4]

The Decentralised Procedure (DCP), in general, follows the same principles of the MRP. A license approved in one Member States (MS) should be mutually recognised in other Member States (MSs) assuming that the evaluation criteria in the EU member states are sufficiently harmonised and are of the same standard.

The DCP is to be used if the aim is to obtain marketing authorisation in several Member States (MSs) where, at the time of application, the medicinal product in question has not yet received a Marketing Authorisation in any MS.

The main difference between the MRP and DCP lies in the fact that the Concerned Member States (CMSs) in a DCP are involved at the onset of the procedure as opposed to waiting for approval before an application is made in the CMS.

The second of these, the decentralised procedure, which was introduced during the changes to the legislation in 2005, aims to avoid some of the potential disputes between Member States and the resulting delays to authorisation by engaging each of the Member States to which the applicant wishes to apply at the time the first marketing authorisation is made. Consequently, this procedure is open only to products that have not yet been granted a marketing authorisation in the EU. Under the decentralised procedure, the applicant chooses one Member State to be its reference Member State.

There are several key advantages of the decentralised procedure. Foremost amongst there is a strong commercial advantage: because the applicant receives identical marketing authorisation for its medicinal product in all chosen member states at the same time, it is possible to launch a product on the market in several different EU countries simultaneously, thus reducing the associated launch costs and potentially creating a strong band and presence for the product in the EU from day one. In addition, the fact that identical marketing authorisation will be issued for the medicinal product concurrently should lead in theory to significant reduction in the regulatory hurdles the applicant must go through in the first instance to obtain the marketing authorisation, and this is coupled with a potential reduction in the future administrative burden of the marketing authorisation holder with regard to the variations, extensions and renewals of the marketing authorisations in each member states. The flow chart of decentralised procedure was provided in figure 8 & table 5.

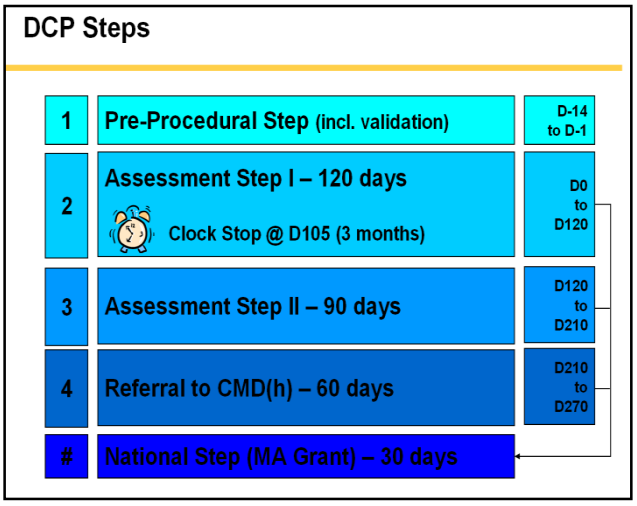

Figure 8: Steps involved in decentralised procedure

5.5. Orphan Drug Procedure

Orphan Drug: EU Regulation on orphan medicinal products EC 141/2000 and EC 847/2000 apply for products intended for treatment of rare diseases. If a medical condition does not affect more than 5 in 10,000 persons in the Community (i.e. appr. 225,000 persons as of 01 April 2004) an orphan designation may be applied for. Prove of the prevalence of a rare condition should follow COMP/436/01. The designation procedure with the COMP takes 90 days plus 30 days for Commission approval. Additionally, the sponsor has to file an application for a marketing authorisation through the centralised procedure and only after approval may bring the orphan drug product on the EU market. The approval includes a 10 years exclusive marketing right. [4]

CONCLUSION

A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorisation has been issued by the competent authority of a Member State (or EEA country) for its own territory (national authorisation) or when an authorisation has been granted in accordance with Regulation (EC) No 726/2004 for the entire Community (a Community authorisation). The marketing authorisation holder must be established within the EEA. The marketing authorisation holder should follow the relevant guideline and directives for manufacturing of the medicinal products to be market in the EEA and he has select to select the relevant legal type of application and relevant procedure based on the product eligibility, for faster drug product approval. Summary of European marketing application options in table 6.

Table 6: Summary of European marketing application options

Process	When used	Pros	Cons
National authorization	Individual applications to each country within the EU. Used for products that fall outside the scope of the EMA centralized procedure.	If application rejected in one country, can still access other EU countries.	Separate applications required for each country. Unique requirements and formats may be required.
Decentralized procedure	Used for products that fall outside the scope of the EMA centralized procedure.	Simultaneous authorization in numerous countries in the EU. May be more efficient than national authorization since a positive outcome results in numerous country approvals. Sponsor can select which countries to apply to; does not have to be all EU countries.	A negative decision on an application may affect numerous countries.
Mutual recognition procedure	Individual application to one country within the EU for products that fall outside the scope of the EMA centralized procedure.	Review by one country and other countries accept the decision. Only one application needs to be submitted.	Individual national approvals can add significant time to the process. A negative outcome can affect numerous countries.
Centralized procedure	Used for biologic products or other products using high-technology procedures; products for HIV/AIDS, cancer, diabetes, neurodegenerative disease, auto-immune or other dysfunctions, and viral diseases; products for orphan conditions; and other new active substances at the request of the applicant.	One application applies to all countries in the EU. Relatively quick procedure. A positive outcome is very beneficial to the sponsor.	A negative outcome will affect access to the entire EU.

Table 5: Flow chart of decentralised procedure

Pre-procedural Step	
Before Day -14	Applicant discussions with RMS, RMS allocates procedure number. Creation in CTS.
Day –14	Submission of the dossier to the RMS and CMSs; Validation of the application.
Assessment step I	
Day 0	RMS starts the procedure.
Day 70	RMS forwards the Preliminary Assessment Report (PrAR) (including comments on SmPC, PL and labeling) on the dossier to the CMSs and the applicant.
Until Day 100	CMSs send their comments to the RMS, CMSs and applicant.
Until Day 105	Consultation between RMS and CMSs and applicant. If consensus not reached RMS stops the clock to allow applicant to supplement the dossier and respond to the questions.
Clock-off period	Applicant may send draft responses to the RMS and agrees the date with the RMS for submission of the final response. Applicant sends the final response document to the RMS and CMSs within a period of 3 months, which can be extended by a further 3 months.
Day 106	RMS restarts the procedure following the receipt of a valid response or expiry of the agreed clock-stop period if a response has not been received.
Assessment step II	
Day 120 (Day 0)	RMS sends the DAR, draft SmPC, draft labelling and draft PL to CMSs and the applicant.
Day 145 (Day 25)	CMSs send comments to RMS, CMSs and the applicant.
Day 150 (Day 30)	RMS may close procedure if consensus reached. Proceed to national 30 days step for granting MA.
Until 180 (Day 60)	If consensus is not reached by day 150, RMS to communicate outstanding issues with applicant, receive any additional clarification, prepare a short report and forward it to the CMSs and the applicant.
Day 195 (at the latest)	A Break-Out Session (BOS) may be held at the European Medicines Agency with the involved MSs to reach consensus on the major outstanding issues.
Between Day 195 and Day 210	RMS consults with the CMSs and the applicant to discuss the remaining comments raised.
Day 210 (Day 90)	Closure of the procedure including CMSs approval of assessment report, SmPC, labelling and PL, or referral to Co-ordination group. Proceed to national 30 days step for granting MA.
Day 210 (at the latest)	If consensus on a positive RMS AR was not reached at day 210, points of disagreement will be referred to the Co-ordination group for resolution.
Day 270 (at the latest)	Final position adopted by Co-ordination Group with referral to CHMP/CVMP for arbitration in case of unsolved disagreement.
National step	
5 days after close of procedure	Applicant sends high quality national translations of SmPC, labelling and PL to CMSs and RMS
30 days after close of The procedure	Granting of national marketing authorisation in RMS and CMSs if outcome is positive and there is no referral to the Co-ordination group. (National Agencies will adopt the decision and will issue the marketing authorisation subject to submission of acceptable translations).
30 days after close of CMD referral procedure	Granting of national marketing authorisation in RMS and CMSs if positive conclusion by the Co-ordination group and no referral to the CHMP/CVMP. (National Agencies will adopt the decision and will issue the marketing authorisation subject to submission of acceptable translations).

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