

**AN INTROSPECTIVE ACCESS IN ASSORTMENT OF DRUG DOSSIER AS PER EU GUIDELINES.****J. Balasubramanian<sup>\*1</sup>, K.S. Lakshmi<sup>2</sup>, E. Pavithra<sup>2</sup> and Sruthi Krishnan**<sup>1</sup>Aeon Formulations Pvt. Ltd., Chennai-600 089, Tamilnadu, India.<sup>2</sup>SRM College of Pharmacy, SRM University, Department of Pharmaceutical Regulatory Affairs, Tamilnadu, India.**\*Corresponding Author: Dr. J. Balasubramanian**

Aeon Formulations Pvt. Ltd., Chennai-600 089, Tamilnadu, India.

Article Received on 19/03/2017

Article Revised on 09/04/2017

Article Accepted on 29/04/2017

**ABSTRACT**

The retrospective approach of the compilation of dossiers for applications of European marketing authorizations is applicable for the centralized procedure and national procedures, including mutual recognition and decentralized procedures. The European Union contains scientific committee, members, European Union member states. The mission of the European Medicines Agency (EMA) is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health in the European Union (EU). The European Medicines Agency's Committee for Medicinal Products for Human Use prepares scientific guidelines in consultation with regulatory authorities in the European Union (EU) Member States, to help applicants prepare marketing authorization applications for human medicines. Guidelines reflect a harmonized approach of the EU Member States and the Agency on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in the Community directives.

**1.0 EUROPEAN MEDICINES AGENCY**

The European Medicines Agency EMA<sup>[1]</sup> is a decentralised agency of the European Union (EU), located in London. EMA protects public and animal health in 28 EU Member States, as well as the countries of the European Economic Area (EEA), by ensuring that all medicines available on the EU market are safe, effective and of high quality. EMA serves a market of over 500 million people living in the EU.

EMA was set up in 1995 to harmonise the work of existing national medicine regulatory bodies.

The Agency's remit has expanded over time, in line with new EU legislation. On top of its remit to evaluate human and veterinary medicines, EMA is also responsible for products developed in the specialised areas of medicines for rare diseases (since 2000), herbal medicines (since 2004), medicines for children (since 2006) and advanced-therapy medicines (since 2007). Acquiring these responsibilities resulted in new scientific committees which provide the expertise in these areas.<sup>[1]</sup>

EMA has a 20-year track record of ensuring efficacy and safety of human and veterinary medicines across Europe, and promoting research and innovation in the development of medicines. In its first two decades, the Agency recommended the authorisation of a total of 975 human and 188 veterinary medicines.<sup>[1]</sup>

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 (SmPC), package information and classification for the supply, readability of the label and package leaflet requirements.<sup>[2]</sup>

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.<sup>[3]</sup>

The 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 fulfil 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.<sup>[4]</sup>

The process of assessing and reviewing the dossier of a pharmaceutical product containing its detailed data like administrative, chemistry, preclinical, clinical and the permission granted by the Regulatory Agencies of a country with a view to support its marketing approval in a country is called as the Marketing Authorization or Marketing Approval. It is commonly called as the New

Drug Application (NDA) in the USA or Marketing Authorization Application (MAA) in the European Union (EU) or simply Registration Dossier.<sup>[5]</sup>

The reasons for revision were minor changes in the numbering and the headings of the CTD, which have been incorporated in the updated Modules 2, 3, 4 and 5 of the EU CTD NTA.

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 all types of products (new chemical entities, radiopharmaceuticals, vaccines, herbals etc.) To determine the applicability of this format for a particular type of product, applicants should consult with the appropriate regulatory authorities.<sup>[6]</sup>

### 1.1 SCIENTIFIC COMMITTEES

The European Medicines Agency (EMA) has seven scientific committees that carry out its scientific assessments.<sup>[7]</sup>

1.1.1 Committee for Medicinal Products for Human Use (CHMP)

1.1.2 Pharmacovigilance Risk Assessment Committee (PRAC)

1.1.3 Committee for Medicinal Products for Veterinary Use (CVMP)

1.1.4 Committee for Orphan Medicinal Products (COMP)

1.1.5 Committee on Herbal Medicinal Products (HMPC)

1.1.6 Committee for Advanced Therapies (CAT)

1.1.7 Paediatric Committee (PDCO)

The work of these committees is supported by Working parties and other groups.

#### 1.1.1 Committee for Medicinal Products for Human Use<sup>[8]</sup>

The Committee for Medicinal Products for Human Use (CHMP) is responsible for preparing the Agency's opinions on all questions concerning 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 or where other Community interests are at stake ('Community referral procedure').

Other important activities of the CHMP and its working parties include

- The provision of assistance to companies researching and developing new medicines
- The preparation of scientific and regulatory guidelines for the pharmaceuticals industry
- Cooperation with international partners on the harmonisation of regulatory requirements for medicines

The CHMP consists of:

- One member and an alternate appointed by each EU Member State and a chairperson, appointed after consulting EMA's Management Board
- One member and an alternate appointed by Iceland and Norway
- Up to five co-opted members, chosen among experts nominated by Member States or the Agency and recruited, when necessary, to provide additional expertise in a particular scientific area
- All members and alternates serve on the committee for a renewable three year period

#### 1.1.2 Pharmacovigilance Risk Assessment Committee<sup>[9]</sup>

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.

The PRAC consists of:

- A Chair and Vice Chair, elected by serving PRAC members
- One member and an alternate nominated by each of the 28 EU Member States
- One member and an alternate nominated by Iceland and by Norway
- Six Independent Scientific Experts nominated by the European Commission
- One member and an alternate nominated by the European Commission after consultation of the European Parliament to represent healthcare professionals
- One member and one alternate nominated by the European Commission after consultation of the European Parliament to represent patient's organisations
- All members and alternates serve on the committee for a once renewable three year period

### 1.1.3 Committee for Medicinal Products for Veterinary Use<sup>[10]</sup>

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 'centralised' or 'Community' procedure, the CVMP is responsible for conducting the initial assessment of veterinary medicines for which an EU-wide marketing authorisation 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 authorisation.
- In the 'mutual-recognition' and 'decentralised' procedures, the CVMP arbitrates in cases where there is a disagreement between Member States concerning the marketing authorisation 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').

Other important activities of the CVMP and its working parties include.

- The provision of assistance to companies researching and developing new veterinary medicines
- The preparation of scientific and regulatory guidelines for the veterinary pharmaceuticals industry
- Cooperation with international partners on the harmonisation of regulatory requirements for veterinary medicines.

The CVMP is composed of.

- A chair, elected by serving CVMP members
- One member and an alternate nominated by each of the 28 Member States
- One member and an alternate nominated by Iceland and by Norway
- Up to five co-opted members, chosen among experts nominated by Member States or the Agency and recruited, when necessary, to provide additional expertise in a particular scientific area

### 1.1.4 Committee for Orphan Medicinal Products<sup>[11]</sup>

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. COMP members are nominated by the Member States, and are chosen on the strength of their qualifications and expertise with regard to the evaluation of medicinal products. They serve on the committee for a renewable period of three years.

The COMP is composed of.

- A Chair, elected by serving COMP members
- One member nominated by each of the 28 Member States
- Three members nominated by the European Commission to represent patient's organizations
- Three members nominated by the European Commission on the Agency's recommendation
- One member nominated by Iceland and one by Norway

All members and alternates serve on the committee for a renewable three year period.

### 1.1.5 Committee on Herbal Medicinal Products<sup>[12]</sup>

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 harmonisation 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.

The HMPC consists of.

- A Chair, elected by serving HMPC members
- One member and an alternate appointed by each EU Member State
- One member and an alternate appointed by Iceland and Norway
- Up to five co-opted members, chosen among experts nominated by Member States or the Agency and recruited, when necessary, to provide additional expertise in a particular scientific area
- All members and alternates serve on the committee for a renewable three year period.

### 1.1.6 Committee for Advanced Therapies<sup>[13]</sup>

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.

### 1.1.7 Paediatric Committee's<sup>[14]</sup>

The Paediatric Committee's (PDCO's) main role is to assess the content of paediatric 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 paediatric population, at the request of the Committee for Medicinal Products for Human Use (CHMP) or a medicines regulatory authority in a European Union (EU) Member State. The PDCO can give an opinion if the data have been generated in accordance with an agreed PIP.
- Advising Member States on the content and format of data to be collected for surveys on the uses of medicines in children.
- Advising and supporting the development of the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)
- Providing advice on questions on paediatric medicines, at the request of the Agency's Executive Director or the European Commission.
- Establishing and regularly updating an inventory of paediatric medicine needs.
- Advising the agency and the European commission on the communication of arrangements available for conducting research into paediatric medicines.

- The PDCO is not responsible for marketing-authorisation applications for medicines for use in children. This remains within the remit of the CHMP.
- For full details on the Committee's responsibilities and composition and on the roles of its members, see the Paediatric Committee rules of procedure.
- The roles and responsibilities of members and alternates, rapporteurs, peer reviewers, observers and experts at the PDCO meetings are described in PDCO – Roles and responsibilities at PDCO meetings.

### 1.2 COMPOSITION<sup>[7]</sup>









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)

### 2.0 EUROPEAN UNION MEMBER STATES<sup>[15-16]</sup>

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). Member State representatives are members of the Agency's management board while the Agency's scientific Committees and its network of 4,500 scientific experts are nominated by the Member States. Without their support and expertise, the Agency would be unable to deliver on its responsibilities and mandate as laid down in European legislation.

**Table 1: European Union Member States.**

S.No	Country and its flag	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	State Agency of Medicines	
9	Finland 	FI	Finnish Medicines Agency	FIMEA
10	France 	FR	The French National Agency for Medicines and Health Products Safety	ANSM

11	Germany		DE	Federal Institute for Drugs and Medical Devices	BfArM
12	Greece		GR	National Organization for Medicines	EOF
13	Hungary		HU	National Institute of Pharmacy	OGYI
14	Iceland		IS	Icelandic Medicines Agency	IMA
15	Italy		IT	Italian Medicines Agency	AIFA
16	Ireland		IE	Irish Medicines Board	IMB
17	Latvia		LV	State Agency of Medicines of Latvia	ZVA
18	Liechtenstein		LI	Office of Health/ Medicinal Products Control Agency	LLV
19	Lithuania		LT	State Medicines Control Agency	VVKT
20	Luxembourg		LU	Ministry of Health	MS
21	Malta		MT	Medicines Authority	
22	Netherlands		NL	Medicines Evaluation Board	CBG-MEB
23	Norway		NO	The Norwegian Medicines Agency	NOMA
24	Poland		PL	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products	URPL
25	Portugal		PT	National Authority of Medicines and Health Products	INFARMED
26	Romania		RO	National Agency for Medicines and Medical Devices	ANM
27	Slovakia		SK	State Institute for Drug Control	SUKL
28	Slovenia		SL	Javna agencija Republike Slovenije za zdravila in medicinske pripomočke	
29	Spain		ES	Spanish Agency of Medicines and Medical Devices	AEMPS
30	Sweden		SE	Medical Products Agency	MPA
31	United Kingdom		UK	Medicines and Healthcare Products Regulatory Agency	MHRA

### 3.0 MARKETING AUTHORISATION IN EU

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. 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.<sup>[17]</sup>



### 3.1 PROCEDURES FOR APPLICATION FOR A MARKETING AUTHORISATION

#### 3.1.1 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.<sup>[18]</sup>

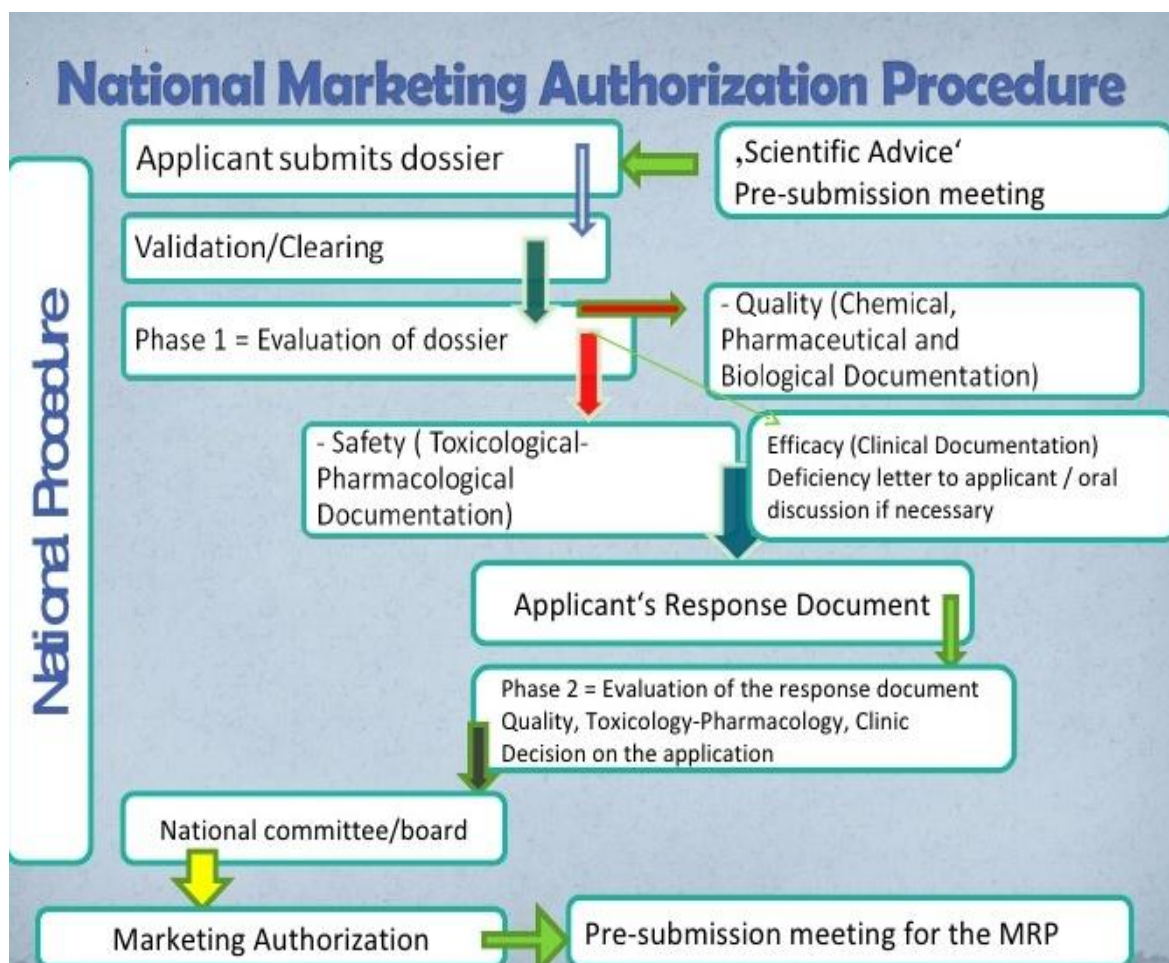


Fig 2: National Marketing authorisation procedure.

- 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.
- 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 only is submitted by the national procedure.<sup>[19]</sup>

#### 3.1.2 Centralised Procedure<sup>[20]</sup>

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).

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).

##### 3.1.2.1 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
- f) Viral diseases

### 3.1.2.2 Optional for the Centralised Procedure

- i) New active substances
- ii) Innovative medicinal products
- iii) In the interests of patients at Community level
  - a) Pandemic
  - b) Generic medicinal products of nationally authorized reference medicinal products
  - c) OTC medicinal products
  - iv) 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.

### 3.1.2.3 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.

### 3.2.1.4 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.

### 3.2.1.5 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.

### 3.2.1.6 EMA requirements

- i) One full copy of the dossier (modules 1-5 according to the EU-CTD format), including the applicant's part of the Active Substance Master File
- ii) Two additional copies of Modules 1 and 2 including the draft summary of product characteristics, labelling and package leaflet in English
- iii) One electronic copy of module 1 and 2 (at least 2.1-2.5) in WORD
- iv) In addition, applicants must submit the dossier to both the Rapporteur and the Co-Rapporteur in parallel to the EMA.

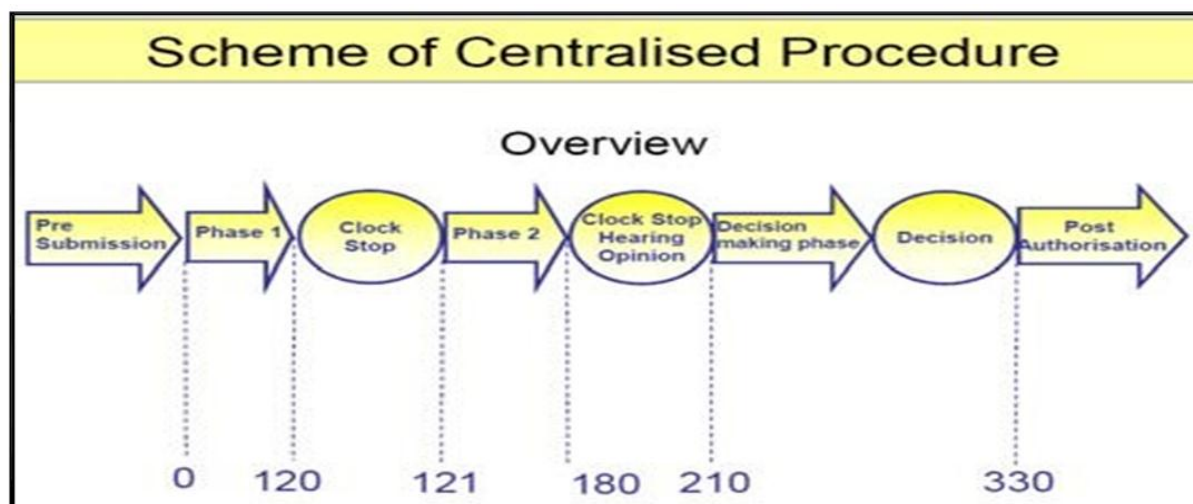
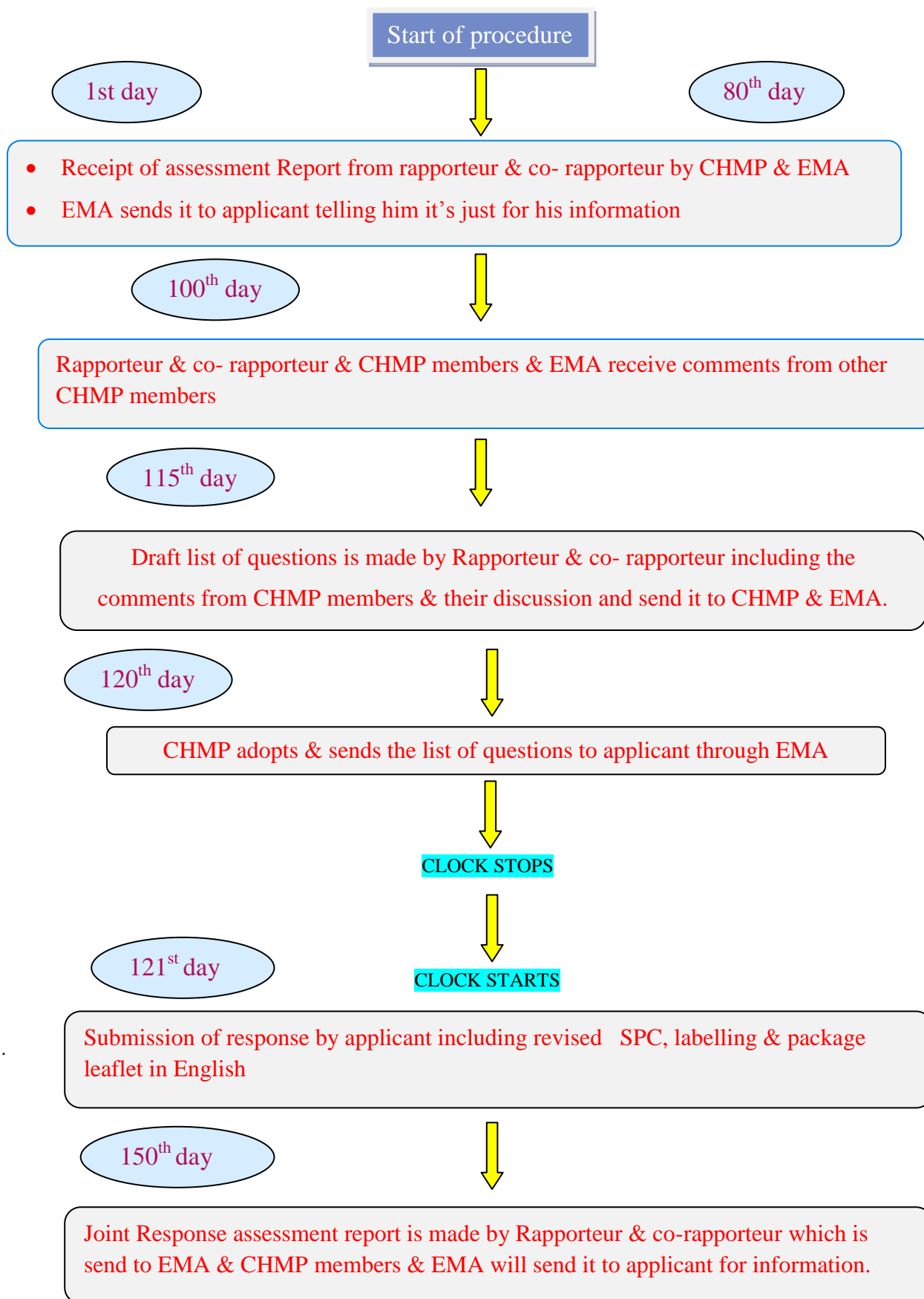
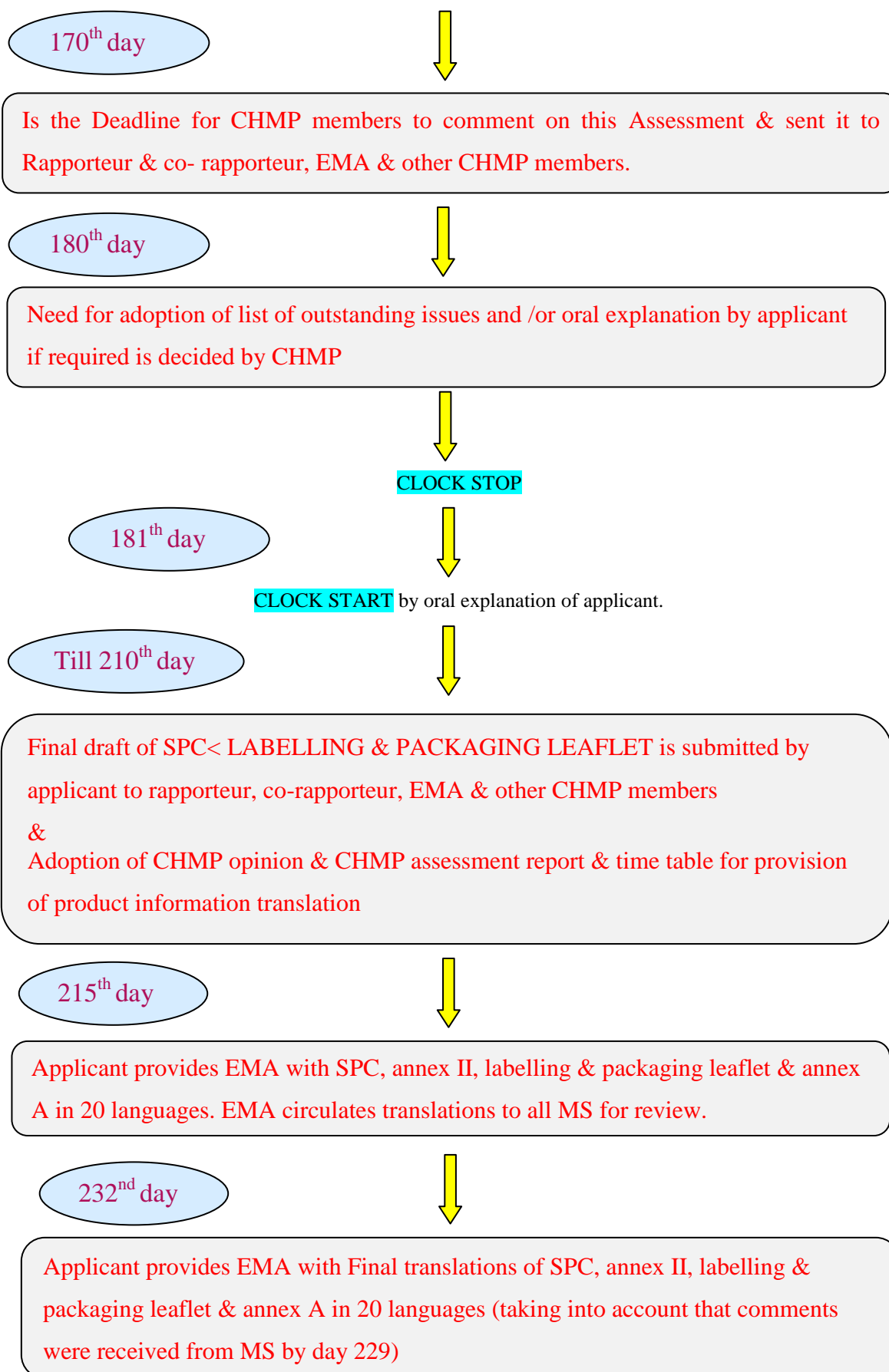


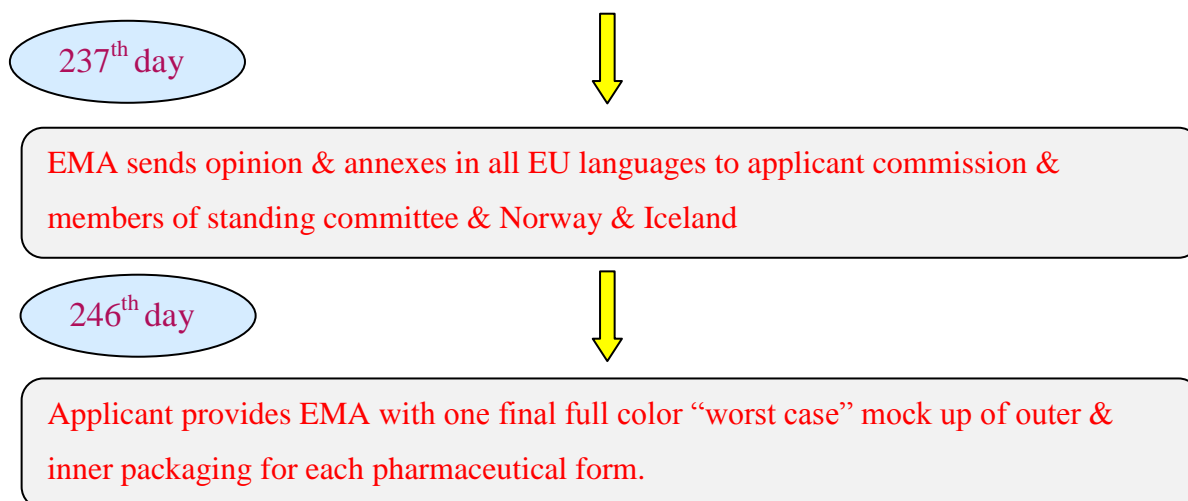
Fig 3: Overview of Centralised procedures.

## 3.1.2.7 The assessment of the application/dossier begins







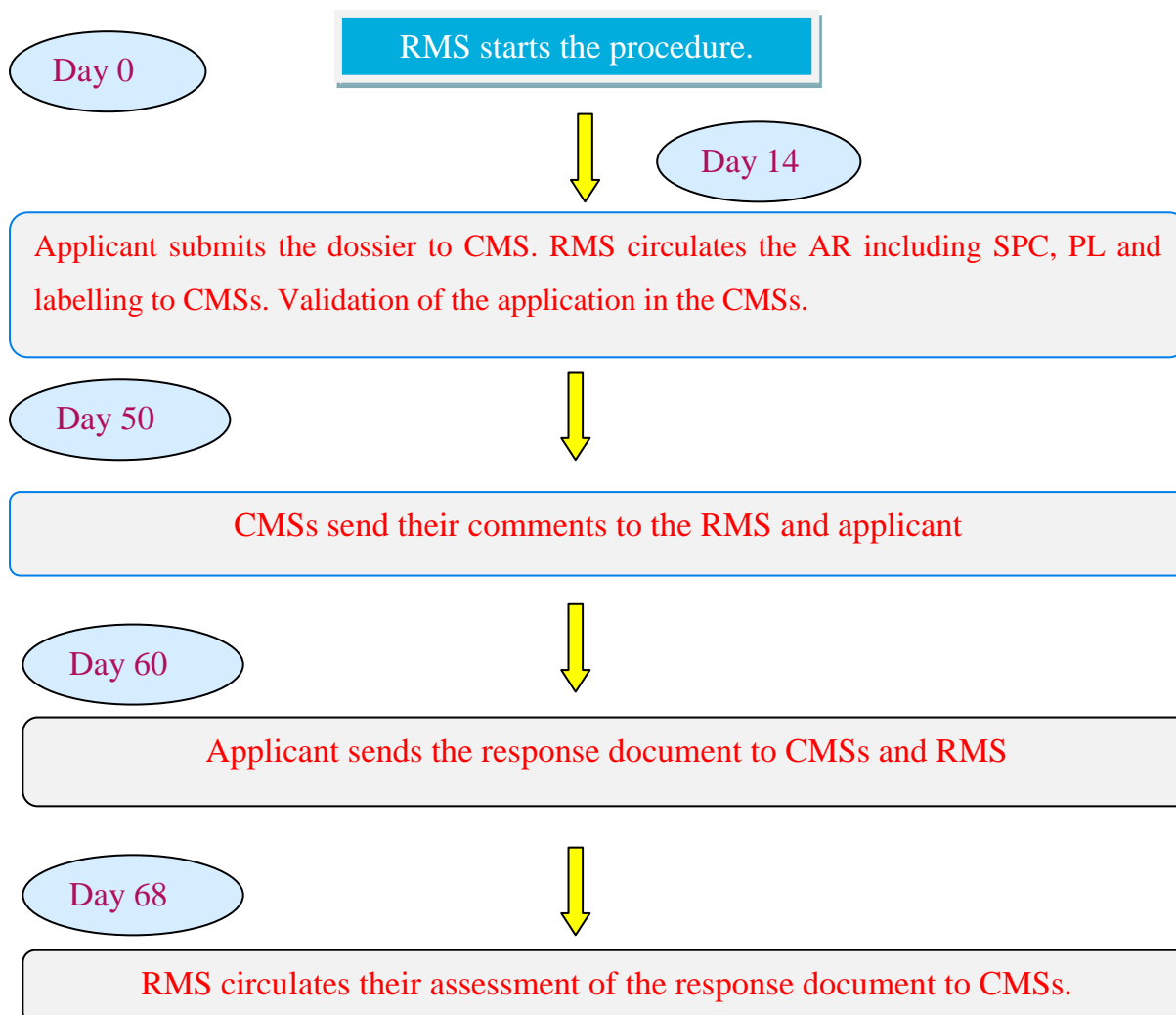


**Fig 4: Flowchart of Centralised Procedure**

### 3.1.3 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 authorisation in any of the Member State at the time of application.



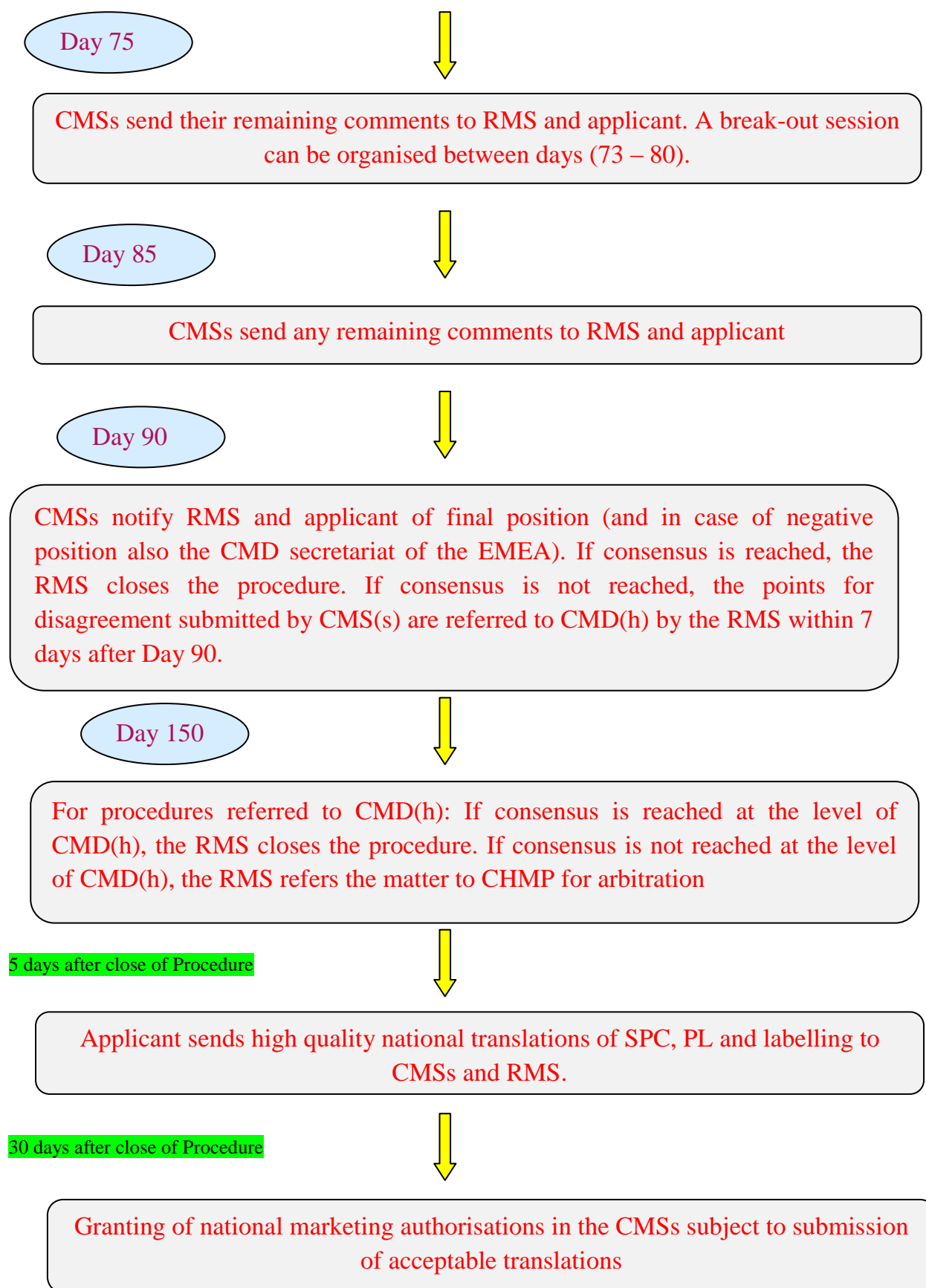


Fig 5: Flowchart of Mutual Recognition Procedure

### 3.1.4 Decentralised Procedure<sup>[21]</sup>

The new Decentralised procedure came into effect in the European Union in 2005 and is regulated by Directive 2004/27/EC. The main purpose of this procedure is to acquire marketing authorizations in several Member States, even though there are no marketing authorization has been granted in the European area.

The decentralised procedure is divided in five steps: (234 days)

- Validation step (14 days)
- Assessment step I (70 +30 days)
- Assessment step II (90 days)
- Discussion at the coordination group level, if needed
- National Marketing Authorisation step (30 days)

**Table 2: Steps of Decentralised Procedure.**

<b>Pre-procedural Step</b>	
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.
<b>Assessment step I</b>	
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.
<b>Assessment step II</b>	
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 steps 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.
<b>National step</b>	
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).

**CONCLUSION**

Having granted some 400 centralized marketing authorizations for medicinal products for human and veterinary use to date, the EMEA, despite some initial skeptics, has proved that a centralized authorization procedure can work successfully by securing consensus among scientists from many different medical cultures. The new legislation and the Agency's numerous initiatives will enable it to do much more - to provide a boost to R&D across Europe.

**REFERENCES**

1. European medicines agency –ema.europa.eu [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/document\\_listing/document\\_listing\\_000426.jsp&mid=](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000426.jsp&mid=).
2. EC Regulation No. 2309/93 as the European Agency for the Evaluation of Medicinal Products, and renamed by EC Regulation No. 726/2004 to the European Medicines Agency, it had the acronym EMEA until December 2009.
3. Santosh Kumar Narla, "Marketing Authorization of Human Medicinal Products to European Union/European Economic Area", *International Journal of Pharmaceutical Sciences Review and Research*, Volume 10, Issue 1, Sept – Oct 2011, Article-001, ISSN 0976 – 044X.
4. Directive 2003/63/EC, OJ L 159 June 2003 p.46.
5. Mo. Nasiruddin I Pawar<sup>1</sup>, \*Darshil B Shah<sup>2</sup>, Dr. Dilip G Maheshwari "REGULATORY REQUIREMENTS FOR MARKETING AUTHORIZATION OF GENERIC DRUG PRODUCT IN BOTSWANA". *European Journal Of Pharmaceutical And Medical Research Volume 2, Issue 3 May 2015*. ISSN 3294-3211.
6. Notice to Applicants (NTA) *Medicinal products for human use* Volume 2B-CTD, foreword & introduction, edition June 2006; 2-4.
7. European Medicines Agency - Committees - Committees, working parties and other groups. [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000217.jsp&mid=](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000217.jsp&mid=).
8. European Medicines Agency - Committees - Committee for Medicinal Products for Human Use (CHMP). [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000094.jsp&mid=WC0b01ac0580028c79](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000094.jsp&mid=WC0b01ac0580028c79).
9. European Medicines Agency - Committees - Pharmacovigilance Risk Assessment Committee (PRAC). [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000537.jsp&mid=WC0b01ac058058cb18](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000537.jsp&mid=WC0b01ac058058cb18).
10. European Medicines Agency - Committees - Committee for Medicinal Products for Veterinary Use (CVMP) [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000262.jsp&mid=WC0b01ac0580028dd8](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000262.jsp&mid=WC0b01ac0580028dd8).
11. European Medicines Agency - Committees - Committee for Orphan Medicinal Products (COMP) [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000263.jsp&mid=WC0b01ac0580028e30](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000263.jsp&mid=WC0b01ac0580028e30).
12. European Medicines Agency - Committees - Committee on Herbal Medicinal Products (HMPC) [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000264.jsp&mid=WC0b01ac0580028e7c](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000264.jsp&mid=WC0b01ac0580028e7c).
13. European Medicines Agency - Committees - Committee for Advanced Therapies (CAT) [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000266.jsp&mid=WC0b01ac05800292a4](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000266.jsp&mid=WC0b01ac05800292a4).
14. European Medicines Agency - Committees - Paediatric Committee (PDCO) [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000265.jsp&mid=WC0b01ac0580028e9d](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000265.jsp&mid=WC0b01ac0580028e9d).
15. European Medicines Agency - EU Member States - National competent authorities (human) [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general\\_content\\_000155.jsp&mid=WC0b01ac0580036d63](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp&mid=WC0b01ac0580036d63).
16. Matrin Johnston and Mendel Goldstein, European Union Development Cooperation Activities in Nicaragua, EU Blue Book 2008.
17. Anthony Warnock-Smith, Bringing a drug to market in the EU using the new decentralised procedure, Euralex, May 2007; 14-16.
18. Dr. Ute Krahl, BioReg Consultancy, July 2005, [www.bioregadvise.com](http://www.bioregadvise.com).
19. Notice to applicants and regulatory guidelines medicinal products for human use. Volume 2A - Procedures for marketing authorization. Chapter 1 – Marketing Authorisation. June 2013.
20. Notice to applicants and regulatory guidelines medicinal products for human use. Volume 2A - Procedures for marketing authorization. Chapter 2 – Mutual Recognition. February 2007.
21. Notice to applicants and regulatory guidelines medicinal products for human use. Volume 2A - Procedures for marketing authorization. Chapter 4 – Centralized Procedure. April 2006.