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REVIEW ARTICLE

REGULATORY DOSSIER SUBMISSION AND REVIEW PROCESS IN EUROPE

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Abstract:

This article discusses the process of marketing authorization application and its regulated evaluation at agency's end in the region of Europe. The cluster of 28 European Union (EU) member states, 3 European Economic Area (EEA) and European Free Trade Association (EFTA) states make European Union. As European nation consists of larger population, the government is alert regarding safety of the public health in EU. In the Europe, authorization of product is mandatory before they can be placed on the market in order to protect public health and ensure the availability of high quality, effective and safe medicines for European citizens. European drug authorization system offers different routes for such marketing authorization and same is discussed in this article.

Keyword: MA, EU, Data protection, Centralized Procedure, Mutual Recognition Procedure, Decentralized Procedure, National Authorization

INTRODUCTION^(1,2):

The European regulation major objective is to protect public health and at the same time encourage the development of the pharmaceutical industry of the EU. Marketing authorization (MA) (i.e. product license) must be obtained before marketing a medicinal product in the EU. The company (it is more specifically called as “Marketing Authorization Holder” in Europe) which is responsible for placing the medicinal product on the market should be established within the European Economic Area (i.e., Iceland, Liechtenstein, Norway and the Member States of the EU). European regulation has established as well as harmonized many aspects of regulating the production, distribution and safe use of medicines in the EU.

A foremost and significant measure was done in the year 1995 by creating the European Medicines Agency (EMA) and the establishment of a Centralized procedure, through which a single EU

wide evaluation was done for granting of approval of new medicines.

Drug approval process in Europe:

The drug approval process is termed as a regulatory process to get authorization to launch the medicinal product in the market for sale. This activity involves different phases : giving application in order to review for conduct clinical trials, then conducting clinical trials and further application to marketing authorization of drug and post-marketing studies. The applicant files a regulatory dossier to apply for marketing authorization (MA) to agency for evaluation. The filing is done by applying suitable regulatory procedure considering the product type. Each nation has its own regulatory drug authority, which is responsible for enforcing rules, regulations and guidelines which are to be followed by applicant. Through this way regulation for marketing of the drugs is controlled. Regulation procedure of agency is shown in Fig 1.

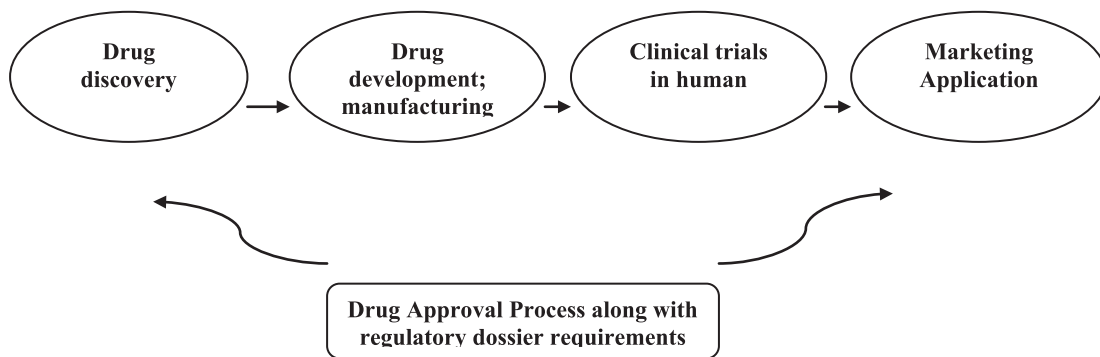


Figure 1 : Regulation procedure

Marketing Authorization Application ⁽²⁾:

Marketing authorization (MA) is defined as the procedure of review and evaluating the dossier to support a medicinal product in view of its requirements for marketing (i.e. registration, license approval) and then issuing a finalized document. The application dossier for marketing authorization is declared as a Marketing Authorization Application (MAA) in the European Union.

Concerned competent regulatory agency monitors Quality, Safety and Efficacy for MA grant.

Only after a marketing authorization (MA) has been issued, medicinal product in the European Union is placed on the market. It can be granted through:

- a) the competent authority of a Member State (National authorizations) or
- b) the Commission for the whole EU (Union authorization).

DATA EXCLUSIVITY/MARKET PROTECTION/GENERICS ^(3,4):

The originators of new drugs have invested a lot of various resources for inventing the new drug. Hence, the regulations are framed in such a way that entry of generic copies of new drug is restricted onto the market for a set time periods. This is done to encourage and reward the innovators.

Data Exclusivity:

It is the duration of time during which an applicant cannot depend on the data in support of another marketing authorization for the purpose of submitting an application, obtaining marketing authorization or placing the product on the market. Health agencies cannot start validation of generics, hybrids or biosimilars during this phase.

Market Protection:

It is the duration of time during which medicinal product cannot be placed on the market even though it has already received a marketing authorization. The medicinal product can be a generic, hybrid or biosimilars.

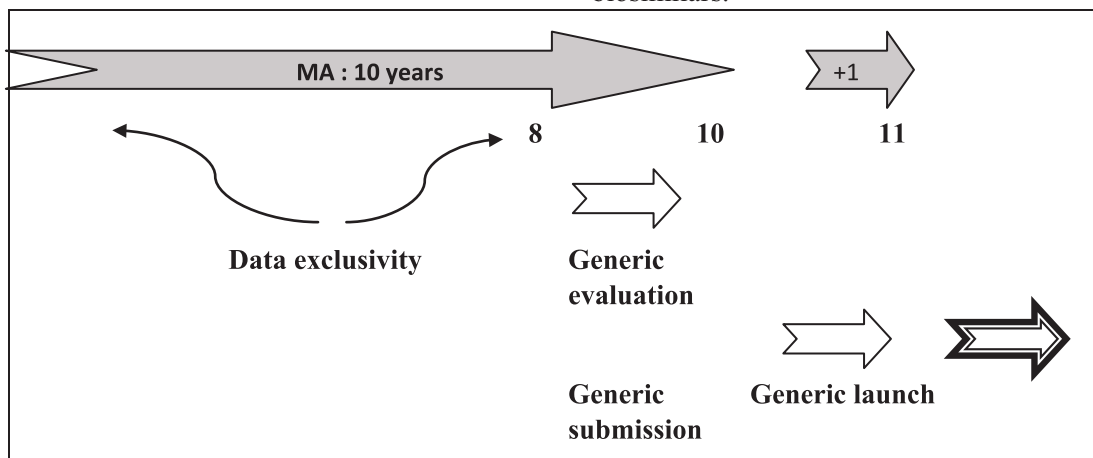


Figure 2 : Data protection

Once an authorized new drug patent expiry happens, manufacturers will wish to introduce generic copies of it in the market to sell their products. However, pre-clinical and clinical data are not submitted, if the bioequivalence with the approved reference drug is demonstrated by the applicant (generic)

The authorization of generic medicinal products is covered by Article 10 of the Human Medicines Directive 2001/83/EC and Article 13 of the Veterinary Medicines Directive 2001/82/EC.

A generic drug is defined as a medicinal product that has:

- the same qualitative and quantitative composition in active substances as the reference product;
- the same pharmaceutical form as the reference medicinal product;

- and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Regulatory submission dossier modules ⁽⁵⁾:

The applicant has to submit regulatory dossier in preferred format for new marketing authorization. All regulatory documents have to be submitted in compliance to the CTD format. The complete guidance on documents requirements for dossier application is presented in volume 2B, NTA, July 2003 edition. Additional guidance is updated on website of European agencies regularly. Five CTD modules are structurally presented in the marketing authorization application. Below is the brief tabulated list of dossier module contents:

Table : 1 - Dossier module contents

Module	Contents	Details
1	EU administrative and prescribing information	Application form Summary of Product characteristics Labelling texts and mock ups Information about the experts Environmental risk assessment Orphan market exclusivity Pharmacovigilance system Risk management plan
2	Summary	Quality Non-clinical overview Non-clinical summary Clinical overview Clinical summary
3	Quality	Body of data References
4	Non-clinical	Study report References
5	Clinical	Study report References

Procedures for marketing authorization of medicinal products in Europe:

The marketing authorization application can be made through four ways as below:

1. Centralized Procedure
2. Mutual Recognition Procedure
3. Decentralized Procedure
4. National Procedure

European Union (EU) ⁽¹⁾:

The EU regulatory systems is one of the most highly regarded reputed systems in the world. The system consists of European parliament, the council of ministers and the European Commission. European Union consists of 28 member states: Austria, Bulgaria, Belgium, Cyprus, Croatia, Czech Republic, Denmark, Estonia, France, Finland, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Latvia, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Spain, Slovenia, Sweden, and the United Kingdom and three countries which are member of European Free Trade Agreement (EFTA) Norway, Iceland and Liechtenstein. These EFTA members are those countries which were not part of the 28 member states as common market. These three EFTA member countries along with 28 EU member states, comprises of the European Economic Area (EEA).

The European Medicines Agency (EMA) is a decentralized agency of the European

Union, located in London. The responsibility of Agency is the scientific evaluation and assessment of medicines developed by pharmaceutical companies for use in the European Union (EU) and applications for European marketing authorizations for both human and veterinary medicines (centralized procedure). Under the centralized procedure, single marketing-authorization application to the Agency is submitted by the applicant. Once marketing authorization is granted by the European Commission, a centralized (or “Community”) marketing authorization is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein and Norway).

This network is what makes the EU regulatory system unique.

Centralized Procedure (CP) ^(6, 7, 8):

As per the regulation (EC) No 726/2004, Centralized procedure is described for marketing application of medicinal products, for which only single application, single evaluation and single authorization is required for marketing medicinal product into entire community market. By this procedure medicinal product can be available into all member states of European Union. The scope of medicinal product for which application is to be made is divided into three parts:

- a) Mandatory
- b) Optional
- c) Generic/Hybrid

a) Mandatory scope:

Medicinal products as per below category fall into the mandatory scope according to EU regulation 726/2004:

- Medicinal products developed by recombinant technology, expression of proteins in prokaryotes and eukaryotes cells & hybridoma and monoclonal antibody methods.
- Medicinal products with a new active substance for the treatment of AIDS, cancer, neurodegenerative disorder, diabetes, auto-immune diseases and other immune dysfunctions and viral diseases.
- Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.

b) Optional scope:

Medicinal products containing other new active substances may, at the request of the applicant, be considered for evaluation under the centralized procedure when it can be shown that the product constitutes a significant therapeutic, technical or scientific innovation, or the granting of a Community authorization is in the best interests of patients at the Community level.

c) Generic/Hybrid:

A generic/hybrid product of a reference medicinal product authorized via the CP has automatic access to the centralized assessment under this scope.

In current scenario, a good number of majorities of new innovative medicines get ahead through the centralized authorization procedure in order to be marketed in the EU.

The schematic procedural timetable for evolution of application is done by EMA is as follows:

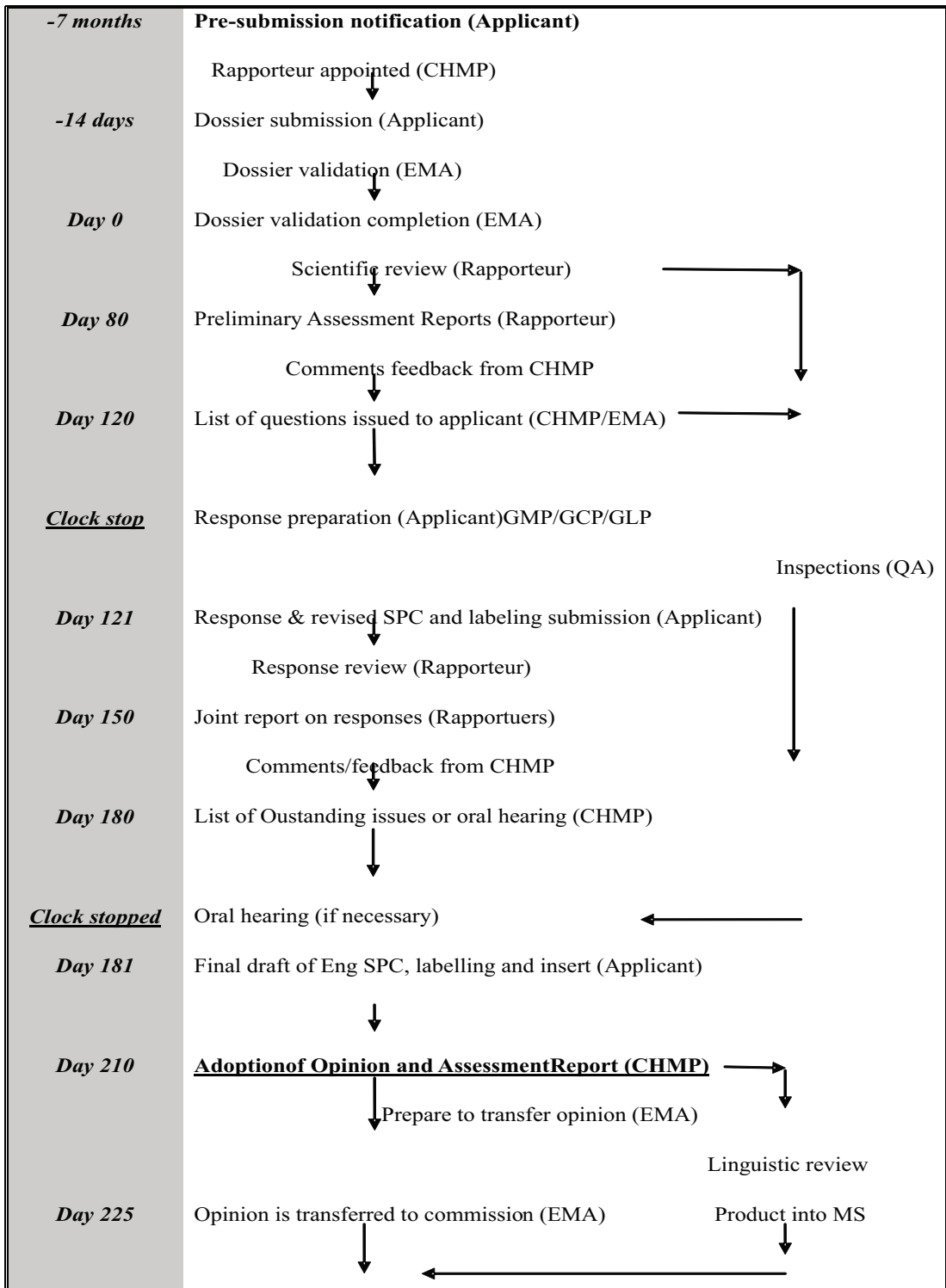


Figure: 3 - Schematic procedural timetable by EMA

Accelerated assessment ⁽⁷⁻¹⁰⁾:

The EU has introduced the accelerated assessment and evaluation in November 2005. The aim for this accelerated assessment is to pace up the regulatory procedure in order to facilitate patients access to new medicines. The request for accelerated assessment and evaluation should be made at least two to three months prior to submitting the marketing-authorization application.

The centralized procedure marketing-authorization application's evaluation can take up to 210 days excluding the procedural clock stops when applicants have to provide additional information. On request, the CHMP can reduce the timeline to 150 days provided if the applicant submits sufficient justification for an accelerated assessment of the MA application.

Article 14 (9) of Regulation (EC) No 726/2004, states that “when an application is submitted for a marketing authorization in respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure”.

Approval of CPMA ⁽⁹⁻¹²⁾:

Assessment of the application by the CHMP is published initially as a summary of Opinion, whether positive or negative.

After the granting of a MA by the EC a more detailed report is published as the EPAR on EMA website.

The EPAR shows the scientific conclusion reached by CHMP at the end of the centralized evaluation process. It is accessible to the public, in which the commercial confidential information is removed. The EPAR gives a summary of the reasons of the CHMP opinion in favour of granting a MA for a specific medicinal product.

EPAR is presented as a sequence of documents and includes: a lay summary, product information (SmPC/PL/label), details about the marketing authorization holder, and discussion about the evaluation carried out at EMA. It comprises based on the review of Committee on the documentation furnished by the applicant & from succeeding discussions held during CHMP meetings. The EPAR is updated throughout the authorization period (life cycle of product) as changes to the original terms and conditions if the authorization (i.e. pharmacovigilance issues, variation, specific obligations) is made. The EPAR also contains a review written in a manner that is understandable to the public.

Mutual Recognition Procedure ^(8, 13-14):

A medicinal product is first authorized by one member state, as per the regulations of its own national procedure. The applicant can seek further authorizations based on that existing MA through a mutual recognition procedure.

The MRP is stated in Council Directive 93/39/EEC. That is, once a drug is approved for marketing authorization (MA) by one member state, the pharmaceutical company can apply for MA in other member states through the MRP.

After getting the first authorization it is easy and quick to get for further member states because medicinal product already exists in European market and it helps to prove that product is therapeutically effective.

The applicant submits identical applications to those member states where marketing authorizations are required.

The member state that reviews the application first is called the 'Reference Member State'.

It notifies other states, called CMS i.e. Concerned Member State. CMS may delay their own evaluations to await assessment by the RMS.

The Reference Member State (RMS) shall prepare or update the assessment report within 90 days of receipt of a valid application. The assessment report together with the approved summary of product characteristics, labeling and package leaflet shall be sent to the Concerned Member States and to the applicant by RMS.

The decision of the RMS is forwarded to the CMS.

If the CMS reject mutual recognition, the subject is referred to the Committee for Medicinal Products for Human Products (CHMP) of EMA for arbitration. EMA forwards its opinion to the EC, which makes the final decision.

Table : 2 - Schematic presentation of mutual recognition procedure

90 days prior to CMS	Applicant requests RMS for AR and procedure number allocation.
Day -14	Applicant submits the dossier to CMS. RMS do circulation of the AR including SmPC/PL/Label to CMSs. Validation of the application is done by CMSs.
Day 0	RMS starts the procedure.
Day 30	CMSs send their comments to the RMS, CMSs and applicant.
Day 40	Applicant sends the response document to CMSs and RMS.
Day 48	RMS evaluates and circulates a report on the applicant's response document to CMSs.
Day 55	CMSs send their remaining comments to RMS, CMS and applicant.
Day 55-59	RMS & Applicant in communication to close the procedure or to submit response.
Day 60	RMS closes procedure if no CMS comments at Day 55.
Day 60-90	Used only if CMS had Day 55 comments.
Day 68	RMS evaluates response and circulate AR.
Day 75	CMS send remaining comments if any.
Day 85	Final CMS position.
Day 90	CMSs give notification to RMS and applicant of final position. "If consensus is reached, then RMS closes the procedure. and if not reached then the points for disapproval submitted by CMS(s) are referred to Co -ordination group for Mutual Recognition and Decentralised Procedures – Human (CMD(h)) by the RMS within 7days".
Day 150	For procedures referred to CMD(h): If consensus is reached at the level of CMD(h), procedure closed and If not reached then, RMS refers the matter to CHMP for arbitration.
5 days after	High quality national translations of SmPC/PL/Label are sent to CMSs by applicant.

Decentralized procedure ^(8, 13, 15):

Directive 2004/27/EC regulates Decentralized procedure that came into effect in the European Union in 2005. The primary aim of this procedure is to obtain marketing authorizations in several Member States, even though there is no existing marketing authorization in the European area. For medicinal products not falls within the mandatory scope of the centralized procedure, the applicant may request one or more concerned Member State(s) to approve a draft assessment report, labeling, summary of product characteristics (SmPC), and package leaflet as proposed by the chosen reference member state. An application is submitted to the competent authorities of the Reference Member State and the concerned member state(s), together with the data and particulars referred to in Articles 8, 10, 10a, 10b, 10c, and 11 of Directive 2001/83/EC.

Steps involved in Decentralized Procedure:

The applicant submits an application to the respective health agencies of each member states, where the applicant wants to acquire a marketing authorization. In contrast to MRP, in DCP the applicant may assign a country to act as the Reference Member State. DCP slot booking procedure is done by applicant. The RMS selection procedure is depended on various criteria like previous experience, workload, interests of the applicant and acceptance of the applied dossier by the RMS.

The RMS will start to assess dossier application once both the RMS and all the CMS(s) agree on validity of procedure. The RMS then prepares and forward a preliminary Assessment Report on the submitted dossier to the CMS(s) and the applicant in a period of 70 days based on assessment. The CMS(s) gives their comments. The RMS will forward all observation and remarks received from the CMS(s) to the applicant on day 105 and stop the clock if required, till the time that the applicant prepares a response document for the comments sent. The RMS prepares a Draft Assessment Report on day 120 and if a consensus has been reached between the CMS(s) and the RMS; the procedure may get closed. Otherwise the CMS(s) has 90 more days to approve the Draft Assessment Report and other documents.

RMS and CMS(s) authorities agree to a decision within 30 days after acknowledgement of their agreement to the Assessment Report and other documents during the national phase. A national marketing authorization will be issued in the RMS and each of the CMS(s) after the positive agreement.

For DCP, it is very much required that competent authorities ensure that assessment reports are released on time in accordance with the DCP timetable. This will be possible by good communication between the applicant and the Reference Member State (RMS).

Competent authorities should do their best endeavor to avoid delay in the start of the procedure.

Table : 3 - Schematic presentation of decentralized procedure

14 days prior	Applicant discusses with RMS. RMS allocate procedure number.
Day -14	Dossier submission to RMS/CMSs
<u>Assessment Step I</u>	
Day 0	RMS starts the procedure.
Day 70	RMS forwards PrAR + comments on SmPC/PL/Label to CMSs & Applicant.
Day 100	CMSs send comments to RMS, CMSs & Applicant. RMS may consult CMS to close procedure.
Day 105	RMS closes the procedure or stops the clock. To allow applicant to respond the comments and supplementation of dossier.
Clock off period	Applicant submit the draft responses to RMS/CMSs. Final responses are sent within a recommended period of 3 months, which could be extended further 3 months if justified.
<u>Assessment Step II</u>	
Day 120 (Day 0)	RMS sends draft AR/SmPC/PL/Label to CMSs + Applicant.
Day 145 (Day 25)	CMS sends comment to RMS/CMSs/Applicant.
Day 150 (Day 30)	RMS may close procedure if consensus reached. Proceed for 30 days National MA Grant.
Day 160	Applicant submits response to RMS/CMSs.
Day 180 (Day 60)	If consensus reached then RMS closes the procedure. If not reached then; RMS prepares AR on outstanding issues.
Day 195	A break out session. CMSs send final comments.
Day 195-210	RMS consults with the CMSs / Applicant to discuss the remaining comments raised.
Day 210 (Day 90)	Closure of the procedure. Proceed for 30 days National MA Grant. or If consensus not reached then referral to the Coordination Group.
Day 270	Final position adopted by Co-ordination Group with referral to CHMP/CVMP for arbitration in case of unsolved disagreement.
National Step	Applicant sends high quality national translations for SmPC/PL/Label.
7 day after EOP	

DCP is a modernized procedure with the possibility for shorter approval times in simple cases. The DCP is a single procedure that could end at different stages taking into account:

- Harmonization of originator SmPCs;
- The quality of the file;
- The assessment report;

It is possible to end the procedure at any time point during the procedure if agreement is reached.

National Authorization Procedure^(8,16):

Apart from the products that fall within the scope of Community Authorizations, all other products can only be licensed via application to the Competent Authorities of individual Member States. However, through the use of either decentralized or mutual recognition procedures it is possible to obtain authorizations on the basis of a dossier assessment conducted by a single Member State.

If the applicant want to get the marketing authorization in only one member state then marketing authorization application should be made to national competent authority of respective member state. In such application while taking the national marketing approval, the medicinal product should not be approved in other member state of European area under same sponsor.

Since the approval for the marketing of product is granted directly by the respective member state authority; sponsor

will get faster approval compared to other procedures.

The competent authority is responsible for reviewing and granting MA. This procedure is applied for new active substances which are not mandatory under Centralized procedure. Most of the regulatory agency requires 210 days for review and approval of MAA; however it may vary slightly from agency to agency of different member states followed by national phase for translation activities.

In current scenario, national procedure application is made very limited in number. In situation when a slot to run DCP with the RMS is not available or in cases when RMS does not want to access the complex molecule as a part of DCP, national procedure is applied. Usually in such instance, the applicant gets approval of medicinal product nationally and then further extends the MA in other member states via Mutual Recognition Procedure.

Well-established Medical Use products⁽⁴⁾:

The EU will accept marketing authorization applications without supporting pre-clinical and clinical studies, if it can be demonstrated that the active substances have been in well-established use in the Community for at least 10 years, with sufficient efficacy and an acceptable level of safety. This route of application can be appropriate for many common over-the-counter (OTC) products. Safety and efficacy is supported by providing copies

of published scientific literature as part of the submission; that is, the submission relies on safety and efficacy data available in the public domain, as opposed to confidential data from authorized applications that is the cornerstone of generic applications.

Renewal ⁽¹⁷⁻¹⁸⁾:

After marketing authorization expiry if applicant wants to continue the sale of the medicinal product into the market; then renewal of the marketing authorization is a must act. For the renewal of the marketing authorization, applicant must apply before nine months of the expiry of medicinal product in market. In this regard, it is noted that the renewal should take place upon the expiry of the period of five years and that decision of granting renewal is based on the consolidated file submitted by MAH for this purpose, that the benefit-risk is positive.

A premature submission for renewal may not be sufficiently up to date for the Commission/Competent Authorities to adopt a decision on the renewal.

If there is agreement at the end of the procedure that the benefit/risk of the product remains favorable and there are no pharmacovigilance issues that would require a further renewal, the MA may be granted unlimited validity.

Sometimes it happens that there are changes in the product information, the renewal documents issued will include the

SmPC and harmonized leaflet and label texts.

On the basis of the overall re-evaluation of the risk-benefit balance, the CHMP may recommend to grant unlimited validity to the Marketing Authorization, or to require one additional five-year renewal. The grounds on which the CHMP may decide to require an additional renewal will be duly justified and mostly it is related to pharmacovigilance. For example, exposure of an insufficient number of patients to the medicinal product.

Conclusion:

The legislations, directives and guidelines as laid by European Commission and CMD (h) are to safeguard public health, safety and patients' well-being. The health agency of various member states follows strict vigilant evaluation of the regulation dossier submitted by the applicant to obtain a marketing authorization. The MAA in Europe can be obtained through any of the regulatory procedure (CP, DCP, MRP and NP) on the basis of application scope. Renewal procedure is filed before nine months of MA expiry if the applicant wants to continue the sale of medicinal product.

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- Abbreviation:**
- CTD: Common Technical Document
- CHMP: Committee for Medicinal Products for Human Use
- CMD (h):Co-ordination group for Mutual recognition and Decentralized procedures – human

EU: European Union

EEA: European Economic Area

EFTA: European Free Trade Association

EOP: End of Procedure

EMA: European Medicines Agency

EPAR: European Public Assessment
Report

PrAR: Preliminary Assessment Report

PL: Patient Leaflet

SmPC: Summary of Product
Characteristics

MA: Marketing Authorization

MAH: Marketing Authorization Holder