Available online on 15 Sept. 2019 at https://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

Published by Diva Enterprises Pvt. Ltd., New Delhi
Associated with Delhi Pharmaceutical Sciences & Research University

Review Article

A New Drug Approval Process in Europe: A Review

Krishnasis Chakraborty*

Department of Quality Assurance, Al-Ameen College of Pharmacy, Lalbagh road, Bangalore, India -560027

Abstract

Current constrain of Regulatory Affairs reveals diverse countries need to follow different regulatory requirements for Marketing Authorization Application (MAA) approval of new drugs. In this present exertion, study expresses the drug approval process and Regulatory requirements according to European Medical Agency (EMA) (1).

Keywords: Drug Approval, Regulatory Requirements, EMA, Marketing Authorization Application (MAA), CHMP, CMS, RMS.

Article Info: Received 26 July 2019; Review Completed 08 Sept. 2019; Accepted 09 Sept. 2019

Cite this article as:
Chakraborty K. A New Drug Approval Process in Europe: A Review. International Journal of Drug Regulatory Affairs [Internet]. 15 Sept 2019 [cited 15 Sept 2019]; 7(3):21-29. Available from: http://ijdra.com/index.php/journal/article/view/332

DOI: 10.22270/ijdra.v7i3.332
*Corresponding author Tel.: +91-9632703191;
E-mail address: krishnasis07p@gmail.com (K. Chakraborty)

1. Introduction

A Patron has multiple possibilities when seeking approval to market a new drug in European countries, a National Authorization Procedure, a Decentralized Procedure, a Mutual Recognition Procedure or a Centralized Procedure. Products that must use the centralized procedure include the following:

- ❖ All biologic agents or other products made using high-technology procedures
- ❖ Products for HIV/AIDS, Cancer, Diabetes, Neurodegenerative diseases, Auto-Immune and Other Immune Dysfunctions and Viral diseases
- ❖ Products for Orphan conditions

Presently different countries must follow different regulatory requirements for sanction of new drug. Marketing Authorization Application (MAA) a single regulatory approach is valid to various countries is almost a difficult task. Therefore, it is essential to have knowledge about regulatory requirement for MAA of each country.

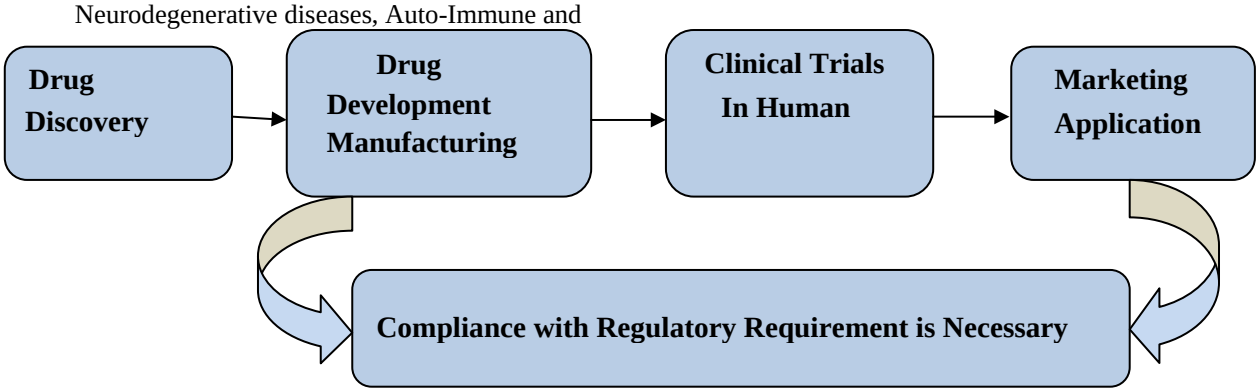


Figure 1. Regulation of Drug Approval Process (1-7)

This report focuses on the centralized procedure, with a brief overview of the other three procedures provided below.

National authorization procedure: Each country within the Europe has its own procedures for authorizing a marketing application for a new drug. A sponsor can consult the website of the regulatory agency in each

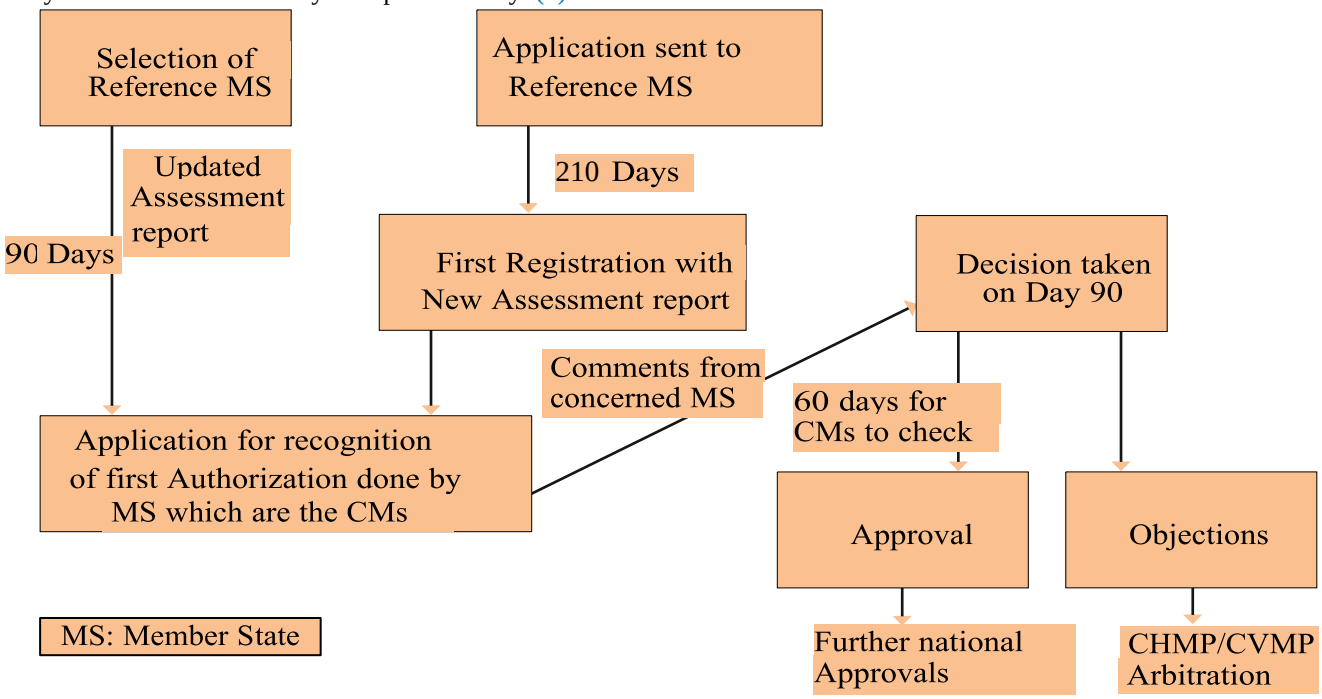
country in which it is interested in obtaining marketing approval to obtain details of the approval process.

A sponsor can also seek approval of several European countries simultaneously using the decentralized or mutual recognition procedure. (8)

Decentralized procedure: Products that fall outside the scope of the European Medicines Agency (EMA) with regard to Centralized Procedures, a sponsor can submit under the Decentralized Procedure. Using this process, a sponsor can apply for simultaneous authorization in more than one European country for products that have not yet been authorized in any European country. (9)

2. Mutual recognition procedure

With the Mutual Recognition Procedure, a product is first authorized by one country in the Europe in accordance with the National Procedures of that country. Later, further Marketing Authorizations can be hunted from other European countries, who rather than conducting their own review, agree to identify the decision of the first country. (10)



CMS: Concerned Member State

Figure 2. Mutual Recognition Procedure for Drug Approval Process in EU (11)

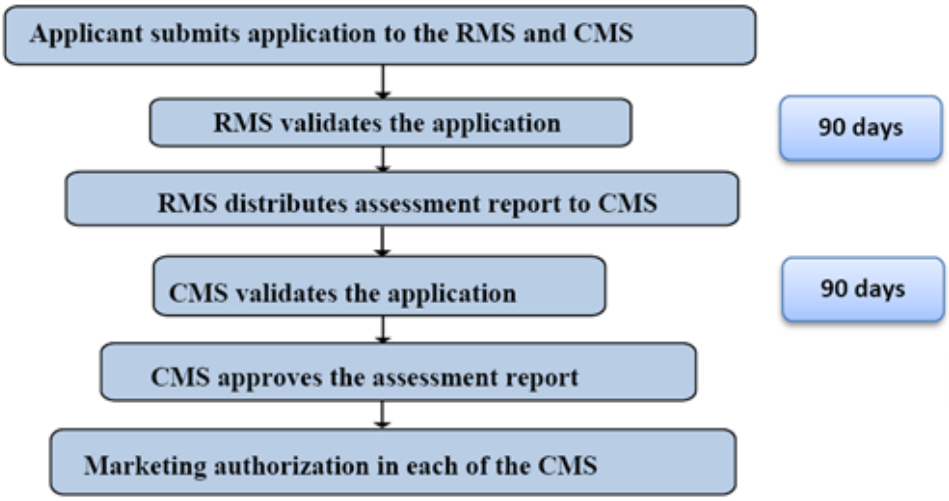


Figure 3. Mutual Recognition Procedure for Drug Approval Process in EU (7-9)

3. Centralized procedure

European drug approvals are overseen by the European Medicines Agency. The EMA is a decentralized body of the EU, with headquarters in London, England. It is responsible for the scientific evaluation of applications for authorization to market medicinal products in Europe (via the centralized procedure).

Marketing applications for drugs for use in humans are evaluated by the Committee for Medicinal Products for Human Use (CHMP).

Products that are eligible for review under the centralized procedure must meet the following criteria:

Biologic drugs developed by recombinant technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, and hybridoma and monoclonal antibody methods

- medicinal products containing new active substances for the following indications: AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, and viral diseases
- orphan medicinal products

Other new active substances may, at the request of the applicant, be accepted for consideration under the centralized procedure when it can be shown that the product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a Community authorization is in the best interests of patients at the Community level. (12)

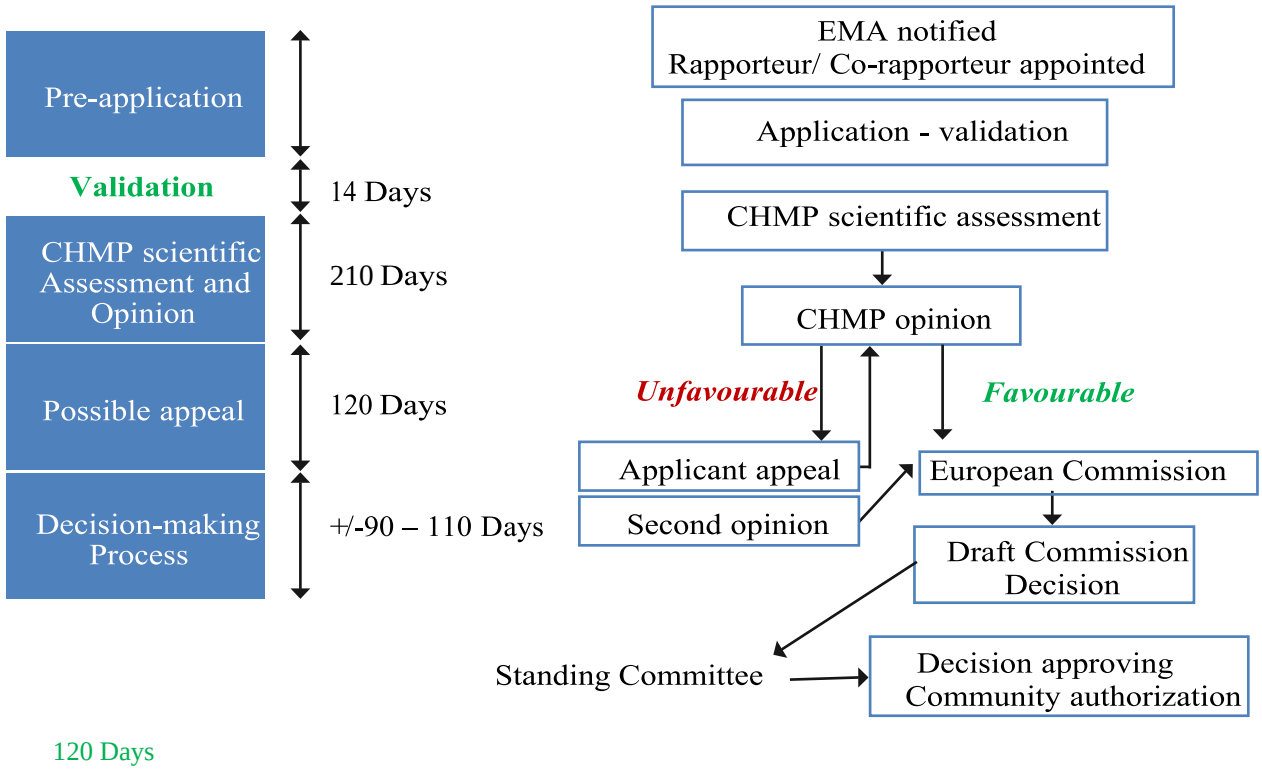


Figure 4. Centralized Procedure for Marketing Authorization in EU (12)

The review process

Companies wishing to market a medicinal product that is eligible for the centralised authorisation procedure, submit their application directly to the European Medicines Agency (EMA). The EMA is responsible for the validation and scientific evaluation of the application.

The EMA's Committee for Medicinal products for Human Use (CHMP) carries out a scientific assessment of the application and give a recommendation on whether the medicine should be authorised or not. A favourable opinion is accompanied by a draft summary of the product's characteristics, the package leaflet, and the proposed text for the packaging.

The time limit for the evaluation procedure is 210 days, subject to extensions if additional questions need to be addressed. Within 15 days of the adoption, the EMA will forward its opinion to the European Commission to start the decision-making phase.

Authorisation

Within 15 days a draft implementing decision is sent by the Commission to the Standing Committee on Medicinal Products for Human Use, allowing for its scrutiny by EU countries. These have fifteen days to return their linguistic comments, and 22 days for substantial ones. Once a favourable opinion is reached, the draft decision is adopted via an empowerment procedure. The adoption of the decision should take place within 67 days of the opinion of the EMA.

The Commission's Secretariat-General then notifies the decision to the marketing authorisation holder. The decision is subsequently published in the Union Register.

Marketing authorisations are initially valid for five years. Applications for renewal must be made to the EMA at least six months before this five-year period expires.

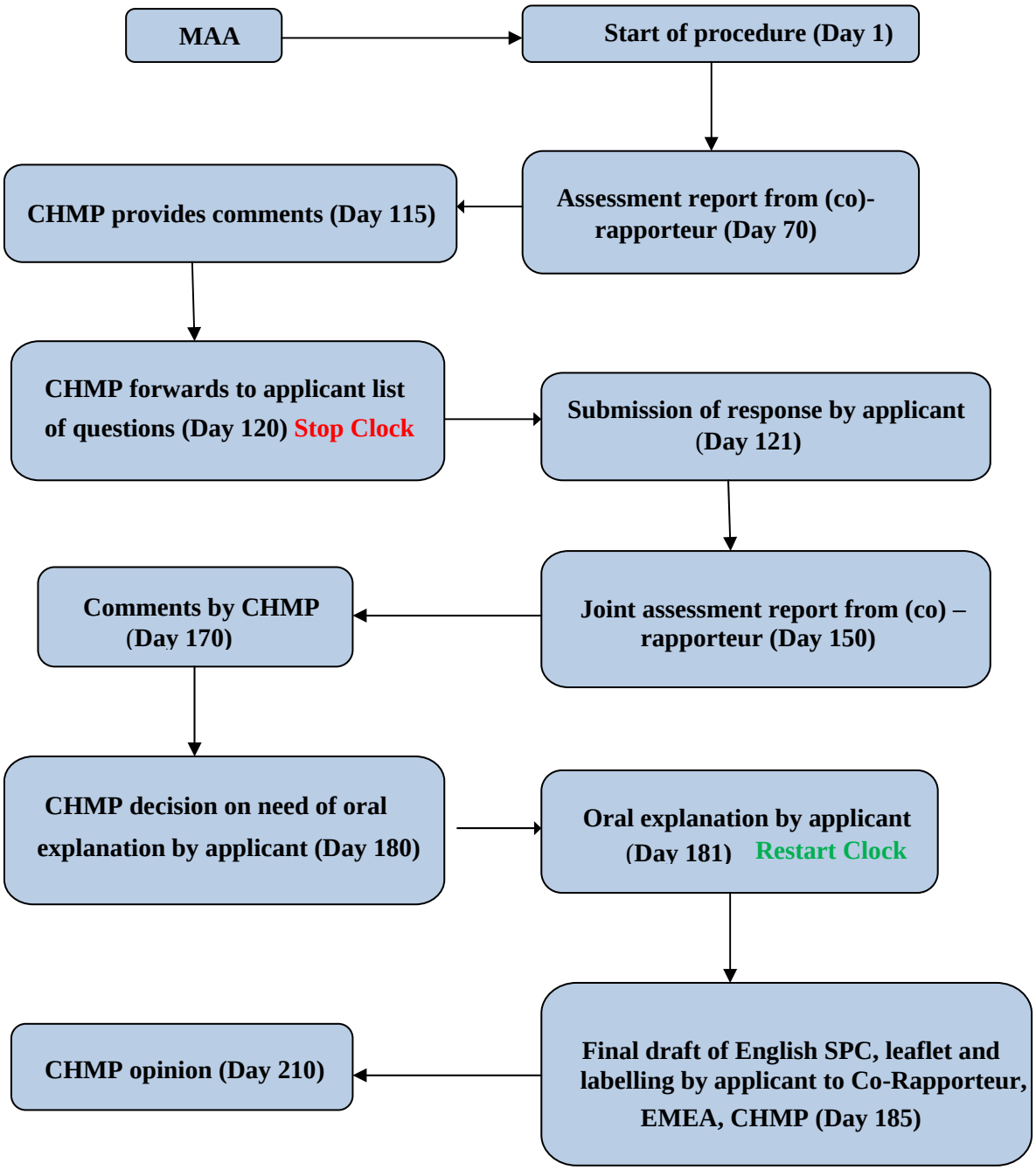


Figure 5. Centralized Procedure for Marketing Authorization in EU (7, 11-13)

4. Decentralized Procedure

To receive marketing authorizations in numerous member states, the centralized procedure is not mandatory; in such case the decentralized procedure is to be used. An application is submitted to competent authorities of each of the member states, where a marketing authorization is to be required. The information like quality, efficacy, safety, administrative information shall be submitted and a list of all Concerned Member States (CMSs) and one-member state to act as Reference Member State (RMS). A draft assessment report on the medicinal product is prepared and the CMS and the RMS confirm the application within a time frame of 14 days. The RMS prepare draft summary of product characteristics, labelling and package leaflet within 120 days. This report can be approved within 90 days.

However, if a medicinal product is supposed to cause potential serious risk to public health, CMS will inform to other CMS, RMS and applicant and further conclusion in this regard is taken within 30 days. Within 60 days of the announcement of the points of disagreement, all member states reach to an agreement on the action to be taken.

After a conclusion to an agreement of the member states, the RMS records the agreement and informs to the applicant.

However, if the member states could not reach an agreement, then CHMP intervenes and take a final decision keeping in view of the written or oral explanations of the applicant. (13)

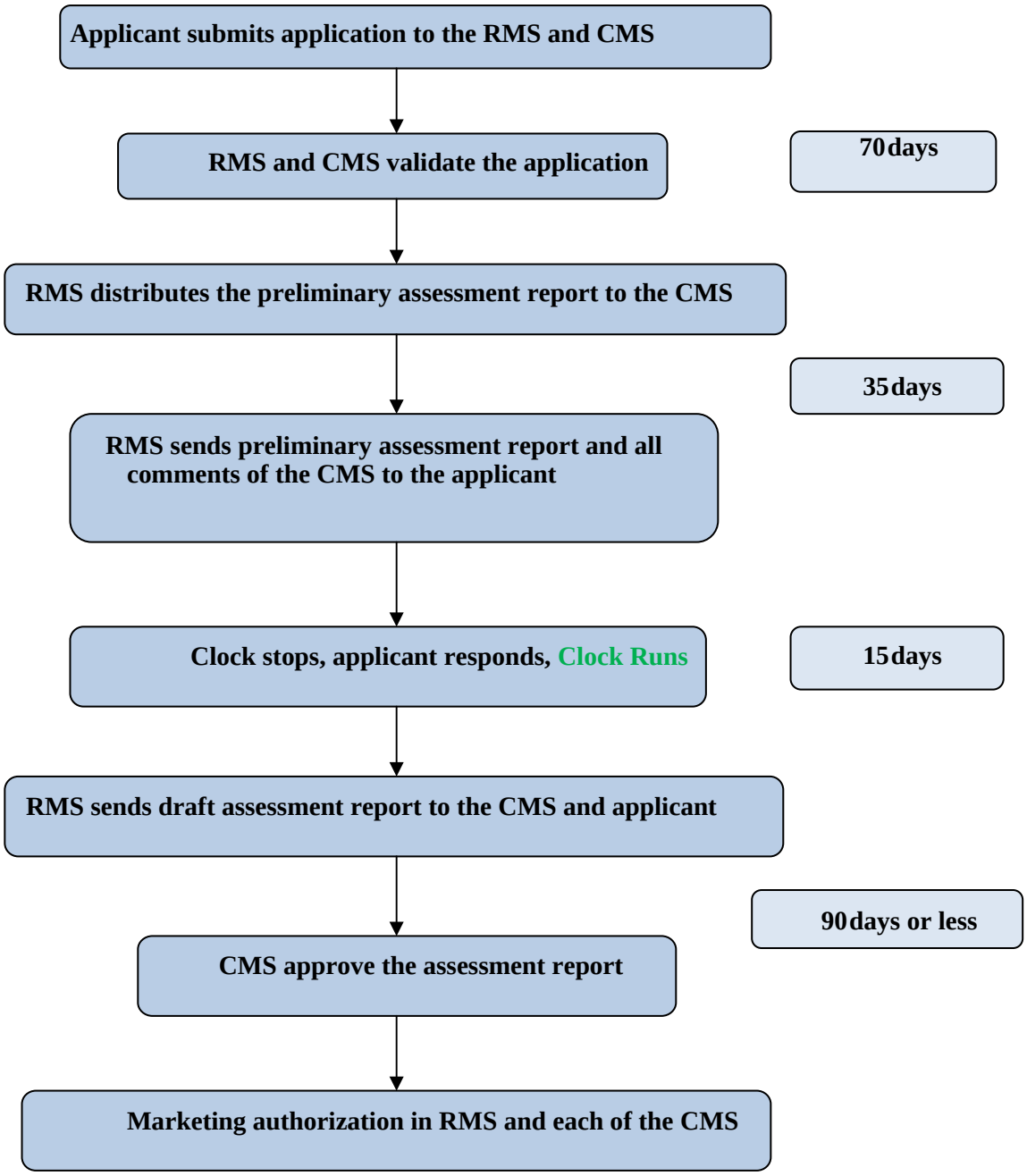


Figure 6. Decentralized Procedure for Marketing Authorization in EU (7, 12-13)

5. Pre-submission process

At least seven months prior to submitting a marketing authorization application (MAA), a sponsor must notify the EMA of their intention to submit and the month of submission. This pre-submission involves a variety of information including a document outlining the reasons the sponsor believes the application should fall under the centralized procedure. The EMA will consider the pre-submission and notify the sponsor of its decision regarding acceptance of the MAA.

Selection of rapporteur/co-rapporteur

The rapporteur is a country-specific regulatory authority within the EU. The rapporteur (reviewer) and corapporteur (if needed) are identified from the CHMP members. The selection of the rapporteur is based on objective criteria, to ensure objective scientific opinion and the best use of available expertise at the EMA.

The role of the rapporteur is to perform the scientific evaluation and prepare an assessment report to the CHMP. If a co-rapporteur is involved, the co-rapporteur will prepare an independent assessment report, or provide a critique of the rapporteur's report, at the discretion of the CHMP.

The process for assigning the rapporteur/co-rapporteur is usually initiated at the CHMP meeting following the receipt of a letter of an intention to submit. The sponsor

is notified of the rapporteur/co-rapporteur once the EMA has deemed a submission admissible.

Product naming

A sponsor's name for the drug product should be the same in all countries within the EU, except where it violates trademark rules. The sponsor should submit the proposed name in advance (usually four to six months, and not more than 12 months) of the marketing authorization application.

Marketing authorization application—submission components

An MAA should be submitted in the EU-CTD (Common Technical Document) format. The five main modules of an MAA are detailed in Exhibit 3.

Marketing authorization application modules

Table 1 Marketing Authorization Application model in EU (14-15)

Module	Content	Details
1	EU administrative and prescribing information	*Application form *Summary of product characteristics *Labelling text and mock-ups *Information about the experts *Environmental risk assessment *Information relating to orphan- market exclusivity *Description of the pharmacovigilance system *Risk management plan
2	High-level summaries	*Quality *Non-clinical overview *Non-clinical summary (pharmacology, pharmacokinetics, toxicology) *Clinical overview *Clinical summary (Biopharmaceutics, clinical pharmacology, efficacy, safety, study synopsis)
3	Quality documentation	*Body of data *References
4	Non-clinical documentation	*Study reports *References
5	Clinical documentation	*Tabular listing of studies *Study reports *References

In addition to the information cited in Exhibit 3, applicants must submit evidence of establishment within the European Economic Area (EEA) and documentation that shows their ability to uphold MAA obligations (such as monitoring pharmacovigilance, identifying a qualified person in the EEA for batch release, and providing a contact person for product defects and product recalls).

Validation

The first step of the review process is for the EMA to assess the MAA to determine whether the reviewers require additional information, data or clarification in order to conduct the review. Once the MAA is deemed valid, the CHMP establishes the timetable for scientific evaluation.

Scientific evaluation

The rapporteur/co-rapporteur conducts the scientific evaluation. As outlined in Exhibit 4, the EMA ensures the CHMP completes the full review within 210 days (less any stops in the timeline for the sponsor to respond to CHMP questions).

Standard timetable for review of a centralized application

Table 2 Standard Timetable for review procedure in EU (16-17)

Day	Action
1	Start of the procedure.
80	Receipt of assessment report or critique from rapporteur and co-rapporteur by CHMP members and EMA. EMA sends assessment report to applicant making clear it only sets out preliminary conclusions and is sent for information only and does not yet represent the position of the CHMP.
100	Rapporteur, co-rapporteur, other CHMP members and EMA receive comments from CHMP members, including peer reviewers.
115	Receipt of draft list of questions (including CHMP recommendation and scientific discussion) from rapporteur and co-rapporteur, as discussed with peer reviewers, by CHMP members and EMA.
120	CHMP adopts list of questions as well as overall conclusions of scientific data to be sent to applicant by CHMP. Clock stops on timetable.

121*	Submission of the responses, including revised summary of product characteristics, labelling, and package leaflet texts in English, restart of clock.
	After receipt of responses:
150	Joint response (assessment report) from rapporteur and co-rapporteur received by CHMP members and EMA. EMA sends joint-assessment report to applicant making clear it only has preliminary conclusions and does not yet represent position of CHMP.
170	Deadline for comments from CHMP members to be sent to rapporteur and co-rapporteur, EMA and other CHMP members.
180	CHMP discussion and decision on the need for adoption of a list of "outstanding issues" and/or an oral explanation by applicant. If oral explanation needed, clock is stopped to allow time for preparation.
181	Restart clock and oral explanation (if needed).
181-210	Final draft of English summary of product characteristics, labeling, and package leaflet sent by applicant to rapporteur and co-rapporteur, EMA and other CHMP members.
By 210	Adoption of CHMP Opinion & CHMP Assessment Report (and timetable for provision of product information translations).
	After adoption of CHMP opinion:
215 at the latest	Applicant provides EMA with summary of product characteristics, labeling, and package leaflet in 20 languages. EMA circulates draft to member states for review.
232 at the latest	Applicant provides EMA with final translations of summary of product characteristics, labelling, and package leaflet in 20 languages, taking into account comments received from member states by day 229.
By 237	Transmission of opinion and annexes in all EU languages to applicant, commission, members of standing committee, Norway and Iceland.
By 246	Applicant provides EMA with one final full-colour mock-up of outer and inner packaging for each pharmaceutical form.

Accelerated assessment

In cases where products are considered to be of major public health interest, a sponsor can apply for accelerated assessment of their application. If granted, the 210-day review procedure is shortened to 150 days.

Committee request for additional information

Once the CHMP has the preliminary assessment reports or critique from the rapporteur and co-rapporteur, it prepares a list of any outstanding issues the sponsor must address. A consolidated list of questions identifying "other concerns" and/or "major objections" is prepared. These are sent to the sponsor with the CHMP recommendation and scientific discussion. The clock will then be stopped (day 120).

The CHMP can make one of two recommendations:

1. The product could be approved provided that satisfactory answers are given to "other concerns," and that the indications, the elements of the summary of product characteristics, and other conditions for marketing are amended as outlined in the list of questions.
2. The product is not approvable since there are "major objections."

The sponsor has three months from the date of receiving the questions to respond to the CHMP. Sponsors are permitted to request a three-month extension, if required.

Oral (or written) explanation

The CHMP will discuss the joint-assessment report and comments of other CHMP members. The CHMP may identify additional issues which the sponsor must address in writing or during an oral explanation. If a sponsor wishes to make an oral presentation, it usually has one month to prepare.

After the oral explanation and the subsequent CHMP discussion, the rapporteur will provide feedback to the sponsor before a formal vote takes place. If the outcome appears it will be positive, a discussion may be held regarding key amendments to the product characteristics summary and draft follow-up measures or conditions to the marketing authorization. If the outcome appears it will be negative, possible procedural options will be discussed with the sponsor.

CHMP opinion

On or before days 210, the CHMP will adopt its final opinion after the final recommendation of the rapporteur. The CHMP opinion, wherever possible, is reached by consensus. If a consensus cannot be reached, the majority opinion will hold (i.e., favourable votes by at least half the members plus one).

Favourable opinion: The sponsor can proceed to preparing the drug for marketing launch.

Unfavourable opinion: The sponsor is informed that the application does not satisfy the criteria for marketing authorization.

Follow-up to the CHMP opinion

Within five days after the CHMP opinion is delivered, the sponsor must provide to the EMA, in the 20 languages of the EU, a summary of product characteristics, the product labelling and the package insert. By day 22 after the final opinion, final translations are due, having taken into account comments received from member states by day 19. A final full-colour mock-up of outer and inner package labelling for each pharmaceutical form is due to the EMA by day 36 after the adoption of the CHMP opinion.

European public assessment report

After authorizing a marketing application, the EMA will publish the assessment report, "EPARs for authorised medicinal products for human use". A sponsor has an opportunity to comment on any issues that it believes are confidential and provide supporting justification. This document is made available from the date of the Commission decision to grant the marketing authorization.

Table 3 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.

6. Conclusion

The Drug approvals in the Europe are most demanding in the world. The primary purpose of the rules governing medicinal products in Europe is to safeguard public health.

The Drug endorsements in the Europe are the most challenging in the world. The primary purpose of the rules governing medicinal products in Europe is to precaution public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trailed, and manufactured in accordance to the guidelines so that they are safe and patient's well-being is protected.

Pharmaceutical company should keep a close eye on the changing regulation and should consult with regulatory consultant for proper filing, so that they can enter without any hurdles.

Acknowledgements

I would like to express my gratitude to International Journal of Drug Regulatory Affairs who gave me the opportunity to publish the article.

Financial Disclosure statement: The author received no specific funding for this work.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

References

1. Rick NG., Drugs from discovery to approval. John Wiley & Sons, New Jersey; 2015.
2. IRA R Berry, Robert P Martin, editors. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare: 45; 2019.
3. Kuhlmann J. Int. Journal of Clinical Pharmacology and Therapeutics. 1999; 37(12): 575-83.
4. Bhatt A. Indian Journal of Pharmacology. 2004; 36(4): 207-8.
5. CDER Guidance: A review for OCRA US RAC Study [Internet]. CDER; 2018 May 25 [cited 2018 May 25]. Available from: https://www.fda.gov/cder/regulatory/applications/
6. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Med. J. 2004; 181:293-4.
7. Krishnasis Chakraborty, Yadav K. Drug approval process in US, Europe and India and its regulatory requirements: A Review. International Journal of Drug Regulatory Affairs [Internet]. 2018 Sept. 15 [cited 2018 Sept. 15]; 6(3):31-9. Available from: http://ijdra.com/index.php/journal/article/view/266
8. European Commission: The Notice to Applicants; Volume 2A; Procedures for marketing authorization [Internet]. EC; 2018 Mar 15 [cited 2018 Mar 15]. Available from: http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_ chap1_2005- 11
9. EMA. Guideline on non-clinical local tolerance testing of medicinal products, EMEA; 2015 [Internet]. EMA; 2018 Jan 10 [cited 2018 Jan 10]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/
10. Ghalamkarpour A. Marketing Authorization Procedures in the European Union - Making the Right Choice [Internet]. 2009 Dec [cited 2018 Jun 10]. Available from: http://www.lsnewscr.sgs.com/lsnewscr/lsnewscr-decemberissue/ Marketing
11. Source: European Commission, Pharmaceuticals in the European Union [Internet]. 2019 Jan 7 [cited 2019 Jan 7] Available from: http://ec.europa.eu/enterprise/newsroom/cf/document.cfm?action=display&doc_id=1684&userservice_id=1&request.id=0
12. Source: European Commission, Pharmaceuticals in the European Union [Internet]. 2019 Jan 07 [cited 2019 Jan 07] Available from: http://ec.europa.eu/enterprise/newsroom/cf/document.cfm?action =display&doc_id=1684&userservice _id=1& request.id=0
13. Kashyap UN, Gupta V. Raghunandan H V. J. Pharm. Sci. & Res. 2013; 5(6): 131-6.
14. Jawahar N, Shrivastava N, Ramachandran, Priyadharshini B R. J. Pharm. Sci. & Res. 2015; 7(4): 219-25.
15. Source: International Conference on Harmonisation. Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 (R3) [Internet]. 2004 Jan 13 [cited 2018 Dec 20]. Available from: http://www.ich.org/LOB/media/MEDIA554.pdf
16. Target dates for the submission of responses are published on the EMA website [Internet]. 2019 Jan 05 [cited 2019 Jan 05]. Available from: (http://www.ema.europa.eu/htms/human/submission/submission.htm)
17. Source: European Commission. Volume 2A, Procedures for marketing authorisation. Chapter 4 Centralised Procedure [Internet]. 2006 Apr 01[cited 2018 Dec 22]. Available from: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/a/chap4rev200604%20.pdf