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Review Article

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Overview of Drug Approval Process and Post Approval Changes in Europe

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Abstract

The European Medicines Agency (EMA) is facilitate development and access to medicine, evaluating applications for marketing authorization, monitoring the safety of medicines across their lifecycle and providing information to healthcare professionals and patients.

In order to obtain a marketing authorization in Europe, a medicine must meet a number of criteria before it can be filed with the European Medicines Agency (EMA). This article is looks at the EMA's Drug approval process and post approval changes. The decentralized regulatory body, or EMA, is in charge of overseeing the safety of food and drug (pharmaceutical products) in Europe. The applications are examined, and member state looks over the safety and effectiveness data before approving the drug. EU establishes 4 different drug approval processes:

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

The goal of the current study is to clarify the function of post-approval change management in preventing non-compliance. The current study has concentrated on locating the current regulations and practices in this field and comprehending the fundamental ideas for post approval compliance for licenses relevant to marketing permission. Though change management is essential to a pharmaceutical's lifespan that is the study's main finding. However, the expense of compliance has escalated due to a lack of a clearly defined framework and a lack of understanding of the same, which has led to step-motherly treatment being applied to compliance and license maintenance.

Conclusion

Europe has the highest thought-due approval rates worldwide. The European Medicines Agency (EMA) aims to guarantee that patients in the EU have access to medicines that are of the highest caliber, are reliable, and are secure. Public regulatory agencies have the responsibility of ensuring that pharmaceutical firms follow the law. In order to ensure patient safety and well-being, laws mandate that pharmaceuticals be created, tested, tracked, and manufactured in compliance with the standards. A guideline, in addition to the European legislation that defines variation types, gives out a harmonized list of anticipated variations with categorization codes. A defined list of variations for European

A MA has existed since 1998. Legislation has been amended on a regular basis, and the most recent amendment, in August 2013, made implementation mandatory at the national level, and the variation process was totally harmonized across the EU.

Keywords: EMA, Drug approval, post approval changes, Market Authorization, Decentralized Procedure, National Procedure, Centralized Procedure, Mutual Recognition Procedure

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1. Introduction

The European Union's (EU) decentralized pharmaceutical regulatory systems are made up of the European Medicines Agency (EMA), National Competent Authorities (NCAs), Heads of Medicines Agencies (HMA), and the European Directorate for the Quality of Medicines (EDQM). Eudralex is a set of laws

and regulations that control the sale of medicines in the EU. (1)

The European Union's (EU) decentralized agency is based in Amsterdam. It started running in 1995. Medicines created by pharmaceutical companies for use in the EU must undergo scientific evaluation, oversight, and safety monitoring by the Agency. EMA protects public and animal health in the 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. The EMA's goal is to support scientific excellence in the assessment and oversight of medications for the benefit of human and animal health in the EU. (2)

For several types of pharmaceutical items, EMA has various committees.

- Committee for Medicinal Products for Human Use (CHMP)
- Pharmacovigilance Risk Assessment Committee (PRAC)
- Committee for Advanced Therapies (CAT)
- Pediatric Committee (PDCO)
- Committee for Orphan Medicinal Products (COMP)
- Committee for Medicinal Products for Veterinary Use (CMVP)
- Committee on Herbal Medicinal Products (HMPC).(1)

A network of about 50 regulatory authorities from the 31 EEA countries forms the foundation of the European Union's regulatory framework for medicines (28 EU member states plus Norway, Iceland, and Liechtenstein), the European Commission and EMA. The regulatory structure of the EU is distinct because of this network. The variety of expertise involved in the EU's regulation of medicines promotes the sharing of knowledge, concepts, and best practices among researchers working to uphold the industry's highest standards.(3)

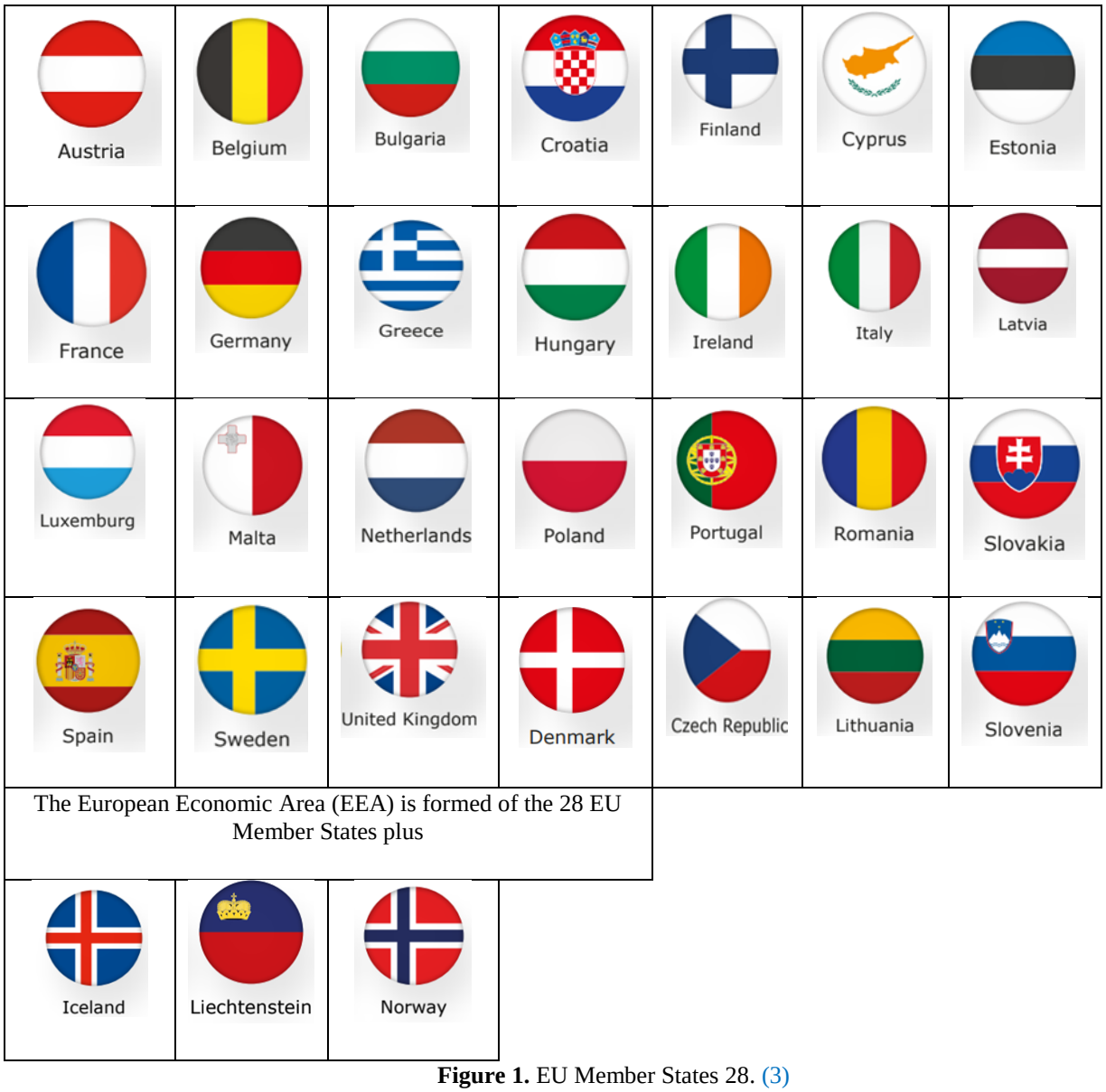

Figure 1. EU Member States 28. (3)

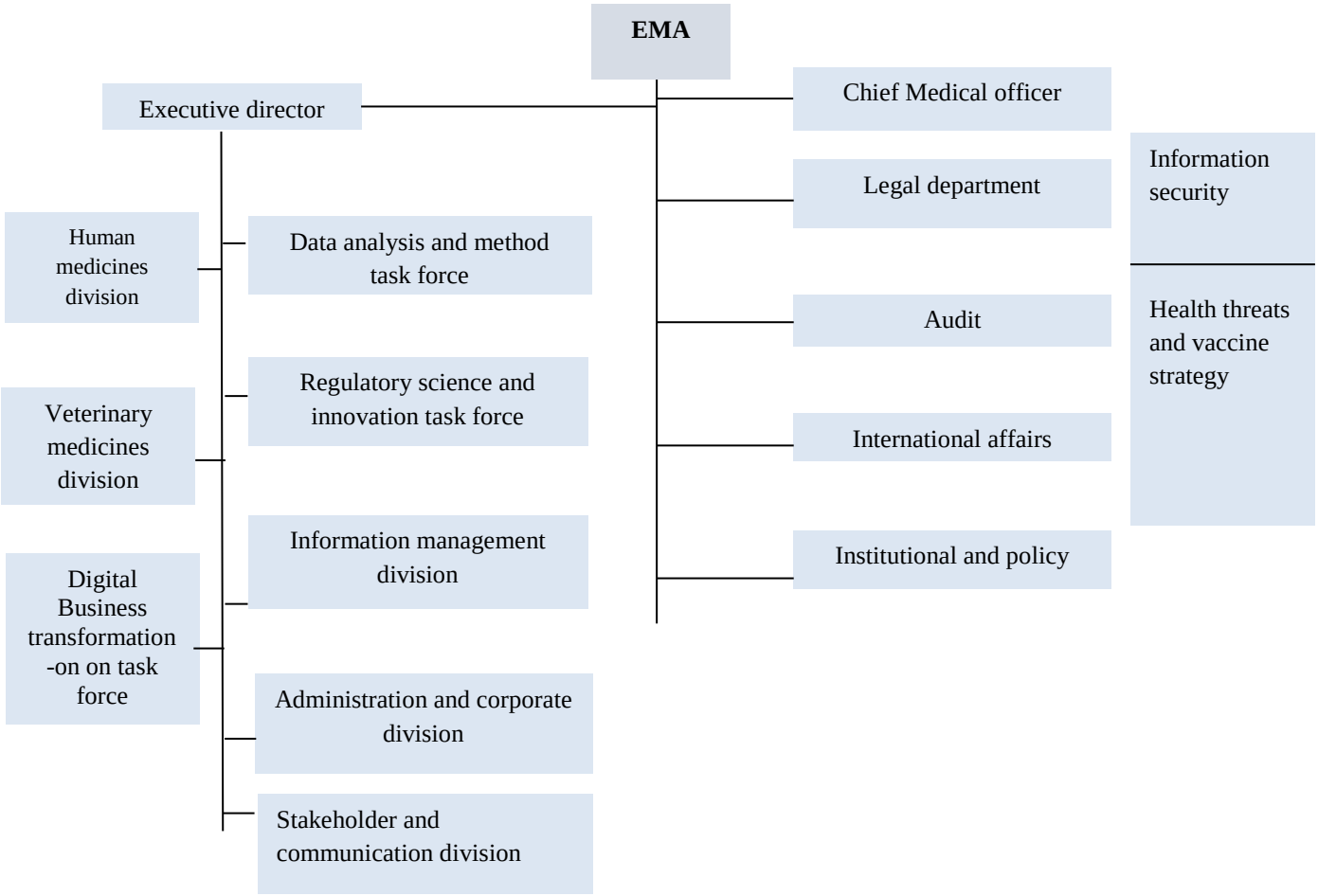

Figure 2. Organization of European Medicines Agency (EMA). (4)

Table 1. EMA: Specific considerations. (5)

1.	Multiple Agencies	▪ EMEA ▪ CHMP ▪ National Health Agencies
2.	Registration Process	Multiple Registration Process ▪ Centralized -(European Community) ▪ Decentralized - (At least 2 member states) ▪ Mutual Recognition -(At least 2 member states) ▪ National - (1 member state)
3.	Specific requirements	TSE / BSE Study data required
4.	Labeling code	Braille code is required on labeling
5.	The changes in the approved drug	▪ Type IA Variation ▪ Type IB Variation ▪ Type II Variation
	Administrative Requirements	
6.	Presentation	eCTD
7.	Approval Timeline	12 Months
8.	Debarment classification	Not Required
9.	Fees	10 - 20 Lakh
10.	Number of copies	1
11.	Application	MAA
	Finished Product Control Requirements	
12.	Water Content	Not Required
13.	Disintegration	Required
14.	Justification	ICH Q6A
15.	Color Identification	Required
16.	Assay	95 - 105%

	Manufacturing & Control Requirements	
17.	Batch Size	Minimum of 1,00,000 Units
18.	Packaging	Units not required
19.	Process Validation	Required
20.	Number of batches	3
	Stability Requirements	
21.	QP Certification	Required
22.	Container orientation	Do not address
23.	Condition	25/60 - 40/75
24.	Clause	Vol. 4 EU Guidelines for medicinal products
25.	Date & Time of Submission	6 Months Accelerate & 6 Months long term
26.	Number of batches	2
	Bioequivalence Requirements	
27.	Retention of samples	No such requirement
28.	Reserve Sample	No such requirement
29.	Fasted / Fed	No such requirement
30.	CRO	Audited by MHRA

2. Drug approval process in Europe

When requesting authorization to commercialize a new drug in European nations, a Patron has a number of options, including a National Authorization Procedure, a Decentralized Procedure, a Mutual Recognition Procedure, or a Centralized Procedure. The following products need to follow the centralized procedure:

- All biologic agents or other products which produced by high-technology procedures.
- HIV/AIDS, cancer, diabetes, neurodegenerative disorders, autoimmunity, and other immune dysfunctions, as well as products for viral diseases.
- Products which using in Orphan conditions.

Currently, different nations must adhere to various regulatory criteria in order to license new drugs. A unified regulatory method for Marketing Authorization Applications (MAA) that is valid in several countries is almost a tough task. As a result, understanding the regulatory requirements for MAA in each country is crucial. (6) All medications must be authorized before they can be sold in the EU in order to safeguard the public's health and guarantee that they are accessible to all European people. The European system provides several options for obtaining such an authorization.(3) The FDA and the EU both have much of the same drug approval procedures. A pre-authorization is initially obtained by an investigator for the use of a proposed medicine in clinical trials. Clinical Trials Directive of the European Commission (2001/20/EC), which was later abolished and replaced in 2014 by Regulation No. 536/2014 of the European Parliament, governed all clinical trials conducted in Europe.(7)

2.1 Marketing Authorization (MA)

A pharmaceutical product must be the subject of a current Marketing Authorization (MA) before it can be offered for sale and supply on the market, whether it is for human or veterinary use. The Marketing Authorization Holder (MAH) is responsible for marketing the product in accordance with the authorization's guidelines.

Unless the product has been authorized through the centralized procedure, in which case a single MA (a Community Authorization) is granted by the European Commission and is regarded as valid in all EU Member States, MAs issued only permit the product in question to be marketed by the MAH in that EU Member State. Based on the safety, quality, and efficacy supporting data offered, all MA applications are evaluated. Only when a product's advantages outweigh its drawbacks is it given an MA. Not all items for which marketing authorization requests are made ultimately receive approval. Some applications are rejected because the data is insufficient or inadequate. (8)

2.2 Validity of Marketing Authorization

Initial validity of a national marketing authorization (MA) is five years from the date of first authorization. It will come up for renewal at the end of the five years, which is a process for examining the product to make sure the benefit/risk balance is still favorable. This evaluation takes into account any new information concerning the product learned through usage experience since it was first approved, such as pharmacovigilance data. This is done to make sure the product's MA is still suitable. After this evaluation, the MA will be permanently valid, or the MAH will be required to submit another renewal within an additional five years.

Volumes 1 and 5 of the book "Rules governing medicinal products in the EU" compile the body of EU legislation pertaining to the pharmaceutical industry. National legislations are used to execute EU Directives. (8)

2.3 Product authorization

A sponsor can use a National Authorization Procedure, a Decentralized Procedure, a Mutual Recognition Procedure, or a Centralized Procedure to request market authorization for a novel medicine in Europe. One of the following methods can be taken depending on the drug category, number of nations proposing to market the drug, timeline for approval, and budget sponsor.(9)

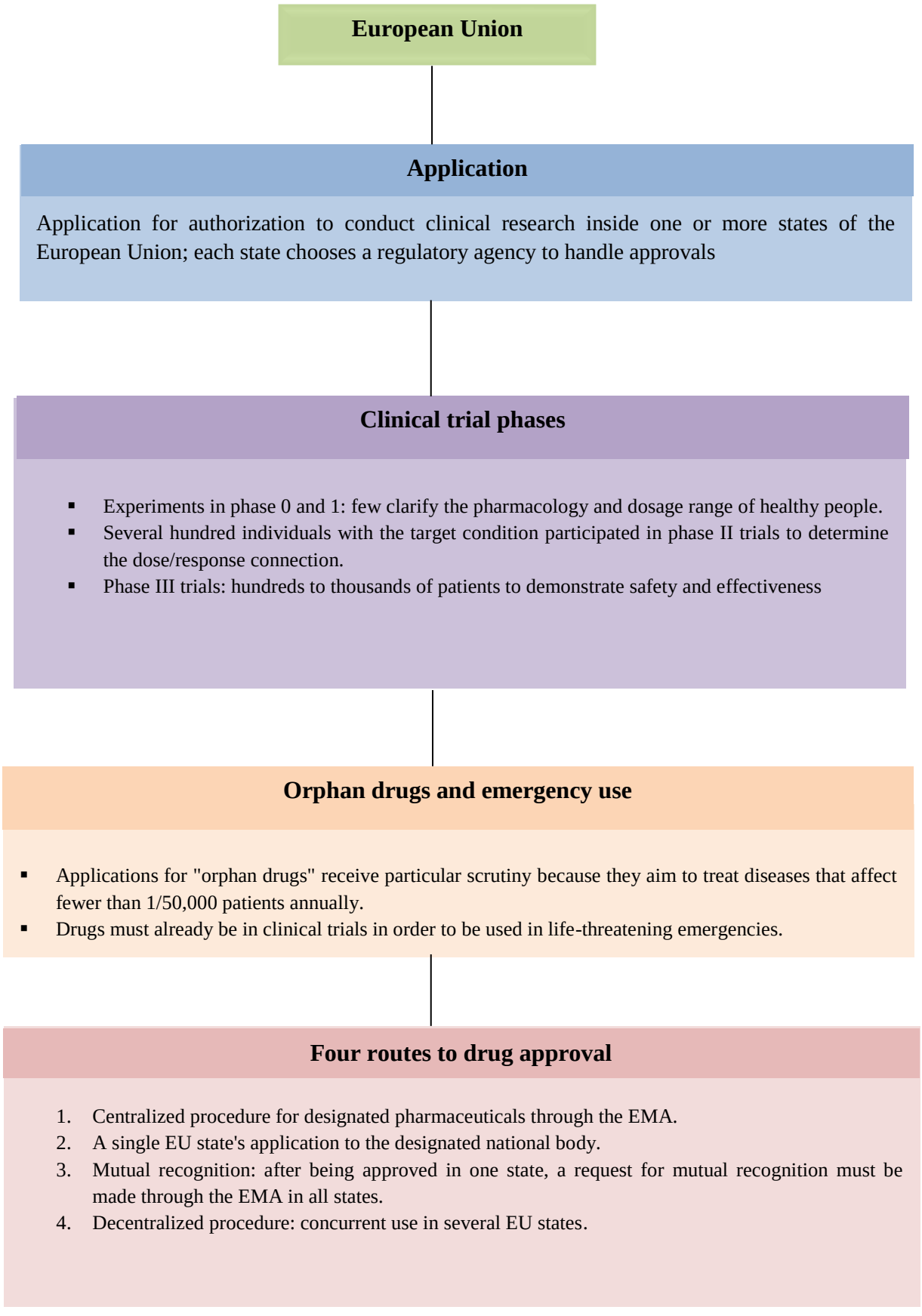

Figure 3. Drug Approval Processes in the EU (7)

2.4 Mutual recognition Procedure (MRP)

In the EU, the MRP has been in force since 1995. When the pharmaceutical product has already received authorization from at least one European Community nation, this procedure's goal is to gain marketing authorizations in one or more Member States. In this situation, the applicant asks one or more CMSs to accept the RMS's authorization as valid. Before beginning the MRP, the dossiers must be reformatted if the marketing authorization in the RMS is based on an outdated dossier format. (10) In this process, pharmaceuticals that have been approved in one European nation then apply for additional marketing permits from other EU nations who accept the first nation's judgment without performing their own reviews.(9)

Review process:

- For first registration, the sponsor is only necessary to submit an application once. Another member country accepts the identical application after making some regional changes.
- The Reference Member State (RMS), which conducts the application evaluation first, notifies the other states—the "Concerned Member States"—through CMS.
- In order to wait for the Reference Member State's evaluation, the concerned Member States may postpone their own assessments.
- The concerned Member States receive notification of the Reference Member State's decision, and if the concerned Member States reject mutual recognition, the CHMP of the EMA is contacted for arbitration.
- The European Commission, which makes the final decision, receives the EMA's recommendation. If no objections are submitted, the decision-making process might take up to 300 days, and if objections are raised, it could take up to 600 days.
- This procedure could take 390 days to complete.(1)

The following product cannot be registered under this program: All biotechnology-based products, specific medicines for cancer and aids, orphan medicines Specific medications for auto immune diseases and dysfunctions, specific antiviral medications, and specific medications for neurodegenerative disorders, including diabetes. (11)

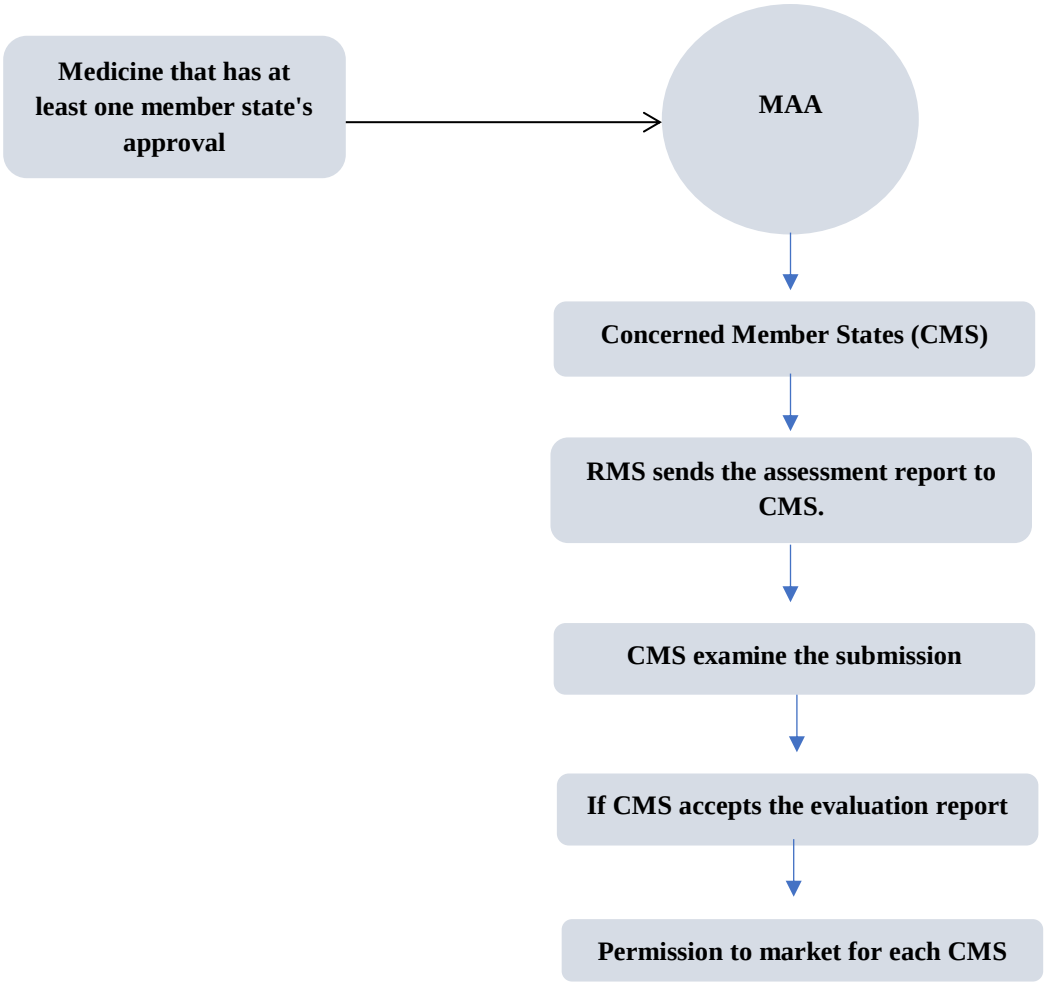

Figure 4. Mutual recognition procedure (1)

2.5 Centralized Procedure (CP)

In 1995, the EU implemented the Centralized Procedure. As previously stated, following the Centralized Procedure is required when requesting authorization for specific pharmaceutical items. (10) It permits the marketing of a medication candidate based on a single EU-wide evaluation and marketing authorization that is accepted across the whole EU. Pharmaceutical firms or sponsors must submit a single application to the EMA, and the agency's Committee for Medicinal Products for Human Use (CHMP) evaluates the application scientifically and makes a recommendation to the European Commission. The suggestion will determine whether marketing authorization is approved or denied.(12)

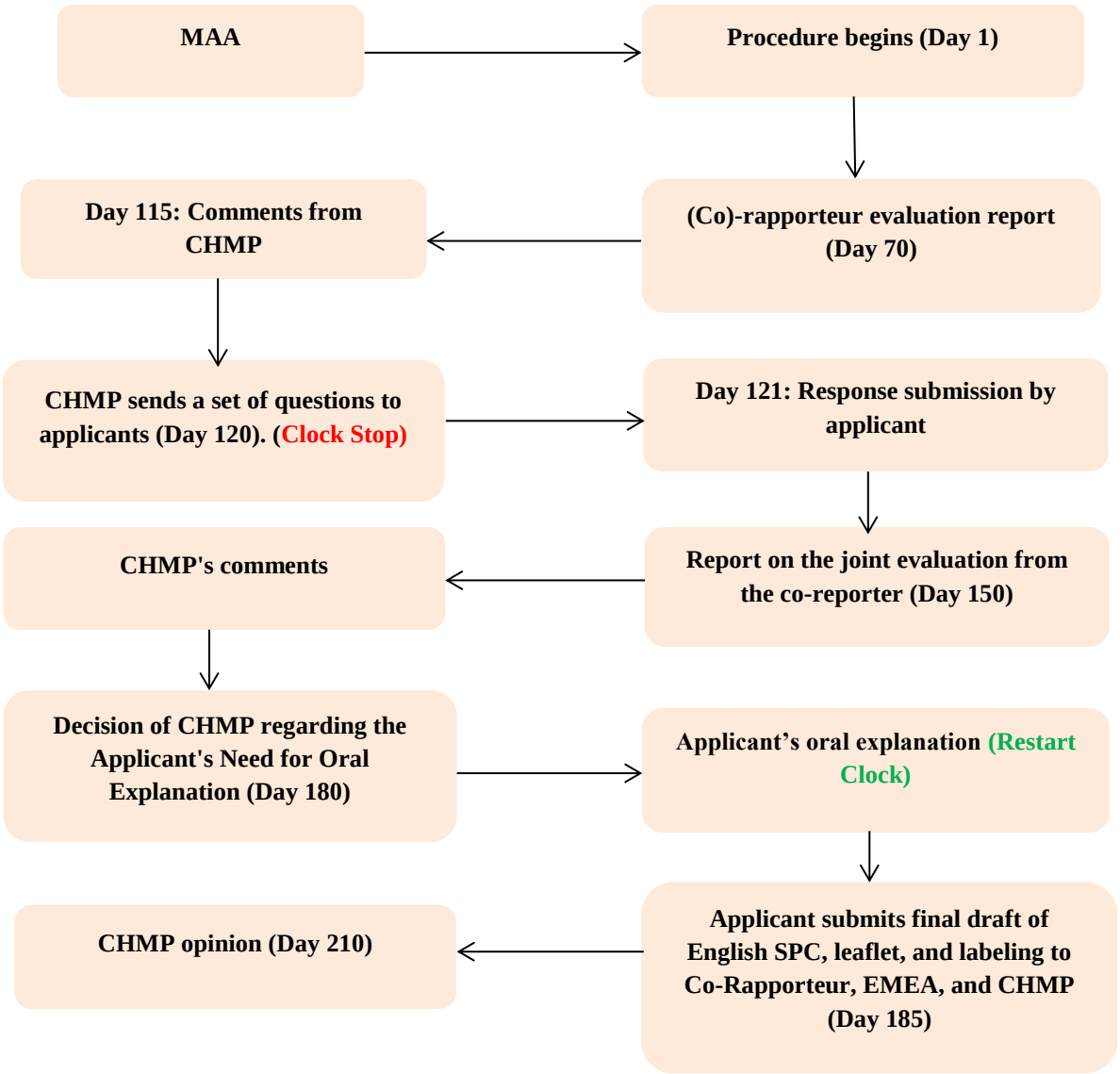

Figure 5. Centralized Procedure for Marketing Authorization in EU (6)

The following requirements must be met by products to be eligible for review under the centralized procedure:

- Recombinant technology, carefully regulated production of genes encoding biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells, hybridoma, and monoclonal antibody techniques are all used to create biologic pharmaceuticals.
- Pharmaceuticals or orphan medicines for rare disorders.
- Novel active ingredients in pharmaceuticals for conditions like AIDS, cancer, neurological diseases, diabetes, and autoimmune disorders.

The centralized procedure was initially only required for biotechnology medications, but over time, it has gradually expanded to include orphan drugs or medications for rare diseases, human medications containing a new active ingredient, advanced therapy medications, and medications intended to treat AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune dysfunctions, viral diseases, and other conditions.(1)

Review process:

- The European Medicines Agency (EMA) receives applications from businesses seeking to commercialize a medicinal product that qualifies for the centralized authorization procedure.
- The application must be validated and subjected to a scientific examination by the EMA.
- The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) evaluates the application scientifically and makes a recommendation on whether or not to approve the medication.
- Along with a positive assessment, there is a draft overview of the product's attributes, a package leaflet, and proposed language for the packaging.
- The evaluation method has a time restriction of 210 days, which can be extended if further questions arise.
- The EMA will transmit its opinion to the European Commission within 15 days of adoption to begin the decision-making process.
- The Commission sends a draft implementing decision to the Standing Committee on Medicinal Products for Human Use within 15 days, allowing EU nations to review it.
- These have fifteen days to respond to linguistic comments and twenty-two days to respond to substantive ones. An empowerment procedure is used to adopt the draft decision once a favorable view has been achieved.
- After receiving the EMA's opinion, the decision must be adopted within 67 days.
- The marketing authorization holder is then informed of the decision by the Secretariat-General of the Commission. The judgment is then made public in the Union Register.(6)

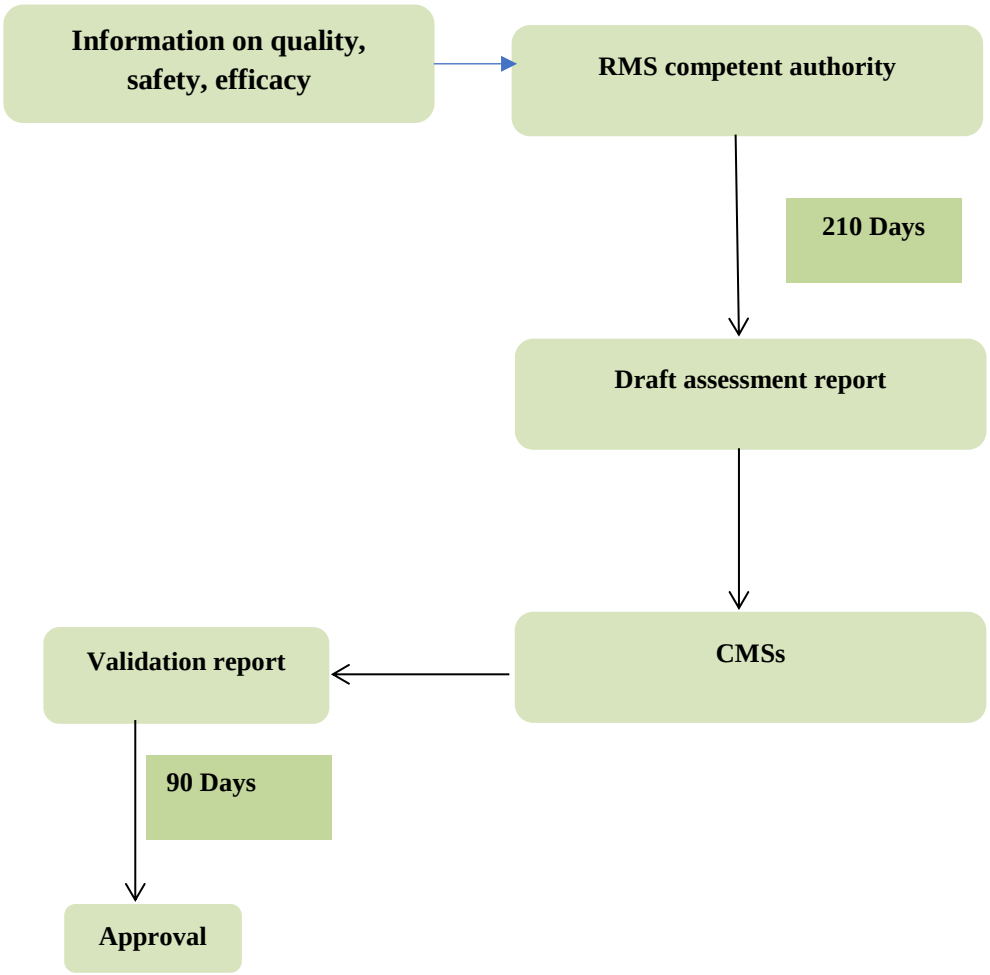

Figure 6. Decentralized Procedure for Marketing Authorization in EU

Validity:

Five years are the expiration date for a national marketing authorization.

The centralized process has a benefit:

The primary benefit of this process is that it calls for a single market approval process, which, if approved, results in an authorization that is valid throughout the entire EU as well as identical product information that is available in all EU languages.(1)

Note: The CP is helpful for producers that intend to market their goods both in the EU and in the EEA

nations of Iceland, Liechtenstein, and Norway. Following European Commission (EC) approval, producers are permitted to promote their products to healthcare professionals under the centralized procedure, which is covered by Regulation (EC) 726/2004. (13)

2.6 Decentralized Procedure

Sponsors may simultaneously apply for market authorization in more than one EU country for items that have not previously been authorized in any EU country and do not fall within the mandatory centralized process.(1) A product is recognized by a group of member countries at the same time under this scheme. It is regarded as a very efficient procedure. In certain member states, a decentralized approach is used to get marketing authorizations. The sponsor sends the application and a list of all Concerned Member States (CMSs) to a national regulatory authority, identifying a Reference Member State (RMS).

- The RMS must validate the application and Summary of Product Characteristics (SPCs); develop a draft assessment report and transmit a copy to the CMSs within 210 days; and approve the report within 90 days.
- If a pharmaceutical product is thought to represent a substantial risk to public health. CMSs may object, and the CHMP will intervene and make a final decision within 30 days.
- However, a negative judgment might have an impact on registration in many countries under this scheme; also, the following products cannot be registered: All biotechnology-based orphan medicinal product, Specific Aids and Cancer Medicines, Specific Antiviral Medicines, Specific Neurodegenerative Disorder Medicines, including Diabetes, and Specific Auto Immune Diseases/Dysfunction Medicines. (11)

Note: The procedure for authorizing medicines in more than one European Union Member State in parallel. It can be used for medicines that do not need to be authorized via the centralized procedure and have not already been authorized in any Member State. (14)

2.7. National Procedure in EU

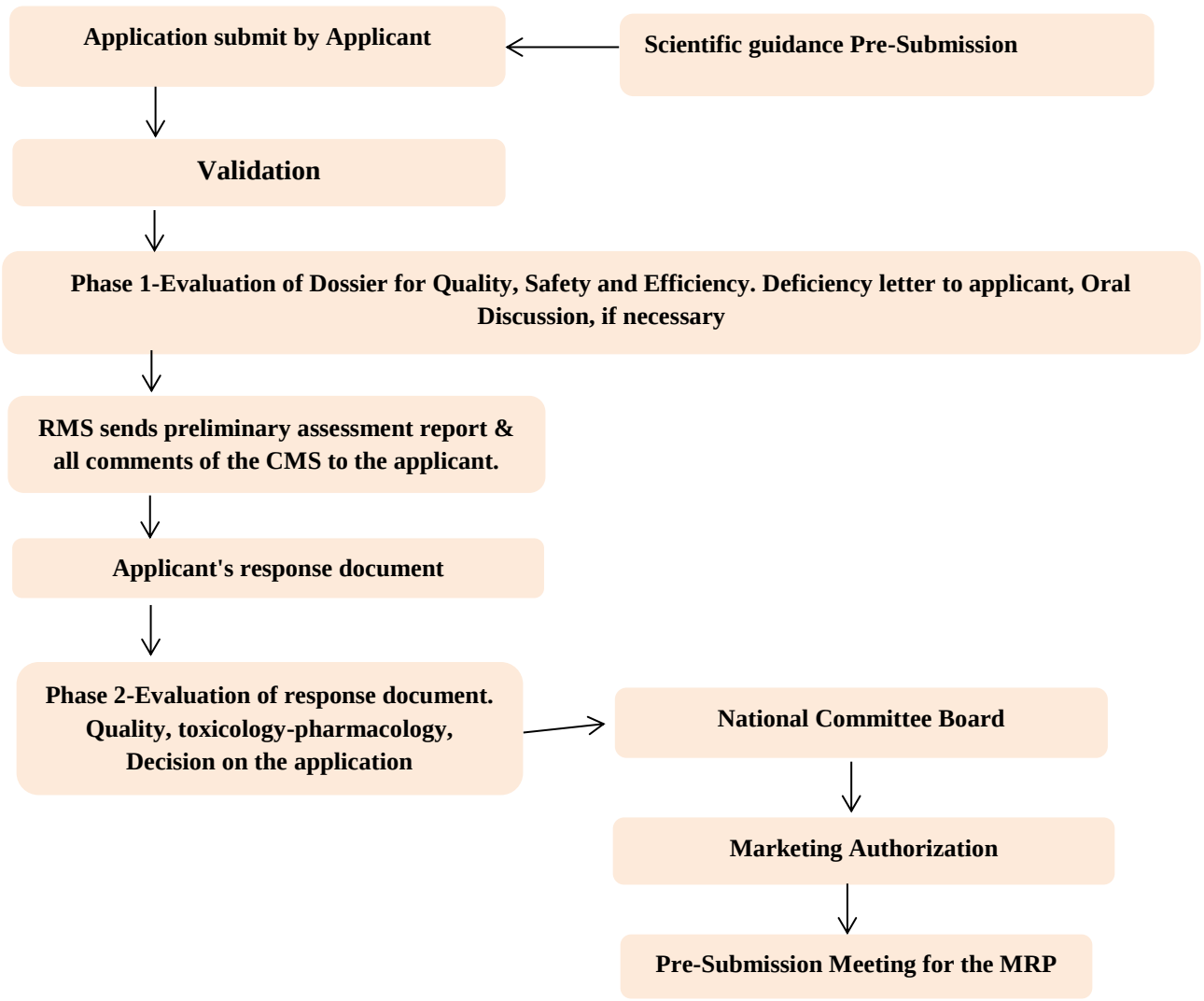

Figure 7. National Procedure in EU (18)

2.8 Market Authorization process difference in EU countries:

1. Germany- The Federal Institute for Drugs and Medical Devices
2. Austria- Austrian Medicines and Medical Devices Agency
3. Hungary- The National Institute of Pharmacy and Nutrition (OGYÉI)
4. Italy- The Italian Medicines Agency
5. Iceland- The Icelandic Medicines Agency (IMA

Table 2. Market Authorization process difference in EU countries

Germany (21)	**Austria** (22)	**Hungary** (23)	**Italy** (24)	**Iceland** (25)
A pharmaceutical business or a team of researchers must first request for approval or a regulatory permit to put this drug on the market, before they can market it or make it available to the general public. Within the EU, there are four different procedural paths to apply for approval depending on where the medicine would be marketed: ➢ The national method allows a medicine to be marketed only in Germany, ➢ whereas the two decentralized procedures allow a drug to be marketed in some EU nations ➢ The centralized procedure allows a drug to be marketed in all European Economic Area (EEA) countries.	The Austrian Medicinal Products Act 1983 governs medicine distribution. In general, to distribute medications in Austria, a marketing authorization that is valid in the country is required. There are several exceptions, such as compassionate usage, herbal pharmaceuticals, specific homeopathic treatments, and parallel imports. There are four procedures that can be utilized to obtain a valid marketing authorization in Austria, which are as follows: ➢ Centralized procedure. ➢ Decentralized procedure. ➢ Mutual recognition procedure. ➢ Austrian national procedure.	Applications should be sent to the National Institute of Pharmacy, which is in charge of pharmaceutical product registration. Applications are evaluated based on the quality, safety, and efficacy of the medicine. The procedure is divided into several steps: evaluation of chemical and pharmaceutical data by the National Institute of Pharmacy staff; evaluation of toxicological and pharmacologic documentation with the assistance of the Committee on Drug Administration; authorized clinical pharmacologic investigations are conducted in the Clinical Pharmacological Network units after consultation with the Committee on Medical Research Ethics (mandatory in cases of original new drugs), Preparations already recorded in another nation may significantly speed up the process.	A medicinal product must be granted a Marketing Authorization (MA) by AIFA or the European Commission before it may be marketed in Italy. To get the MA, the applicant must submit an application that includes a dossier containing information on chemical-pharmaceutical, preclinical, and clinical aspects in a specified format (CTD - Common Technical Document). The data and studies provided to support MA applications must adhere to European-level requirements. The authorization procedures provided for in European legislation are: ➢ National procedure ➢ Mutual recognition procedure and decentralized procedure ➢ Centralized procedure ➢ Parallel import	The Iceland Medicines Agency has dispensed with its practice of formally approving variations to medicinal products that have been evaluated through the European Union's centralized procedure

2.8.1 Latest approval in EU

Six new medications, including Genmab/AbbVie's Tepkinly, have been added to the EU's centralized approvals of novel active substances list for treating adult patients with relapsed or refractory diffuse large B-cell lymphoma complying with two or more lines of systemic therapy.

Givinostat, Italfarmaco's investigational treatment for Duchenne muscular dystrophy, is among the latest products that have been filed for review by the European Medicines Agency for potential EU marketing approval on 27 Sep. 2023 (26)

2.9 Regulatory submission dossier modules (27, 28)

For a new marketing authorization, the applicant must submit a regulatory dossier in the preferred format. Every regulatory document must be submitted using the CTD format. *Volume 2B, NTA, July 2003 edition*, provides comprehensive information on document

requirements for dossier applications. Additional guidance is periodically updated on the websites of European agencies. The marketing authorization application structurally presents five CTD sections. The following is a brief tabular list of the dossier module contents:

Table 3. Dossier module contents

Module	Contents	Details
1.	EU administrative and prescribing information	▪ Application form Summary of Product characteristics Labeling 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

3 Post approval changes in Europe

Pharmaceutical product life cycle management includes post-approval adjustments as a crucial component. These adjustments need to be closely watched and must adhere to the correct regulatory framework for the applicable country. The European Medical Agency (EMA) has outlined the regulatory framework for post-approval adjustments, often known as variant filings in Europe, in a number of guidelines.(29) In a post-approval change management, specific changes that a company would like to implement throughout the product's lifecycle are outlined, along with how they would be prepared and confirmed; Such a stepwise approach can result in faster and more predictable implementation of changes after approval because the Marketing Authorization Holder (MAH)will have obtained agreement from the Regulatory Authorities about the proposed strategy and tests to verify the effect of the change on product quality.(30)

The need to maintain current and updated dossiers is a need across the pharmaceutical business, regardless of a product's route or country of registration. Marketing authorization holders (MAHs) have a crucial role to play in the post-approval lifecycle management activities, regardless of whether changes are prompted by advances in technology and science or a need to cut costs. The procedures for filing and processing variants are starting to converge as regulatory agencies around the world modernize.(31) For any type of alteration to a drug product that has been approved by EMA, a variant method was first developed in 1995. The two categories of variations—type-I for small modifications and type-II for large changes—were first introduced by EMA in 1995. In 2003, type-I was further divided into two categories—type-IA for minor changes and type-IB for moderate alterations.(32)

3.1 Variation classification:

Through the filing of a modification, the agency may be notified of any post-approval changes. This method can be used for all types of applications, including centralized (CP), national (NP), decentralized (DCP), and mutual recognition (MRP) procedures. Variations can be divided into four groups, including types IAIN, IA, IB, type II, and Extensions

Minor variations of Type IA

i. Type-IA:

These variations do not require any prior approval, but MAH should notify within 12 months (“Do and Tell”)

ii. Type-IAIN:

It requires immediate notification after implementation.

Minor variations of Type IB

These must be informed prior to implementation. The holder must wait 30 days for the notification to be considered acceptable ("Tell, Wait, and Do").

Major variations of Type II

Before they may be implemented, these changes must be approved by the relevant competent authorities.

Extension

These notifications will be assessed similarly to the first MAA. The extension may be included in the initial MA to which it refers or may be issued as a new MA.(32)

Urgent Safety Restrictions

According to Article 22 of the Variations Regulation, the holder may implement temporary "urgent safety restrictions" if there is a risk to the public health in the case of pharmaceuticals intended for human use or a risk to the environment, human or animal health, or both, in the case of pharmaceuticals intended for veterinary use.(33)

3.2 Variations

The marketing authorization holder (MAH) is accountable for the product for the duration of its shelf life and must take appropriate action in response to any information that could affect the assessment of the risks and benefits of the specific medicinal product.

The MAH is necessary

- to regularly update the dossier to take account of technical and scientific advancements and to introduce any change that may be required for the manufacture and control of the medicine

- To guarantee that the product information (SmPC, labeling, and PL) is kept current with the state of science.(34)

Minor variations of Type IA

Minor modifications of Type IA can be used by the holder without being reviewed by the authorities first. However, the holder must simultaneously send a notification of the pertinent variation(s) to all Member States involved, the national competent authority, or the Agency (as appropriate), at the latest within 12 months of the date of implementation. A holder may submit a minor Type IA variation for immediate notification or submit any other variation along with a small Type IA variation that is not subject to immediate notification. (35)

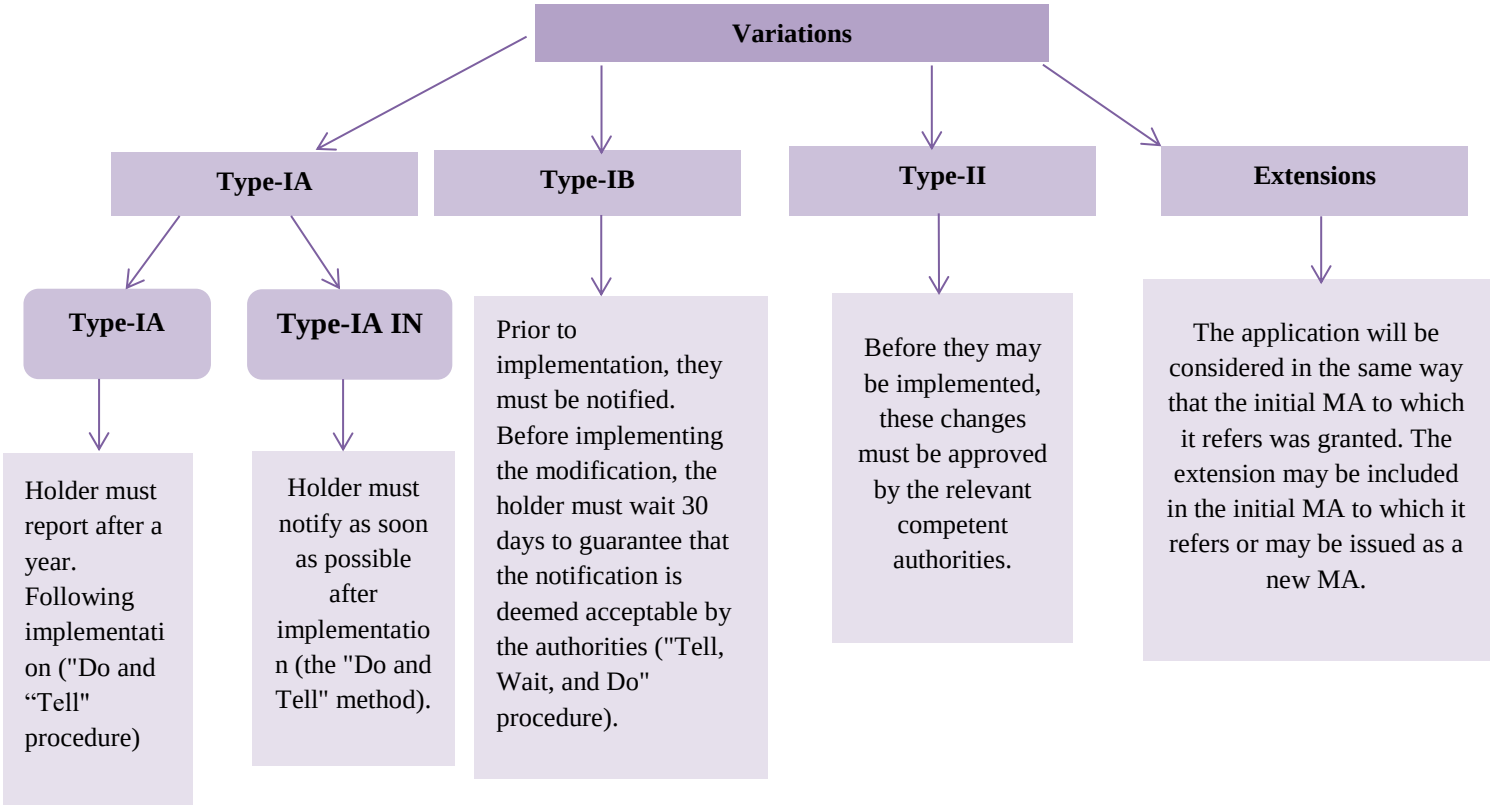

Figure 8. Classification of Variations (32)

Type IAIN Variations:

Variations are also minor variations but require immediate notification to the competent authority on implementation. The Annexes to the Variations Regulation specifies which minor Type IAIN variations must be notified immediately on implementation. Type IA and Type IAIN variations typically have a 30-day review cycle. Changes of Type IA and Type IAIN may be made before the variation is submitted, but the MAH must stop using the rejected changes as soon as the variation is rejected by an authority. (36)

Type IB Variations:

The Marketing Authorization Holder (MAH) must notify the National Competent Authority/European Medicines Agency (the Agency) prior to the implementation of any minor modification that is neither a Type IA variation, Type II variation, nor an Extension. Before making the change, MAH must wait 30 days to confirm that the notification has been approved by the National Competent Authority or the Agency. (37)

Type II

Variations are major variations which are not extensions and which may have a significant impact on the quality, safety and/or efficacy of the medicinal product concerned.(38) A type II variation will be validated and assessed.(39) Before implementation, approval from the appropriate authorities is required. Type II variations generally have a 60-day assessment timetable, however this can be shortened to 30 days for urgent safety issues and prolonged to 90 days for therapeutic indication expansions. (36)

Extension:

Changes that may have a major impact on the medicinal product's quality, safety, or efficacy must be reported as a Type II variant. Changes necessitating the use of an extension application-

- Changes to the active substance(s)
- Changes to strength, pharmaceutical form and route of administration. (37)

The Variations Regulation Annex I details extension applications, which include modifications to strength, method of administration, and pharmaceutical form. Before implementation, approval from the appropriate authorities is required. In general, extension applications are evaluated within 210 days. (36)

Table 4. Periods of Time (37)

Periods of Time: (Working Days)	Type of Application Days	Days
	Type IAIN	30
	Type IB	30
	Type II	30, 60, 90
	Type II Extension	210

Urgent Safety Restrictions

Urgent safety restrictions are temporary modifications to the marketing authorization's requirements brought on by new knowledge that m ay have an impact on the medicine's safe usage. Subsequently, these critical changes must be implemented via a corresponding modification to the marketing authorization. The holder shall immediately notify all affected Member States, the national competent authority, or the Agency (as appropriate) of the impending restrictions. The urgent safety restrictions are regarded acceptable if no objections have been raised by the relevant authority or the Agency (for centrally licensed medical products) within 24 hours of receipt of that information. The reference Member State, the national competent authority, or the Agency (where applicable) and the holder must agree on a timeline for their implementation. The holder shall submit within 15 days the necessary variation application reflecting the urgent safety limitations (whether sought by the holder or imposed by the Commission or the national competent authorities). (33)

3.2 Classifying variations related to: (40)

Table 5. Variation classification

A. Administrative changes
B. Quality changes
I. Active substance ▪ Manufacture ▪ Control of active substance ▪ Container closure system ▪ Stability ▪ Design space
II. Finished Product ▪ Description and composition ▪ Manufacture ▪ Control of excipients ▪ Control of finished product ▪ Container closure system ▪ Stability ▪ Design Space
III. CEP/TSE/monographs
IV. Medical Devices
V. Changes to a marketing authorization resulting from other regulatory procedures ▪ PMF/VAMF ▪ Referral ▪ Change management protocol
C. Safety, efficacy, Pharmacovigilance Changes
I. Human and Veterinary medicinal products
II. Veterinary medicinal product – specific changes
D. Plasma master file/ vaccine antigen master file

4. Conclusion

Europe has the highest thought-due approval rates worldwide. The European Medicines Agency (EMA) aims to guarantee that patients in the EU have access to medicines that are of the highest caliber, are reliable, and are secure. Public regulatory agencies have the responsibility of ensuring that pharmaceutical firms follow the law. In order to ensure patient safety and well-being, laws mandate that pharmaceuticals be created, tested, tracked, and manufactured in compliance with the standards. A guideline, in addition to the European legislation that defines variation types, gives out a harmonized list of anticipated variations with categorization codes. A defined list of variations for European

A MA has existed since 1998. Legislation has been amended on a regular basis, and the most recent amendment, in August 2013, made implementation mandatory at the national level, and the variation process was totally harmonized across the EU

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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