Comprehensive Review on Guidelines for Drug Approval in European Union

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ABSTRACT:

This current article reviews and simplifies the Regulatory Framework and strategy for filing application (Marketing Authorisation Application) across the EU, along with a brief introduction on the dossier submission requirements and EU Variations. European regulations are legislative acts that are directly applicable and binding in all member states of the European Union. It aims to ensure the harmonization of rules and standards across the EU, promoting a common market and the free movement of goods. Following the Thalidomide Catastrophe, the EU began to regulate pharmaceuticals. The first pharmaceutical Directive 65/65/EEC was adopted in the EU as a result of this catastrophe. In order to assure the highest standard of scientific review and monitoring of medications created by pharmaceutical firms for use in the European Union, the Agency draws together the scientific resources of the EU member states and operates as a network.

Keywords: EU, EMA, MAA, ASMF, CEP

INTRODUCTION:

Following the Thalidomide Catastrophe, the EU began to regulate pharmaceuticals. The first pharmaceutical Directive 65/65/EEC was adopted in the EU as a result of this catastrophe (1). The teratogenicity of this moderate sedative shocked public health officials and the broader public, making it very evident that no pharmaceutical product should ever again be promoted without prior authorisation (2).

The EMA, with its headquarters in London, UK, started operating in 1995. In order to assure the highest standard of scientific review and monitoring of medications created by pharmaceutical firms for use in the European Union, the Agency draws together the scientific resources of the EU member states and operates as a network (3).

27 member nations (Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden) in Europe make up the European Union (EU), which is a political and economic union (1,3). The EU is home to 508 million people, making it the third-largest population in the world after China and India. It has a land area of nearly 4 million km^2. France is the largest and Malta is the smallest EU nation by surface area (4).

The EU is run via a system of supranational organisations and agreements reached between member states during intergovernmental meetings. The European Central Bank, the European Court of Auditors, the European Parliament, the European Council, and the European Court of Justice are the key institutions of the EU. Every five years, EU people choose a new member of the European Parliament (5).

European Council: The European Council is where the political agenda for the EU is decided. The amount of political collaboration between EU member states is at its greatest (6).

European Commission: The politically impartial executive branch of the EU is known as the European Commission (EC). It is alone in charge of creating new legislative proposals for the EU and carrying out the decisions made by the EU Council and European Parliament (7).

Court of Justice of the European Union: The Court of Justice resolves legal disputes between national governments and EU institutions and interprets EU law to ensure that it is enforced uniformly in all EU nations.

Iceland, Liechtenstein, and Norway are also included in the EEA together with the EU. It enables them to participate in the EU single market (8). Despite not being a member of the EU or EEA, Switzerland participates in the single market. This implies that Swiss nationals enjoy the same rights to reside and work in the UK as other EEA nationals.

MARKETING AUTHORIZATION

A pharmaceutical product must first get marketing permission in order to be sold and promoted lawfully in the European Union (EU). The European Medicines Agency (EMA), which is in charge of evaluating the efficacy, quality, and safety of new medications, is in charge of overseeing the procedure (9).

A drug producer must submit a marketing authorization application (MAA) to the EMA in order to receive marketing authorisation in Europe. The MAA provides details on the drug's quality, manufacturing process, and labelling in addition to data from preclinical and clinical trials that show its safety and effectiveness (10).

The MAA is subsequently subjected to a thorough scientific review by the EMA, which also involves interaction with national regulatory agencies and evaluation by an expert committee. If a medication is discovered to be safe, effective, and of high quality, the EMA will grant a marketing authorization that allows the drug to be sold in all EU member states (9, 11). The marketing authorization process in Europe is based on a centralized system, which means that a single application is submitted to the EMA for review and approval. This allows for a streamlined process and ensures that the same standards are applied across all EU member states.

Marketing authorization in Europe is a key step in the drug development process and is required before a drug can be marketed and sold to patients in the EU. It ensures that medicines are safe, effective, and of high quality, and provides patients with access to the latest treatments and therapies (12).

Marketing Authorization Application:

A Marketing Authorization Application (MAA) is a formal request submitted by a pharmaceutical company to the European Medicines Agency (EMA) for approval to market a medicinal product in the European Union (EU). The MAA is a comprehensive document that includes all the data and information required to support the safety, efficacy, and quality of the medicinal product (13). The MAA submission process in Europe is centralized, which means that a single application is submitted to the EMA for review and approval, instead of submitting separate applications to each member state. This ensures that the same standards are applied across all EU member states. The MAA must include a detailed description of the medicinal product, including its composition, pharmaceutical form, method of administration, and indications for use. The application must also include results from pre-clinical and clinical studies that demonstrate the safety, efficacy, and quality of the product (13, 14).

The EMA assesses the MAA based on a range of criteria, including the quality of the product, its safety and efficacy profile, and its benefit-risk balance. The review process involves a scientific assessment by the relevant scientific committee, followed by a decision-making process by the EMA's Committee for Medicinal Products for Human Use (CHMP) (15). If the MAA is approved, the EMA grants a marketing authorization that allows the pharmaceutical company to market and distribute the medicinal product in all EU member states. The marketing authorization is valid for five years and can be renewed thereafter, subject to ongoing monitoring and evaluation of the product's safety and efficacy.

Marketing Authorization Holder:

A Marketing Authorization Holder (MAH) is the entity that is responsible for obtaining and maintaining a marketing authorization for a medicinal product in the European Union (EU). The MAH is the holder of the marketing authorization and is responsible for ensuring that the medicinal product is manufactured, marketed, and distributed in compliance with the regulatory requirements of the EU (15, 16).

The MAH is typically the pharmaceutical company that developed the medicinal product or a subsidiary of that company. However, in some cases, the marketing authorization may be transferred to a different company, such as a generic drug manufacturer, through a process called "marketing authorization transfer." The MAH is responsible for a range of activities related to the marketing of the medicinal product, including:

1. Manufacturing and quality control: The MAH is responsible for ensuring that the medicinal product is manufactured and tested according to the standards set out in the marketing authorization.
2. Labelling and packaging: The MAH is responsible for ensuring that the labelling and packaging of the medicinal product comply with the regulatory requirements of the EU.
3. Pharmacovigilance: The MAH is responsible for monitoring the safety of the medicinal product and for reporting any adverse events to the relevant regulatory authorities.
4. Sales and distribution: The MAH is responsible for marketing and distributing the medicinal product in compliance with the regulatory requirements of the EU.

In summary, the MAH plays a crucial role in ensuring that medicinal products are marketed and distributed safely and effectively in the EU.

Authorisation Procedures:

European Medicines Agency (EMA), Heads of Medicines Agencies (HMA), National Competent Authorities (NCAs), and European Directorate for the Quality of Medicines (EDQM) are the decentralised bodies that make up the EU's pharmaceutical regulatory systems. The EU's set of laws and regulations controlling pharmaceuticals is known as EudraLex. After obtaining a marketing permission in the EU, a Marketing permission Holder (MAH) may introduce a pharmaceutical product there. Any of the four main procedures—centralized (CP), decentralised (DCP), mutual recognition (MRP), and national procedure—can be used to get the marketing authorisation (17). The authorisation requested using the centralised method is authorised in all EU member states, including the European Economic Area (EEA), while the marketing authorization requested using the DCP and MRP procedures is approved in EU member states chosen by the applicant. A pharmaceutical product must be approved within 210 days under both centralised and decentralised procedures. An EU marketing licence is typically given for a period of five years. When marketing authorizations are granted, they are renewed through a renewal procedure, and any adjustments to a marketing authorisation can be made by filing variant applications. The MAH is accountable for complying with the regular batch release and pharmacovigilance duties in addition to acquiring and maintaining the marketing authorizations (18).

- **The Centralised Procedure:**

The Centralised Procedure is the regulatory pathway for the authorization of medicinal products in the European Union (EU). It is one of three main procedures that can be used to obtain marketing authorization for a medicinal product in the EU, alongside the Mutual Recognition Procedure (MRP) and the Decentralised Procedure (DCP). Und er the Centralised Procedure, the European Medicines Agency (EMA) is responsible for the evaluation of the application for marketing authorization (19). The EMA's Committee for Medicinal Products for Human Use (CHMP) reviews the application and provides a recommendation to the European Commission, which makes the final decision on the authorization of the product. The Centralised Procedure provides a single marketing authorization that is valid throughout the EU, as well as in Norway, Iceland, and Liechtenstein. It is intended to ensure that all patients in the EU have access to safe, effective, and high-quality medicinal products.

Flowchart of Centralized Procedure:

Day	Action
1	Start of procedure
80	Receipt of assessment reports from rapporteur and co-rapporteur(s) by CHMP members and EMA. Sent to applicant for information only
100	Rapporteur, co-rapporteur, other CHMP members and EMA receive comments from members of the CHMP.
115	Receipt of draft list of questions (including the CHMP recommendation and scientific discussion) from rapporteur and co-rapporteur.
120	CHMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMA.
Clock stops	
121	Submission of the applicant's responses, including revised SmPC, labeling and package leaflet texts in English.
Restart of clock	
150	Joint response assessment report from rapporteur and co-rapporteur received by CHMP members and the EMA. Sent to applicant for information only.
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 to adopt a list of "outstanding issues" and/or an oral explanation by the applicant. If an oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation.
Clock stops	
181	**Restart of the clock** and oral explanation (if needed).
210	Adoption of CHMP opinion and CHMP assessment report (and timetable for the provision of product information translations).

If an applicant decides to withdraw their application before an opinion is adopted, the EMA makes this public on its website along with the relevant assessment report (19, 20). Applicants are required to submit a risk management plan at the time of marketing application and keep it updated during the lifecycle of the product. The RMP will be subject to review by the pharmacovigilance risk assessment committee (PRAC) in parallel to the CHMP review.

- **The Mutual Recognition Procedure:**

The Mutual Recognition Procedure (MRP) is a regulatory pathway for the authorization of medicinal products in the European Union (EU). It is one of three main procedures that can be used to obtain marketing authorization for a medicinal product in the EU, alongside the Centralised Procedure (CP) and the Decentralised Procedure (DCP). The MRP is typically used for medicinal products that have already been authorized in one member state and are intended for marketing in other member states (20). It allows for the recognition of the authorization granted by the reference member state (RMS) and the subsequent authorization of the product in other member states, known as the concerned member states (CMS). It is possible to use the mutual recognition procedure more than once for subsequent applications to other Member States in relation to the same medicinal product (so called repeat use). It is recommended that, wherever feasible, the MAH considers involving all Member States where the product is intended to be marketed, in the first use of mutual recognition procedure or decentralized procedure.

Flow chart of Mutual Recognition Procedure:

Day	Action
-14	Applicant submits the dossier to CMS. RMS circulates the AR including SmPC, PL, and labeling to CMSs. Validation of the application in the CMSs.
0	RMS starts the procedure.
30	CMSs send their comments to the RMS, CMSs, and applicant.
40	Applicant sends the response document to CMSs and RMS.
48	RMS evaluates and circulates a report on the applicant's response document to CMSs.
55	CMSs send their remaining comments to RMS, CMSs, and applicant.
59	The applicant and RMS are in close contact to clarify if the procedure can be closed at day 60 or if the applicant should submit a further response at day 60.
60	If CMS have no remaining comments at Day 55, the RMS closes the procedure.
68	RMS evaluates and circulates a report on the applicant's response document to CMSs.
75	CMSs send their remaining comments to RMS, CMSs, and applicant.
90	CMSs notify RMS and applicant of final position (and in case of negative position also the CMDh secretariat of the EMA). If consensus is reached, the RMS closes the procedure.

	If consensus is not reached, the points for disagreement submitted by CMSs are referred to CMDh by the RMS within 7 days after Day 90.
150	Final position adopted by the CMDh: If consensus is reached at the level of CMDh, the RMS closes the procedure. If consensus is not reached at the level of CMDh, the RMS immediately refers the matter to EMA for CHMP arbitration
5 days after close – CMS's & RMS's	Applicant sends high quality national translations of SmPC, PL, and labeling to of procedure

- **The Decentralised Procedure:**

The decentralized procedure can be used in cases where the product has never been authorized in any of the Member States, and the applicant wishes to obtain a license in a number of states simultaneously. The applicant must submit applications with the complete dossier to the Competent Authorities of each of the Member States where authorization is desired (21, 22). A single Member State should be chosen as the reference member state to undertake the scientific assessment of the complete dossier, while the other states are designated as concerned states. The review process has many parallels with the centralized procedure, in that similar timelines exist, the Reference Member State (RMS) plays the role of the rapporteur, and the Concerned Member States (CMS) replace the CHMP.

Flow chart of the Decentralized Procedure:

Day	Action
Before Day-14	**Applicant discussions with RMS.**
-14	RMS allocates procedure number. Submission of the dossier to the RMS and CMSs. Validation of the application.
Assessment Step I	
0	RMS starts the procedure.
70	RMS forwards the Preliminary Assessment Report (PrAR) (including comments on SmPC, PL and labeling) on the dossier to the CMSs and the applicant.
100	CMSs send their comments to the RMS, CMSs, and applicant. It may also be sufficient for the CMS to indicate in CTS only in case there are no additional comments.
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
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. The CMS are informed via e-mail and CTS will be updated accordingly.
Assessment Step II	
120	RMS sends the DAR, draft SmPC, draft labeling and draft PL to CMSs and the applicant.
145	CMSs send comments to RMS, CMSs, and the applicant. It may also be sufficient (Day 25) for the CMS to indicate in CTS only in case there are no additional comments.
150	RMS may close procedure if consensus reached.
180	If consensus is not reached by day 150, RMS to communicate outstanding issues (Day 60) with applicant, receive any additional clarification, prepare a short report, and forward it to the CMSs and the applicant.
195	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.
195-210	RMS consults with the CMSs and the applicant to discuss the remaining comments raised. Closure of the procedure including CMSs approval of assessment report, SmPC, (Day 90) labeling and PL, or referral to Co-ordination group. Proceed to national 30 days step for granting MA.

- **Nationalised Procedure:**

The National Procedure is a regulatory pathway for the authorization of medicinal products in the European Union (EU) that allows a company to apply for marketing authorization in one member state only. The National Procedure is used when a company intends to market a product in only one EU member state (23). The National Procedure timeline is determined by the individual member state's regulatory authority and may vary between countries. However, the general steps involved in the National Procedure include the following:

- Submission of the Marketing Authorization Application (MAA) to the national regulatory authority, including all relevant documentation such as the product dossier, clinical trial data, and labeling information.
- The regulatory authority evaluates the MAA, including quality, safety, and efficacy data, and may request additional information from the applicant.
- The regulatory authority prepares an assessment report and, if necessary, seeks input from relevant expert committees or advisory groups.

- The regulatory authority makes a decision on whether to grant national marketing authorization based on the evaluation of the MAA and assessment report.
- If national marketing authorization is granted, the product can be marketed in the respective member state.

The timeline for the National Procedure can vary depending on the specific requirements of the individual member state's regulatory authority. Typically, the timeline may take several months or longer to complete, depending on the complexity of the product, the data submitted, and the regulatory workload. It is important to note that the National Procedure only allows for marketing authorization in one EU member state. If a company intends to market a product in multiple member states, they may need to consider other regulatory pathways such as the Mutual Recognition Procedure (MRP) or the Decentralized Procedure (DCP). In general, national regulatory procedures for the authorization of medicinal products may involve the submission of an application to the national regulatory authority, followed by an evaluation of the application by a committee of experts. The evaluation process may involve the review of clinical data, non-clinical data, and quality data, as well as an assessment of the benefit-risk balance of the product (23, 24). If the national regulatory authority determines that the product meets the regulatory requirements, it may grant marketing authorization for the product in that member state. The marketing authorization granted by a national regulatory authority is only valid in the member state in which it was granted. However, the EU has established a harmonized regulatory framework for the authorization of medicinal products, which is designed to ensure that all medicinal products authorized in the EU meet the same high standards for safety, efficacy, and quality (24). The EU regulatory framework includes the Centralised Procedure, the Decentralised Procedure, and the Mutual Recognition Procedure, which provide a streamlined and efficient pathway for the authorization of medicinal products that is valid throughout the EU.

Differences Between Different Marketing Authorization Procedures

Procedures	Brief Description
National Authorization	Used for products that fall outside the scope of the EMA centralized procedure. Where MA is required in one country. Simple procedure involving one Member State.
Decentralised Procedure	Used for products that fall outside the scope of the EMA centralized procedure. Simultaneous authorization in numerous countries in the EU.

	A positive outcome results in numerous country approvals. Sponsor can select which countries to apply to. The number of countries is more than one and doesn't have to be all EU countries.
Mutual Recognition Procedure	Used for products that fall outside the scope of the EMA centralized procedure. Individual application to one country within the EU, followed by subsequent applications to other countries. Generally used for extending marketing approvals in other Member states. When the procedure is repeated to extend MAs in other Member States, it is called Repeat Use Procedure.
Centralized Procedure	Mandatory for certain types of Human Medicinal Products such as those developed by certain biotechnological processes, advanced therapy medicinal products, designated orphans, and those containing new active substances for the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorders, diabetes, autoimmune diseases, other immune dysfunctions, and viral diseases. One application applies to all EU countries.

EU Active Substance Master File (EU - ASMF)

The main objective of the Active Substance Master File (ASMF) procedure, formerly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or "know-how" of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorization (MA) holder to take full responsibility for the medicinal product and the quality and quality control of the active substance (25). NCA/ EMA thus have access to the complete information that is necessary for an evaluation of the suitability of the use of the active substance in the medicinal product. The ASMF procedure can be used for the following active substances, including herbal active substances/preparations, i.e.,

- New active substances
- Existing active substances not included in the European Pharmacopoeia (Ph. Eur.) or the pharmacopoeia of an EU Member State
- Pharmacopeial active substances included in the Ph. Eur. or in the pharmacopoeia of an EU Member State

Note: The ASMF procedure cannot be used for biological active substances.

EDQM Certificate of Suitability (EDQM - CEP)

A Certificate of Suitability (COS) is a document issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM), which is part of the Council of Europe. The COS certifies that a substance, such as an active pharmaceutical ingredient (API), complies with the European Pharmacopoeia (Ph. Eur.) monograph and with the relevant European Union (EU) regulations (26).

- The COS is required for certain substances that are used in the manufacture of pharmaceutical products, including human and veterinary medicines. It demonstrates that the substance has been subjected to a thorough evaluation by the EDQM and is of appropriate quality for use in pharmaceutical products that are intended for sale in the EU.
- The COS includes information about the substance, such as its name, chemical structure, and purity, as well as details of the tests that were carried out to evaluate its quality. The certificate also includes the name and address of the holder of the COS and the date of issue.
- The COS is an important document for pharmaceutical companies that use substances in the manufacture of their products. It provides assurance that the substance is of suitable quality for use in pharmaceuticals and can help to expedite the regulatory approval process for new drugs or variations to existing drugs that contain the substance.
- A pharmaceutical product must first get marketing permission in order to be sold and promoted lawfully in the European Union (EU). The European Medicines Agency (EMA), which is in charge of evaluating the efficacy, quality, and safety of new medications, is in charge of overseeing the procedure.
- A drug producer must submit a marketing authorization application (MAA) to the EMA in order to receive marketing authorisation in Europe. The MAA provides details on the drug's quality, manufacturing process, and labelling in addition to data from preclinical and clinical trials that show its safety and effectiveness.

CONCLUSION:

The use of European drug regulations has been crucial in ensuring that drugs used in the European Union (EU) are safe, effective, and of high quality. The European Medicines Agency (EMA) is responsible for the regulation of medicines in the EU, and it oversees the authorization, monitoring, and assessment of medicines for human and animal use. The regulatory framework provided by the EU ensures that pharmaceutical companies follow strict guidelines during the development, manufacturing, and distribution of drugs. Overall, the use

of European drug regulations has been beneficial for patients, healthcare providers, and pharmaceutical companies, and it will continue to play an important role in ensuring the safety and efficacy of medicines in the EU.

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