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Alternative Marketing Authorisation Routes for ASMF Submissions Across the Europe

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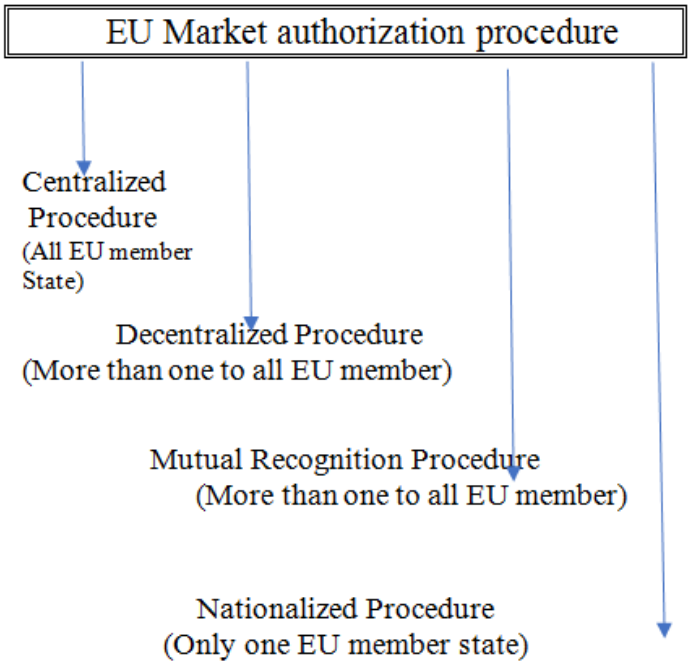
Abstract: *The European regulatory framework provides several pathways for obtaining Marketing Authorisation (MA) for medicinal products, including those involving Active Substance Master Files (ASMF). An ASMF is a detailed document submitted by the manufacturer of the active substance (API), containing confidential information about the manufacturing process, quality control, and other critical data. This allows the marketing authorisation holder to reference the ASMF without disclosing information.Traditionally, medicines are authorised through national procedures when intended for a single Member State or through centralized procedures, mutual recognition procedures, or decentralised procedures when multiple Member States are involved.*

Keywords: Marketing Authorisation, ASMF, API, Centralized procedure, Mutual recognition, National procedures, Decentralised procedures

I. INTRODUCTION

The EU's pharmaceutical regulatory framework maintains the safety, effectiveness, and quality of medicines by working through a combined network of national agencies and the European Medicines Agency (EMA).One of the most critical component of this process is the Active Substance Master File (ASMF) procedure, which enables the confidential submission of comprehensive information regarding the active pharmaceutical ingredient (API).



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Although the ASMF procedure is broadly recognized, the procedures for obtaining marketing authorisation differ among European countries, influenced by national regulatory rules and the selected authorisation pathway. As a result, alternative marketing authorisation routes have been developed and implemented to better meet applicants' specific requirements and to make an evaluation process very simple. This introduction discusses the different alternative pathways for ASMF submissions across Europe, outlining their regulatory foundations, main variations, and the strategic significance for pharmaceutical companies.

II. AIM & OBJECTIVES

Aim

It aims to provide a comprehensive understanding of how these routes—namely the National Procedure, Mutual Recognition Procedure (MRP), Decentralised Procedure (DCP), and Centralised Procedure—can be effectively utilized to obtain marketing authorisation in different EU Member States.

Objectives

- To explore and critically evaluate alternative marketing authorisation (MA) routes applicable to Active Substance Master File (ASMF) submissions across the European regulatory landscape.
- To assess the regulatory frameworks that allow the use of ASMFs in centralised, decentralised, mutual recognition, and national procedures.
- To provide guidance on regulatory best practices and harmonization opportunities for pharmaceutical applicants and active substance manufacturers.

III. METHODOLOGY

The approach used to explore alternative marketing authorisation pathways for Active Substance Master File (ASMF) submissions across Europe followed a series of steps intended to provide a detailed and structured examination of the regulatory landscape.

The method of submitting an ASMF is determined by the type of Marketing Authorisation Application (MAA) being followed, which may include the Centralised, Decentralised, Mutual Recognition, or National procedures.

Centralized Procedure :

To centralize an Active Substance Master File (ASMF) in Europe for a product under the Centralised Procedure, a single EU-wide ASMF submission must be made to the European Medicines Agency (EMA) through their eSubmission Gateway, using the electronic Common Technical Document (eCTD) format.

It is a single, EU wide pathway which is governed by European Medicines Agency (EMA). It allows manufacturer to sell their medicine throughout the EU, Iceland and Norway with one application and one authorization.

The Manufacturer submits application to European Medicines Agency (EMA).

EMA's Committee for Medicinal products for Human Use (CHMP) carry out to assess the application and provides a recommendation on whether the medicine should be approved for marketing.

However, according to EU law, the EMA does not have the power to grant marketing authorisation in individual EU member states. Instead, the European Commission serves as the authorizing authority for all centrally approved products and makes a legally binding decision based on the EMA's recommendation. This decision is issued within 67 days of receiving the EMA's opinion.

Once approved by the European Commission, the centralised marketing authorisation becomes valid across all EU Member States, as well as in the European Economic Area (EEA) countries, including Iceland, Liechtenstein, and Norway.

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Benefits:

- To authorized in all EU countries at same time.
- To monitor centralize safety.
- Avaibility of Product detail in all languages at same time.

Limitations:

- Higher application and maintenance fees.
- Requirement of more comprehensive and robust data.
- No Flexibility for National Approval. (If the marketing authorisation is refused via CP, the product cannot be marketed in any EU member state.)

Scope:

- Orphan Medicines
- New active substances for certain diseases
- Biotechnological products
- Veterinary medicinal products

Flowchart

Presubmission Meeting with EMA
↓
Submit application through submission Gateway
↓
Start the procedure (Day 1)
↓
Preparation of assessment report (AR)
↓
List of Questions (Day 120)
↓
3 -6 months to answer question
(Clock stop)
↓
Assessment of responses
(Restart the clock)
List of outstanding issues (Day 180)
↓
Company Response
1-3 months
(Clock stop)
↓
Oral Explanation (Day 181)
(Restart the clock)
↓
CHMP Final opinion (Day 210)
↓
Possible Re-examination
Final opinion
Max. 60 days

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↓

Publish Commission decision
(Day 277)

Timelines:

Stage	Timeline (approx.)
Submission to EMA	0 – 30 days
Evaluation (CHMP)	0-210 Days
EC decision	~ 67 days after CHMP opinion
Total time	~277 days

(Table-1: Timeline for Centralized Procedure)

Step	Authority involved	Key activities
1.Pre- submission phase	EMA	Applicant requests a product Team Meeting for scientific advice or protocol assistance.
Submission of MAA	EMA	Marketing Authorization Application (MAA) submitted to EMA. EMA performs technical validation (0-30 days)
Evaluation phase I (0 to 120 Day)	CHMP (Committee for medical products for Human use)	Assessment of Full dossier and CHMP issues List of Questions
Clock Stop	Sponsor	Applicant responds to List of Questions. (Approx. 1 to 3 months)
Evaluation phase II (Day 121-210)	CHMP	Review of responses. List of Outstanding Issues may be raised. And Oral Explanation may be requested.
CHMP Final opinion (Day 210)	CHMP	Final Positive or Negative opinion
EC Decision (Day 277)	European Commission	CHMP sent opinion to EC. EC issues Legally MA decision
Publication	EC && EMA	Decision published on the Official journal of EU

(Table-2: Overview of Stepwise key activities forCentralized Procedure)

Examples:

i. Dapagliflozine (Forxiga)
MAH: AstraZeneca AB
Type: Small –molecule antidiabetic
Approved: 2012 (CP)

ii. Dolutegravir (Ticicay)
MAH: ViiV Healthcare UK Ltd
Type: HIV integrase inhibitor
Approved: 2014 (CP)

Decentralised procedure :

It is used for the drug which has not received market authorization in any EU country.

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The Decentralised Procedure permits a company to request marketing authorisation in several EU/EEA countries at the same time, provided the medicine has not been approved in any EU country yet.
One Member State (MS) serves as the Reference Member State (RMS) and leads the procedure, which may be proposed by the sponsor.
In this procedure, the application is submitted at the same time to multiple Member States. One country takes on the role of Reference Member State (RMS), carrying out the initial evaluation, while the remaining Member States, known as Concerned Member States (CMSs), review and comment on the draft assessment report.
If a medicine might seriously harm public health, the Concerned Member State (CMS) will notify the other CMSs.
All Member States come to an agreement on the necessary action. If they are not come on one platform, then CHMP involve and take final decision.

Benefits:

- To Speed up access to multiple markets without repeating the same process in each country.
- To Facilitates earlier availability of medicines to patients across the EU/EEA.
- To minimize repetitive work and results in a more streamlined regulatory assessment.

Limitations:

- Collaboration between RMS and CMS is crucial.
- Objections from CMSs may lead to delays.
- Limited to products which are not previously authorized in any EU state.

Scope:
Applicable to generic, biosimilar, or other medicinal products not yet approved in any EU country

Flowchart

Start
↓
Applicant prepare dossier
↓
Select RMS & CMS
↓
Submit application to RMS and all CMA
↓
Validation phase (14 days)
↓
Assessment phase I (0-70 days)
↓
Start procedure by RMS and inform to CMS (Day 0)
↓
CMS submit comments to RMS and applicant (Day 100)
↓
Clock stop
Applicant respond to all equations
(within 3 months it can be extended if required.)
↓
Assessment phase II
RMS send to CMS and applicant (Day 120)

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↓

If agreement reached: End the procedure (Day 210)

↓

Each Concerned Member State (CMS) grants a national marketing authorization.

Timelines:

Phase	Timeline (approx.)
Validation	~ 14 days
Assessment I	Day 0-70
CMS feedback	Day 70-100
Clock stop	3 months it can be extended if required.
Assessment II	Day 105-120
Closure	Day ~120

(Table-3: Timelines for Decentralised procedure)

Step	Responsible party	Key activities
Pre-procedural phase	Applicant	Applicant chooses RMS & CMS, confirms slot with RMS, prepares dossier (Module 1-5) and ASMF if applicable.
Validation phase	RMS/CMS	Validate the dossier for completeness and acceptability
Assessment Phase I	RMS	RMS evaluate dossier and issues Preliminary Assessment Report (AR)
Comments Phase I	CMS	CMS review AR and provide comments to RMS/Applicant.
Applicant Response	Applicant	Applicant provides written response and revised dossier (if needed)
Assessment phase II	RMS	RMS updates AR based on responses and prepare Final Assessment report.
Agreement Phase	RMS/CMS	CMSs agree or raise issues; if agreement reached, procedure closed positively.
National Phase	RMS/CMS	Each Member state grants its national marketing authorization based on the Final Assessment.

(Table-4: Overview of Stepwise key activities for Decentralised procedure)

Example:

Atorvastatin Teva(Atorvastatin calcium tablets)

Procedure Type : Decentralised (RMS: Netherlands , CMSs: Germany , France , Spain, Italy)

Product Typpe : Generic (small molecule)

Mutual recognition procedure:

The Mutual Recognition Procedure enables a marketing authorisation approved in one EU Member State (also called Reference Member state or RMS) to be acknowledged by one or more additional EU/EEA countries (also called Concerned member State or CMS).

It is applied when a medicinal product has already been granted a national marketing authorisation in at least one EU/EEA country, and the company seeks to extend that authorisation to additional countries.

The applicant is required to submit the same application for mutual recognition to all Concerned Member States and nominate one Member State to act as the RMS.

The Reference Member State (RMS) is either requested to prepare a new assessment report for the medicine or, if needed, to revise an existing one.

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Once the assessment report is finalized, it is distributed to all Concerned Member States along with the approved Summary of Product Characteristics (SmPC), labelling, and package leaflet.

Benefits:

- To improve regulatory efficiency without compromising the high standards of safety and efficacy.
- To reduce duplication of work and speed up the availability of important medicine.

Limitations:

- Timelines may be extended if CMSs require additional clarification or data.
- Coordinating with multiple agencies and managing country-specific requirements (like translations) can be complex.

Flowchart

Start
↓
Applicant submit application to RMS / CMS
↓
RMS circulate Assessment report to CMS
(14 Days)
(Validation phase by CMS)
↓
CMS review and revert with comments if any
↓
Comments/Objections (50-60 days)
↓
Clock stop (If CMS raise concerns)
↓
Applicant response
↓
RMS close the procedure consensus is reached. (90 Days)

Step	Key activities
Existing Marketing Authorization	The product needs to be authorized at the national level in the RMS.
MRP Application	Submission of the dossier and assessment report to the RMS and CMS
Validation phase	To check dossier by each CMS (~14 days)
CMS Evaluation	To review RMS's assessment and raise concern by CMSs
Procedure closure	If all agree each CMS issue its own national MA (~ 90 days)

(Table-5: Overview of Stepwise key activities for Mutual Recognition Procedure)

Examples:

i. Ibuprofen tablets (Generic Medicines)

A generic version of ibuprofen receives national marketing authorisation in Germany (RMS). The marketing authorisation holder (MAH) then applies via MRP to extend the approval to Austria, the Netherlands, and Spain (CMSs).

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ii. Paracetamol oral suspension (Over-the-Counter (OTC) Products)
After national authorisation in Sweden, the company uses MRP to expand the product to other Nordic countries like Finland and Denmark.

iii. Clotrimazole cream (antifungal) (Dermatological Products)
Approved nationally in Poland; then recognition is sought in Hungary, Czech Republic, and Slovakia through MRP.

National Procedure
The National Procedure is applied when a Marketing Authorisation Application is filed with just one EU Member State, and the medicine is intended to be marketed exclusively within that country.
It is applicable when the product has not been approved in any other EU Member State.
They apply to variations or extensions—like adding new strengths, pharmaceutical forms, or routes of administration—of marketing authorisations previously granted at the national level.
It is beneficial for manufacturers to secure marketing authorisation in particular EU Member States.
In this procedure, the applications are evaluated by the relevant authorities of the corresponding EU Member State.

Benefits:
- Simpler and faster for products intended for one market.
- The regulatory process is simpler than that of other EU authorisation pathways.
- Provides an opportunity to launch in a single country before pursuing wider market access.

Limitations:
- Restricted to one Member State and cannot be used for marketing in other EU/EEA countries.
- Requires separate applications if the product is to be marketed in other countries.

Scope:
For small companies looking to test a product in a local market.
For OTC or generic drugs.

Flow chart:

Start
↓
Dossier preparation by Applicant in CTD format
↓
To submit market authorization application to National competent Authority (NCA)
↓
Validation phase (~ 30 days)
↓
Assessment phase (~ 150-210 days)
↓
Issue Query by NCA
↓
Response by Applicant against Query
↓
Final decision by NCA
↓
Market Authorization granted

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Examples:

Generic paracetamol tablets

A generic drug manufacturer chooses to launch a low-cost generic in Hungary only, using the national procedure via the Hungarian Medicines Agency (OGYÉI).

Vitamin D drops formulated for the Nordic population

A product formulated to meet local guidelines or consumer preferences is authorised only in **Sweden** via the national procedure. This is common when formulations differ from EU-wide standards.

Post approval Life cycle Management for Marketing Authorization Routes:

Post-approval life-cycle management (PALM) refers to the ongoing regulatory activities carried out after a medicinal product has received marketing Authorisation (MA). It ensures that any changes (variations) to the product, it's manufacturing, quality, safety, or labelling are properly assessed and approved through the appropriate regulatory route.

Types of variations:

Type IA:

Minor change with no significant impact on the quality, safety or efficacy of the product (e.g. change in batch size of excipient, minor administrative change).

These variations are mainly administrative or technical and can be implemented without prior approval but must be notified immediately after implementation.

Type IA variations are listed as below:

Administrative Changes (Change in the name or address of the MA holder , Change in the name/address of the manufacturer (no change in site) .

Quality Changes (Change in batch size (within approved limits) , Minor change in the specification of an excipient , Introduction of a new certificate of analysis template, Changes to analytical methods)

Submission Requirements:

Cover letter

Application form (variation form)

Updated documents (e.g., module 1- 3)

Proof of implementation (if applicable)

Declaration of classification as Type IA

Type IB:

A Type IB variation is a minor change to the terms of a marketing authorisation (MA) that is not classified as Type IA, but also does not have a significant impact on the quality, safety, or efficacy of the medicinal product.

These variations require notification before implementation and cannot be made until the competent authority has conducted a regulatory check (30-day "do and wait" rule).

Type IB variations are listed as below:

Administrative Changes (Change of MAH legal entity , Change in company name (legal entity)

Quality Changes (Addition of a new manufacturer , Change to in-process controls or specifications , Minor changes in synthesis route, Change in packaging components, Change to analytical method)

Manufacturing changes (Change in batch size outside approved range , Change in manufacturing process (non-significant), Change of storage conditions during transportation)

Submission Requirements :

Cover letter

Application form (variation form)

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Revised documentation (e.g., Module 1-3)
Justification and supportive data
Declaration of classification as Type IB

Type II:

A Type II variation is a major change to the terms of a marketing authorisation (MA) that may have a significant impact on the quality, safety, or efficacy of the medicinal product.
These changes require full assessment and prior approval from the relevant authority before implementation.
Type II variations are listed as below:
Changes involving the addition of a new therapeutic indication or a modification to an existing one.
Major changes to the manufacturing process, formulation, product specifications, or impurity profile of either the active substance or the finished product, which could significantly affect the quality, safety, or efficacy of the medicine.
Variations relating to modifications in the manufacturing process or manufacturing sites for the active substance of a biological product.

Submission Requirements

Cover letter
Completed application form (variation form)
Revised documentation (Modules 1–5, as relevant)
Justification and full supporting data
Updated RMP (if applicable)

Extension:

An extension application for a marketing authorisation will be reviewed following the same procedure as the original marketing authorisation to which it pertains.
An extension shall either be granted a separate marketing authorisation following the same procedure as the initial authorisation to which it relates, or it shall be incorporated into the existing marketing authorisation.
Extension of a marketing authorisation' or 'extension' means a variation which is listed as below:

1. Changes to the active substance

Changing the chemical active substance to an alternative form, such as a different salt, ester, complex, or derivative.
Replacement involving a different isomer, an alternative composition of isomers, or the conversion of a mixture into a single isolated isomer.
Alteration of the vector used for antigen production or a change in the source material, including the use of a new master cell bank from a different origin, provided there is no significant impact on the efficacy or safety profile.
Modification of the extraction solvent or the herbal drug-to-preparation ratio, provided that the change does not significantly affect the efficacy or safety profile.

2. Changes to strength, pharmaceutical form and route of administration

Modification in the pharmacokinetics
Modification in the bioavailability profile
Modification or inclusion of a new route of administration
Modification or inclusion of a new pharmaceutical form
Modification or inclusion of a new strength/potency

Submission Requirements

Cover Letter
Application Form

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Comprehensive Dossier (Modules 1–5)
Product Information
Risk Management Plan (RMP)
Additional Data (Stability data, Bioequivalence studies)

Centralized Procedure:

Applicable Authority:
European Medicines Agency (EMA)
(Committee for medicinal Products for Human Use-CHMP and CMDh if required)

Variation Types	Examples	Handled by	Timeline (approx.)
Type IA	Administrative changes (e.g. Manufacturer address)	EMA	~ 30 days (post Implementation)
Type IB	Minor process change	EMA	30 days
Type II	Major change (e.g. new manufacturing site)	EMA / CHMP	60-90 days
Line Extension	New strength / Form /route	EMA (New MA)	Full MA procedure

Table-6: Overview of variation for Centralized Procedure

Decentralised procedure:
Applicable Authority: Reference Member State (RMS) and Concerned Member State (CMS)

Variation Types	Examples	Handled by	Timeline (approx.)
Type IA	Administrative or Minor Quality changes	RMS (informs CMS)	30 days
Type IB	Minor process or control change	RMS / CMS coordination	30 days
Type II	Major change / safety / efficacy change	RMS coordinates joint assessment with CMS	60-90 days
Line Extension	New strength / Form /route	RMS / CMS as a new application	Full MA procedure (DCP)

(Table-7: Overview of variation for Decentralized Procedure)

Mutual recognition procedure:
Applicable Authority: Reference Member State (RMS) and Concerned Member State (CMS) (Similar to DCP but product already authorized in one member state)

Variation Types	Examples	Handled by	Timeline (approx.)
Type IA	Administrative changes	RMS (informs CMS)	30 days
Type IB	Minor manufacturing change	RMS and CMS coordination	30 days
Type II	Major safety or quality change	RMS and CMS coordination	60-90 days
Line Extension	New strength , Form , route	New application	Full MRP timeline

(Table-8: Overview of variation for Mutual recognition Procedure)

National Procedure
Applicable Authority: Single National Competent Authority (NCA)

Variation Types	Examples	Handled by	Timeline (approx.)
Type IA	Change in manufacturer adress	NCA	30 days
Type IB	Minor Quality control update	NCA	30 days
Type II	Major Formulation or safety update	NCA	60-90 days

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Line Extension	New strength , Form , route	New application	Full procedure

(Table-9: Overview of variation for National Procedure)

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