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European Union Marketing Authorisation Procedures

"WHICH REGISTRATION STRATEGY TO FOLLOW?"

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The European Medicines Regulatory System

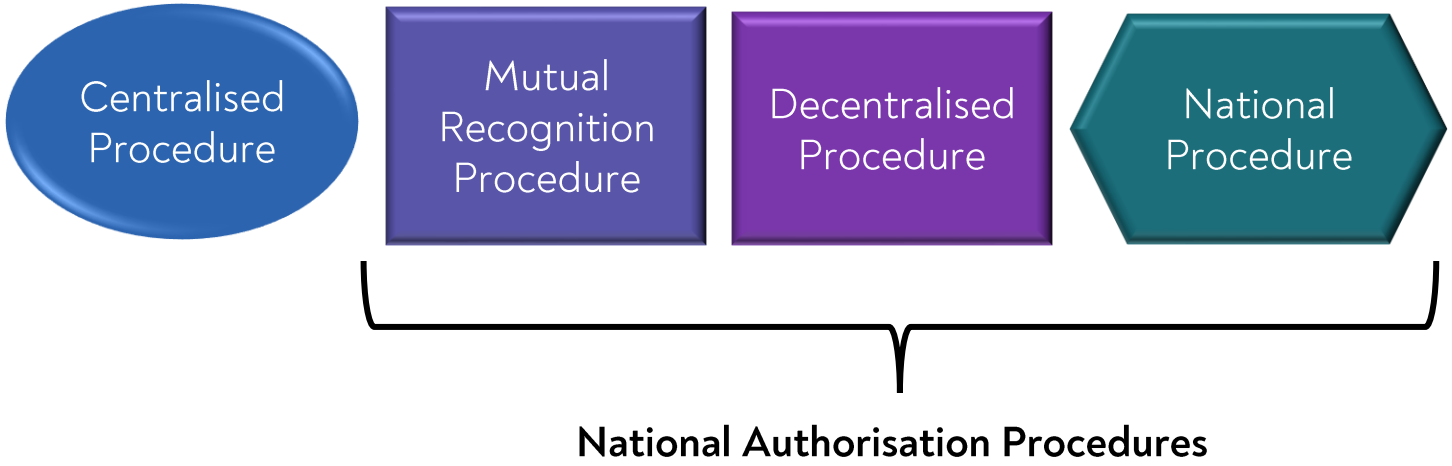
The European Medicines Regulatory System is based on a network of around 50 regulatory authorities from the **30 EEA countries (27 EU Member States plus Iceland, Liechtenstein and Norway), the European Commission and the European Medicines Agency (EMA)**. This network is what makes the EU regulatory system unique.

To protect public health and ensure the availability of high **quality**, **safe** and **effective** medicinal products for European citizens, all medicines products must be authorised before they can be placed on the market. And the Marketing Authorisation Holder must be situated in the EEA.

European Economic Area (EEA) + European Commission + EMA

Marketing Authorisation Routes in the EU

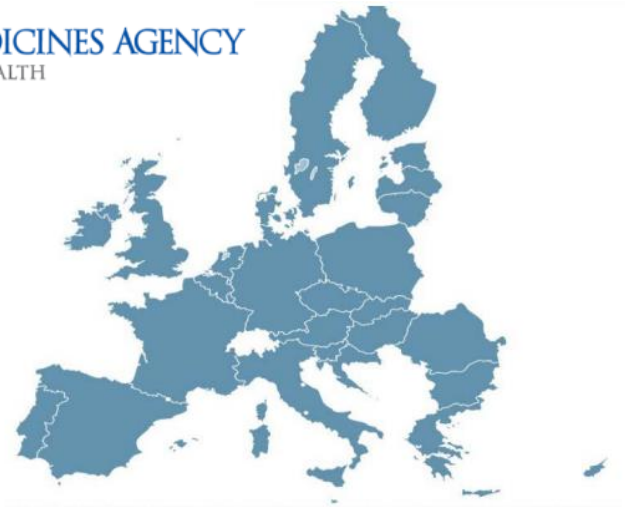
All medicinal products must be authorised before they can be marketed and made available to patients. In the European Union (EU), there are two main routes for authorising medicines: a **centralised route** and a **national route**.



Directive 2004/27/EC – Article 6:
"No medicinal product may be placed on the market of a Member State unless a Marketing Authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EC) nº 726/2004/EC".

- **Do you know the differences between each type of procedure? Let's check…**

Centralised Procedure



The **centralised procedure** allows the marketing of a medicinal product on the basis of a single EU-wide assessment and Marketing Authorisation (MA) which is valid throughout the EEA.

Pharmaceutical companies submit a single authorisation application to EMA. The Agency's Committee for Medicinal Products for Human Use (CHMP) or Committee for Medicinal Products for Veterinary Use (CVMP) then carries out a scientific evaluation of the application and gives a recommendation to the European Commission on whether or not to grant a MA.

Once granted by the European Commission, the centralised MA is valid in all EU Member States, Iceland, Norway and Liechtenstein.

- **The use of the centralised procedure is mandatory in some cases in accordance with the Annex to Regulation (EC) nº 726/2004…**

Centralised Procedure

MANDATORY CP:

1. **Orphan Medicinal Products**

2. **Medicinal products developed by means of one of the following biotechnological processes:**
   - recombinant DNA technology
   - controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells
   - hybridoma and monoclonal antibody methods

3. **Medicinal products for human use containing a new active substance indicated in:**
   - acquired immune deficiency syndrome
   - cancer
   - neurodegenerative disorder
   - diabetes
   - auto-immune diseases and other immune dysfunctions
   - viral diseases

4. **Veterinary medicinal products for use as growth or yield enhancers**

OPTIONAL CP:

1. **Medicinal product that contains a new active substance other than those previously indicated**

2. **Medicinal product constitutes a significant therapeutic, scientific or technical innovation**

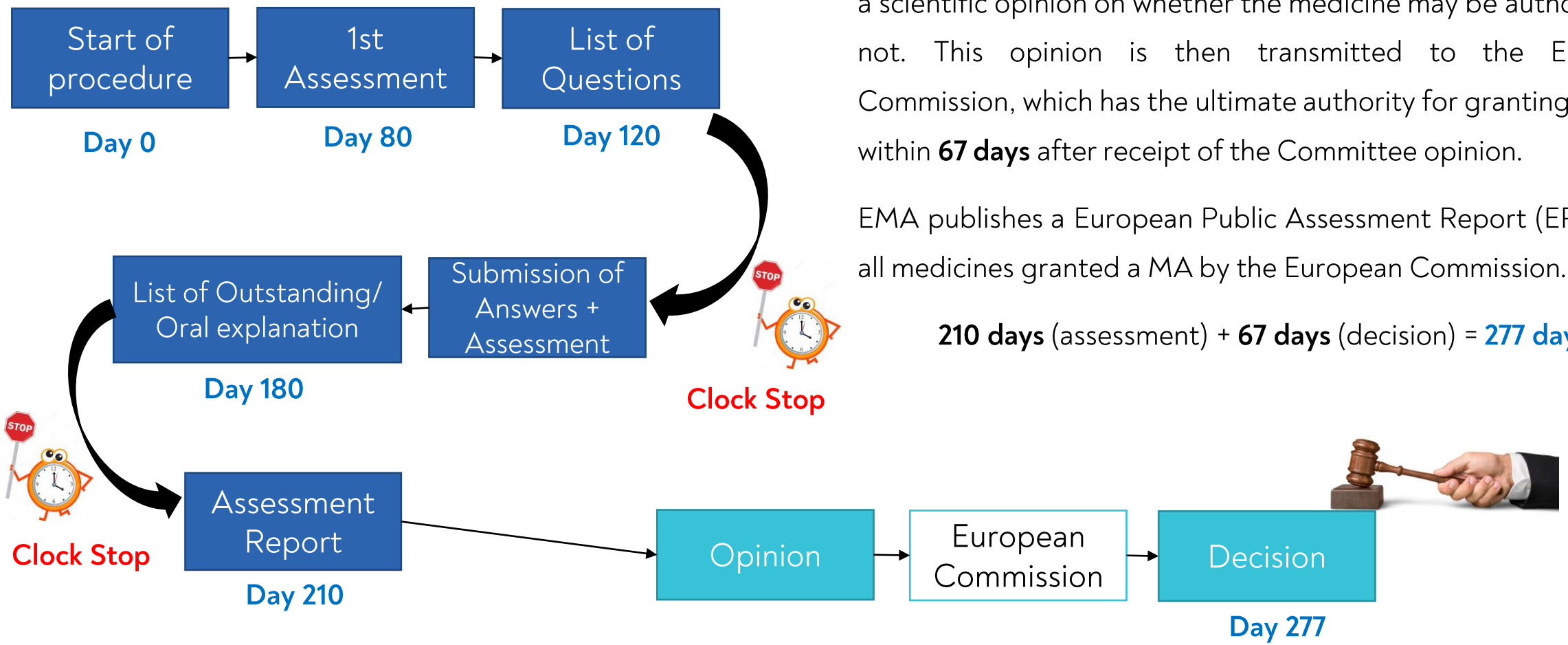
3. **The medicinal product is in the interests of patients or animal health at Community level**

4. **Immunological veterinary medicinal products for the treatment of animal diseases that are subject to Community prophylactic measures**

5. **A generic medicinal product of a reference medicinal product authorised by the Union**

Centralised Procedure

How long does it take?



Upon submission of a valid application, the evaluation takes up to **210 days**, at the end of which the Agency's Committee must issue a scientific opinion on whether the medicine may be authorised or not. This opinion is then transmitted to the European Commission, which has the ultimate authority for granting the MA within **67 days** after receipt of the Committee opinion.

EMA publishes a European Public Assessment Report (EPAR) for all medicines granted a MA by the European Commission.

210 days (assessment) + **67 days** (decision) = **277 days**

Centralised Procedure

Advantages:

1. One single submission to EMA
2. One single Quality, Safety and Efficacy Assessment
3. One single decision in the EEA
4. One single MA simultaneous and valid in all EU Member States and EEA
5. Medicinal products are authorized for all EU citizens at the same time
6. Product information available in all EU languages at the same time (Summary of the Product's Characteristics, Package, Leaflet and Labelling)

Disadvantages:

1. "All or nothing"
2. Less flexible for marketing arrangements
3. The Rapporteur is not selected by the company (chosen among EMA's Committee members and responsible for coordinating the team that assesses the application).

National Procedure

The Competent Authorities of the Member States are responsible for granting MA for medicinal products which are placed on their markets, except for medicinal products which are authorised under Regulation (EC) nº 726/2004 ("Union Authorisations"). In order to obtain a National Marketing Authorisation, an application must be submitted to the Competent Authority of the Member State (the Competent Authority responsible for grating MA for medicinal products for human use in Portugal is INFARMED I.P.).

How long does it take?

Infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

210 days

1. **Submission**
2. **Validation**
3. **Assessment**
4. **Request for supplementary information/ clarifications**
5. **Plenary meeting of CAM ("Comissão de Avaliação de Medicamentos")**
6. **Final Decision**

Mutual Recognition Procedure

A Mutual Recognition Procedure (MRP) is based on existing national decisions. The first step in this procedure is to obtain an MA in a member state of the EU (Reference Member State - RMS). This member state carries out the first evaluation and authorises the medicine nationally. This authorisation is the basis of the application to be submitted in other Member States.

The MA holder shall submit an application in the Concerned Member States (CMS) using the procedure of mutual recognition. The CMS should then recognise the MA already granted by the Reference Member State (RMS) and authorize the marketing of the product on their national territory.

"The starting point for the Mutual Recognition Procedure is always the pre-existence of a purely national MA, that will afterwards be recognised by the CMS"

Mutual Recognition Procedure

How long does it take?

210 days (National Procedure) + **90 days** + **90 days** + **30 days** = **420 days**

National Procedure → Preparation/update of AR → Submission → Validation

210 days

Approx. 90 days before submission to CMS: Applicant requests RMS to update Assessment Report (AR) and allocate procedure number

The RMS shall prepare or update the AR within **90 days** of receipt of a valid application. The AR together with the approved Summary of Product Characteristic (SPC), Package Leaflet (PL) and labelling shall be sent to the CMS and to the applicant.

90 days

Day 0

Assessment → Final Decision → National Step

Day 30: CMSs send their comments to the RMS, CMSs and applicant.
Day 40: Applicant sends the response document to CMSs and RMS.
Until Day 48: RMS evaluates and circulates a report on the applicant's response document to CMSs.
Day 55: CMSs send their remaining comments to RMS, CMS and applicant
Day 55-59: 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.
Day 60: If CMS have no remaining comments at Day 55, the RMS closes the procedure. In case a CMS has remaining comments, the applicant sends the response document to CMSs and RMS.
Day 60-90: The period 60-90 will only be used if a CMS has remaining comments at Day 55.
Until Day 68: RMS evaluates and circulates a report on the applicant's response document to CMSs.
Day 75: CMSs send their remaining comments to RMS, CMSs and applicant.
Until Day 80: A break-out session can be organised around Day 75.
Day 85: CMSs send any remaining comments to RMS, CMS and applicant.

90 days

Day 90: CMS notify RMS and applicant of final position. If consensus is reached, the RMS closes the procedure.

7 days after close of procedure: applicant sends high quality national translations of SmPC, labelling and PL to CMSs.
30 days after close of the procedure: Granting of National Marketing Authorisation in the CMSs subject to submission of acceptable translations.

30 days

Decentralised Procedure

Procedure that can be used only when the medicinal product in question does not have a MA in any Member State of Union.

If no MA has been granted in the Union, the applicant may make use of a decentralised procedure and submit an application in all the Member States where it intends to obtain a MA at the same time and choose one of them as Reference Member State (RMS).

One of the proposed Member States will be asked by the applicant company to act as RMS. The RMS does the initial evaluation of the product and issues a Draft Assessment Report. The other Member States, known as the Concerned Member States (CMS), either agree with the RMS's evaluation or they ask further questions/raise objections.

If all the issues are resolved and the application is successful, each Member State will then issue a MA for that product permitting it to be marketed in their country.

- **New MA where the centralized procedure is not mandatory**
- **Allows for a company to submit a MA application simultaneously in several Member States**

Decentralised Procedure

210 days + 30 days = 240 days

How long does it take?

Submission → Validation → Assessment I → Clock Stop → Submission of response → Assessment II → Final Decision → National Step

Day 0

Day 70: RMS forwards the Preliminary Assessment Report (including comments on SPC, PL and labelling) to CMSs and applicant
Day 100: CMSs send their comments to the RMS, CMSs and applicant.
Until Day 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 Stop

Max 6 Months

Day 106: RMS restarts the procedure following the receipt of a final response

120 days

Day 120 (Day 0): RMS sends the Draft Assessment Report and draft SPC/PL/labelling to CMSs and the applicant.
Day 145 (Day 25): CMSs send comments to RMS, CMSs and the applicant.
Day 150 (Day 30): RMS may close procedure if consensus reached.
Until 180 (Day 60): If consensus is not reached by day 150, RMS to communicate outstanding issues with applicant, receive any additional clarification, prepare a short report and forward it to the CMSs and the applicant.
Day 195 (at the latest): A Break-Out Session may be held at the EMA with the involved MSs to reach consensus on the major outstanding issues.

90 days

Day 210 (Day 90): RMS closes the procedure if consensus is reached thar the product is approvable.

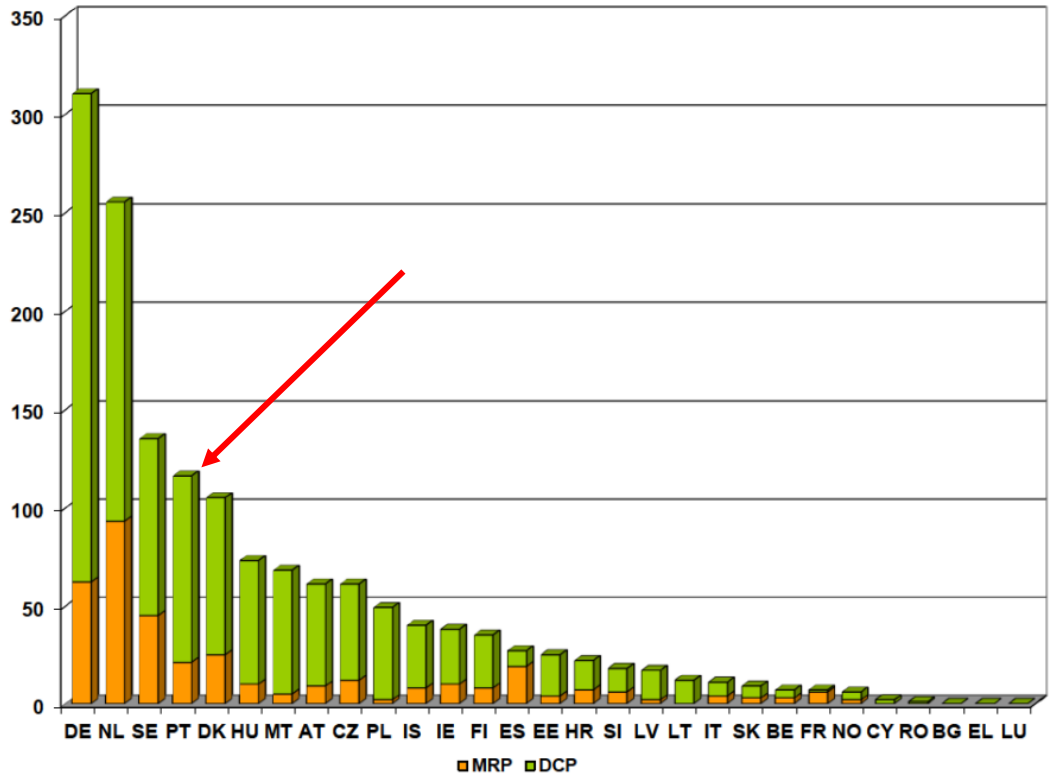
7 days after close of procedure: applicant sends high quality national translations of SmPC, labelling and PL to CMSs and RMS.
30 days after close of the procedure: Granting of National Marketing Authorisation in RMS and CMSs (National Agencies will adopt the decision and will issue the MA subject to submission of acceptable translations).

30 days

Portugal as Reference Member State (RMS)

STARTED Procedures – MRP/DCP per RMS

Total: 366 MRP and 1144 DCP (regarding 703 and 2342 products respectively)



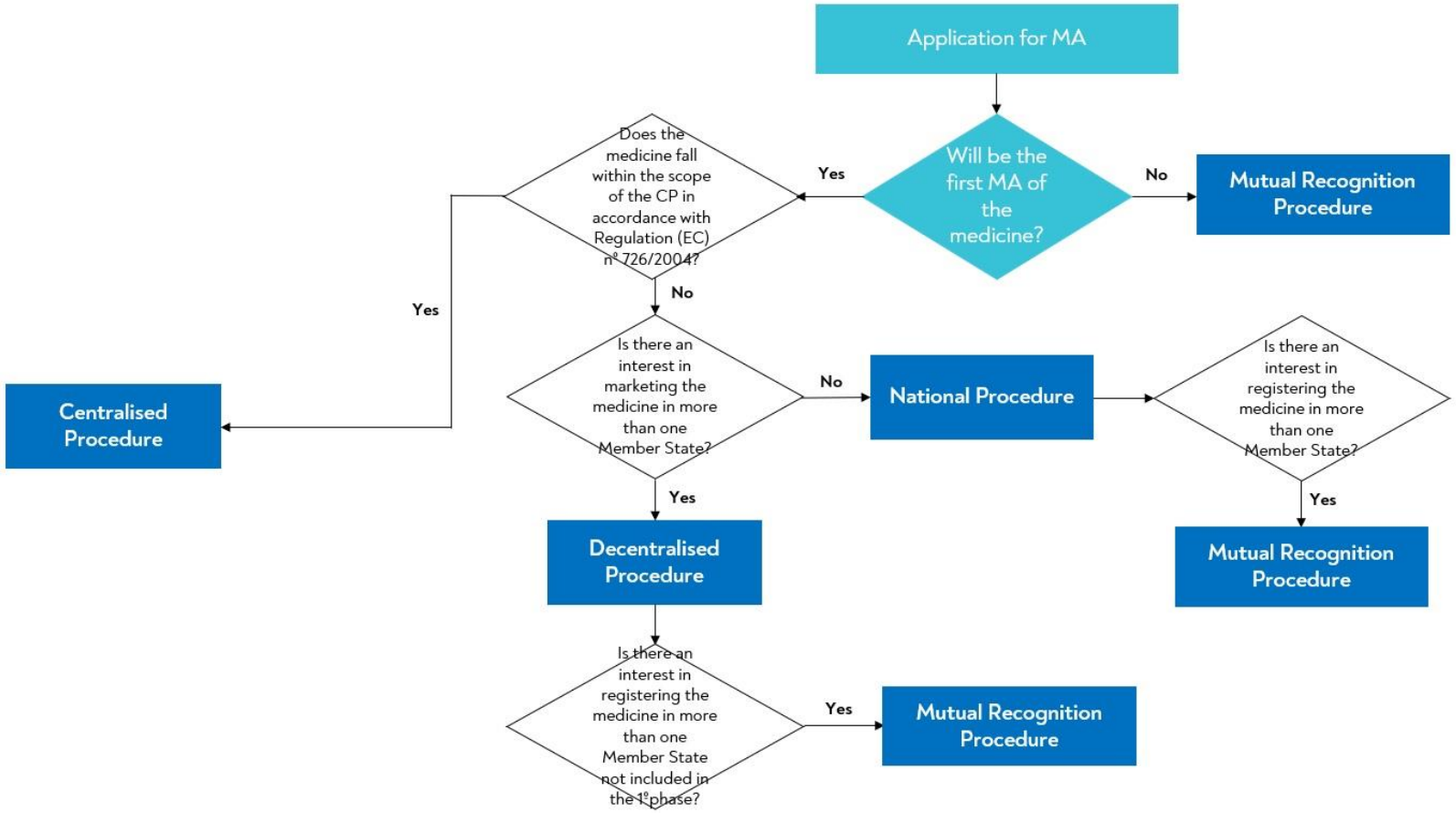
Source: CMDh Statistics 2021.

INFARMED, I.P. participates actively in the Mutual Recognition and Decentralised procedures as RMS.

In 2021, INFARMED, I.P. was one of the Member States that most contribute to the European evaluation system (it was the 4th Member State in number of start procedures as Reference Member State).

Final Remarks

What strategy to obtain a MA in the EU?



Decision on strategy depends on:

a. Type of product

b. Authorisation history in EU

c. Regulatory and Marketing strategy

References

- Regulation (EC) nº 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
- Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use
- Eudralex, Volume 2A – Procedures for Marketing authorization. [Online]. Available: https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-2_en#volume-2a---procedures-for-marketing-authorisation (Last Visited Mar. 16, 2022).
- European Union – country profiles. [Online]. Available: https://european-union.europa.eu/principles-countries-history/country-profiles_en (Last Visited Mar. 16, 2022).
- The centralized procedure at the EMA [Online]. Available: https://www.ema.europa.eu/en/documents/presentation/presentation-centralised-procedure-european-medicines-agency_en.pdf (Last Visited Mar. 16, 2022).
- Marketing Authorisation. [Online]. Available: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation (Last Visited Mar. 16, 2022).
- Marketing Authorisation Procedures. [Online]. Available: https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/autorizacao-de-introducao-no-mercado/procedimentos_de_aim (Last Visited Mar. 16, 2022).
- CMDh Statistics. [Online]. Available: https://www.hma.eu/human-medicines/cmdh/statistics.html (Last Visited Mar. 16, 2022).
- Flow chart of the Mutual Recognition Procedure. [Online]. Available: https://www.hma.eu/human-medicines/cmdh/procedural-guidance/application-for-ma/mrp/rup.html (Last Visited Mar. 16, 2022).
- Flow chart of the Decentralised Procedure. [Online]. Available: https://www.hma.eu/human-medicines/cmdh/procedural-guidance/application-for-ma/dcp.html (Last Visited Mar. 16, 2022).

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