
NAVIGATING THE EMA

*The EMA procedures for
marketing authorisation
applications and the way
Horizon Scanning in
Amgros uses the data*

FOREWORD

Establishing a better decision base for the healthcare sector is a very important task for Amgros. We monitor the market so that we keep ourselves at the forefront of developments and so that we can build bridges between political, administrative and clinical environments.

Horizon Scanning also contributes to this task.

Our aim is to provide a full overview of new medicines, indications and pharmaceutical forms two to three years before a drug obtains marketing authorisation in Denmark, and to make it easier to predict therapeutic changes and costs.

Our primary source of information is the European Medicines Agency; often abbreviated to the EMA.

We register and monitor applications sent by pharmaceutical companies to the EMA. These can be applications for marketing authorisation for new medicines, as well as applications for major changes to existing marketing authorisations, such as extensions of indications and other extensions. Other extensions include new strengths, as well as new pharmaceutical forms and routes of administration.

We collate information on each type of application in briefings, overviews and lists.

As a service for our stakeholders, we have prepared an easy-to-read introduction to the regulatory procedures at the EMA. These are the same procedures as we follow in Horizon Scanning.

You can either read the introduction in its entirety or just use it as a reference. We hope that this publication will make it easier for you to find exactly what you need more information about.

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DEFINITIONS AND ABBREVIATIONS

CHMP	The Committee for Medicinal Products for Human Use - a committee within the EMA, responsible for scientific assessment of applications for marketing authorisation for medicines.
Clock stop	The time period in which assessment of an application at the CHMP is officially stopped while the applicant prepares replies to questions from the CHMP. The clock starts again when the applicant has submitted the replies.
EMA	The European Medicines Agency
Extension	Changes to the marketing authorisation, such as changes in the active substance, strength, pharmaceutical form and/or route of administration as well as supplementary indications.
D150 Assessment Report	A report prepared by the CHMP on day 150 in the procedure for evaluating applications for marketing authorisation for new medicines
LoOI	List of Outstanding Issues - a series of questions from the CHMP to the applicant in connection with the second clock stop, and any further clock stops, in the procedure to evaluate an application for marketing authorisation for a new medicine. LoOI also applies for the evaluating process for other extensions.
LoQ	List of Questions - a series of questions from the CHMP to the applicant in connection with the first clock stop in the procedure to evaluate an application for marketing authorisation for a new medicine. LoQ also applies for the evaluating process for other extensions.
Opinion	The recommendation from the CHMP, which can be positive or negative, in relation to whether a new medicine, an extension of indication or any other extension should be approved by the European Commission.
Orphan drug	A status designated by the CHMP to a medicine for a specific condition, such as life-threatening diseases or chronic disabling disease. The disease must be rare (less than five cases, per 10,000 inhabitants in the EU). There shouldn't be any existing treatment for the relevant illness, but if it does the medicine must have significant additional benefits for those affected by the disease.
RSI	Request for Supplementary Information - a series of questions sent from the CHMP to the applicant in connection with clock stops in the procedure to evaluate an application for an extension of indication.
Variation	Additional changes to the terms of the original initial application for a marketing authorisation.

A MEDICINE'S STAGES ON THE JOURNEY THROUGH THE EMA

In simple terms, a medicine goes through a lifecycle, which involves research and development, application for marketing authorisation and subsequent changes to this authorisation. Ultimately, the pharmaceutical can be de-registered.

Figure 1 illustrates four different situations in which pharmaceutical companies can ask the EMA to assess whether a new medicine should have marketing authorisation, or an existing authorisation should be changed.

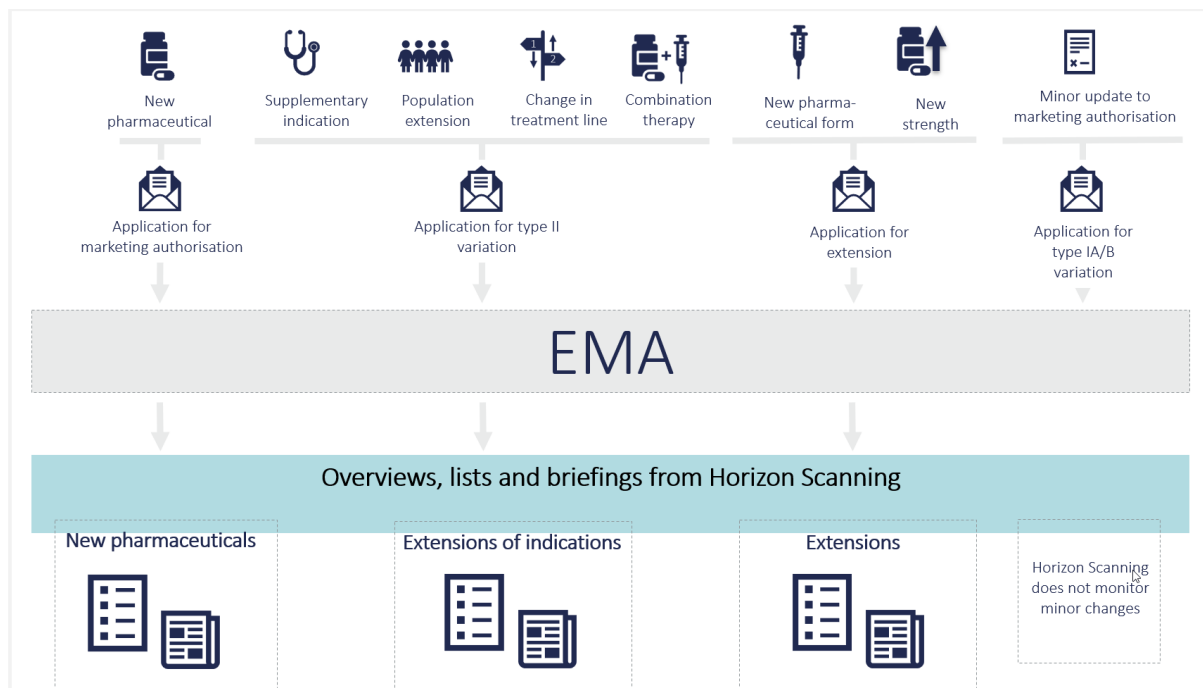


Figure 1 Events in the lifecycle of a medicine in relation to the EMA and Horizon Scanning outputs

When the EMA assesses a new medicine

A marketing authorisation for a new medicine can be obtained throughout the entire EU. This is done by sending an application to the EMA via the centralised procedure for approval of medicines.¹ The EMA coordinates the scientific evaluation of applications for centralised marketing authorisations. The Committee for Medicinal Products for Human Use (CHMP) is responsible for this scientific evaluation. The CHMP meets once a month. The European Commission then issues the final marketing authorisation following a recommendation from the CHMP.

¹ Pharmaceuticals can also be approved via a decentralised procedure in which the marketing authorisation is issued by a national authority

The EMA must assess all medicinal products for human use that originate from biotechnological and other high-technology processes. The same applies for all advanced therapy and medicines for treating HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune diseases and other disorders of the immune system, as well as viral diseases and orphan drugs for rare diseases.

For medicines that do not fall under the categories mentioned above, companies can apply to the EMA for marketing authorisation for a new medicine. This applies if the medicine contains a new active substance and constitutes a significant therapeutic, scientific or technical innovation or in some other way has interest for patients throughout the EU. Finally, generics of centrally authorised medicines and applications for some medicines for paediatric use can go through the centralised procedure.²

When the EMA assesses changes to an existing marketing authorisation

The EMA and the European Commission must approve or register changes to an existing marketing authorisation.

These changes can be divided into four categories:

- Type IA variations
- Type IB variations
- Type II variations
- Extensions

Type IA variations are minor variations to the marketing authorisation. The changes only have a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned. A type IA variation does not require approval from the EMA and the European Commission - applicants just notify the EMA that there have been changes.

Type IB variations are minor variations that are neither a variation of type IA nor a type II nor an extension.

Type II variations are major variations to the marketing authorisation. The changes have a significant impact on the quality, safety or efficacy of the medicinal product concerned. Examples of changes under type II variations are a supplementary indication or changes to an already approved indication.

Extensions are certain changes to the marketing authorisation. Extensions fundamentally change the terms and conditions of the original authorisation. Examples of changes that require an application for extension are changes in the active pharmaceutical substance, strength, pharmaceutical form or route of administration.³

Common for types IB and II variations as well as extensions is that, prior to implementation, they require evaluation from the EMA and approval from the European Commission.

² European Medicines Agency (18 May 2015). Applying for EU marketing authorization. For medicinal products for human use. Localised 1 November 2017 at: http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2011/03/WC500104233.pdf

³ European Commission (24 November 2008). Commission Regulation (EC) No 1234/2008. Localised 1 November 2017 at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2008_1234_cons_2012-11-02/reg_2008_1234_cons_2012-11-02_en.pdf

Processing times for applications to the EMA

The EMA has stipulated time limits for processing the different types of applications. The guarantee only applies for the periods when the EMA is actively evaluating the application. The active evaluation time will be interrupted by at least one clock stop when the applicant is preparing answers to the questions from the CHMP. The clock at the EMA is not running during a clock stop. The clock will start again when the CHMP resumes processing of the application on the basis of the new input from the applicant.

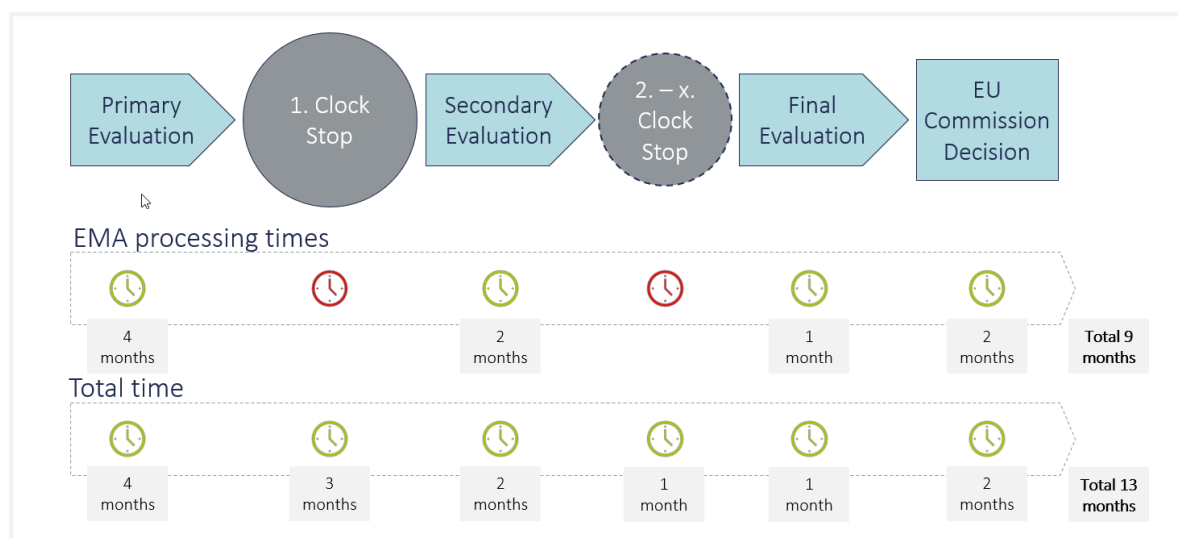


Figure 2 Example of the length of time spent by the EMA and the European Commission on processing an application

There are differences between how much time it takes for an application to go through the procedure for evaluation at the EMA. The number and duration of clock stops can vary considerably. Therefore, it is difficult to assess how long the different stages will take, and when the EMA will be able to issue its final statement. Figure 2 illustrates an example of the difference between the active processing time at the EMA and the total processing time. The total processing time includes processing by the EMA and the European Commission.

HOW HORIZON SCANNING MONITORS A MEDICINE'S JOURNEY THROUGH THE EMA

Horizon Scanning at Amgros registers and monitors the applications submitted to the EMA for marketing authorisation for new medicines, as well as major changes to an existing marketing authorisation (type II variations and extensions). We gather information primarily from the monthly meetings of the CHMP.

We collate information on each application in briefings, overviews and lists for each type of application, as illustrated in figure 1. The overviews show when we expect the applications to reach selected stages in the procedures for evaluation. We have described this in more detail below.

When Horizon Scanning categorises applications to the EMA

For *new medicines*, we distinguish between applications evaluated via the normal procedure and the accelerated procedure.

For *type II variations*, which we refer to as extensions of indication, we make a distinction between applications for:

- Supplementary indication: The applicant applies for authorisation for a new indication for an already approved medicine.
- Change in treatment line: The applicant wants to change the position in the treatment regime for the already approved medicine.
- Combination therapy: The applicant applies for the already approved medicine to be used in combination with another medicine for an approved indication.
- Population extension: The applicant wants to add a new group of patients, for example children, to an approved indication.

Applications for type II variations can include several of the above sub-categories. Finally, a type II variation can relate to the safety of a medicine in the form of restrictions in the marketing authorisation. Horizon Scanning does not register this type of change.

For other *extensions*, we distinguish between applications for:

- A new strength for an approved pharmaceutical form
- A new pharmaceutical form
- A new route of administration

Applications for extensions can also include several of the above sub-categories or type II variations.

Horizon Scanning uses the same standards as the EMA

We also use standards in Horizon Scanning. We work with standards in order to be able to answer questions about when a medicine is likely to be approved. As shown in figure 3, the timeline for the different types of applications varies. The standards are associated with some uncertainty due to variations in the overall timeline, as we described in the section above.

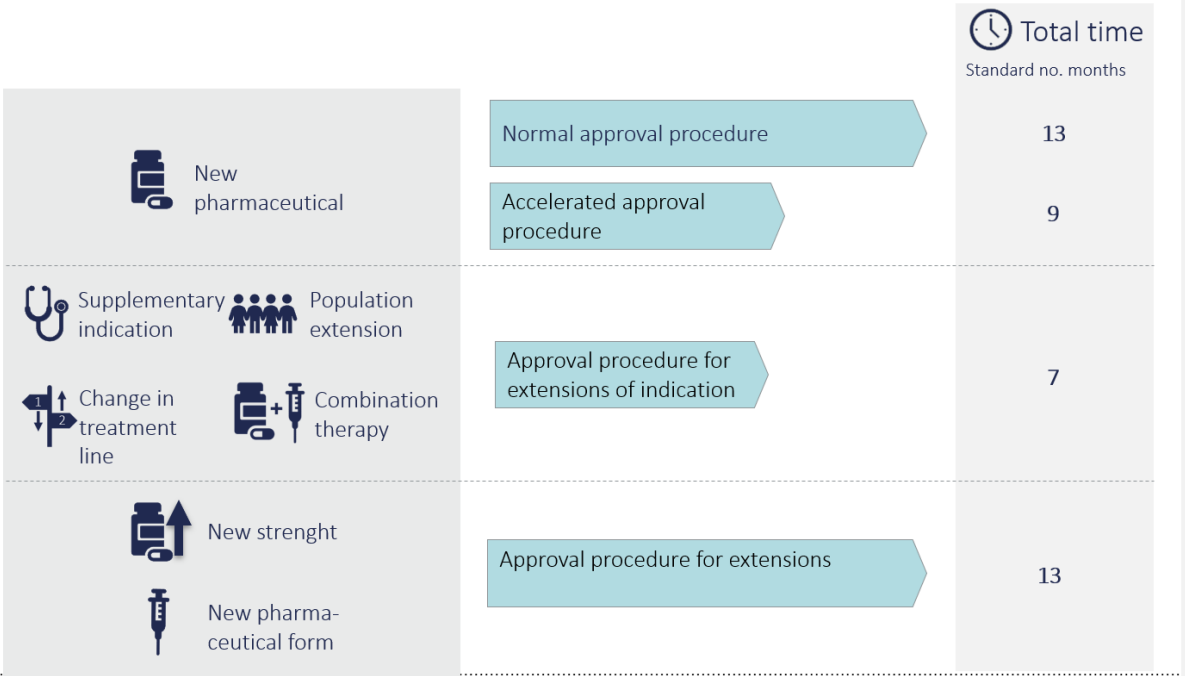


Figure 3 Standards for overall timeline for approval used by Amgro, Horizon Scanning

HOW THE EVALUATION PROCEEDS AT THE EMA

Applications for marketing authorisation for new medicines

Normal procedure

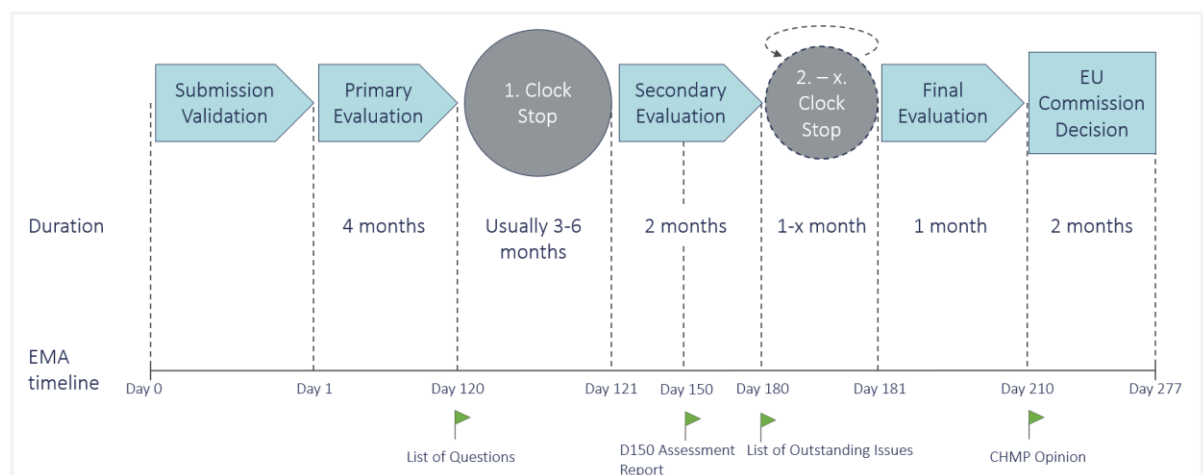


Figure 4 Normal procedure at the EMA and the European Commission for evaluating new medicines

Day 0-120

The normal procedure for evaluating a marketing authorisation for a new medicine starts when the application is validated by the EMA. The procedure starts on the first day of the EMA timeline, as illustrated in figure 4. Day 1 is the start date for the monthly CHMP meeting in the relevant month. Over the following four months, selected rapporteurs from the CHMP conduct the preliminary evaluation of the application. The preliminary evaluation culminates in a List of Questions (LoQ) for the applicant. The CHMP agrees on the questions at a monthly meeting on day 120. After this, the first clock stop begins, when applicants have time to prepare their answers to the CHMP.

Day 121-180

When the applicant is ready with the answers, the CHMP again looks at the application at a monthly meeting and the clock starts at day 121. In the course of the secondary evaluation of the application at around day 150, the selected CHMP rapporteurs draw up a D150 Assessment Report. The applicant receives the report as information about the process. If necessary, at day 180 the reporters draw up a List of Outstanding Issues (LoOI) and/or invite the applicant to an oral explanation at one of the monthly CHMP meetings. After this, the second clock stop begins, when the applicant again has time to prepare answers for the CHMP.

Day 181-277

When the applicant returns from the second clock stop, the clock starts again at the EMA at day 181. If the CHMP considers it necessary, there may be yet another or several rounds of LoOI and/or oral explanations including clock

stops. Then, the CHMP makes its final evaluation. The CHMP adopts an updated report by no later than day 210. At the same time, the CHMP issues a scientific recommendation - its Opinion. This states whether the new drug should be approved. The Opinion can be positive or negative. The European Commission then processes the application and decides finally whether to issue a marketing authorisation for the application. This is by no later than 67 days after the CHMP opinion, i.e. day 277 at the latest.

We estimate when the application will reach selected stages

Horizon Scanning publishes overviews and lists that state when an application is likely to reach specific stages at the EMA. These are day 120 and day 150 in the normal procedure for new pharmaceuticals. Furthermore, we estimate when the CHMP will issue its Opinion, and when the European Commission will finally approve the application.

Accelerated procedure

The CHMP can process an application quicker, if a new drug is particularly important for the public health. This is primarily for therapeutic innovations. The EMA calls these accelerated procedures. In these circumstances, at the request of the applicant, the CHMP decides whether an application is entitled to an accelerated procedure. An accelerated procedure usually takes 150 days, as illustrated in figure 5.

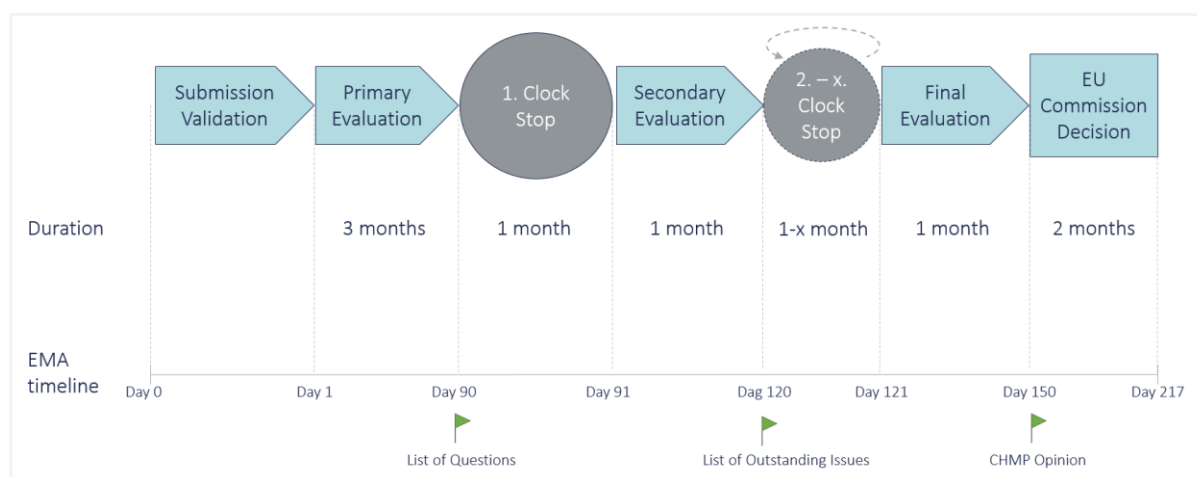


Figure 5 Accelerated procedure at the EMA and the European Commission for evaluating new pharmaceuticals

Day 0-90

The accelerated procedure starts at day 1 with a preliminary assessment after the application has been validated. It usually takes about three months. At day 90, the selected rapporteurs from the CHMP adopts the LoQ. This is done at one of the monthly CHMP meetings. The applicant receives the LoQ, after which the EMA implements the first clock stop.

Day 91-120

When the applicant reports back from the first clock stop with replies to all the questions, the CHMP again looks at the application at a monthly meeting and the clock starts at day 91. The secondary assessment of the application may give rise to a LoOI at day 120. This may result in one or, if necessary, several additional clock stops.

Day 121-217

The final assessment of the application starts at day 121 and by no later than day 150 results in the CHMP adopting an updated report. At the same time, the CHMP issues a scientific recommendation - its Opinion. This states whether the new drug should be approved. The Opinion can be positive or negative. The European Commission then processes the application and decides finally whether to issue a marketing authorisation for the application. This is by no later than 67 days after the CHMP opinion, i.e. day 217 at the latest.

We estimate when the application will reach selected stages

Horizon Scanning publishes overviews and lists that state when an application is likely to reach specific stages. This will be day 90 and day 120 in the accelerated procedure for evaluating new pharmaceuticals. Furthermore, we estimate when the CHMP will issue its Opinion, and when the European Commission will finally approve the application.

Applications for extensions of indication

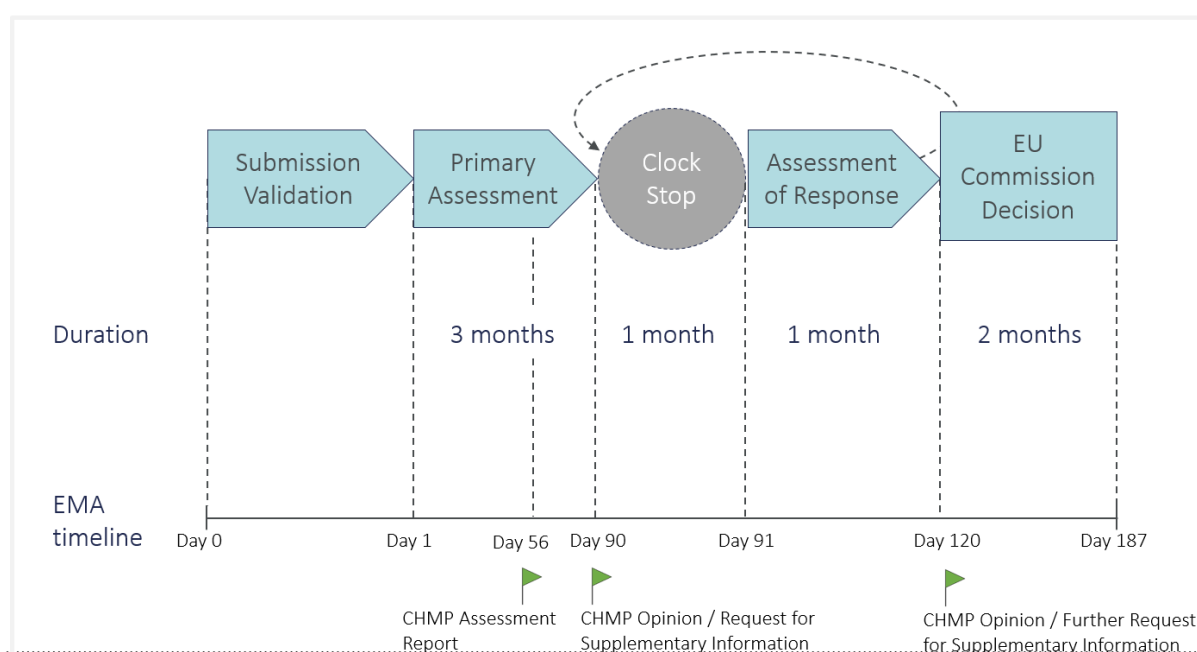


Figure 6 Procedure at the EMA and the European Commission for evaluating extensions of indication for already approved medicines

Day 0-90

The preliminary assessment of an application for an extension of indication for an already approved medicine, starts on the first day after the CHMP has validated the application. The preliminary process usually takes three months, as illustrated in figure 6. During the preliminary evaluation, at day 56 the CHMP prepares a CHMP Assessment Report. If the CHMP does not have any questions about the report, at one of its monthly meetings at day 90, the committee can adopt the final report. At the same time, the CHMP issues a scientific recommendation - its Opinion. The Opinion is about whether the CHMP recommends the extension of indication for approval. If, on the other hand, the reporters have identified unresolved issues regarding the application, they will send the RSI to the applicant. Then the EMA initiates a clock stop, and the applicant typically has a month to respond.

Day 91-187

At day 91, the CHMP starts to assess the applicant's replies. This may give rise to another round of RSI and clock stops. But it may also mean that the CHMP adopts a final report and issues an Opinion. This is by no later than day 120. The Opinion can be positive or negative. After this, the European Commission processes the application and makes a final decision on whether to approve the extension of indication. This is done by no later than 67 days after the CHMP-opinion, i.e. day 187 at the latest.

We estimate when the application will reach selected stages

Horizon Scanning publishes overviews and lists about when an application is likely to reach specific stages. This will be day 56 in the procedure for evaluating extensions of indication. Furthermore, Horizon Scanning estimates when the CHMP will issue its Opinion, and when the European Commission will finally approve the application.

Applications for other extensions

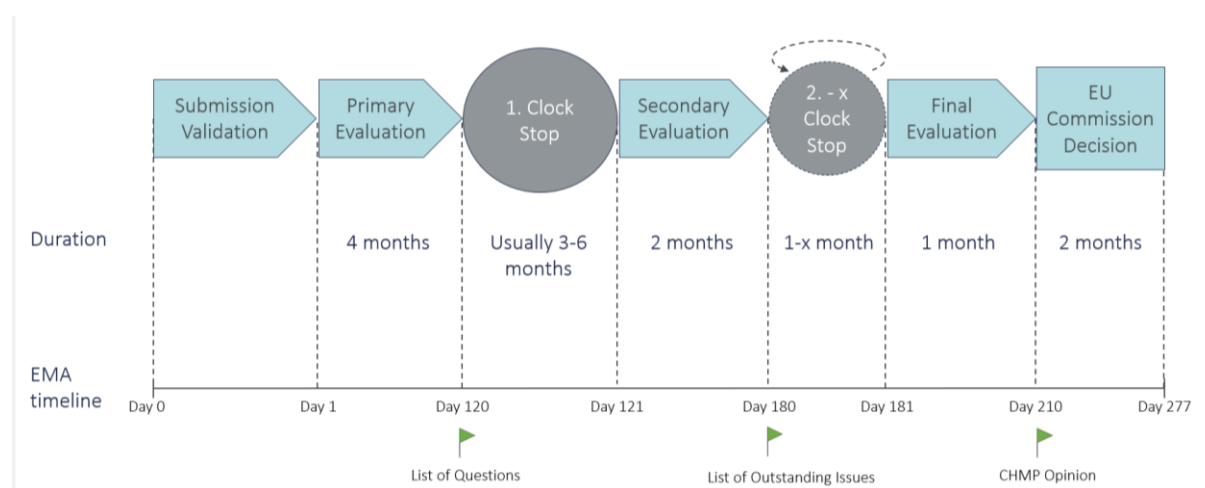


Figure 7: Procedure at the EMA and the European Commission for evaluating extensions for already approved medicines.

Day 0-120

The procedure for evaluating an application for extensions to an existing medicine begins when the EMA has validated the application. The procedure starts at day 1 on the EMA timeline, as illustrated in figure 7. This corresponds to the day the CHMP holds its monthly meeting. Over the following four months, selected rapporteurs from the CHMP conduct the preliminary evaluation of the application. The evaluation culminates in the LoQ for the applicant. The CHMP adopts the questions at a monthly meeting at day 120. After this, the first clock stop begins, when applicants have time to prepare their answers for the CHMP.

Day 121-180

When the applicant returns with answers to the LoQ, the CHMP again assess the application at one of their monthly meetings. EMA starts the clock again at day 121. During the secondary evaluation of the application, around day 150, the CHMP-rapporteurs compile a report, the D150 Assessment report. The applicant receives the report as an information on how the process continues. If necessary, the rapporteurs issue a LoOI at day 180. Hereafter the second clock stops start, were the applicant can prepare answers to the questions issued by the CHMP.

Day 181-277

When the applicant returns from the second clock stop, the clock starts again at the EMA at day 181. If the CHMP considers it necessary, there may be yet another or several rounds of LoOI and/or oral explanations and clock stops. Then, the CHMP makes its final evaluation. The CHMP adopts an updated report by no later than day 210. At the same time, the CHMP issues a scientific recommendation - its Opinion. This states whether the extension should be approved. The Opinion can be positive or negative. After this, the European Commission processes the application and makes a final decision on whether the applicant is to have the marketing authorisation. This is by no later than 67 days after the CHMP-opinion, i.e. day 277 at the latest.

We estimate when the application will reach selected stages

Horizon Scanning publishes overviews and lists about when an application is likely to reach specific stages. This will be day 120 and day 150 in the procedure for evaluating extensions. Furthermore, we estimate when the CHMP will issue its Opinion, and when the European Commission will finally approve the application.



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