


# How new drugs are approved in Europe



A sponsor has several options when seeking approval to market a new drug in Europe: a national authorization procedure, a decentralized procedure, a mutual recognition procedure, or a centralized procedure. Products that must use the centralized procedure include the following:

- all biologic agents or other products made using high-technology procedures
- products for HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions and viral diseases
- products for orphan conditions

This report focuses on the centralized procedure, with a brief overview of the other three procedures provided below.

## **National authorization procedure**

Each country within the EU has its own procedures for authorizing a marketing application for a new drug. A sponsor can consult the website of the regulatory agency in each country in which it is interested in obtaining marketing approval to obtain details of the approval process.

A sponsor can also seek approval of several EU countries simultaneously using the decentralized or mutual recognition procedure.

## **Decentralized procedure**

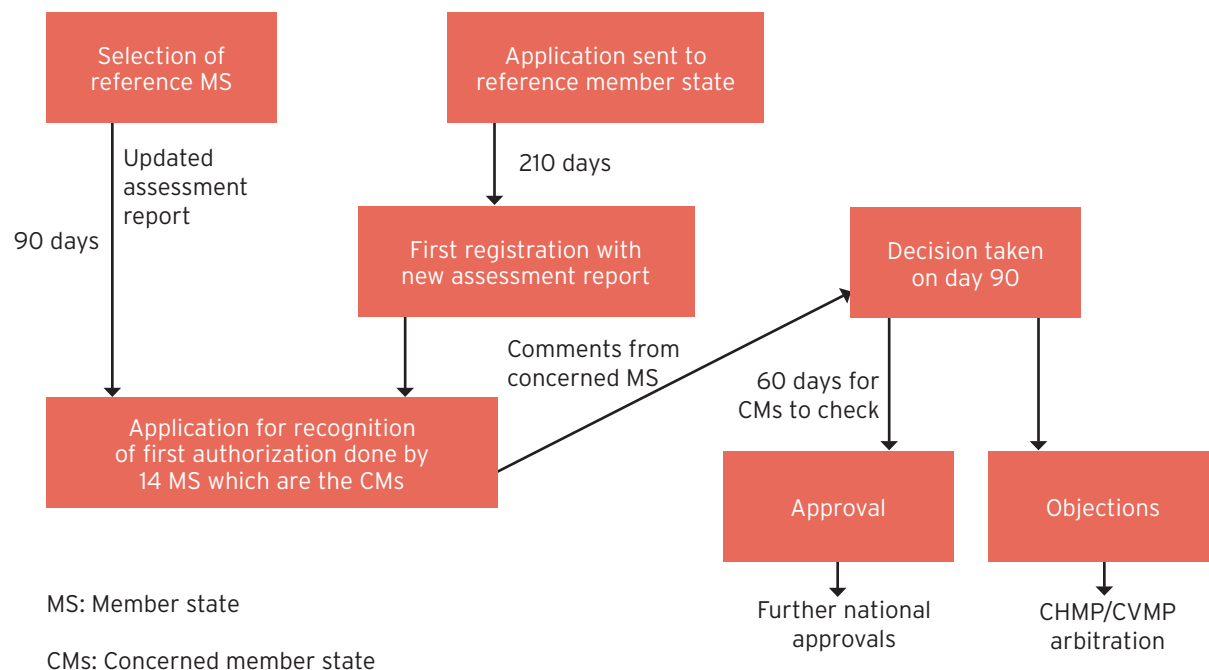
For products that fall outside the scope of the European Medicines Agency (EMA [[www.ema.europa.eu](http://www.ema.europa.eu)]) with regard to centralized procedures, a sponsor can submit under the decentralized procedure. Using this process, a sponsor can apply for simultaneous authorization in more than one EU country for products that have not yet been authorized in any EU country.

## **Mutual recognition procedure**

With the mutual recognition procedure, a product is first authorized by one country in the EU in accordance with the national procedures of that country. Later, further marketing authorizations can be sought from other EU countries, who, rather than conducting their own review, agree to recognize the decision of the first country.

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## Exhibit 1: Mutual recognition procedure



Source: European Commission, *Pharmaceuticals in the European Union*, [http://ec.europa.eu/enterprise/newsroom/cf/document.cfm?action=display&doc\\_id=1684&userservice\\_id=1&request.id=0](http://ec.europa.eu/enterprise/newsroom/cf/document.cfm?action=display&doc_id=1684&userservice_id=1&request.id=0)

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### Centralized procedure

European drug approvals are overseen by the European Medicines Agency. The EMA is a decentralized body of the EU, with headquarters in London, England. It is responsible for the scientific evaluation of applications for authorization to market medicinal products in Europe (via the centralized procedure).

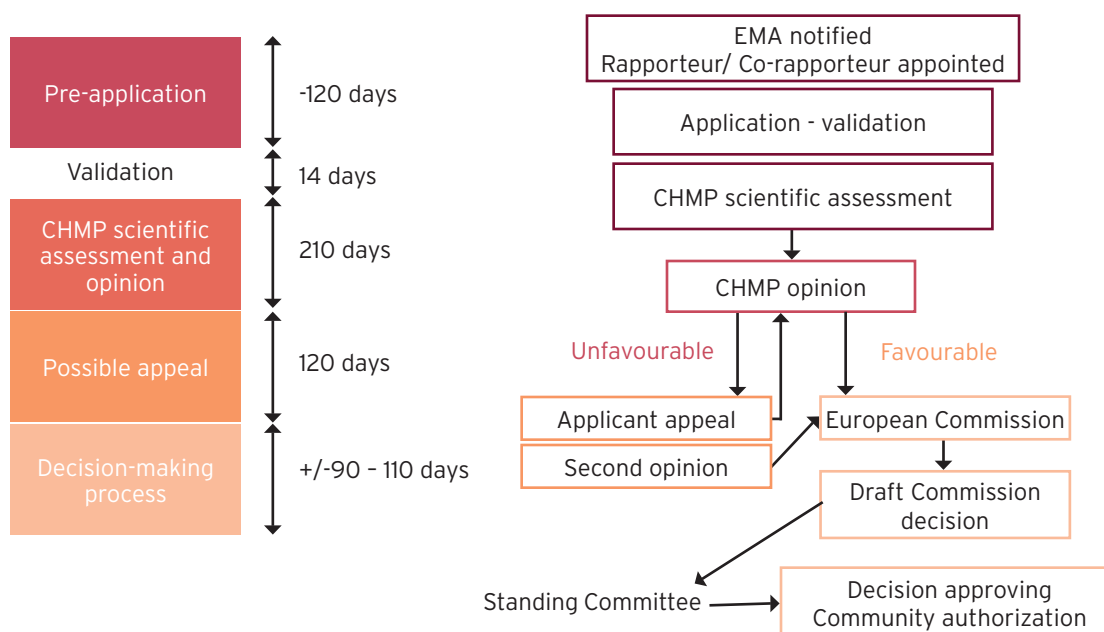
Marketing applications for drugs for use in humans are evaluated by the Committee for [Medicinal Products for Human Use](#) (CHMP).

Products that are eligible for review under the centralized procedure must meet the following criteria:

- biologic drugs developed by recombinant technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, and hybridoma and monoclonal antibody methods
- medicinal products containing new active substances for the following indications: AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, and viral diseases
- orphan medicinal products

Other new active substances may, at the request of the applicant, be accepted for consideration under the centralized procedure when it can be shown that the product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a Community authorization is in the best interests of patients at the Community level.

## Exhibit 2: Centralized procedure



Source: European Commission, *Pharmaceuticals in the European Union*, [http://ec.europa.eu/enterprise/newsroom/cf/document.cfm?action=display&doc\\_id=1684&userservice\\_id=1&request.id=0](http://ec.europa.eu/enterprise/newsroom/cf/document.cfm?action=display&doc_id=1684&userservice_id=1&request.id=0)

### Pre-submission process

At least seven months prior to submitting a [marketing authorization application](#) (MAA), a sponsor must notify the EMA of their intention to submit and the month of submission. This pre-submission involves a variety of information including a document outlining the reasons the sponsor believes the application should fall under the centralized procedure. The EMA will consider the pre-submission and notify the sponsor of its decision regarding acceptance of the MAA.

### Selection of rapporteur/co-rapporteur

The rapporteur is a country-specific regulatory authority within the EU. The rapporteur (reviewer) and co-rapporteur (if needed) are identified from the CHMP members. The selection of the rapporteur is based on objective criteria, to ensure objective scientific opinion and the best use of available expertise at the EMA.

The role of the rapporteur is to perform the scientific evaluation and prepare an assessment report to the CHMP. If a co-rapporteur is involved, the co-rapporteur will prepare an independent assessment report, or provide a critique of the rapporteur's report, at the discretion of the CHMP.

The process for assigning the rapporteur/co-rapporteur is usually initiated at the CHMP meeting following the receipt of a letter of an intention to submit. The sponsor is notified of the rapporteur/co-rapporteur once the EMA has deemed a submission admissible.

### Product naming

A sponsor's name for the drug product should be the same in all countries within the EU, except where it violates trademark rules. The sponsor should submit the proposed name in advance (usually four to six months, and not more than 12 months) of the marketing authorization application.

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## Marketing authorization application–submission components

An MAA should be submitted in the EU-CTD (Common Technical Document) format. The five main modules of an MAA are detailed in Exhibit 3.

### Exhibit 3: Marketing authorization application modules

Module	Content	Details
1	EU administrative and prescribing information	*Application form *Summary of product characteristics *Labelling text and mock-ups *Information about the experts *Environmental risk assessment *Information relating to orphan-market exclusivity *Description of the pharmacovigilance system *Risk management plan
2	High-level summaries	*Quality *Non-clinical overview *Non-clinical summary (pharmacology, pharmacokinetics, toxicology) *Clinical overview *Clinical summary (biopharmaceutics, clinical pharmacology, efficacy, safety, study synopsis)
3	Quality documentation	*Body of data *References
4	Non-clinical documentation	*Study reports *References
5	Clinical documentation	*Tabular listing of studies *Study reports *References

Source: International Conference on Harmonisation. *Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 (R3)*, January 13, 2004.

<http://www.ich.org/LOB/media/MEDIA554.pdf>

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In addition to the information cited in Exhibit 3, applicants must submit evidence of establishment within the European Economic Area (EEA) and documentation that shows their ability to uphold MAA obligations (such as monitoring pharmacovigilance, identifying a qualified person in the EEA for batch release, and providing a contact person for product defects and product recalls).

### Validation

The first step of the review process is for the EMA to assess the MAA to determine whether the reviewers require additional information, data or clarification in order to conduct the review. Once the MAA is deemed valid, the CHMP establishes the timetable for scientific evaluation.

### Scientific evaluation

The rapporteur/co-rapporteur conducts the scientific evaluation. As outlined in Exhibit 4, the EMA ensures the CHMP completes the full review within 210 days (less any stops in the timeline for the sponsor to respond to CHMP questions).

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## Exhibit 4: Standard timetable for review of a centralized application

### Standard timetable for the evaluation of a centralized application

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Day	Action
1	Start of the procedure.
80	Receipt of assessment report or critique from rapporteur and co-rapporteur by CHMP members and EMA. EMA sends assessment report to applicant making clear it only sets out preliminary conclusions and is sent for information only and does not yet represent the position of the CHMP.
100	Rapporteur, co-rapporteur, other CHMP members and EMA receive comments from CHMP members, including peer reviewers.
115	Receipt of draft list of questions (including CHMP recommendation and scientific discussion) from rapporteur and co-rapporteur, as discussed with peer reviewers, by CHMP members and EMA.
120	CHMP adopts list of questions as well as overall conclusions of scientific data to be sent to applicant by CHMP. Clock stops on timetable.
121*	Submission of the responses, including revised summary of product characteristics, labelling, and package leaflet texts in English, restart of clock.
<b>After receipt of responses:</b>	
150	Joint response (assessment report) from rapporteur and co-rapporteur received by CHMP members and EMA. EMA sends joint-assessment report to applicant making clear it only has preliminary conclusions and does not yet represent position of CHMP.
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 for adoption of a list of "outstanding issues" and/or an oral explanation by applicant. If oral explanation needed, clock is stopped to allow time for preparation.
181	Restart clock and oral explanation (if needed).
181-210	Final draft of English summary of product characteristics, labeling, and package leaflet sent by applicant to rapporteur and co-rapporteur, EMA and other CHMP members.
By 210	Adoption of CHMP Opinion & CHMP Assessment Report (and timetable for provision of product information translations).
<b>After adoption of CHMP opinion:</b>	
215 at the latest	Applicant provides EMA with summary of product characteristics, labeling, and package leaflet in 20 languages. EMA circulates draft to member states for review.
232 at the latest	Applicant provides EMA with final translations of summary of product characteristics, labelling, and package leaflet in 20 languages, taking into account comments received from member states by day 229.
By 237	Transmission of opinion and annexes in all EU languages to applicant, commission, members of standing committee, Norway and Iceland.
By 246	Applicant provides EMA with one final full-colour mock-up of outer and inner packaging for each pharmaceutical form.

\*Target dates for the submission of responses are published on the EMA website (<http://www.ema.europa.eu/htms/human/submission/submission.htm>)

Source: European Commission. Volume 2A, *Procedures for marketing authorisation*. Chapter 4, Centralised Procedure, April 2006, <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/a/chap4rev200604%20.pdf>

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## Accelerated assessment

In cases where products are considered to be of major public health interest, a sponsor can apply for accelerated assessment of their application. If granted, the 210-day review procedure is shortened to 150 days.

## Committee request for additional information

Once the CHMP has the preliminary assessment reports or critique from the rapporteur and co-rapporteur, it prepares a list of any outstanding issues the sponsor must address. A consolidated list of questions identifying "other concerns" and/or "major objections" is prepared. These are sent to the sponsor with the CHMP recommendation and scientific discussion. The clock will then be stopped (day 120).

The CHMP can make one of two recommendations:

1. The product could be approved provided that satisfactory answers are given to "other concerns," and that the indications, the elements of the summary of product characteristics, and other conditions for marketing are amended as outlined in the list of questions.
2. The product is not approvable since there are "major objections."

The sponsor has three months from the date of receiving the questions to respond to the CHMP. Sponsors are permitted to request a three-month extension, if required.

## Oral (or written) explanation

The CHMP will discuss the joint-assessment report and comments of other CHMP members. The CHMP may identify additional issues which the sponsor must address in writing or during an oral explanation. If a sponsor wishes to make an oral presentation, it usually has one month to prepare.

After the oral explanation and the subsequent CHMP discussion, the rapporteur will provide feedback to the sponsor before a formal vote takes place. If the outcome appears it will be positive, a discussion may be held regarding key amendments to the product characteristics summary and draft follow-up measures or conditions to the marketing authorization. If the outcome appears it will be negative, possible procedural options will be discussed with the sponsor.

## CHMP opinion

On or before day 210, the CHMP will adopt its final opinion after the final recommendation of the rapporteur/co-rapporteur. The CHMP opinion, wherever possible, is reached by consensus. If a consensus cannot be reached, the majority opinion will hold (i.e., favourable votes by at least half the members plus one).

*Favourable opinion:* The sponsor can proceed to preparing the drug for marketing launch.

*Unfavourable opinion:* The sponsor is informed that the application does not satisfy the criteria for marketing authorization.

## Follow-up to the CHMP opinion

Within five days after the CHMP opinion is delivered, the sponsor must provide to the EMA, in the 20 languages of the EU, a summary of product characteristics, the product labelling and the package insert. By day 22 after the final opinion, final translations are due, having taken into account comments received from member states by day 19. A final full-colour mock-up of outer and inner package labelling for each pharmaceutical form is due to the EMA by day 36 after the adoption of the CHMP opinion.

## European public assessment report

After authorizing a marketing application, the EMA will publish the assessment report, "EPARs for authorised medicinal products for human use" (<http://www.ema.europa.eu/htms/human/epar/a.htm>). A sponsor has an opportunity to comment on any issues that it believes are confidential, and provide supporting justification. This document is made available from the date of the Commission decision to grant the marketing authorization.

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## Exhibit 5: Summary of European marketing application options

Process	When used	Pros	Cons
National authorization	Individual applications to each country within the EU. Used for products that fall outside the scope of the EMA centralized procedure.	If application rejected in one country, can still access other EU countries.	Separate applications required for each country. Unique requirements and formats may be required.
Decentralized procedure	Used for products that fall outside the scope of the EMA centralized procedure.	Simultaneous authorization in numerous countries in the EU. May be more efficient than national authorization since a positive outcome results in numerous country approvals. Sponsor can select which countries to apply to; does not have to be all EU countries.	A negative decision on an application may affect numerous countries.
Mutual recognition procedure	Individual application to one country within the EU for products that fall outside the scope of the EMA centralized procedure.	Review by one country and other countries accept the decision. Only one application needs to be submitted.	Individual national approvals can add significant time to the process. A negative outcome can affect numerous countries.
Centralized procedure	Used for biologic products or other products using high-technology procedures; products for HIV/AIDS, cancer, diabetes, neurodegenerative disease, auto-immune or other dysfunctions, and viral diseases; products for orphan conditions; and other new active substances at the request of the applicant.	One application applies to all countries in the EU. Relatively quick procedure. A positive outcome is very beneficial to the sponsor.	A negative outcome will affect access to the entire EU.

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