EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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European Medicines Agency Guidance for applicants seeking access to PRIME scheme

This guidance document addresses questions that applicants seeking support through the PRIME scheme may have.

This guidance also explains the scope and features of PRIME. It provides an overview of the procedure to obtain support through the scheme and gives guidance to companies in preparing their requests.

This guidance will be updated regularly to reflect new developments as experience is gained with the scheme.

It should be read in conjunction with:

Enhanced early dialogue to facilitate accelerated assessment of PRIority MEdicines (PRIME)

Guidance on accelerated assessment

European Medicines Agency Guidance for applicants seeking scientific advice and protocol assistance

If you require further information on any of the included topics, do not hesitate to send your request to prime@ema.europa.eu and we will deal with your query in a timely manner.

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1. What is PRIME?

PRIME is a scheme to reinforce scientific and regulatory support in order to optimise development and enable accelerated assessment of new medicines.

The scheme is voluntary and subject to application justifying that the eligibility criteria are met. All requests to enter the scheme must be based on adequate data to justify a potential major public health interest. Applicants will be informed in writing of the acceptance or refusal of their eligibility request.

Support provided through the scheme will be tailored to meet the needs of development at different stages.

Key benefits for applicants are:

- Early appointment of a rapporteur from EMA's Committee for Medicinal Products for Human Use (CHMP) or the Committee for Advanced Therapies (CAT), to provide continued support and help to build knowledge ahead of a marketing authorisation application (MAA);
- An initial kick-off meeting with the CHMP/CAT rapporteur and a multidisciplinary group of experts from relevant EMA scientific committees and working parties and EMA staff to (1) provide preliminary guidance on the overall development plan, (2) discuss key development steps subject of future advice and (3) open the discussion on the recommended regulatory strategy;
- EMA dedicated contact point who will coordinate the support offered throughout the scheme
- Scientific advice on the overall development plans, at major development milestones and on key issues, with possibility to involve additional stakeholders (e.g. health technology assessment (HTA) bodies and patients).
- Confirmation of the potential for accelerated assessment at the time of an application for marketing authorisation.

The scheme enables early proactive, continuous and strengthened regulatory dialogue between the applicant and the EU regulatory network, ensuring generation of a robust data packages designed to address MAA requirements. This will also raise awareness of applicants towards the use of existing tools (e.g. parallel EMA/HTA advice, conditional marketing authorisation…) relevant to their development programme.

Overall, the intensive guidance is expected to lead to more efficient medicines development and high quality marketing authorisation applications thus allowing for review within an accelerated timeframe to ensure authorisations meeting high standards of quality that will facilitate patients access to these promising medicines in the shortest possible timeframe.

2. What are the eligibility criteria for PRIME?

The PRIME scheme is limited to medicines under development which are not authorised in the EU and for which the applicant intends to apply for an initial MAA through the centralised procedure.

The eligibility criteria for PRIME are identical to EMA's accelerated assessment criteria, and target medicinal products of **major public health interest** and in particular from the viewpoint of therapeutic innovation.

Products eligible to PRIME support shall:

- Target conditions where there is an **unmet medical need**, i.e. for which there exists no satisfactory method of diagnosis, prevention or treatment in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected;
- Demonstrate the **potential to address the unmet medical need** for maintaining and improving the health of the Community, for example, by introducing new methods of therapy or improving existing ones.

The available data should support the claim that the product has the potential to **bring a major therapeutic advantage to patients** in a given indication, through a clinically meaningful improvement of efficacy, such as having an impact on the prevention, onset and duration of the condition, or improving the morbidity or mortality of the disease.

3. At which phase of development can I apply for PRIME ?

Any sponsor engaged in the exploratory clinical trial phase of development can submit a request to enter the PRIME scheme, based on the availability of preliminary clinical evidence in patients to demonstrate the promising activity of the medicinal product and its potential to significantly address an unmet medical need (**proof of concept**).

In exceptional cases, applicants from the academic sector[1] and micro-, small-and medium-sized-enterprises (SME) may submit an eligibility request at an earlier stage of development if

- compelling nonclinical data in a relevant model provide early evidence of promising activity (**proof of principle**) and
- first in man studies indicate adequate exposure for the desired pharmacotherapeutic effects and tolerability.

SMEs should register with the Agency's SME office in advance of submitting an eligibility request. Applicants who consider they meet the definition of academic sector should contact the Agency prior to submitting an eligibility request.

[1] Applicant established in the EEA and fulfilling the definition of public or private higher education establishments awarding academic degrees, public or private non-profit research organisations whose primary mission is to pursue research, or international European interest organisations as set out in Commission Regulation (EU) No 1290/2013 of 11 December 2013. Applicants should not be financed or managed by private profit organisations in the pharmaceutical sector ("PPO"), nor should have they concluded any operating agreements with any PPO concerning their sponsorship or participation to the specific research project for which a fee exemption is sought for scientific advice under the PRIME scheme.

PRIME is not the right support tool for you if:

- You are already in the MAA pre-submission phase (i.e. you have submitted a letter of intent for a MAA). In this case, you should consider alternative tools (e.g. pre-submission meeting request, request for accelerated assessment).
- You are seeking support for development in a new indication for an already authorised product for which you are the marketing authorisation holder. In this case, you should consider alternative tools (e.g. scientific advice, pre-submission meeting with EMA and rapporteur).

4. How can I apply?

You should submit a request for eligibility to PRIME via Eudralink[2] to prime@ema.europa.eu, using the

- Pre-submission request form (selecting 'Human Medicinal Product', 'Eligibility' and then 'PRIME'),
- the Applicant's justification template,

in accordance with submission deadlines, all of which are published on our website.

There is no fee payable for submission of a request to enter the PRIME scheme.

Your request should be duly substantiated and justify the expectation that the medicinal product is of major public health interest particularly from the point of view of therapeutic innovation.

The justification should be presented as a short but comprehensive document (not more than 30 pages in length), using the template provided.

When preparing the justification, you should consider aspects as detailed in the CHMP document entitled Enhanced early dialogue to facilitate accelerated assessment of PRIority MEdicines (PRIME) and its Annex 1.

Information included in the application form will also be used to confirm eligibility to the centralised procedure should your product be granted eligibility to PRIME (see also question 7. What happens once my product is granted eligibility to PRIME?).

5. How will my request for eligibility to PRIME be reviewed?

Once EMA has received your request, the Agency will confirm whether it is within the scope of the scheme (see question 3) and that the format and content is adequate to support the review of the request.

If deemed acceptable, one Scientific Advice Working Party (SAWP) reviewer and one EMA scientific officer will be appointed. You will be informed of the start of the procedure.

Review of PRIME eligibility requests will be conducted through the SAWP. The reports will be forwarded for comments to the SAWP and CHMP, prior to final adoption. If you develop an advanced therapy medicinal products, the CAT will also be review the eligibility request and provide their recommendation to the CHMP.

The CHMP will aim to have outcomes adopted **within 40 days of the start of the procedure.** The submission deadlines and procedural timetables are published on the EMA website as a standard calendar.

[2] Applicants without a EudraLink account are invited to complete the EudraLink Account Request Form and submit it to Eudralink@ema.europa.eu.

After adoption by the CHMP, you will receive a letter summarising the outcome of the evaluation with the reasons for acceptance or rejection to the scheme. Reports prepared to support the final outcome will not be shared with the applicant.

6. Will the outcome of the review of PRIME eligibility requests be made public?

Yes, the outcome adopted by the CHMP will be made public. After each CHMP meeting, an overview of the number of recommendations adopted will be published in the CHMP monthly report, including:

- the type of product (chemical, biological or advanced therapy),
- the intended indication,
- the type of data supporting the eligibility request and,
- the type of applicant (SMEs, applicants from the academic sector or others).

For products that are deemed eligible to PRIME, the name of the active substance/INN will also be made public, whilst it will not be published in case of negative outcome.

In case of a subsequent centralised marketing authorisation, eligibility to the PRIME scheme granted by the CHMP will be reflected in the European Public Assessment Report.

7. What happens once my product is granted eligibility to PRIME?

Confirmation of eligibility to the centralised procedure

When access to the scheme is recommended by the CHMP, you will also receive that same month confirmation of eligibility to the centralised procedure, which will be based on information provided in the PRIME eligibility request form.

Appointment of the Rapporteur

The appointment of the CHMP rapporteur will also be initiated (unless you are an SME or applicant from the academic sector and applied to enter the scheme based on data showing proof of principle, see below).

For advanced-therapy medicinal products (ATMP), a CAT rapporteur and a CHMP co-ordinator will be appointed.

The appointment procedure will be conducted in line with the Procedural Advice on CHMP/CAT/PRAC Rapporteur/Co-Rapporteur appointment principles, objective criteria and methodology in accordance with Article 62 (1) of Regulation (EC) No 726/2004.

The appointment procedure takes one month. You will be notified about the outcome after the CHMP meeting subsequent to the confirmation of eligibility to PRIME scheme.

CHMP co-rapporteur and PRAC rapporteur appointment will not occur until you submit a letter of intent (**approximately 6-7 months prior to submission of MAA**).

For SMEs or applicants from the academic sector who enter the scheme based on data showing **proof of principle**, the appointment of the rapporteur will occur once they have generated data confirming eligibility at **proof of concept stage**. You will be required to submit relevant data and justification as the product development reaches this stage.

EMA dedicated contact point

You will also benefit from a dedicated EMA contact point during the development, who will coordinate the support offered throughout the scheme. Name and details will be included in the eligibility outcome letter.

EMA will further support the development through guidance on regulatory pathways, and where relevant, raise awareness of the use of regulatory/legislative tools (e.g. conditional marketing authorisation, marketing authorisation under exceptional circumstances) or other initiatives in order to facilitate timely access to patients.

Kick-off meeting

The EMA contact point will liaise with you to organise a kick-off meeting as soon as possible after entering into the scheme with

- the main SAWP coordinator,
- CHMP rapporteur,
- relevant experts from the EU network (particularly from PDCO, COMP and CAT in case of ATMP) and
- relevant EMA staff.

The meeting will preferably be held in the context of a scientific advice procedure, but may be arranged as a stand-alone meeting depending on the status of your development.

The objective of this meeting is to facilitate the initial interaction between the applicant and the multi-disciplinary assessment team of experts and EMA. In the meeting, you will present the development programme and regulatory strategy for the product. You will receive recommendations on interactions through relevant regulatory procedures (e.g. adequate timepoints to submit request for scientific advice, paediatric investigation plan). In addition, regulatory aspects can also be discussed during this meeting.

The kick-off meeting may be an opportunity for early dialogue between applicants and the EMA/PDCO regarding the strategy for the paediatric development programme of the medicine, in advance of a PIP application (that can otherwise take place during early paediatric interaction meetings).

Scientific advice

Scientific guidance will be provided in the context of scientific advice procedures, where you will be able to receive broad advice on your development plan as well as on major issues or key topics for the marketing authorisation application.

Two coordinators from SAWP will be appointed to each procedure, in line with current practice. One of these SAWP coordinators will be appointed through each iterative scientific advice request submitted: this continuity is expected to facilitate sharing of knowledge from development to life-cycle and the preparation of SAWP/CHMP advice. Wherever possible, this SAWP coordinator will be chosen from the same delegation as the CHMP rapporteur.

Where relevant, other committees (e.g. CAT, COMP, PDCO) will be involved in the preparation of the final advice letters. Furthermore, applicants will be encouraged to request parallel EMA/HTA advice.

If you are an SME or an applicant from the academic sector, you may also request fee reduction on scientific advice requests related to a product within the PRIME scheme, upon case-by-case decisions. This can be discussed with your EMA dedicated contact point.

Accelerated assessment

Medicinal products that have been granted PRIME support are expected to benefit from the accelerated assessment procedure, although this will have to be formally confirmed 2-3 months before submission of the application for marketing authorisation (see guidance on accelerated assessment).

8. Will support from PRIME be withdrawn if the data emerging during development no longer support the criteria?

Development progress of products successfully entering the scheme will be monitored on a regular basis as part of the scientific advice procedures. Based on the data presented in the scientific advice requests, the SAWP and CHMP will, in the scientific advice letter:

- Advise the applicants on the next milestone/key points for which scientific advice should be requested.
- For products that entered the scheme in early development stages, advise whether the data support proof of concept and enable access to incentives provided by the scheme in later phases of development (i.e. CHMP rapporteur appointment).

In case no scientific advice requests are submitted in a period of a year, applicants would be asked to provide the EMA contact point with a progress report on development.

Over the course of drug development, it can be expected that some products granted PRIME support will no longer meet the eligibility criteria of major public health interest as defined in Section 3 of CHMP document entitled Enhanced early dialogue to facilitate accelerated assessment of PRIority MEdicines (PRIME).

In these situations, the applicant/sponsor will be contacted by EMA and requested to provide a justification whether the criteria for eligibility to PRIME are still met for review and assessment by the SAWP/CHMP.

PRIME support may be withdrawn if emerging data were to show that the criteria are no longer met. However, this should not impact on the eligibility of the product to the centralised procedure.

Furthermore, you should inform your EMA contact point if you no longer intend to pursue the development of an eligible PRIME medicine.

9. What happens if my product is not granted eligibility to PRIME?

In view of the proposed eligibility criteria, while many new medicinal products add value to the therapeutic armamentarium by providing alternatives and incremental benefits over established products, they may not necessarily qualify for eligibility to PRIME. However, this should not be seen as a negative view of the regulators on the merit of the product and on any development plans put forward so far.

Applicants not eligible to PRIME are still encouraged to engage with scientific advice in order to obtain the CHMP views on their development plans.

Furthermore, applicants may submit a new request if new clinical evidence is obtained that demonstrates the product has potential to be of major public health interest.

See also Question 10 below.

10. Can I still request accelerated assessment if my product is not part of PRIME?

Yes, applicants not applying for, or not qualifying for PRIME support, will still be able to request accelerated assessment prior to filing provided that the criteria are met.

11. How does PRIME differ from adaptive pathways?

PRIME aims to provide early and enhanced scientific and regulatory support to promising new medicines that fulfils the criteria for accelerated assessment, while adaptive pathways is for treatments in high medical need areas where collection of data via traditional routes is difficult and where large clinical trials would unnecessarily expose patients who are unlikely to benefit from the medicine. It relies on the targeted development of a medicine in a restricted patient population as an initial step and the progressive gathering of evidence through real-life data prospectively planned, as a supplement to clinical trials data and with the view to expand the patient population in which the medicine can be used.

As part of PRIME, EMA will provide advice to medicines developers on the possible authorisation routes for their medicine as well as on the overall development plan; as part of these discussions, the adaptive pathways approach can be envisaged if the medicine fulfils the criteria (e.g. potential for a gradual extension of the target population and possibility to collect and use real-world data). In such case, the medicine will continue to benefit from PRIME support.

However, the adaptive pathways approach to medicine development may not be appropriate for all medicines that are eligible for PRIME. Vice-versa, a medicine eligible to adaptive pathways may not be eligible to PRIME if it does not fulfill the eligibility criteria.

The table below provides an overview of common features and differences between PRIME and adaptive pathways:

	PRIME	Adaptive pathways
What it is about?	Early and enhanced scientific and regulatory support to medicine developers to optimise the generation of robust data and enable accelerated assessment.	Scientific concept of medicines development and data generation with lifespan approach, which relies on the targeted development of a medicine in a restricted patient population as an initial step and the progressive gathering of evidence through real-life data prospectively planned to supplement clinical trials data and with the view to expand the patient population in which the medicine can be used. Level of evidence addresses not only the needs of regulators, but of HTA bodies as well.

	PRIME	Adaptive pathways
Which medicines are eligible	Accelerated assessment criteria, i.e. medicinal products of a major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation (unmet medical need).	Medicines (in areas of high medical need), with: • An iterative development plan (either gradual expansion of the target population or progressive reduction of uncertainty after initial authorisation); • Ability to engage HTA bodies and other stakeholders; • Use of real-world data to supplement clinical trials
Which medicines are not eligible	Medicines which are already authorised. Medicines which are not addressing an unmet medical need.	Medicines that do not fulfil the criteria above (please refer to decision tree).
Key features	Identify potential for accelerated assessment earlier in development, Early rapporteur appointment, Reinforced scientific and regulatory support from the SAWP/ CHMP, other scientific committees and EMA, Dedicated contact point within EMA	Early multi-stakeholder dialogue with feedback on suitability of a prospectively planned data collection making use of real-world data.
Who is involved (stakeholders)	Multidisciplinary expertise from regulators with possibility to involve patients and HTAs (in particular, through the use of the parallel scientific advice with HTAs).	Multidisciplinary expertise from regulators, HTA, patients. Potential involvement of payers on an ad-hoc basis.
Post-authorisation implications	On a case by case basis, depending on the authorisation route and development plan followed	Yes, in view of real-world data acquisition requirement.
How to apply	Submit request supported by justification on the claim that the medicinal product addresses to a significant extent the unmet medical needs.	Guidance for submission can be found here. Applicants are also invited to contact EMA, should they wish to discuss the content and suitability of their request.
Most appropriate stage when to request	At least first in man. During the development, based on preliminary clinical evidence (proof of concept). Exceptionally earlier access to SMEs and academia (proof of principle).	At least first in man. Early stages of development offer the highest opportunity for a meaningful dialogue and input from regulators, HTAs and patients.
Contact point	prime@ema.europa.eu	adaptivepathways@ema.europa.eu

12. What are other regulatory tools and scientific support available to developers?

Other tools supporting early access to medicines include conditional marketing authorisation, accelerated assessment and compassionate use. These are available to applicants, irrespective of their eligibility to PRIME scheme. Further information, including a comparative overview of these tools is included here.

EMA also offers a range of advisory services to companies working in research and development of medicines, including scientific advice and protocol assistance, the small and medium-sized enterprise office, and the Innovation Task Force (ITF) and early paediatric interaction meetings.