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Human Medicines Research and Development Support Division

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 ? *Rev. May 2018*

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 address to a significant extent 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.

In the case where a product is already advanced in its development programme (e.g. pivotal trial ongoing and for which scientific advice has been received), the applicant will require to elaborate on the remaining development and post-authorisation activities for which PRIME would bring benefits.

[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? *Rev. May 2018*

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 (this should be submitted in MS Word format),
- Literature references cited in the justification (this should be appended in a zip file).

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? *Rev. May 2018*

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, a CAT reviewer will also be appointed and the CAT will provide their recommendation to the CHMP.

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

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.

After adoption by the CHMP, you will receive a letter explaining the outcome of the evaluation with the reasons for acceptance or rejection to the scheme. There is the possibility to contact the Agency should further clarification on the reasons for acceptance or rejection be needed. 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? *Rev. May 2018*

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.

A list of products granted eligibility to PRIME is also published and updated on a monthly basis. Products are removed from this list when a marketing authorisation application is submitted or if a product is withdrawn from the scheme if emerging data show that the eligibility criteria are no longer met.

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? *Rev. May 2018*

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

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

The objective of this meeting is to facilitate the initial interaction between the applicant and the multi-disciplinary assessment team of experts and EMA. While the participants will not engage into detailed scientific and technical discussions around the identified topics, during the kick-off meeting, the aim is to agree on the next steps on how best to address any identified issues or to identify potential additional issues. 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).

Further details are provided in the European Medicines Agency Guidance on interactions in the context of PRIME.

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 specific 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.

Regular updates

After the kick-off meeting, the Applicant should keep the EMA dedicated contact point informed of submission of procedures to the Agency. In case the applicant identifies a topic warranting further discussion with regulators, they should contact the EMA who will advise on the suitable way to address the matter. Where appropriate, the Agency can support interactions with the CHMP/CAT Rapporteur (e.g. ad hoc teleconferences) with a view to resolve minor issues or for the applicant to provide updates on their development. Further details are provided in the European Medicines Agency Guidance on interactions in the context of PRIME.

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? *Rev. May 2018*

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. Different SAWP reviewer and EMA scientific officer will be appointed to review such new request.

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. What are other regulatory tools and scientific support available to developers? *Rev. May 2018*

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, parallel consultation with regulators and health technology assessment bodies, the small and medium-sized enterprise office, and the Innovation Task Force (ITF) and early paediatric interaction meetings.

12. What information is exchanged between the EMA and the US Food and Drug administration on the EU PRIME scheme and US Breakthrough Therapy designation programme? *New. May 2018*

PRIME and the US breakthrough therapy designation share the same objective (timely patient access to innovative medicines) but have a different legal basis, hence comparison and harmonization is difficult.

In late 2016, as part of the confidentiality arrangements, FDA and EMA began regular exchange of information and meetings regarding breakthrough therapy designation and PRIME eligibility requests,

focusing on high level topics and comparing general experience and program implementation challenges.

In this context, FDA and EMA track submitted requests for PRIME and breakthrough therapy designations and compare final review outcomes, including specific reasons for a designation request denial.

These meetings facilitate increased awareness of FDA/EMA dually designated products and stimulate early dialogue by therapeutic area experts in both regions on an ad hoc basis within the existing clusters, or in the context of Parallel Scientific Advice (PSA) program via a formal meeting.

The agencies do not routinely share scientific and regulatory reviews regarding dually designated product development programs or marketing applications, unless a topic of specific interest has been defined by the agencies' subject matter expert teams or sponsors.

When requesting breakthrough therapy designation or eligibility to PRIME, sponsors are encouraged to inform the agency whether they have submitted a request for designation or eligibility to the other agency and the outcome of this request.

For successful planning of global development and clinical studies, both agencies encourage sponsors to contact FDA and EMA on a dually designated product's development program and seek joint advice under the PSA program. Sponsors wishing to nominate a product for a PSA procedure should address one single "Request for PSA" letter to both emainternational@ema.europa.eu at EMA and OC-OIP-Europe@fda.hhs.gov at FDA.