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Committee for Medicinal Products for Human Use

Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME)

Draft

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Comments should be provided using this template. The completed comments form should be sent to prime@ema.europa.eu.

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Glossary

ATMP	Advanced therapy medicinal products
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
HTA	Health Technology Assessment
MAA	Marketing authorisation application
SAWP	Scientific Advice Working Party
SME	Micro-, small- and medium-sized-enterprise

1. Drivers for change

The development of promising new medicines to address unmet medical needs is challenging from the scientific and regulatory point of view. Early consultation and scientific advice with regulators and other healthcare decision-makers is key to ensuring data is generated to the standards required for regulatory approval and market access.

Over the past year, the European Medicines Agency (EMA) and its scientific committees have worked on a number of initiatives to further support development with a view to accelerating patients' access to medicines that address unmet medical needs. These include:

- The Adaptive Pathways pilot, an opportunity for early and open dialogue with applicants and other stakeholders, to explore ways to optimise development pathways and accelerate patients' access to medicines.
- Revisions of guidance on accelerated assessment and conditional marketing authorisation, two key tools in the EU legislation to accelerate approval of medicines that address unmet medical needs.

There is, however, a need to further reinforce regulatory and scientific support to foster development of new medicines addressing major public health needs. The EU Medicines Regulatory Network has, therefore, highlighted in its Strategy to 2020[1] the need to work towards ensuring timely access to new beneficial and safe medicines for patients, supporting patient focused innovation and contributing to a vibrant life science sector in Europe.

2. Background and objectives

In December 2014, a group composed of members of the Committee for Medicinal Products for Human Use (CHMP) and EMA representatives was established to explore ways, within the current regulatory framework, to further support the development of new medicines addressing major public health needs. As a result of that work, a scheme has been developed to reinforce early dialogue and regulatory support to stimulate innovation, optimise development and enable accelerated assessment of PRIority MEdicines (referred to as PRIME). An overview of the PRIME scheme is provided in this reflection paper.

According to Recital 33 and Article 14(9) of Regulation (EC) No 726/2004, an applicant may request an accelerated assessment procedure in order to meet, in particular the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, for medicinal products of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation.

To date, the evaluation of a centralised marketing authorisation application (MAA) to an accelerated timetable has been confirmed just prior to filing. With a view to improving early access tools and regulatory support to promising new medicines, the PRIME scheme would introduce the possibility not only to identify products fulfilling the criteria for accelerated review earlier, but also to enhance the regulatory and scientific support on offer to these products through advice at key milestones in development.

[1] EU Medicines Agencies Network Strategy to 2020, Working together to improve health, Consultation draft (EMA/MB/151414/2015, 27 March 2015)

Eligibility to the PRIME scheme will depend on the availability of adequate non-clinical and exploratory clinical data to justify a potential major public health interest prior to the initiation of confirmatory clinical studies at proof of concept stage (prior to confirmatory clinical studies).

The support on offer through the PRIME scheme will be tailored to the stage of development and provided through scientific advice, with products achieving proof of concept benefiting from early CHMP Rapporteur appointment, a kick-off meeting with the experts from the Scientific Advice Working Party (SAWP), relevant committees and the CHMP Rapporteur to discuss development plans, regulatory pathways and confirmation of eligibility for accelerated assessment (subject to the criteria still being met at the time of MAA).

There is also value in opening the scheme to SMEs and applicants from the academic sector at an earlier stage as progressing to proof of concept stage is often a difficult step for these smaller actors with limited regulatory and medicine development experience. Exceptionally, eligibility to the scheme is therefore being considered at the earlier proof of principle stage (prior to exploratory clinical studies), provided compelling data can be presented to justify a products potential public health impact.

Ultimately, the scheme is expected to lead to better informed development plans, to improve the quality of marketing authorisation applications and to promote regulatory awareness thus allowing for a shortened timeframe for review and earlier patient access to promising new medicines.

Applicants not applying for, or not qualifying for PRIME support, will continue to be able to request accelerated assessment prior to filing provided that the criteria are met. Eligibility criteria and requests for accelerated assessment of the MAA are covered within the *Guideline on the procedure for accelerated assessment pursuant to Article 14 (9) of Regulation (EC) No 726/2004,* which should be read in conjunction with this document.

3. Proposed Eligibility criteria and procedure

The PRIME scheme is limited to products under development which are innovative and yet to be placed on the EU market, i.e. where there is an intention to apply for an initial marketing authorisation application through the centralised procedure.

The scheme aims to support medicinal products of **major public health interest** and **in particular from the viewpoint of therapeutic innovation (i.e. those which fulfil the accelerated assessment criteria)**.

As such, products eligible for PRIME support are expected to 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.

In these conditions, a product eligible for PRIME support should demonstrate the **potential to address to a significant extent 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.

Data available to support a request for eligibility should support the claim that the product has the potential to bring a major therapeutic advantage to patients, through a meaningful improvement of efficacy, such as having an impact on the onset and duration of the condition, or improving the morbidity or mortality of the disease.

Detailed guidance on the justification to be submitted by applicants to be part of the scheme is provided in Annex 1.

Review of PRIME eligibility requests will be conducted through the SAWP, with recommendations forwarded to the CHMP for final adoption. In case of advanced therapy medicinal products (ATMP), the Committee for Advanced Therapies (CAT) will also be involved in the review of requests for eligibility.

One SAWP reviewer and one EMA scientific officer will be appointed to review each eligibility request. Details of the proposed procedure are provided in Annex 2.

As the data submitted will vary depending on the product, stage of development and therapeutic area, the appointed co-ordinators will consider each request on a case by case basis. An oversight group will be established to monitor output, ensure consistency and update guidance to reflect the experience gained.

When access to the scheme is recommended by CHMP, eligibility to the centralised procedure will also be confirmed at the same time.

Each month, an overview of the number of recommendations adopted will be published in the CHMP Monthly report, including broad characteristics on the substance(s) (chemical, biological or ATMP), the therapeutic area, the type of data on which the eligibility to access the scheme was granted or rejected, its phase of development, and the type of applicant (SMEs, applicants from the academic sector or others). The individual outcome adopted by the CHMP for a given medicinal product will not be made public. In case of a subsequent centralised marketing authorisation, reference to eligibility to the PRIME scheme granted by the CHMP will be mentioned in the European Public Assessment Report.

4. Proposed support features

Support provided through the scheme will be tailored to meet the needs of developers at different stages of development and provided up to the submission of the marketing authorisation application. Successful applicants will receive written confirmation of eligibility to the PRIME scheme, which will include early confirmation of potential for accelerated assessment of MAA.

The following key benefits for applicants are considered:

In early stages of development, following demonstrated proof of principle, focusing on SMEs and applicants from the academic sector:

- Scientific advice (with fee reductions for SMEs) on the overall development plan and at major development milestones, with the potential to involve multiple stakeholders (e.g. Health Technology Assessment (HTA) bodies, patients).

In clinical stages of the development, following demonstrated proof of concept:

- Early appointment of CHMP/CAT Rapporteur (in line with current process, objective criteria and methodology).
- An initial kick-off meeting with multidisciplinary participation from the EU network (SAWP and relevant committees members and experts), including the CHMP/CAT Rapporteur, to understand the proposed development programme, give preliminary guidance on requirements for MAA, and to develop of schedule for giving regulatory and scientific advice.

- Scientific advice (with fee reductions for SMEs) on key decision points/issues for the preparation of MAA with the potential to involve multiple stakeholders (e.g. Health Technology Assessment (HTA) bodies, patients), when relevant.

Eligible products will also receive coordinated support from EMA throughout the development to address matters related to regulatory aspects.

The early appointment of the CHMP/CAT Rapporteur will enable continuity in a life-cycle approach and support the development of important innovative medicines based on relevant expertise in the therapeutic area and/or product type (e.g. ATMP). The Rapporteur will support the development by directing applicants towards the EMA scientific advice on data requirements for the future MAA as well as raising awareness on the use of early access tools where relevant (e.g. conditional marketing authorisation) or other initiatives (e.g. parallel EMA/HTA advice, adaptive pathways) to facilitate timely access to patients.

This support will be channelled mainly through scientific advice by the SAWP/CHMP where the applicant will be able to discuss the detailed development plan and the design of pivotal studies. Two coordinators from SAWP will be appointed to each procedure, in line with current practice. Wherever possible, one of the SAWP coordinator will be appointed from the same delegation as the Rapporteur in order to facilitate continuity in support and sharing of knowledge gained throughout the development.

Such early dialogue between the applicant and the EU regulatory network, through the CHMP Scientific advice, will ensure generation of a robust data package designed to address MAA requirements and support a thorough Benefit/Risk evaluation of the new medicine.

Products granted PRIME support are anticipated to benefit from the accelerated assessment procedure, which is to be formally confirmed shortly before submission of the application for marketing authorisation. In line with the current practice, CHMP Co-Rapporteur, CHMP peer reviewer and PRAC Rapporteur will be appointed approximately 6-7 months prior to submission of MAA.

Overall, the intensive guidance is expected to lead to better informed development plans, better planning of resources for the EU network and to improve the quality of marketing authorisation application thus allowing for review within an accelerated timeframe and aiming overall to ensure patients access to these promising medicines in the shortest possible timeframe.

5. Monitoring of development

Development progress of products successfully entering the scheme will be monitored at regular checkpoints. 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, applicants would be asked to provide an update on development progress (as defined with the SAWP/CHMP during the scientific advice procedure, e.g. at relevant milestones).

Over the course of drug development, it can be expected that some products granted PRIME support will no longer meet the eligibility criteria (e.g. further to data derived from confirmatory study or availability of other therapies fulfilling the unmet medical need). In these situations, the SAWP/CHMP will re-assess whether the criteria for eligibility to PRIME are still met and notify the applicant/sponsor of its conclusions. PRIME support may be withdrawn if emerging data were to show that the criteria are no longer met.

Furthermore, the Agency should be informed when the applicant no longer intends to pursue the development of an eligible PRIME medicine.

Guidance for applicants in this respect will be prepared for the launch of the scheme.

6. Next steps

The proposed scheme was developed in consultation with the Agency's scientific committees, the EC and its expert group STAMP as well as the regulatory network.

The scheme is proposed to be launched by Q1 2016, after finalisation of the reflection paper following public consultation.

Relevant procedural documents (including 'question and answer' guidance to applicants, templates) will be published prior to launch. The mandate of the SAWP will be revised to include objectives related to PRIME scheme eligibility and support.

The EMA will report at regular intervals on the uptake into and the operation of the 'PRIME' initiative. The scheme will be subject to review as experience is gained.

Annex 1 – Justification for eligibility to PRIME

The request should be submitted with justification that the eligibility criteria are met in a given indication and should be presented as a short but comprehensive document (not more than 30 pages in length). The following aspects could be considered, as appropriate, in the justification:

Unmet medical need

- In general, the justification may be more convincing if based as much as possible on epidemiological data about the disease (e.g., life expectancy, symptoms and duration, health-related quality of life). The claims could be substantiated e.g., from published literature or registries or healthcare databases.
- Where relevant, the unmet medical need could be described separately for different indications or subpopulations.
- A description of the available treatment options/standard of care (SOC), including all relevant treatment modalities, e.g., medicinal products used in clinical practice (whether approved or not), devices, surgery, radiotherapy could be included. The effect of available treatments could also be described together with a description of how the medical need is not fulfilled by the available treatments.

Potential to significantly address the unmet medical need

- The extent to which the medicinal product is expected to address the unmet medical need (described in the above bullet point) is essential to its eligibility for PRIME support. The justification could include a description of the medicinal product's observed and predicted effects, their clinical relevance, the added value of the medicinal product and its impact on medical practice. It is noted that a new mechanism of action or a technical innovation *per se* may not necessarily represent a valid argument for justifying major interest from the point of view of public health.
- In case authorised treatments or established methods exist, the expected improvements should be discussed through a critical review comparing authorised or clinically established treatments and the proposed product.

Data required at different stages of development

The applicant will need to discuss the strength of evidence to support justifying major interest from the point of view of public health, for example, the available evidence to establish that the product has the potential to fulfil an unmet medical need. The description of the strength of evidence should include a brief outline of the main available evidence on which the applicant bases its claim of addressing a major public health interest.

Assumptions of potential benefit(s) should be plausible and where possible based on a sound understanding of the product's pharmacology and relationship of pharmacological effects to clinical outcome. In addition to any data on clinical activity, a summary of all available safety data obtained in the nonclinical and clinical setting should be included in the request. If the product is under development for other conditions, a very brief description of any relevant supporting data should be included but should be clearly separated from the data which relates directly to the condition which is the subject of the PRIME request.

Clinical stages of development (Proof of concept)

In order to access the breadth of regulatory support during the clinical stages of development, the potential promising activity of the medicinal product should be based on proof of concept in man to justify that clinical benefit can be expected.

- Entry to the scheme for the majority of products is therefore expected to be at stages of the development where the strength of evidence would typically be based on clinical response and safety data in patients (i.e. generated in exploratory clinical studies) substantiating the product's potential to significantly address the unmet medical need by providing a clinically relevant advantage for patients.

- Preliminary clinical evidence should indicate substantial improvement in patients. The appropriateness for access to the PRIME scheme is judged on a case by case basis and depends on both the magnitude of the treatment effect, which could include duration of the effect, and the relevance of the observed clinical outcome. Relevant clinical outcomes generally refer to an endpoint that predicts an effect on associated morbidity, mortality or progression of the underlying disease (e.g. response rate in certain cancers). Established surrogate, other intermediate endpoint or pharmacodynamic marker that strongly suggest the potential for a clinically meaningful effect can also be used to justify eligibility for PRIME support.

- In general, it will be difficult to justify eligibility to the PRIME scheme on the safety aspects alone during the development, as the safety profile of a medicinal product is usually fully characterized only after a medicinal product is placed on the market. Nevertheless, this may be justified, on a case-by-case basis, where safety is a major limiting factor in whether a patient can receive the full benefit of existing treatment or where safety issues of existing treatments are known to severely limit the patient's quality of life.

Early stages of development (Proof of principle/proof of mechanism)

Medicinal products in early stages of development could also access the PRIME support scheme based on nonclinical data and very early clinical data showing the promising activity of the medicinal product. Entry at this early stage will be exceptional and directed to provide SMEs and applicants from the academic sector with advice on tests and trials to support confirmation of eligibility through to later clinical phases of development.

- At this stage, the most important criterion will be the convincing scientific concept and the magnitude of the observed effect in non-clinical studies supported by indicators of an acceptable/proportionate safety in clinical studies. The observed effect must be sufficiently large and/or of long duration in order for the drug to be eligible for the PRIME scheme. Overall, the results of the non-clinical and early clinical studies should be extremely compelling to outweigh the many remaining uncertainties at this early stage of development.

- Relevant in vitro and in vivo data in appropriate preclinical models should be submitted, with their relevance discussed preferably in the context of the use with other products known to be successfully developed for the condition. If available, established in vivo models for the condition should be preferably used. Unless adequately justified, in vitro evidence alone will generally not be considered sufficient evidence to support eligibility to PRIME support.

- A new pharmacological target or mechanism of action will not, in and of itself, therefore be viewed as sufficient to justify PRIME support.

- When available, discussion of the results obtained with the product compared to those obtained with comparators should be provided to substantiate the major advantage in the diagnosis,

prevention or treatment of the condition applied for. The preclinical data should be discussed in full even if preliminary results from first administration to humans are available.

- Product should have shown acceptable tolerability in early clinical studies to support further progress of development in clinical phases. Early clinical data to evidence initial safety at exposures sufficient that the proof of principle/proof of mechanism may translate into man should be submitted if available.
- Furthermore, the application should contain a brief outline on the future plans regarding the preclinical and clinical development; future studies should be easily distinguishable from studies already performed or ongoing.

The items to be described in the justification and the appropriate level of detail should be evaluated on a case-by-case basis.

Annex 2 – Procedure for review of requests for eligibility

Review of requests of eligibility to PRIME are proposed to be conducted by the SAWP and CHMP will be responsible for the adoption of recommendations.

The applicant should submit a request for PRIME support electronically to EMA including a justification and summary of available data. Specific deadlines will be published to that effect.

Upon receipt of the request, one SAWP reviewer and one EMA scientific officer will be appointed for the procedure to start in accordance with published timetables, as follows:

Day 1 Start of procedure (SAWP 1 meeting).

Day 30 Discussion and recommendation during SAWP plenary (SAWP 2 meeting).

Day 40 The CHMP final recommendation is adopted during the plenary meeting.

Of note, SAWP recommendations on requests related to ATMPs will also be circulated to the CAT prior to finalisation and adoption by CHMP.

The outcome, including the reasons that led to the CHMP's decision, will be sent by EMA to the applicant. An appeal mechanism is not foreseen. The applicant may, however, submit a new request should new evidence or data be considered to support eligibility to the scheme.

Templates will be developed to support the procedure.