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Committee for Medicinal Products for Human Use

## Enhanced early dialogue to facilitate accelerated assessment of PRiority Medicines (PRIME)

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## Glossary

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

## 1. Background

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 that 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 been working on a number of initiatives aimed at further supporting development with a view to accelerating patients' access to 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<sup>1</sup> 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.

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 document.

## 2. Objectives

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 is confirmed just months prior to filing. With a view to improving early access tools and regulatory support to promising new medicines, the PRIME scheme introduces the possibility not only to identify products fulfilling the criteria for accelerated review earlier, but also to enhance the regulatory and scientific support for these products through advice at key milestones in development.

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 (i.e. where data in patients justify that clinical benefit can be expected).

With PRIME, products will benefit from support tailored to the stage of development, which will not only be provided through scientific advice, but, for products achieving proof of concept, through: early CHMP Rapporteur appointment<sup>2</sup>; a kick-off meeting involving also experts from the Scientific Advice Working Party (SAWP), relevant committee members (particularly from the Paediatric Committee

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<sup>1</sup> [EU Medicines Agencies Network Strategy to 2020, Working together to improve health](#) (EMA/MB/151414/2015, 17 December 2015)

<sup>2</sup> In case of advanced therapy medicinal products (ATMP), the Committee for Advanced Therapies (CAT) Rapporteur and CHMP co-ordinator will be appointed.

(PDCO), Committee for Orphan Medicinal Products (COMP) and Committee for Advanced Therapies (CAT) in case of advanced therapy medicinal products (ATMP)) and EMA to discuss development plans and regulatory pathways; and confirmation of eligibility for accelerated assessment (subject to the criteria still being met at the time of MAA).

Progressing to proof of concept stage is often a difficult step for smaller actors with limited experience in regulatory aspects and medicine development. This may hinder the development of promising products. Therefore, there is value in opening the scheme to SMEs and applicants from the academic sector at an earlier stage. This additional support is expected to be exceptional and limited to situations where earlier proof of principle/proof of mechanism stage (prior to, or during, early exploratory clinical studies) is supported by compelling data that can be presented to justify a product's potential public health impact. Such requests would typically be based on a convincing scientific concept and the magnitude of the observed effect in non-clinical studies in appropriate models; in addition, indicators of an acceptable toxicity at exposure levels required for the desired pharmacological effect in first in man studies need to be provided.

Overall, 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. Ultimately, this will promote the possibility of earlier patient access to promising new medicines.

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. It is also acknowledged that some development programmes (including certain orphan conditions) do not fit into a conventional series of exploratory and confirmatory clinical trials. Consequently, decisions on eligibility will need to take account of the spectrum of clinical contexts and experiences that exist.

Applicants not applying for, or not qualifying for PRIME support, will continue to be able to request Scientific Advice / Protocol Assistance and accelerated assessment prior to filing a marketing authorisation. 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. PRIME Eligibility criteria**

The PRIME scheme is limited to products under development which are innovative and yet to be placed on the EU market. There should be an intention to apply for its initial marketing authorisation 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, medicines eligible for 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.

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

The appropriateness for access to the PRIME scheme 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.

Consequently, entry to the scheme for the majority of products is expected to be supported by evidence of clinical response 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.

As the data submitted will vary depending on the product, stage of development and therapeutic area, each request will be considered on a case by case basis.

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

## 4. PRIME eligibility procedure

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 review the requests and provide their recommendation to CHMP.

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.

An oversight group composed of CHMP members and representatives from the CAT, COMP, PDCO and Pharmacovigilance Risk Assessment Committee (PRAC) will be established to ensure the consistency of the scheme, monitor output 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.

An overview of the number of recommendations adopted will be published in the CHMP Monthly report. The EMA will also publish information on products for which eligibility to the scheme has been granted, including the name of the active substance/INN, 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 have been denied eligibility, similar information will be published, with the exception of the name of the active substance/INN, to avoid unintended negative connotations on the merit of the product at the early stage of its development. In case of a subsequent centralised marketing authorisation, reference to eligibility to the PRIME scheme and relevant information will be mentioned in the European Public Assessment Report.

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.

## 5. PRIME 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. Applicants will receive written confirmation of the outcome of the eligibility to the PRIME scheme, which in positive cases will include early confirmation of potential for accelerated assessment of MAA.

The following key benefits for applicants are provided:

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

- Raising awareness of regulatory requirements early in the development, by providing scientific and regulatory advice on the overall development plan and at major development milestones, with the possibility to involve multiple stakeholders (e.g. Health Technology Assessment (HTA) bodies, patients).
- Eligibility to PRIME may help these applicants to overcome financial hurdles<sup>3</sup> to progress through later stages of the development.
- Upon request, SMEs and applicants from the academic sector<sup>4</sup> may also be eligible for fee reductions on their scientific advice requests, upon case-by-case decisions.

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

- Early appointment of CHMP Rapporteur<sup>5</sup> (in line with current process, objective criteria and methodology).
- An initial kick-off meeting with multidisciplinary participation from the EU network (SAWP, CAT, COMP, PDCO and experts, as relevant), including the CHMP Rapporteur<sup>5</sup>, to discuss the proposed development programme, give preliminary guidance on requirements for MAA, and to develop a schedule for giving regulatory and scientific advice and for submissions of applications to fulfil legislative requirements (e.g. paediatric investigation plan).
- Scientific advice on key decision points/issues for the preparation of MAA with the possibility 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.

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<sup>3</sup> In light of Recital (5) of COMMISSION REGULATION (EC) No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises.

<sup>4</sup> 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.

<sup>5</sup> In case of advanced therapy medicinal products (ATMP), the Committee for Advanced Therapies (CAT) Rapporteur and CHMP co-ordinator will be appointed.

The early appointment of the CHMP Rapporteur<sup>6</sup> is a key feature of the scheme that 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 and its assessment team will discuss preparatory aspects of the MAA from both a technical and scientific viewpoint and ensuring that important aspects of the development programme are brought to discussion at CHMP through Scientific Advice or Protocol Assistance in a timely and comprehensive manner. This engagement also provides the possibility for greater regulatory preparedness to support scientific opinions at PDCO, COMP and CHMP/CAT at the time of MAA.

This assistance will be channelled through scientific advice by the SAWP. In this framework the applicant will be able to discuss the detailed development plan; the design of pivotal studies; post-authorisation activities, in particular if a conditional marketing authorisation is envisaged; as well as quality and non-clinical aspects. Two coordinators from the SAWP will be appointed to each procedure, in line with current practice. One of these coordinators will follow each advice request received, which may enable the use of shorter procedural timelines. Wherever possible, one of the SAWP coordinators will be appointed from the same delegation as the Rapporteur in order to facilitate continuity in support and knowledge sharing.

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. The EMA will also contribute to the regulatory support by 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. The EMA will also facilitate collaboration and coordination of support across committees.

Products granted PRIME support are anticipated to benefit from the accelerated assessment procedure, which is to be formally confirmed 2-3 months before submission of the application for marketing authorisation. In line with the current practice, CHMP Co-Rapporteur<sup>5</sup>, 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, improved resource planning for the EU network and higher quality of marketing authorisation applications, thus allowing assessments within an accelerated timeframe aiming to promote the possibility of earlier patients' access to these promising medicines in the shortest possible timeframe for the benefit of public health.

## 6. Monitoring of development

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).

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<sup>6</sup> In case of ATMP, this refers to the CAT Rapporteur and Co-Rapporteur.

If no scientific advice requests are submitted in a period of one year, applicants would be asked to provide 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 (e.g. further to data derived from confirmatory study or availability of other therapies fulfilling the unmet medical need). In these situations, the applicant/sponsor will be requested to provide a justification on whether the criteria for eligibility to PRIME are still met; this will be assessed by the SAWP/CHMP<sup>7</sup>. PRIME support may be withdrawn if emerging data were to show that the eligibility 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 after the launch of the scheme.

## 7. Collaboration

**Innovation offices** exist in a number of EU Member States. These offices are in contact and support applicants in very early stages of developments. They will have an important role in raising awareness to PRIME and directing possible candidates towards the scheme. The Agency collaborates with the Innovation offices and will exchange information on the scheme and its output on a regular basis.

EMA is committed to facilitating as much as possible the assessment of priority medicines done by **health technology assessment (HTA) bodies**, which inform reimbursement decisions by Member States. This is vital so that patients can access new medicines in a timely manner. In the last years the Agency has launched various initiatives to strengthen collaboration with these bodies. In view of its aim to promote the possibility of earlier patients' access, as part of PRIME, EMA will encourage medicine developers to make use of relevant tools supporting early dialogue with HTAs, such as the parallel EMA/HTA advice.

The importance of considering PRIME in the context of global developments and **international cooperation** is acknowledged. As part of their confidentiality agreements, EMA and other agencies may exchange information on specific medicines' development and experience on development support tools.

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<sup>7</sup> And CAT in case of ATMP.



## 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 will 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 should be described separately for different indications or subpopulations.
- A description of the available diagnostic, prevention or 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 should be included. The effect of available methods should also be described together with a description of how the medical need is not fulfilled by the available methods.

### 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 should 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 (in comparison with existing methods when those exist). 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. Established surrogate or pharmacodynamic marker that strongly suggest the potential for a clinically meaningful effect maybe 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 early clinical studies. The observed effect must be sufficiently large and/or of long duration in order for the medicinal product to be eligible for the PRIME scheme. Overall, the results of the non-clinical and early clinical studies should be 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, 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, requests related to ATMPs will also be circulated, after the SAWP, to the CAT for review and recommendation 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 have been developed to support the procedure.