



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Outcome of the public consultation on the Reflection paper on PRIME

Summary of the comments received during the public consultation and the EMA / CHMP responses

1. Background and outline of the public consultation process

PRIME is a scheme 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 was provided in the draft *Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME)* (EMA/CHMP/57760/2015).

Prior to its publication, the proposal and draft reflection paper was subject to extensive discussions with the EU Regulatory network and the Agency stakeholders and partners:

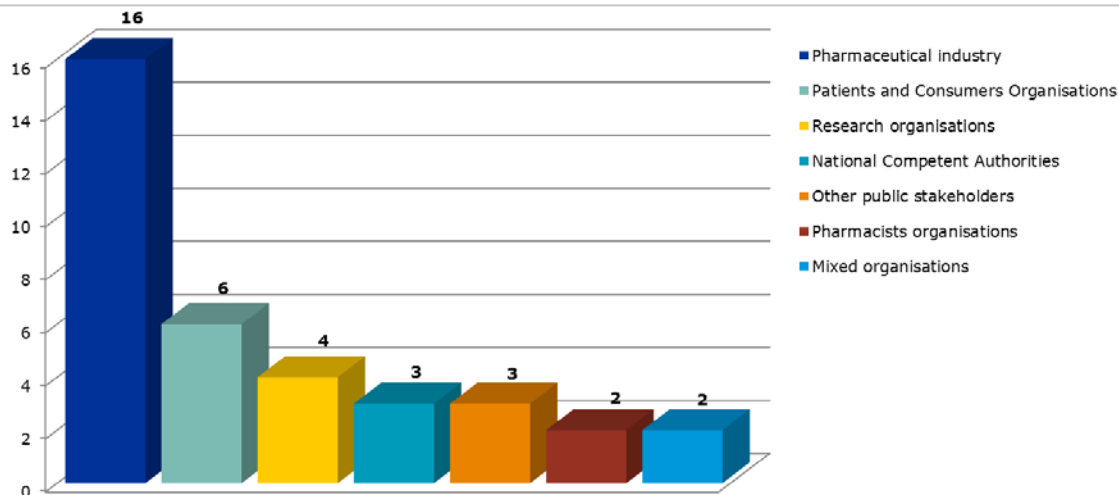
- Between May and October 2015, it was presented and actively discussed on several occasions with the Agency scientific committees that contribute to development support and evaluation of medicines for human use and the Scientific Advice Working Party (SAWP).
- In September 2015, it was also presented to the Patients' and Consumers' Working Party (PCWP) and Healthcare Professionals' Working Group (HCPWG).
- In October 2015, the Agency organised a targeted consultation meeting with industry stakeholders in order to obtain feedback on the potential interest of industry in such a scheme, and to provide an opportunity for high level questions.
- The scheme was presented to Heads of Medicines Agency and the EMA Management Board in July and October 2015, respectively.
- Important contributions were received from the Commission Expert Group on Safe and Timely Access to Medicines for Patients ("STAMP") when the scheme was discussed at each of their meetings in 2015.

Overall, this dialogue has offered the opportunity to receive feedback on the scheme with the view of refining it prior to the publication of the draft Reflection paper for consultation on the EMA website on 26 October 2015 following its adoption at the October 2015 CHMP meeting. Comments were invited through a public consultation until 23 December 2015.



2. Contributors

In total, 36 contributions (from 42 stakeholders) were received in writing with 303 comments (97 general and 206 specific comments) submitted. These came from the pharmaceutical industry (16) but also from a wide range of other stakeholders (20). The detailed distribution of respondents was as follows:



3. Summary of the main points raised during the public consultation

All comments received in writing during the public consultation have been analysed. Overall, the feedback received was positive, with a wide range of stakeholders recognising the need to launch such scheme and its objectives.

Due to the amount and diversity of the comments made, this summary report will focus on the recurrent issues raised and recommendations/suggestions made. Likewise, section 4 of this document will provide the Agency's response to the points expressed.

These comments relate to the following areas:

3.1. Eligibility criteria and timing of entry into the scheme

- The need for clear and robust criteria, clarifications on underlying definitions and data requirements was highlighted.
- Comments on possible similarity and/or links of the PRIME criteria with the criteria for orphan designation.
- Comments on the proposed restriction of entry into early stages (proof of principle) to micro-, small- and medium-sized-enterprise (SMEs) and applicants from the academic sector, not to be driven by the developer status but the unmet medical need of the product.
- Proposal for eligibility to PRIME to also include extensions of indications or line extensions of authorised medicinal products that meet a significant unmet medical need.
- The need for clarifications on criteria for withdrawal of PRIME eligibility and further details with regards to monitoring was highlighted.

3.2. Support provided by EMA and European Union (EU) network upon eligibility to the scheme

- Several Pharmaceutical Industry Stakeholders highlighted the early appointment of the Rapporteur as a key benefit of the PRIME scheme and requested further clarity or made suggestions on criteria for selection of the Rapporteur.
- Other stakeholders (Patient and Consumer Organisations, National Competent authorities, Pharmacist organisations) raised concerns on the risk of regulatory capture and potential conflicts of interests further to regulator's involvement in scientific advice and in view of early dialogue and appointment of the Rapporteur in PRIME.
- Further clarity on the advantages of PRIME and differences with scientific advice outside of the scheme were requested. Several stakeholders made suggestions for process improvements of the scientific advice procedure for PRIME, in particular, in case of iterative procedures.
- The need for clarifications on coordination and collaboration across the Agency's scientific committees, and particularly the involvement of the Committee for Orphan Medicinal Products (COMP) and Paediatric Committee (PDCO), was highlighted.
- Clarifications were sought on the provision of coordinated support by the Agency.

3.3. Collaborations and involvement of stakeholders

- The critical importance of involving HTA bodies into early dialogue was highlighted.
- Considerations and suggestions were made on PRIME in the context of global development and international cooperation with other regulatory authorities, particularly the United States (US) Food and Drug Administration (FDA) and Japanese Ministry of Health, Labour and Welfare (MHLW) and Japanese Pharmaceuticals and Medical Devices Agency (PMDA) which have similar initiatives in place.
- Comments were raised on the collaboration and involvement of national innovation offices in PRIME.
- Comments were made with respect to the role and involvement of patients and healthcare professionals in the scheme.

3.4. Other issues

- The need to ensure patient's safety is not compromised by expedited evaluation was highlighted.
- Several comments were raised with regards to transparency:
 - Highlighting the need for greater transparency on the oversight of the scheme and management of conflict of interests;
 - Patients/consumer and research organisations made suggestions to increase transparency of eligibility to PRIME and supporting data;
 - Pharmaceutical industry organisations highlighted the need and made suggestions with respect to non-disclosure of commercially confidential information.

- Several clarifications were requested with regards to fees; particularly comments were raised by several stakeholders whether fee reductions would be proposed for academic/research organisations.
- A number of clarifications and suggestions were made on operational aspects of PRIME eligibility and provision of support in the scheme.
- Clarifications were requested on how PRIME fits other Agency's initiatives, particularly adaptive pathways.

4. EMA/CHMP responses to the main points raised

As already mentioned, this section elaborates on the response to the recurrent points raised. Changes have been made to the Reflection paper as indicated below; however, since it is a high-level document, several comments made have not been addressed in the document as such, but will be taken into account in other documents (e.g. guidance for applicants) and in the processes underpinning the implementation of PRIME.

4.1. Eligibility criteria and timing of entry into the scheme

- Where relevant, clarifications or stronger wordings with respect to eligibility criteria have been introduced in the reflection paper. Definitions used such as unmet medical need, major interest from the point of view of public health and therapeutic innovation are in line with other existing legislation and guidances (i.e. conditional marketing authorisation and accelerated assessment), on which the CHMP and EU regulatory network has experience in implementing. The level of guidance provided is similar to the level provided as part of the accelerated assessment guideline. As experience is gained, further guidance building on examples may be provided in the relevant documents.
- PRIME eligibility and orphan designation are different and originate from different legislations. Orphan designation is granted based on the potential for use in a specific rare condition; PRIME eligibility would be granted on the potential use in a specific therapeutic indication. In addition, criteria and data requirements for eligibility to PRIME and orphan designation are different, particularly with respect to addressing a major therapeutic advantage for PRIME versus the significant benefit in the context of an orphan drug designation. For being eligible to PRIME enough evidence will be required while for the orphan designation it can be based on an assumption to be demonstrated only at time of the marketing authorisation application.
- The objective of PRIME is to provide tailored support to products for which evidence is available to demonstrate the promising activity of the medicine and its potential to significantly address the unmet medical need. Upon eligibility based on proof of concept data, the EMA and EU network will provide enhanced scientific and regulatory support, through the organisation of a multidisciplinary kick-off meeting and appointment of the Rapporteur, in addition to the scientific advice from the CHMP's Scientific Advice Working Party (SAWP). It is however considered that there is value in supporting SMEs and applicants from the academic sector at an earlier stage, if their product demonstrates a convincing scientific concept and relevant non-clinical effects of sufficiently large magnitude and duration. This support, facilitated by the EMA dedicated contact point, will help them progress through to the proof of concept stage, which is often a difficult step for these smaller actors with limited experience in regulatory aspects and medicine development, and therefore prevent the discontinuation of the medicine development. In that regards, PRIME

complements the support available for all applicants with emerging therapies through other EMA initiatives such as the Innovation Task Force (ITF).

- In addition to scientific advice, the main added benefits of the support provided during development to products eligible to PRIME compared to other products, are the EMA dedicated contact point and early appointment of the CHMP (CAT as well for ATMP) Rapporteur. Once authorised products can already benefit from such support through the EMA Product Lead & Procedure Manager as well as appointed Rapporteur and Co-Rapporteur. Furthermore, PRIME targets products with a potential for accelerated assessment, which is a regulatory pathway only applicable to initial marketing authorisation applications (MAA). Consequently, it is believed that an already authorised product showing promising data in a new indication, can benefit of support from other existing tools such as the scientific advice procedures or discussion meetings with EMA and Rapporteur, outside of the PRIME scheme. Involvement of relevant committees (e.g. COMP, PDCO) can also be considered on an ad hoc basis after discussion with EMA.
- Clarifications have been introduced in the reflection paper with regards to monitoring and criteria and applicability of withdrawal. Need for additional templates or supportive documents will be considered as experience is gained.

4.2. Support provided by EMA and EU network upon eligibility to the scheme

- The appointment of the Rapporteur is made on the basis of objective criteria, which will ensure the provision of objective scientific opinions and will allow the use of the best and available expertise in the European Economic Area (EEA) on the relevant scientific area, as detailed available [Procedural advice](#).
- Early appointment of the Rapporteur is considered a key feature of the scheme as it will enable continuity in support with life-cycle approach from development to marketing authorisation. It should be emphasized that the Agency has rigorous processes and procedures in place that ensure the independence of the assessment of marketing authorisation applications and handling of conflicts of interest:
 - Each application is reviewed independently by a Committee member who acts as rapporteur and a Committee member who acts as co-rapporteur. Rapporteur and co-rapporteur prepare their assessment independently from each other and are supported by assessment teams to do so.
 - The assessments are commented by the other Committee members and discussed several times within the Committee. Further clarifications are often sought from the companies for the Committee to reach its final opinion on the benefit/risk balance of the medicinal product.
 - In PRIME, only the CHMP Rapporteur will be appointed early. Co-Rapporteur, peer reviewer and PRAC Rapporteur will be appointed a few months before the MAA, in line with EMA current practice.
 - Advice during development on scientific aspects will be formalised through the existing scientific advice framework, which also involves two co-ordinators, peer review within the SAWP and SAWP agreement prior to formal adoption at the level of the plenary CHMP.
 - Scientific advice aims to help developers of medicines design trials that are scientifically sound and generate adequate data for the benefit-risk assessment of medicines. It is the Agency's

key instrument to support the development of high-quality, effective and safe medicines that meet patients' needs.

- In addition to the early Rapporteur appointment, enhanced scientific and regulatory support will be provided through the kick-off meeting with input from experts across the Agency's committees, scientific advice and EMA dedicated contact point. The reflection paper has been updated to indicate that continuity in the scientific advice procedure may enable the use of shorter procedural timelines in the provision of the advice.
- It is intended to enhance cross-committee collaboration within the PRIME scheme; this is expected mainly through the coordinated support and guidance provided e.g. as part of the kick-off meeting to enable applicants' preparations of relevant submissions and their adequate planning; expedited assessment of other procedures (e.g. paediatric investigation plan, orphan designation) should not be expected as sufficient time should be given to Committees to conduct robust assessment of these pre-authorisation applications. The reflection paper has been updated to clearly refer to participation of PDCO and COMP representatives in the support provided; Furthermore, it is also foreseen that all the Agency's scientific committees are represented in the oversight group.
- Applicants will be provided with a dedicated PRIME contact point within the EMA Product Development scientific Support Department when eligibility to the scheme is confirmed. The contact point will address or direct queries as relevant and support the monitoring of development.

4.3. Collaborations and involvement of stakeholders

- Decision on the pricing and reimbursement of medicines are taken at national level and are not in the remit of EMA. However, EMA is committed to facilitating as much as possible the assessment 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. This procedure enables medicine developers to gain feedback from regulators and HTA bodies at the same time, early in the development of a medicine. This can streamline the generation of evidence needed to determine both a medicine's benefit-risk balance and its relative effectiveness so that patients can access new medicines in a timely manner. The Reflection paper has been updated accordingly.
- The reflection paper has been updated to acknowledge the importance of considering PRIME in the context of global developments and international cooperation. The US FDA's expedited programmes, Japanese Sakigake and EMA's early access tools (including PRIME), cannot be directly compared because of differences between the US, Japan and the EU legislations. However, medicines that are eligible to the FDA breakthrough therapy designation or Japan's Sakigake may in some instances be eligible for EMA PRIME scheme, and vice-versa, should they meet criteria for eligibility to respective initiatives. As part of their confidentiality agreements, EMA and other agencies may exchange information on specific medicines' development and experience on development support tools. Furthermore, applicants wishing to receive advices from EMA and FDA may use the existing procedure for [parallel advice with the FDA](#).
- Innovation offices exist in a number of EU Member States and are in contact and support applicants in very early stages of development. 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. The reflection paper has been updated accordingly.

- Involvement of patient representatives in the eligibility process is not foreseen routinely; however, this may be considered on a case by case basis when additional expertise is needed. This aspect may be reconsidered after experience is gained. The Agency intends to report on a regular basis to the Patients' and Consumers' Working Party (PCWP) and Healthcare Professionals' Working Group (HCPWG).

4.4. Other issues

- PRIME will not lower the marketing authorisation requirements standards. The objective of PRIME is to provide support to lead to better informed development plans and advice on the generation of robust high quality data to support marketing authorisation, while still ensuring that expedited access is not at the expense of inappropriate risk to patients.
- With regards to comments on transparency:
 - Further information has been included in the reflection paper with regards to composition of the oversight group. With regards to the transparency in relation to conflict of interest, as indicated above, the Agency has rigorous processes and procedures in place that ensure the independence of the assessment of marketing authorisation applications and handling of conflicts of interest.
 - With regards to transparency with respects to eligibility to PRIME, the Reflection paper has been updated in view of comments received: additional information, namely the name of active substance/INN, will be published when eligibility to PRIME is granted by the CHMP. This proposed increased level of transparency is believed to benefit patients and other important stakeholders by raising awareness on development of promising products in a given indication, whilst respecting confidentiality in case of negative outcome so as not to allow for unintended negative connotations on the merit of the product at the early stage of its development.
- No fees will be payable for eligibility requests. No changes to the fee structure are proposed, where reduced fees are applied to follow-up advices, and level of fees adapted to the aspects of the development (e.g. for advice on quality aspects only) addressed in the request (see [Explanatory note on fees payable to the European Medicines Agency](#)). The reflection paper has been updated to indicate that SMEs and applicants from the academic sector may also be eligible for fee reductions upon request.
- Guidance for applicants seeking entry to PRIME scheme has been prepared and published on the [EMA website](#). It provides further details and clarifications on procedural aspects. This guidance will be updated regularly to reflect new developments as experience is gained with the scheme.
- This guidance for applicants also includes additional clarifications on how PRIME fits with other initiatives, particularly how it differs from adaptive pathways. SME office and the ITF will continue to provide support. When applicable, they may participate to the support provided in the context of PRIME.