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3 Committee for Medicinal Products for Human Use

4 **Reflection paper on a proposal to enhance early dialogue**
5 **to facilitate accelerated assessment of priority medicines**
6 **(PRIME)**
7 **Draft**

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Date for coming into effect	

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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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Keywords	<i>Accelerated assessment, unmet medical need, development support, scientific advice, early dialogue</i>
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12 **Glossary**

13	ATMP	Advanced therapy medicinal products
14	CAT	Committee for Advanced Therapies
15	CHMP	Committee for Medicinal Products for Human Use
16	EMA	European Medicines Agency
17	HTA	Health Technology Assessment
18	MAA	Marketing authorisation application
19	SAWP	Scientific Advice Working Party
20	SME	Micro-, small- and medium-sized-enterprise
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22 **1. Drivers for change**

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

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

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

35 There is, however, a need to further reinforce regulatory and scientific support to foster development
36 of new medicines addressing major public health needs. The EU Medicines Regulatory Network has,
37 therefore, highlighted in its Strategy to 2020¹ the need to work towards ensuring timely access to new
38 beneficial and safe medicines for patients, supporting patient focused innovation and contributing to a
39 vibrant life science sector in Europe.

40 **2. Background and objectives**

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

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

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

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

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

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

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

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

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

82 **3. Proposed Eligibility criteria and procedure**

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

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

89 As such, products eligible for PRIME support are expected to target conditions where there is an
90 **unmet medical need**, i.e. for which there exists no satisfactory method of diagnosis, prevention or
91 treatment in the Community or, even if such a method exists, in relation to which the medicinal
92 product concerned will be of major therapeutic advantage to those affected.

93 In these conditions, a product eligible for PRIME support should demonstrate the **potential to**
94 **address to a significant extent the unmet medical need** for maintaining and improving the health
95 of the Community, for example, by introducing new methods of therapy or improving existing ones.

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

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

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

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

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

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

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

120 **4. Proposed support features**

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

125 The following key benefits for applicants are considered:

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

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

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

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

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

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

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

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

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

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

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

166 **5. Monitoring of development**

167 Development progress of products successfully entering the scheme will be monitored at regular
168 checkpoints. Based on the data presented in the scientific advice requests, the SAWP and CHMP will, in
169 the scientific advice letter:

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

175 In case no scientific advice requests are submitted, applicants would be asked to provide an update on
176 development progress (as defined with the SAWP/CHMP during the scientific advice procedure, e.g. at
177 relevant milestones).

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

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

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

187 **6. Next steps**

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

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

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

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

197

198 **Annex 1 – Justification for eligibility to PRIME**

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

202 **Unmet medical need**

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

214 **Potential to significantly address the unmet medical need**

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

224 **Data required at different stages of development**

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

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

237 *Clinical stages of development (Proof of concept)*

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

- 241 • Entry to the scheme for the majority of products is therefore expected to be at stages of the
242 development where the strength of evidence would typically be based on clinical response and
243 safety data in patients (i.e. generated in exploratory clinical studies) substantiating the product's
244 potential to significantly address the unmet medical need by providing a clinically relevant
245 advantage for patients.
- 246 • Preliminary clinical evidence should indicate substantial improvement in patients. The
247 appropriateness for access to the PRIME scheme is judged on a case by case basis and depends on
248 both the magnitude of the treatment effect, which could include duration of the effect, and the
249 relevance of the observed clinical outcome. Relevant clinical outcomes generally refer to an
250 endpoint that predicts an effect on associated morbidity, mortality or progression of the underlying
251 disease (e.g. response rate in certain cancers). Established surrogate, other intermediate endpoint
252 or pharmacodynamic marker that strongly suggest the potential for a clinically meaningful effect
253 can also be used to justify eligibility for PRIME support.
- 254 • In general, it will be difficult to justify eligibility to the PRIME scheme on the safety aspects alone
255 during the development, as the safety profile of a medicinal product is usually fully characterized
256 only after a medicinal product is placed on the market. Nevertheless, this may be justified, on a
257 case-by-case basis, where safety is a major limiting factor in whether a patient can receive the full
258 benefit of existing treatment or where safety issues of existing treatments are known to severely
259 limit the patient's quality of life.

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

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

- 266 • At this stage, the most important criterion will be the convincing scientific concept and the
267 magnitude of the observed effect in non-clinical studies supported by indicators of an
268 acceptable/proportionate safety in clinical studies. The observed effect must be sufficiently large
269 and/or of long duration in order for the drug to be eligible for the PRIME scheme. Overall, the
270 results of the non-clinical and early clinical studies should be extremely compelling to outweigh the
271 many remaining uncertainties at this early stage of development.
- 272 • Relevant in vitro and in vivo data in appropriate preclinical models should be submitted, with their
273 relevance discussed preferably in the context of the use with other products known to be
274 successfully developed for the condition. If available, established in vivo models for the condition
275 should be preferably used. Unless adequately justified, in vitro evidence alone will generally not be
276 considered sufficient evidence to support eligibility to PRIME support.
- 277 • A new pharmacological target or mechanism of action will not, in and of itself, therefore be viewed
278 as sufficient to justify PRIME support.
- 279 • When available, discussion of the results obtained with the product compared to those obtained
280 with comparators should be provided to substantiate the major advantage in the diagnosis,

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

283 • Product should have shown acceptable tolerability in early clinical studies to support further
284 progress of development in clinical phases. Early clinical data to evidence initial safety at exposures
285 sufficient that the proof of principle/proof of mechanism may translate into man should be
286 submitted if available.

287 • Furthermore, the application should contain a brief outline on the future plans regarding the
288 preclinical and clinical development; future studies should be easily distinguishable from studies
289 already performed or ongoing.

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

292

293 **Annex 2 – Procedure for review of requests for eligibility**

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

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

298 Upon receipt of the request, one SAWP reviewer and one EMA scientific officer will be appointed for the
299 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.

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

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

305 Templates will be developed to support the procedure.