7 March 2016
EMA/136751/2016
Human Medicines Research and Development Support Division

Overview of comments received on 'Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME)' (EMA/CHMP/57760/2015)

Comments

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
1	24-25	Early consultation and scientific advice with regulators and other healthcare decision-makers	Early consultation and scientific advice with regulators and other healthcare decision-makers and patients' representative
1	117-119	The individual outcome adopted by the CHMP for a given medicinal product will not be made public. In case of a centralised marketing authorisation, reference to eligibility to the PRIME scheme granted by the CHMP will be mentioned in the European Public Assessment Report.	The individual outcome adopted by the CHMP for a given medicinal product will be made public and the centralised marketing authorisation, reference to eligibility to the

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			PRIME scheme granted by the CHMP will be mentioned in the European Public Assessment Report.
1	128-130	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	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). and healthcare decision makers.
1	180-181	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.	In these situations, the SAWP/CHMP will re-assess whether the criteria for eligibility to PRIME are still met , particularly regarding the potential to address to a significant extent the unmet medical needs for maintaining and improving health, as provided in Section 93, for eligibility criteria , and subsequently notify the applicant/sponsor of its conclusions
1	205	The claims could be substantiated e.g., from published literature or registries or healthcare databases.	The claims could be substantiated e.g., from published literature or registries or healthcare databases and patient organizations surveys and other specific documents on epidemiological data. .

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1	294-295	Review of requests of eligibility to PRIME are proposed to be conducted by the SAWP and CHMP will be 294 responsible for the adoption of recommendations.	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. Representatives of patients' organizations should be duly represented throughout the reviewing procedures.
2	General	BEUC welcomes the opportunity to comment on the EMA's *Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME)*. Consumers welcome improvements to the design and conduct of clinical trials in order to maximize the quality of data collected while minimizing the risk to participants and adhering to good governance standards. Consumers also see the value in developing an expedited process to bring a limited number of medicines with a clearly defined and demonstrated impact on public health to the market. Regardless of which process is followed, consumers trust regulators to ensure that the benefits of medicines available on the market outweigh their risks. However, experiences in the US show that expedited regulatory evaluation programmes have resulted in safety implications for patients, including a higher risk of serious adverse drug reactions (ADRs) and higher rate of patient information leaflet (PIL) revisions for dose, safety and efficacy issues.[1] Any move to bring unproven medicines to the market sooner raises many questions about patient safety and consumer protection. With these general concerns in mind, we wish to make the following specific recommendations	

1 Kesselheim et al. JAMA 2011;305:2320-6 and Berlin. Am J Pub Hlth 2009;99:1693-8

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		to the *Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME)*.	
2	43	The PRIME scheme focuses on developing new medicines to address major public health needs. A clear definition of a major public health need is lacking. This is necessary to set the scope and boundaries of the PRIME scheme.	
2	52	There are many conceptions of what medicines innovation means and it is necessary to specify how the EMA defines 'therapeutic innovation'. BEUC highlights that true therapeutic innovation is the development of medicines that have added value compared to existing alternatives.	
2	90	A clear definition of an 'unmet medical need' should be agreed**.** A lack of a definition could enable the excessive use of the PRIME scheme in inappropriate situations, thereby wasting resources and potentially exposing consumers to unnecessary risks associated with expedited assessment.	
2	89; 93; 203; 205; 209; 218	There should be a clear link between the unmet medical need and the product considered for PRIME. Three elements of justification are crucial to ascertain the suitability of potential products for the PRIME scheme: the scope of the unmet medical need, the extent to which the product fulfils that need and is safe for consumers to use, and the strength of the evidence.	(line 89) As such, products eligible for PRIME support **shall** target conditions where there is an unmet medical need,… (line 93) In these conditions, a product eligible for PRIME support **shall** demonstrate a positive benefit/risk ratio **and** the potential to address to a significant extent the unmet medical need for maintaining and improving the health of the

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			Community… (line 203) In general, the justification may be more convincing if based ~~**as much as possible**~~ on epidemiological data about the disease… (line 205) These claims **shall** be substantiated e.g., from published literature or registries or healthcare databases. (line 209) A description of the available treatment options/standard of care (SOC), including all relevant treatment modalities, …, radiotherapy **shall** be included. The effect of available treatments **shall** also be described together with a description of how the medical need is not fulfilled by the available treatments. (line 218) The justification **shall** 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.
2	98	Only clinically significant impacts are valuable for patients and should be part of	Data available to support a request for eligibility should support the claim that the

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		the eligibility criteria for PRIME.	product has the potential to bring a major therapeutic advantage to patients, through a meaningful improvement of efficacy, such as having a **clinically significant** impact **for the patient** on the onset and duration of the condition…
2	118	Disclosure of the data used to determine a product's eligibility for the PRIME scheme aids patients' and healthcare professionals' understanding of the rationale for regulators' decisions and contributes to a restoration of public confidence in regulators following recent scandals which have affected the medical sector.	In case of a subsequent centralised marketing authorisation, ~~**reference to**~~ **the data used to show the product's** eligibility to the PRIME scheme granted by the CHMP will be mentioned in the European Public Assessment Report **and the summary**.
2	132-149	It is vital to ensure that regulators' involvement in scientific or regulatory advice does not undermine their independence. The Reflection Paper indicates that the CHMP/CAT Rapporteur will be appointed at an early stage (line 132) to 'enable continuity in a lifecycle approach' (line 143), will participate in meetings with the applicant (line 134-135) and will provide scientific and regulatory advice (lines 146-149). BEUC would have strong reservations about this scheme if the CHMP/CAT Rapporteur is the same individual who will serve as Rapporteur for a future market authorization application for this product. To avoid any potential conflict of interest, those individuals involved in scientific or regulatory advice on behalf of the EMA should not be involved in the evaluation of the marketing authorization application. To maintain public trust in the EMA's objectivity, there should be a section	

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		introduced in the reflection paper to indicate how conflicts of interest will be identified and prevented.	
2	166	When monitoring development (chapter 5), the product being tested should always be compared with available alternatives/standard treatment. This is essential if PRIME is to target unmet medical needs and to determine if products are still eligible for PRIME (line 179).	
2	251-253	We note that the use of intermediate endpoints is most valuable and certain when their relationship with clinical outcomes is validated.	Established surrogate, other **validated** intermediate endpoint or pharmacodynamics marker ~~**that strongly suggest the potential for a clinically meaningful effect**~~ can be used to justify eligibility for PRIME support.
3	General	The opportunity for increasing early dialogue and regulatory support to enable accelerated assessment via new initiatives such as PRIME is welcomed, however, it is difficult to fully understand the specific differences between PRIME and a regular drug development for a product with unmet medical need other than the early appointment of the Rapporteur (i.e. does the Agency direct proceedings as opposed to the Sponsor)	
3	General	It is not explicitly clear from the guidance when during the development an applicant can submit a request for eligibility to PRIME to the 40 day procedure. It is assumed that this could be at any time point when the applicant believes they have sufficient data to fulfil the eligibility criteria, however, it would be helpful if this is clarified, or whether it is envisaged that in general this could be done at the proof of principle or proof of concept stages only.	

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3	96-99	It should be clarified that the mentioned request for eligibility in the context of this section refers to PRIME (as opposed to accelerated review).	Data available to support a request for eligibility for PRIME should support…
3	125-130 & 138-140	It is not clear how scientific advice is a specific benefit for PRIME when it can be requested at any time during the development program. It would be helpful to understand the key differences of the scientific advice procedure within the context of the PRIME scheme versus a standard drug development.	
3	137	Typo 'develop of'	Develop ***a*** schedule
3	141-142	It would be helpful to add examples of the types of regulatory aspects that might be addressed.	
3	150-154	Not clear whether this refers to the usual scientific advice procedure which is usually a written procedure, unless the company is invited to a discussion meeting, or a specific scientific advice procedure for PRIME where the company can automatically have a discussion meeting with the agency.	Typo on line 153 – 'SAWP coordinator**s**'
3	162	When it is referred to 'intensive guidance' this implies that it is not a consultative procedure. It is not clear how such guidance should work in practice and if this is driven by the company or the regulators.	
3	178-183	It should be confirmed that the Sponsor is still eligible to apply for an accelerated review in the event that PRIME support is withdrawn.	
3	198-229	The Annex describes the justification for eligibility to PRIME, however this seems no different to the requirement for the justification for accelerated assessment. It would be helpful to clarify any differences or alternatively cross reference could be made to the requirements in the accelerated assessment guidance document for any overlapping parts.	

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3	224	In terms of the data required at different stages of development, it is felt that it would be clearer if this section was ordered with the data required at the early stages of development first and then the later stages.	
4	General	As a developer of innovative, transformative medicines, Vertex welcomes and commends initiatives such as PRIME that aim to foster development of new medicines addressing major public health needs.	
4	General	The reflection paper frames PRIME as a scheme to reinforce early dialogue and regulatory support to stimulate innovation, optimise development and enable accelerated assessment of priority medicines. In the "Drivers for Change" section of the reflection paper, the need for PRIME is linked to other initiatives that aim to accelerate patients' access to medicines (e.g. Adaptive Pathways, Accelerated Assessment and Conditional Marketing Authorisation). While some of the measures detailed within the reflection paper regarding PRIME may reinforce early dialogue and regulatory support, the link with a wider aim to ensure expedited and timely access to medicines that address unmet medical needs is not clear. The reflection paper suggests that PRIME relies primarily on the current regulatory procedures conducted by the Committees of the EMA, particularly CHMP Scientific Advice. It is not clear how development will be substantially accelerated by PRIME designation unless some flexibility is provided in the review and evaluation procedures during development. Further comments are provided below in relation to this point. In addition, more details about how PRIME fits with other initiatives (e.g. Adaptive Licensing, Conditional Marketing Authorisation, Member States' Early Access initiatives) would be welcomed. Given the major public health impact that new	

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		transformative, precision medicines are having for an increasing number of rare diseases, the fit between PRIME and orphan designation might also be expanded upon. There is a need to ensure that the various initiatives and designations are complementary and mutually reinforcing.	
4	General	It is noted that eligibility to the PRIME scheme may be possible at an early stage of development following demonstrated proof of principle. However, this early point of entry seems to be restricted to medicinal products being developed by SMEs or academia, rather than being available to all Sponsors, including established biotech or pharmaceutical companies. This distinction is inappropriate and somehow contradictory to the overarching (and welcomed) aims of PRIME. PRIME aims to reinforce early dialogue and regulatory support to stimulate innovation, optimise development and enable accelerated assessment to new medicines addressing major public health needs. The source of a promising, innovative new medicine should not be relevant in this context – the unmet need should be the driver for the regulatory support offered by PRIME. The importance of supporting SMEs/academia in accessing and navigating the EU regulatory system is acknowledged but this would be better served via other initiatives such as fee reductions/waivers, or broader initiatives in European Community policy and investment.	EMA is requested to consider this comment and the need for resultant changes
4	General	The development of innovative, transformational medicines addressing major public health needs is usually a global process. More details about how PRIME will work in the context of a global development paradigm would be welcomed. It might be envisaged that many promising medicines eligible for PRIME designation will also request Breakthrough Designation from the US FDA. Breakthrough Designation is generally been viewed as successful in its ambitions to expedite the	

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		development and review of drugs for serious or life-threatening conditions and the designation has increasing value for innovator companies. With this in mind, an explicit allowance for joint FDA-EMA dialogue, if desired by the applicant, might be considered for the PRIME scheme. Such a provision may assist with agreeing an acceptable global development plan without major divergences between regions, and bolster the overarching objective of timely access of priority medicines to patients.	
4	62-63	In the reflection paper, it is written that "*the support on offer through the PRIME scheme will be tailored to the stage of development and provided through scientific advice*". From the reflection paper, it is understood that Scientific Advice will continue to be the main method by which the Agency will work with Sponsors on development plans. If this is indeed the case, then the advantages of the PRIME initiative are not likely to have a great impact, unless there are differences in the Scientific Advice procedure for PRIME-designated products. At the moment, the CHMP Scientific Advice procedure is often viewed as being less expeditious than equivalent procedures with US FDA, where meetings/written feedback are generally provided within 30 days of submitting the Sponsor's briefing package (in our experience this is the key metric – submitting a meeting request can be done ahead of time if data generation timelines are well planned and understood). Although it is possible for the SAWP to conclude Scientific Advice procedures at Day 40 (~60 days after initial submission of the briefing package to EMA), this shorter timeline does not allow a meeting with the Applicant. In addition, the uncertainty of whether the advice will be provided at Day 40 or Day	EMA is requested to consider this comment and the need for resultant changes.

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		70 does not help with planning of expedited development, especially for medicines with high potential to meet major public health needs. The Agency is asked to consider whether shorter Scientific Advice procedures can be conducted for PRIME-designated products. Based on the expected familiarity of the SAWP coordinators with the data and development plan for PRIME-designated products, could a ~ 30 day review of the briefing package be envisaged? To facilitate this, review of the briefing package could begin at the time of initial submission to EMA rather than waiting for formal validation from the EMA Scientific Administrator for PRIME-designated medicines. This approach would be supported by the familiarity that the SAWP coordinators would be expected to have with the product and development plan from the PRIME eligibility request and subsequent interactions between the Company, CHMP Rapporteur and the wider Agency.	
4	63-64	It is noted that a benefit of the PRIME scheme will be the early appointment of a CHMP Rapporteur for designated products. If PRIME is to contribute to a more efficient, streamlined regulatory environment then some measures to allow for faster, simpler forms of interactions would be welcomed. The current trend as experienced during MAA review and post-marketing activities is that Sponsors are having less direct access to Rapporteurs, with even straightforward clarification calls being mediated by the EMA, requiring advanced notice and scheduling. Some provision and direction for more informal interactions and correspondence with the CHMP Rapporteur would be welcomed for PRIME-designated products – the advantages of early appointment of a CHMP Rapporteur might be largely negated otherwise.	EMA is requested to consider this comment and the need for resultant changes.
4	64-65	It is noted that an initial kick-off meeting for PRIME-designated medicines will be held with the experts from the SAWP, relevant committees and the CHMP Rapporteur. However, more granularity as to how the other committees within	EMA is requested to consider this comment and the need for resultant changes.

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		EMA will be involved in PRIME would be welcomed. One of the critical pieces of support that could be provided as part of PRIME is assistance in navigating and coordinating across Committees, particularly when interacting and working with the PCDO and COMP. This applies both early in development and closer to submission of the Marketing Authorisation Application. The extent to which PRIME may allow more flexibility in procedures supported by other committees should be considered by the Agency. For example, PIP modifications can frequently take 2-3 months and the progress of development plans can often hinge on the PDCO's response to such modifications. Expedited assessment procedures for all committees might be considered for PRIME-designated products. In order to facilitate this, the Agency might consider whether PDCO Rapporteurs and COMP Coordinators for PRIME-designated products should be assigned from the same delegation as the CHMP Rapporteur to ensure greater familiarity with the product and development plan across Committees.	
4	66-67	It is noted in the reflection paper that an advantage of PRIME will be confirmation of eligibility for accelerated assessment, subject to the criteria still being met at the time of MAA. A confirmation step is appropriate but it might be considered to increase uncertainty in the planning of MAA submission and review for PRIME-designated products. Although the criteria for PRIME are linked to the criteria for accelerated assessment in Regulation (EC) No 726/2004, it might be considered that the reassessment of these criteria at the time of MAA might be considered with a different mindset. For PRIME-designated products it should be shown that the product is not eligible anymore rather than assessing whether the product is eligible. Conceptually this may provide a way to ensure that PRIME-designated products have more reassurance of eventually being evaluated via an accelerated	EMA is requested to consider this comment and the need for resultant changes.

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		assessment for the MAA.	
4	83-85	It is noted in the reflection paper that the PRIME scheme is limited to products under development which are innovative and yet to be placed on the EU market. The Agency is asked consider PRIME designation for development programmes that aim to extend the therapeutic indication for approved medicinal products (and line extensions for such products as well). Although such products will likely already have access to the EMA and a CHMP Rapporteur, there are additional benefits from PRIME designation that could be derived in terms of additional regulatory support to stimulate innovation and optimise development. This includes the potential for an initial kick-off meeting with members (see line 134-137) from the EU network, involvement of SAWP coordinators appointed from the same delegation as the CHMP Rapporteur (see line 153) and potential involvement of HTA in Scientific Advice (see line 139). In addition, it should be considered if PRIME could provide a setting, or at least impetus, for accelerated assessment of Type II variations for extension of the therapeutic indication for approved products. Currently, approval of new/extended indications usually takes >150 days (the standard being an initial 90 day assessment, with a 60 day assessment for Responses to RSI), despite such filings normally containing far less CMC and nonclinical information than an Marketing Authorisation Application.	EMA is requested to consider this comment and the need for resultant changes.
4	150-154	It is noted that one of the SAWP coordinators for PRIME-designated products will be from the same delegation as the CHMP Rapporteur to aid continuity of support and sharing of knowledge gained during development. The Agency should consider whether the SAWP reviewer involved in the initial PRIME eligibility request might serve as the 2nd SAWP coordinator in any Scientific Advices - again this would	EMA is requested to consider this comment and the need for resultant changes.

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		serve to increase consistency of review and familiarity with data. Such a provision might be helpful when considering some of the comments above concerning shorter Scientific Advice procedures to expedite development of priority medicines.	
4	163	It is noted that one of desired outcomes of PRIME is better planning of resources for the EU network. It should be considered whether the resources for PRIME within the EU network should be additive. Whilst the intention to prioritise new medicines addressing major public health needs is supported, there needs to be careful provision not to substitute from the regulatory support including those whose potential for accelerated assessment might only be apparently later in development.	EMA is requested to consider this comment and the need for resultant changes.
4	296-297	More details would be welcomed regarding the lead-times for the documentation for PRIME eligibility requests and how the initial kick-off meeting with multiple stakeholders will be scheduled in relation to a positive CHMP decision on eligibility. Since clinical data is effectively needed for PRIME, once promising data is secured there will be an understandable push to progress to the next stage of development. It may be difficult for Sponsors to wait 40 days for PRIME designation and then for an initial kick-off meeting with multiple stakeholders. Perhaps there can be scope for PRIME eligibility to be reviewed in parallel to a regular SAWP request, in order to allow progress of development to continue.	EMA is requested to consider this comment and the need for resultant changes.
4	178-180	It should be clarified only negative or equivocal data from confirmatory studies would lead to reassessment of the PRIME eligibility criteria for a specific product.	*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~~*

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			~~derived from confirmatory study~~ availability of data from confirmatory studies suggesting that the product does not meet the unmet need or availability of other therapies fulfilling the unmet medical need).
4	182-183	It is stated that PRIME support may be withdrawn if emerging data were to show that the criteria are no longer met. Some clarification would be welcomed as to how regulatory support would be continued in such instances. For example, will the appointed CHMP Rapporteur still remain with the product through the Marketing Authorisation Application (and beyond)?	EMA is requested to consider this comment and the need for resultant changes.
4	251-252	It should be further clarified that data related to established surrogate, other intermediate endpoint or pharmacodynamic markers will not be a pre-requisite for entry into PRIME but rather supportive. Indeed, establishing such surrogate endpoints could be the subject of Scientific Advice through PRIME.	*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 (if such endpoints are available and established).*
4	296	More clarification on electronic submission requirements (e.g. Eudralink, eSubmission Gateway, CD-ROM) would be welcomed either in an updated paper or within more detailed guidance for Sponsors.	EMA is requested to consider this comment and the need for resultant changes.
4	299	More details of the procedure for evaluating PRIME eligibility requests would be welcomed. For example, will the preliminary reports shared with CHMP be made available to Sponsors as part of the procedure or will Sponsors only receive the final CHMP decision?	EMA is requested to consider this comment and the need for resultant changes.

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		On a similar theme, the Agency is asked to consider building in opportunities for Sponsors to provide responses to questions for clarification purposes during the review of PRIME eligibility requests. This could help avoid negative outcomes for Sponsors as appeals are not foreseen with respect to PRIME eligibility requests and a new request should only be made with new evidence or data.	
5	General	**EFPIA, EBE, VE welcome the PRIME scheme and wish to provide constructive input to fully optimise its implementation.** PRIME has the potential to greatly impact the EU research and development environment. We appreciate that some of our proposals and requests for clarification may only be possible once experience is gained.	
5	General	**Early regulatory advice on product development**: *EFPIA, EBE, VE highlight that in order to have the greatest positive impact on public health, all applicants (public and private sectors, SME/ non-SME) should be permitted to request PRIME designation at an early phase of a product's development (i.e., after the 'proof of principle' stage or phase 1 using historic nomenclature). Moreover, once a product which is expected to address unmet medical need in a specific indication has entered the scheme, a second product should be considered eligible to enter PRIME for the same indication until and unless it is demonstrated that there is no longer an unmet medical need. In addition, clarification that a combination of several products[2] can be eligible for the scheme will provide reassurance.* <u>Rationale and Considerations:</u> According to the draft Reflection paper, the aim of PRIME is, not only to identify	

[2] Combination products are medicines that include more than one individual active substance. The individual active substances may each already be authorised, not authorised, or a blend of authorised and not authorised products.

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		products fulfilling the criteria for accelerated assessment, but also to reinforce early dialogue and enhance support throughout the development program. Indeed, PRIME should optimally introduce a holistic approach to medicine development and regulatory review. These aims will ultimately accelerate patient access to safe and efficacious promising medicines, thus improving public health. Supporting this objective, data demonstrate that early advice from regulatory agencies increases the likelihood of a positive result in development of a new medicine. As initially suggested, it may run contradictory to this objective for 'proof of concept' to be the timing for eligibility requests for most applicants. Innovative product development is transitioning away from the historical definitions and distinct transition phases of development (i.e., Phase 2 and 3). Furthermore, novel product development often entails adaptive clinical trial design and adaptive manufacturing process development progressing along a broader variety of methods for evidence generation over the lifecycle of a product. Additionally, limited patient numbers and severity of the disease for rare conditions imply a short exploratory phase followed by confirmatory trials. Since the PRIME entry criteria are limited to products expected to address unmet medical need situations, the use of the system will be restricted. Insofar, an equal approach to allow all applicants to enter the scheme at "proof of principle" seems proportionate for well justified applications of promising products, also from a resource perspective. An alignment of underlying definitions for eligibility (e.g. unmet medical need, products of major interest from the point of view of public health and therapeutic	

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		innovation, significant benefit) will be needed to allow for consistency between different schemes (*e.g.,* Accelerated Assessment or AA, Conditional Marketing Authorisation or CMA). As another important justification, allowing all applicants to apply for PRIME after proof of principle will ensure that the applicant has the chance to optimally engage with other committees (e.g., PDCO which is available after proof of concept and COMP), and on CMC aspects, when relevant. This is particularly important for products that fulfil an unmet medical need in a paediatric indication. Failing this, a PIP may need to be agreed well in advance of the PRIME designation. For those products where the development path is very rapid and expect to file a marketing authorisation application with more limited data (i.e., after phase 2 using historical terminology), the proof of concept entry point into PRIME would be too late to enable the benefits that the scheme offers. These development plans are likely for the very products that would optimally benefit from early, ongoing regulatory advice – a key benefit of PRIME. EFPIA is conscious of the potential resource implications for offering PRIME at proof of principle for all applicants and believes that resource implications should be carefully tracked for future discussion, if special consideration becomes necessary. Yet, given the high potential impact for patients, PRIME should not be restricted due to resource considerations but be prioritised and resourced within the Agency and the EU Network[3]. A sustainable solution should be sought between stakeholders to address any resource aspect and clarify the fee structure.	

[3] Likewise, the Agency's PRIME efforts should not delay the evaluation of products not eligible for PRIME, which should experience timely access to regulatory procedures, as usual.

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5	General	**Scientific advice tailored for the PRIME scheme**: *The SA process should be tailored for PRIME to expedite iteration and, in addition, should be adapted to offer timely, less formal advice to companies in well justified situations. Ideally, the scientific advice process under PRIME will synchronise or link with other committees (e.g. PDCO). More details on how interactions would work in practice (i.e. milestones, triggers for interaction) should be provided to manage expectations in terms of resources and time commitments both from regulators and applicants. EFPIA considers that SA should be timely and adaptable, such that where appropriate, depending on the compound's developmental milestones, it is formal, and at the same time, where appropriate, informal. EFPIA would welcome the opportunity to provide further ideas on the operational enhancements to better tailor SA for PRIME.* <u>Rationale and Considerations:</u> As noted, since potential products for areas of high unmet need often require adaptive approaches to development, a level of flexibility in the scientific advice (SA) process is necessary. There is a need for flexible and less formal advice by rapporteur/ co-rapporteur in addition to iterative scientific advice steps. Particularly, when considering situations where it will be important for a product developer to understand the current regulatory thinking before it makes decisions. In these cases, the full involvement of the SAWP/ CHMP is not yet needed. For PRIME to foster the early development of innovative medicines in Europe and to accelerate patient access to innovative new medicines, the scheme will require	

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		effective cooperation including the EMA with the different working parties, national Agencies, HTA bodies and the European Commission, also in connection with European and national innovation schemes. PRIME designation will meet its goals more successfully if SA is offered to cover discussion for clinical development milestones as well as non-clinical, manufacturing process and CMC related topics. For the conditions mainly affecting paediatric populations, processes should also be identified to allow simultaneous consultation of the PDCO. Of note, currently, only one PDCO member is participating in SAWP/ CHMP meetings, and the CHMP opinion on SA affecting a certain clinical programme does not overlap with the PDCO opinion on the same programme, which can risk delays to development. Ultimately, industry' s expectation on PRIME is to have a better understanding of the regulators' expectations of a product's development with a view to generate the relevant data leading to a high quality dossier and hence a swift assessment with potential approval. The general framework of continuous monitoring by the SAWP during the development suggests iterative interactions and it will be important that the SA[4] process is adapted: • Today, although there is the possibility for Day 40 or Day 70 SA processes, any interaction beyond written communication is currently applied to trigger a Day 70 procedure. This approach may be too restrictive for the PRIME scheme in which flexibility to have timely (and eventually several)	

[4] Note: SA should also cover IVD's, biomarkers, and administration devices. Especially considering that emerging classes of medicines (e.g. biotherapeutics and ATMPs in immune-oncology) all have a series of associated biomarkers and administration devices.

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		face-to-face dialogues is needed. SA interactions for Day 40 could occur more timely via teleconference or videoconference for all aspects of development. • The possibility for a 'discussion meeting' for SA should not be limited to 'cases of disagreement' under PRIME.[5] • The timing and content of the submission package(s) should also be adapted. • It would be interesting to understand whether the fee structure would also be modified. Likewise, specifically for PRIME, early appointment of and interactions with the Rapporteur should be possible to allow for ongoing dialogue, and the SA pre-submission phase should be streamlined. EFPIA, EBE, VE consider that, under PRIME, the first SA interaction would be most detailed, while ongoing dialogue would be streamlined and more efficient than traditionally provided, given the idea that companies would have a consistent point of contact and the Agency would already have background knowledge. The flexible, rapid SA described here is likely to support the future of 'disruptive innovation' recently discussed by an EU Commission expert panel[6].	
5	General	**Involvement of HTA bodies early in PRIME discussions:** *EFPIA, EBE, VE would like to underline that ultimately, a substantial move towards early patient access to innovative medicines in Europe will not be possible without HTA bodies' early involvement and commitment to the concept[7]. Products with*	

[5] EMA/691788/2010 Rev. 7; points 20 and 21.
[6] Disruptive Innovation - Considerations for health and health care in Europe; October 2015; http://ec.europa.eu/health/expert_panel/opinions/docs/011_disruptive_innovation_en.pdf [accessed 13 November 2015]
[7] Although the MAA review remains focused on Quality, Safety and Efficacy aspects, we fully welcome EMA initiatives to stimulate and coordinate HTAs' involvement in the PRIME process.

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		PRIME designation should be early signalled to HTA national agencies so that local assessment could be managed without delays in decisions after the medicines have been approved for marketing. It will likewise be important that national HTA bodies assign resources to cooperate in the above schemes. Rationale and Considerations**:** Products with PRIME designation should allow the involvement of HTA bodies into the early discussions in order to avoid delays in decisions after the medicines have been approved for marketing. EFPIA, EBE, VE understand that the cooperation between the Agency and HTA bodies is currently subject to other initiatives beyond PRIME, such as parallel SA. Further, we anticipate that evolution and outcome on these projects will also be considered for PRIME.	
5	General	**Product eligibility based on potential to address unmet medical need**: *The PRIME scheme should also encourage innovation related to extensions of indications (i.e., Type II variations seeking a new indication) line extensions (i.e., new formulations/route of administrations) and new combinations meeting a significant unmet medical need.* Rationale and Considerations. After authorisation, a product may show promise for an area of high unmet need with the potential to have a positive impact on public health. In these cases, access to the PRIME scheme would ensure that the most efficient and effective development path was implemented for these additional uses of an already marketed medicine. EFPIA, EBE, VE envisions medicines that initially were designated as PRIME for their preliminary indication with potential extensions of indications that would also be eligible for PRIME. In other scenarios, a medicine	

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		authorised without a PRIME designation may have an extension of indication that would qualify for PRIME. Actually, the potential impact on public health should be the determining factor rather than the order of indication development or the type of product (i.e., preventative or therapeutic; individual or combination).	
5	General	**Impact of PRIME designation on subsequent authorisation procedure:** When a product has been granted a PRIME designation, it *de facto* is expected to follow an accelerated centralised procedure. However, the link between the early PRIME designation and the subsequent marketing authorisation application are unclear. Therefore, it should be further clarified: • whether the applicant will need to apply for eligibility to the centralised procedure in order to have the PRIME rapporteur appointed, and how this will be handled. • how the 'coordinated support from EMA' (see page 6) will be provided, in particular whether there will be the concept of an EMA Product Lead during the PRIME development. Additionally, it should be clearly stated whether a request for eligibility for the centralised procedure would need to be submitted again in the event that the PRIME designated product no longer meets the PRIME eligibility criteria and the applicant/sponsor was informed accordingly by the EMA.	
5	General	**Integration with other EMA schemes aimed at promoting innovation:** A number of other schemes have been put in place at EMA in order to foster innovation. These may be established by law (*e.g.,* ATMP certification) or run as pilot schemes (*e.g.,* adaptive pathways, early paediatric interaction). It would be	

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		helpful if EMA could, in its PRIME documents, discuss how these fit together with the PRIME scheme, and how the Agency is anticipating the evolution and outcome of the pilot projects and their possible impact/interaction with PRIME.	
5	7	Although the Reflection paper does not include a 'date for coming into effect', given the potential positive impact for PRIME, EFPIA, EBE, VE supports expediency in implementing the final policy and remains readily available should further input be useful.	
5	30	EMA makes reference to the Adaptive Pathways Pilot and we understand that PRIME is one regulatory tool which can support adaptive pathways. We also understand that PRIME will be available for products which are not included in EMA's Adaptive Pathways Pilot. However, EFPIA, EBE, VE would appreciate additional details on how these two regulatory initiatives will operationally coincide.	
5	23	The availability of the PRIME scheme may also be valuable for the accelerated development and assessment of innovative prophylactic vaccines for which there is a major public health interest. Therefore, the PRIME proposal should acknowledge its applicability to both therapeutics and preventatives.	"The development of promising **new therapeutic and preventive** medicines to address unmet medical needs…."
5	45	It would be helpful if it were explicitly stated that one of the overall objectives of the scheme is to accelerate development and not only assessment. Acceleration can be achieved by using and encouraging innovative approaches to development (e.g. adaptive clinical trials and Adaptive Pathways) and would not imply a lowering of regulatory standards.	'…a scheme has been developed to reinforce early dialogue and regulatory support to stimulate innovation, optimise *and where possible accelerate development* and assessment….'

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
5	53-56	As described, designating an MAA to an accelerated timetable occurs just prior to filing. EMA intends for the PRIME scheme to 'identify products fulfilling the criteria for accelerated review earlier'. This is most welcome by EFPIA, EBE, and VE since early preparations for accelerated review help streamline the applicant's filing process. Many companies must coordinate submissions globally including the timing for Certificate of Pharmaceutical Product (CPP) dependent countries. Companies must also plan for use of their resources globally (*e.g.*, manufacturing preparations, IT dossier support, and regulatory responses to questions) in advance and the earlier the review procedure timelines are known, the more efficient the planning process becomes. For example, if a product will be sourced for the global market from a manufacturing site in Europe, early knowledge about the potential timelines for site inspections and product approval can be helpful from a scenario planning perspective. Considering that Accelerated Assessment (AA) and Conditional Marketing Authorisation (CMA) are key tools in the EU legislation to accelerate approval of medicines that address unmet medical needs, the PRIME scheme can assist in early identification and communication to the applicant of products likely to fulfil the respective eligibility criteria.	'…but also to enhance the regulatory and scientific support on offer to these products through advice at key milestones in clinical and CMC development.'
5	59-61	The text suggests it is the early data from the new medicinal product that will help justify a major public health issue. It would be valuable to have some clarification on the role of clinical and scientific data for the disease area of interest as this may constitute the primary source of justification to the definition of a major public health issue.	
5	68-73	As mentioned under 'General Comments', data demonstrate that early advice from regulatory agencies increases the likelihood of a positive result for developing a	Delete 1st sentence on lines 68-70 – "~~There is also value in opening the scheme~~

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		new medicine. Therefore, EFPIA, EBE, VE believe that the PRIME scheme should be available to <u>all</u> applicants at the time of proof of principle. There are several other important incentives to assist SME product development such as a reduction of regulatory fees (Line 128) and availability of dedicated EMA expertise for query responses.	~~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.~~"
5	86	It should be noted that PRIME is available to both therapeutic and preventative medicinal products.	"The scheme aims to **support therapeutic and preventive medicinal** products of major public health interest and in particular from the viewpoint of therapeutic **and prophylactic** innovation (i.e. those which fulfil the accelerated assessment criteria)."
5	87-88	It is important to ensure that the criterion for PRIME of major public health interest will also apply to orphan drugs. Orphan drugs have been granted AA in the past and thus EFPIA assumes orphan drugs will not be, at the outset, excluded from the PRIME scheme.	
5	89-92	For the justification of unmet medical need, it is important to compare the new treatment to current standard of care in Europe – independent of licencing status. The notion of "satisfactory method" similar to the orphan drug regulation is a formalistic requirement to compare the potential benefit of the new product to approved methods (the interpretation of "satisfactory" as per the orphan regulation). However, licencing status is much less relevant in order to determine medical need than current standard of care independent of licencing status. Including the "satisfactory method" definition will focus the discussion on approved medicines rather than defining the expected clinical benefit compared to current	

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		standard of care, which is the most relevant aspect for consideration.	
5	93-99	EMA describes the eligibility requirements for PRIME as a product "should demonstrate the potential to address to a significant extent the unmet medical need for maintaining and improving the health of the Community; potential to bring a major therapeutic advantage to patients, through a meaningful improvement of efficacy…" EFPIA also believes that this eligibility criterion is sufficiently detailed while still necessarily flexible. There may also be cases where it would be possible for a product to be eligible for PRIME through 'meaningful improvement of safety'. EMA seems to recognise this situation within the text (Annex, line 254). Though, EFPIA, EBE, VE request that the main body of the reflection paper include this criteria for consistency and clarity. There could be a product that is expected to have similar efficacy to one already on the market, but with an expectation of an improved safety profile. For example, an autoimmune therapy in development for a condition of patient need may have a very similar expected efficacy profile to a marketed product, but may have anticipated improvements in its safety/tolerability profile and thus should be considered for PRIME eligibility. Also, the PRIME initiative, and particularly this section, could benefit from referring to and suggesting inclusion of surrogate biomarkers and other intermediate endpoints, so as to accelerate development programmes. **Proposed change:** • Alignment and reference with the interpretation in the revised guideline on conditional marketing authorisation.	

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		• Expand eligibility criteria statements to include situations of meaningful improvement of patient safety. • Suggest additional words within text: *potential to bring a major therapeutic advantage to patients, through a **clinically** meaningful improvement of efficacy **or of the benefit-risk balance** …* Include a reference to the current EMA mechanism to qualify biomarkers and other drug development tools (Qualification of Methodologies for Drug Development; EMA/CHMP/SAWP/72894/2008).	
5	98	Since in the case of prophylactic medicinal products, including vaccines, the main expected impact is prevention, we propose to amend the text as follows.	"**Prevention**, onset and duration **of the condition, or on** …."
5	113-118	EMA describes the types of information about PRIME applicant requests that it will list in its monthly reports. EFPIA, EBE, VE appreciate EMA's acknowledgement of the importance of communicating program metrics. However, if there's a therapeutic area with only one or a few products in development (i.e., ultra orphan condition), releasing a product's 'therapeutic area' along with its 'phase of development' may allow for deduction as to the product's status and company's identity. This may be particularly pertinent for a product that was not accepted into the PRIME scheme. Therefore, EFPIA, EBE, VE believe that only summary information and data should be released within the monthly reports.	EMA should simply make available summary PRIME metrics such as total number of requests, numbers of requests granted/denied and percentage within different general therapeutic areas.
5	126-127	See also general comment. To meet the goal of the PRIME initiative, the innovative clinical development of drugs eligible for PRIME needs to be aligned by a new concept, faster-paced manufacturing process development. Therefore, the possibility of gaining agreement on CMC development plans at the earlier stages should be listed among	*In early stages of development, following demonstrated proof of principle, focusing on **but not limited to** SMEs and applicants from the academic sector.* Add a separate bullet point for CMC

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		the benefits of PRIME and should be included in the bullet points.	development, as follow: • Scientific advice (with fee reductions for SMEs) on the overall **clinical** development plan and at major development milestones, with the potential to involve multiple stakeholders (e.g. Health Technology Assessment (HTA) bodies, patients) When applicable, scientific advice on innovative CMC development approaches, which otherwise have the potential to delay the availability of the drug and equal out the benefit of PRIME designation"
5	126-140	It would be helpful to add the possibility of gaining agreement on CMC development plans at the earlier stages listed among the benefits of PRIME in the included bullet points.	
5	128-130	EMA notes the need to involve multiple stakeholders including HTA bodies. EFPIA, EBE, VE support that iterative steps on scientific advice should allow involvement of HTA bodies building upon the current parallel scientific advice established by EMA. This will be key for the ultimate success of the scheme and Member States should ensure HTA bodies will have the resources to contribute to the discussion. Also in terms of stakeholder engagement, EMA, FDA and PMDA should develop regular mechanisms for an exchange on scientific discussions. The use and operation of PRIME should be monitored, and further opportunities for global	

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		cooperation explored and implemented as experience is gained. This will be paramount for global development considerations.	
5	132	The early appointment of the CHMP/CAT Rapporteur is a welcome feature of the PRIME scheme. It will be important however that the selection criteria for Rapporteurs is highly robust and based on an appropriate level of skill and experience not just in the therapeutic area but also in assessment of highly innovative products and developments in areas of high unmet medical need (e.g. Prior experience of products authorised via Accelerated Assessment, Conditional Marketing Authorisation or other tools). The success of PRIME is particularly dependent upon the rapporteur.	Early appointment of CHMP/CAT Rapporteur (based on objective criteria and methodology and experience of assessment of products in areas of high public health need).
5	140	There is a need for flexible and less formal advice by rapporteur/ co-rapporteur in addition to iterative scientific advice steps. Particularly, when considering situations where it will be important for a product developer to understand the current regulatory thinking before it makes a decision and full involvement of the SAWP/ CHMP is not yet needed. Examples of such situations: • Potential compliance issue or safety signal where a product developer requires a more rapid decision than the formal SA route • New technologies not covered by guidance (*e.g.,* drug-device combination) that are beyond the stage of ITF advice, but directly before the product developer will make a development decision • Other emerging issues where a product developer needs advice (*e.g.,* for Ebola or new clinical rating scales). It is understood that such possibilities for additional flexible guidance may impact resources at the level of EMA and the agencies. Consequently, it is understood that	" - flexible and informal advice by rapporteur/ co-rapporteur in well-justified situations should be possible."

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		this additional option will be applied to well justified situations.	
5	145-149	EMA's proposal states, "The Rapporteur will support the development by directing applicants towards the EMA scientific advice on data requirements for the future MAA…" The intentions of this statement would benefit from further clarification.	We suggest the text of the PRIME proposal could be amended as follows: "The Rapporteur will support the development by directing applicants towards the EMA scientific advice on data requirements for the future MAA. **Scientific advice may also be used to examine whether the investigational product and development plan might qualify for a Conditional Marketing Authorisation. The Rapporteur may raise sponsor awareness of alternative early access tools where relevant (e.g., parallel EMA / HTA advice, adaptive pathways) to facilitate timely access to patients.**"
5	150-157	**Comment 1:** While much of the attention of PRIME support may be on clinical development, it will be necessary for chemistry, manufacturing and control (CMC) and quality aspects to be considered within PRIME along with the clinical development plans. **Comment 2**: limiting interactions to formal SA by the SAWP/CHMP may be too restrictive for the PRIME scheme in which flexibility to have timely, face-to-face dialogue is needed. SA interactions for Day 40 could occur more timely via teleconference or videoconference.	"*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.* ***If appropriate, and in order to guarantee appropriate input in discussions on the***

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			chemistry, manufacturing and control development of a compound with a PRIME designation, a quality expert will also be included. *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.* ***It will be possible for the applicant to have interactions with the SA coordinators and Rapporteur via TC or VC if necessary."***
5	162-165	EMA describes its encouraging expectation for 'intensive guidance…to lead to better informed development plans…aiming overall to ensure patients access to these promising medicines in the shortest possible timeframe'. EMA does not mention the types of data that it will collect internally to measure how the program is functioning to realise this goal. There should be a thorough review and possible adjustments to the PRIME scheme after several years of experience. Also, through its PRIME experience, EMA will certainly uncover novel approaches to SA, engagement of stakeholders and regulatory procedures. EFPIA, EBE, VE encourage EMA to consider which of these regulatory ideas and tools may be more broadly applicable to all MAAs.	EFPIA, EBE, VE suggest that EMA note the PRIME experiential data that it will collect, the metrics that will be important, the frequency by which it will analyse the data, and the stakeholder input needed once the program becomes operational.
5	167-168	It would be helpful if the Agency would specify and clarify the "regular checkpoints" it envisions.	

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5	178-183	EMA notes that "PRIME support may be withdrawn if emerging data were to show that the criteria are no longer met". EFPIA, EBE, VE understand the need to maintain regulators' flexibility; however, EMA should also clarify that withdrawal of PRIME will not be based on having another similar product (*e.g.*, same mechanism, target) achieving PRIME status or authorised for marketing. If this was not to be the case, the development of the 'leading' candidate could be delayed / terminated with the consequence that the availability of a suitable treatment for patients could be delayed as an unintended consequence of another product receiving a PRIME designation in the particular disease area first. Further, appreciating that the eligibility status of a product may change over time, if EMA considers that an initial PRIME designation no longer applies, there should be a process for the applicant to discuss this with EMA before a final decision is taken. The applicant may have generated new data and/or information since it submitted its initial PRIME application, which could impact EMA's final decision.	A discussion process should be envisaged with the applicant prior to a final decision on withdrawal of a PRIME designation.
5	192	In cases where products have already received a similar designation(s), there should be tick boxes within the application for the applicant to note other pertinent designations such as for U.S. Breakthrough Therapy and Japan SAKIGAKE. This may be helpful also to EMA when considering global information sharing across agencies.	
5	198	In Annex 1, EMA describes the content to be submitted as a justification by the applicant for inclusion within PRIME. In order to streamline the application process and to reduce unnecessary administrative burden, it should be possible for Sponsors to easily reuse or refer to existing documents (such as the Investigator's Brochure for a summary of available data, Orphan drug applications for justification of unmet need, etc.). The future PRIME application template should	

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		mirror as much as possible the structure of these and other existing documents.	
5	198-292	The Annex 1 of the document is mainly referring to treatments.	To ensure the applicability of the document to prophylactic medicinal products, including vaccines we propose to replace the words 'treatment(s)' by 'treatment(s) **or prevention(s)**' in Annex 1.
5	225-229	The paper refers to 'robust data package' and to the 'strength of evidence to support justifying major interest from the point of view of public health'. In early stages of development, the evidence package will be somewhat limited and may include short-term or surrogate outcomes only. Based on the proposal, it is not clear whether there will be allowances for different data requirements if there is significant unmet medical need that the investigational product may fulfil. Although some flexibility should be maintained, we expect that guidances would be developed with some suggestions of expectations for appropriate descriptions of strength of evidence, for example, ensuring the level of uncertainty in the data of treatment benefit is quantified, Within the scheme, noting the use of modelling and simulation may be useful to show the potential benefits if using a short-term or surrogate endpoint and how this may translate to address the significant unmet medical need.	
5	237 ff, 260 ff	For applicants to be able to select appropriate products for submission to PRIME, further clarification of the criteria for "proof of principle" will be most helpful, *e.g.,* through examples. More clarification will help enhance efficiency of the scheme both for regulators and for applicants.	Question and answer guidance should provide further insight into EMA's expectation on acceptable cases for submission at "proof of principle".
5	246	Since in the case of prophylactic medicinal products, including vaccines, the main	"…. indicate substantial improvement in

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		expected impact is prevention we propose to amend the first sentence as follows.	patients **or in the case of prophylactic medicinal products, including vaccines, indicate substantial potential to prevent disease**."
5	249-253	One absolute key factor for PRIME to work most effectively is the preliminary clinical evidence needed to be designated with PRIME status. The current text suggests that an endpoint used to demonstrate activity should "[predict] an effect on associated morbidity, mortality or progression". Of note, in many cancer studies -both early and proof of concept studies – there may not be any meaningful information on these endpoints due to low numbers of participants, uncontrolled settings, or last line populations. Thus, the current text should include surrogate endpoints as well as other means by which to demonstrate the treatment effect – such as response to prior treatment vs current treatment – and the nature of the population treated. Further, there are some therapeutic fields, e.g. neurodegenerative diseases, with high unmet medical needs where currently there is neither established surrogate or other intermediate endpoint nor pharmacodynamic marker that strongly suggest the potential for a clinically meaningful effect. In order to avoid a *de facto* exclusion of these therapeutic fields from the PRIME scheme, alternative data should be considered for assessing eligibility to the scheme.	"*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. Exceptionally, for therapeutic fields with high unmet medical needs and where such surrogate or markers have not yet been established, applicants may propose alternative data in their eligibility request."*
5	299	Having submitted a PRIME request, a company will receive a response 40 days following the start of the procedure (i.e., SAWP 1 meeting). Efforts should be made to expedite the process and minimise any delays. Also, additional logistical details would be appreciated within EMA's PRIME	

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		guidances such as will applicants be required to submit a Letter of Intent and be invited to a Pre-submission meeting? Will there be a (formal) validation of the PRIME request prior to start of the clock?	
6	General	EuropaBio and its members welcome the new PRIME scheme which offers greater support to developers of priority medicines that address unmet medical needs within the exiting EU regulatory framework. We value the positive engagement with the European Medicines Agency, as well as participating in the consultation meeting with Industry Stakeholders on 1st October 2015, and see this as benefiting research and development of new, innovative medicines which may significantly improve patients' lives. EuropaBio welcomes the opportunity to submit these comments and observations on the proposed features of the scheme outlined in the draft reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (EMA/CHMP/57760/2015). As discussed at the consultation meeting with Industry Stakeholders last October, we fully appreciate the need for the scheme to be flexible and refining eligibility criteria as experience is gained. Having consulted with our members we believe that the following five key areas require consideration in order to make the scheme truly beneficial for both life science companies and patients.	
6	General	**1. Eligibility criteria to include indications with a clear impact on an unmet medical need**	

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		The principles of the PRIME scheme should allow for applicants to engage, at an early stage of development, for new products or additional uses for existing products where the potential to benefit public health and address an unmet need can be anticipated. This is especially of relevance for biological products, which often acquire new indications during the course of their entire life cycle. a. This could apply to existing products which are in development for major new indications or combination products; for example, where the product is to be used in a completely new patient population and/or a full clinical development is required. b. This principle is also important for products being developed via Adaptive Pathways. The product may already be on the market for a small sub-population, but it can be foreseen that enhanced and ongoing regulatory support could be crucial to the expansion of the label given the innovative nature of the use of real world data in this approach (e.g. registries, healthcare databases). For products which remain eligible to the PRIME scheme for later indications/label expansion, enhanced support should be available after the initial approval. c. It is recognised that the EMA has resource constraints, but it is important that eligibility to the scheme is focused primarily on products in areas of high medical need and the need for increased regulatory support to proceed quickly through development, rather than the product lifecycle's stage. d. Three examples of new indications with a clear impact on an unmet need are provided below: i. EMA has recommended extending the use of Humira (adalimumab) to include treatment of adults with active moderate to severe	

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		hidradenitis suppurativa (acne inversa), who have failed to respond to conventional systemic treatments. […] Humira is the first medicine that is recommended for approval for the treatment of this disease in the European Union (EU). Official Press Release ii. In 2014, Keytruda (pembrolizumab) was approved by the US Food and Drug Administration (FDA) to treat patients with advanced melanoma following treatment with ipilimumab. Following this first approval the FDA granted breakthrough therapy designation and subsequently approved Keytruda in 2015 to treat patients with advanced (metastatic) non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments and with tumors that express a protein called PD-L1. The FDA granted Keytruda breakthrough therapy designation for this indication because the applicant demonstrated through preliminary clinical evidence that the drug may offer a substantial improvement over available therapies. The drug also received priority review status, which is granted to drugs that, at the time the application was submitted, have the potential to be a significant improvement in safety or effectiveness in the treatment of a serious condition. Official Press Release The FDA granted a breakthrough therapy designation to crizotinib (Xalkori) as a potential treatment for patients with ROS1-positive NSCLC, based on phase I findings published in the New England Journal of Medicine. In the study, treatment with crizotinib demonstrated an overall response rate of 72% in patients with ROS1-rearranged NSCLC. The median progression-free survival with crizotinib was 19.2 months. This is an example of a personalised medicine (drug and companion	

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		diagnostic) which addresses an unmet medical need in the identified sub group of patients, as implied by the award of breakthrough therapy designation. Official Press Release	
6	General	**2. Rapporteur appointment** The early appointment of the CHMP/CAT Rapporteur is a key benefit of the PRIME scheme. The success of the scheme will depend upon the relevant expertise of the Rapporteur and of the assessment team in the concerned therapeutic area. In order to identify the most appropriate Rapporteur, the EMA should consider any prior engagement of the applicant with Member States' competent authorities or scientific advice taken at a national level. Furthermore, for biotech medicines, it would be helpful if the Rapporteurs have prior experience with early access tools (i.e. adaptive pathways, products authorised via accelerated assessment or conditional marketing authorisation).	
6	General	**3. Flexibility on point of entry** When developing drugs to address high-unmet medical needs, all companies try to design compressed development programmes and apply for marketing authorisation based on early data. Therefore, the scheme should allow flexibility as regards to timing for granting PRIME status, and should assess the entry point on a case by case basis irrespective of the company's size. We recommend that the Guidance Document for applicants contains clear recommendations for SMEs to engage at an earlier stage for enhanced scientific and regulatory support.	
6	General	**4. Scientific advice processes**	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		It is important that the existing scientific advice process is shortened and information requirements are streamlined to ensure that the benefits of the scheme are not offset by the administrative burden. The latter is especially significant in the case of SMEs. Moreover, receiving prompt regulatory feedback at key milestones is important for sponsors to ensure a fast and seamless progression of the clinical development programme. To complement the CHMP Scientific advice, it would be important that the opportunity for national scientific advice is retained within the scheme. The Rapporteur could also provide support by directing the applicant towards the Member State's competent authority where the company is based to seek national scientific advice, where this is appropriate. There may be cases where 'narrower scope' advice can be managed more quickly and efficiently with a National Competent Authority. The output of such a procedure would be shared with the Rapporteur. Finally, developers of advanced therapy medicinal products and emerging technologies - which are often SMEs - would welcome guidance in particular on the CMC aspects at an early stage of the development plan.	
6	General	**5. Globalisation of product development** The global nature of product development should be recognised and therefore the ability to allow for FDA-EMA dialogue, if desired by the applicant, ought to be	

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		accommodated within the scheme. This is because major divergences in approach between regions could undermine the key objective of timely patient access to medicines that PRIME has.	
7	General	ESIP welcomes the opportunity to comment on the EMA "Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME)". ESIP supports the focussing on major public health interests and substantial benefits for patients. The goal of improved quality of marketing authorisation application should lead to better comprehensive premarket approval evidence. Problems concerning conditional or exceptional market approvals have already been identified (Banzi et al., Eur J Int Med 26 (2015) 572-584). Importantly, obligations imposed due to limited evidence supporting a positive benefit-risk-balance at the time of approval, are often not fulfilled correctly or fulfilled only with delay. Therefore, measures to ensure generation of a more robust data package at the time of approval (as foreseen in the reflection paper, line 155 on) are welcomed. Since medicines of major public interest and addressing unmet medical need are often granted conditional approval due to immature data, these drug candidates would seem to be the right targets for PRIME.	
7	General	The reflection paper stresses early dialogues as a crucial part of the PRIME concept. In our view, early dialogue carries a risk of jeopardising the independence of the engaged institution. Authorities taking part in these dialogues have to advise on the desired parameters of the next steps of development of the drug without adequate data on which to base this advice. Yet, they may feel some sort of obligation to decide later on the basis of the advice given, even if further development proves initial hypotheses wrong. While this has not been a major issue at the current level of scientific advice, it may become more important as the	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		scope and extent of the advice is intensified. The draft currently lacks measures to sufficiently guard against this potential conflict of interest. It should be re-emphasized that all advice given is legally non-binding (for all parties).	
7	143	Line 143 and on (and implied elsewhere in the paper) states that the rapporteur will raise the applicant's awareness on the use of other early access tools. Conditional marketing authorisation is explicitly mentioned as an example. Having in mind that PRIME aims to ensure the creation of a robust data package (see above) at the time of approval there should be only very limited need for conditional marketing authorisation for medicines developed under PRIME. The paper clearly indicates that the applicant will be given coordinated support at every step of development, starting with the overall development plan and proof of principle, and continuing through to the design of clinical trials. It should therefore be possible to ensure that clinical trials are designed well enough to generate data on relevant outcomes, reducing the need for conditional approvals and even in part, post-marketing data generation.	We therefore propose revising these passages and including the reduction of conditional approvals as a goal of PRIME that should be measured when evaluating the success of PRIME.
7	74-76 148-149 164-165	Lines 74-76 and 148-149 and 164-165 clearly state that the objective of PRIME is, ultimately, a “shortened timeframe for review and an earlier access to promising new medicines”. This is desirable, not only for patients urgently in need of a new therapy, but also for the applicant, as it can lead to an increase of the time during which the medicine can be marketed under patent protection (market exclusivity). Therefore, we need to point out that PRIME may come at a not insignificant cost to society, because, in Europe such medicines are not paid for out of pocket, but through social health insurance or a government-funded national health service and highly desirable medicines tend to command a high price.	
7	General	Agency support in the form of PRIME can be of major benefit for an applicant. It is also to be expected - extensive scientific advice notwithstanding - that in some cases, marketing authorisation will still be contingent on the fulfilment of	

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		obligations, as already stated (e.g. in the case of orphan medicinal products). PRIME should be an opportunity to introduce mechanisms for further safeguarding that these obligations are met. For example, EMA should require full compensation for the resources invested in the support given to an applicant, if post-marketing commitments are not met. This, as a minimum, in view of the additional burden on EMA resources. Finally, how these additional resources will be financed is not sufficiently addressed in the reflection paper.	
8	General	The principle of PRIME is strongly supported.	
8	General	From a Quality (Chemistry and Pharmacy or Chemistry, Manufacturing and Controls (CMC)) perspective the following general comments are suggested for consideration by EMA: 1. Projects, which meet the PRIME definition of Unmet Medical Need, are very likely to face significant Quality challenges. Please refer to the article: CMC Considerations when a Drug Development Project is Assigned Breakthrough Therapy Status, Pharmaceutical Engineering, January/February 2015, E S Dye, J Groskoph, B Kelley, G Millili, M Nasr, C J Potter, E Thostesen, H Vermeersch. The article refers to US FDA definition of Breakthrough Therapy, however, some clinical developments may meet EMA definition of Unmet Medical Need.	
8	General	2. Access to the PRIME scheme at early stages of development should be available to all companies rather then just SMEs and academic groups for the following reasons: a. New therapies meeting the Unmet Medical Need criteria may be identified from Phase 1 clinical studies in patients (proof of principle/proof of mechanism) from any size of company and there	

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		almost certainly will be significant CMC issues to discuss with EMA – please refer to the above article. b. For exciting new therapies, companies not fitting the definition of SMEs may not have the previous experience of regulatory requirements for these new therapies and would welcome regulatory advice to ensure the CMC programme is optimised alongside the proposed clinical programme – please refer to the above article for potential CMC issues. Delaying CMC interaction with EMA for a non SME company until Proof of Concept i.e. end of a Phase 2/3 clinical study would (Figure 1 in the above article) mean that most CMC studies to support a marketing application would be well advanced or completed based on a company's judgement without a desired interaction with EMA. This CMC programme may not meet the 'normal' CMC marketing application requirements and there would be little time to adjust or supplement the CMC programme to meet regulators' requirements.	
8	General	3. Use of the formal scientific advice process with associated fees to discuss CMC issues alone could be a barrier to efficient interaction between a company and quality regulatory experts. Some relatively small but formal interactions with the quality regulator could be beneficial to both the regulator and the company. Companies may benefit with interactions, which are facile to arrange and formal and from which answers are provided by quality regulators relatively quickly.	
8	General	4. The level of fees for a quality-only interaction at an early stage of development should be clarified. At the early stage of development, there may be examples where it is not efficient for the company or EMA to have clinical and quality development discussions at the same time.	

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8	General	In summary, ISPE supports the PRIME scheme and recommends that consideration is given to include processes and procedures applicable to all companies to discuss and agree quality issues with EMA regulators and provide responses in a relatively quick timescale at any stage when a project is identified as meeting the criteria for Unmet Medical need.	
9	General	Voisin Consulting Life Sciences (VCLS) welcomes this initiative which gives companies and academics developing priority medicines that target high unmet medical needs the opportunity to have greater support from the European Medicines Agency. VCLS welcomes the opportunities to present these comments and observations on the different sections of the draft reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (EMA/CHMP/57760/2015).	
9	30-32	The EMA mentions the existing initiatives to support development and accelerated patients' access to medicines that address unmet medical needs. It is unclear how Adaptive pathways and PRIME scheme tools will complement each other.	We suggest to clarify this in the final EMA guidance documents.
9	70-72	It is mentioned that eligibility to PRIME scheme is being considered exceptionally at the earlier proof of principle stage (prior to exploratory clinical studies), provided compelling data can be presented to justify a product potential public health impact.	Further clarification on the term 'compelling data' would help SME's determine if their product shows potential. This is also an opportunity for us to help prospective clients define data requirements, for their specific developments.
9	66		We suggest to specify among benefits of

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			PRIME scheme: "… **early** confirmation of eligibility for accelerated assessment (subject to the criteria still being met at the time of MAA)."
9	83-85	The scope of PRIME scheme is limited to innovative products under development intended for MAA application in EU through the centralised procedure. We understand that centrally authorized products being developed for a new innovative indication (to be applied via a type II variation) are not eligible to PRIME scheme.	This should be specified.
9	90	An 'unmet medical need' is also part of the Orphan Drug Designation criteria. How does the PRIME reflection paper relate to the Orphan Drug Pathway?	The paper could make specific reference here or at least acknowledge orphan drug pathway as part of the preamble.
9	After 95		We suggest to specify that there will be dedicated slots for submission of eligibility requests to PRIME. We assume that the EMA guidance documents will specify submission timelines (as mentioned in Annex 2) and provide a template for the eligibility request.
9	113-119	With regards to transparency and publishing recommendation in the CHMP monthly Report. Will applicants have an opportunity to vet the information before it is published? Though EMA state individual outcome for a medicinal product will not be disclosed, we think that it is important for applicants to have an opportunity, ensuring it's in line with EMA's current transparency mandate.	

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		Orphans We suggest that orphan medicinal products should qualify in priority and the eligibility criterion linked to the 'unmet medical need' should be waived for these applications as they would have been already assessed by COMP at time of ODD request. We also suggest that early agreement on how to substantiate significant benefit should be considered as a priority within the PRIME scheme with involvement of COMP (and ideally HTA bodies) as key stakeholders – for those products where demonstration of significant benefit is required.	
9	120-165	Is it likely that the same person (rapporteur) would be engaged for the entire development program?	
9	128-132	Will Scientific Advice/Protocol Assistance in context of PRIME be the same procedure as current SA/PA? Will non-SMEs still pay the standard SA fees?	
9	132-133	Early appointment of CHMP/CAT Rapporteur. Will the CHMP/CAT Rapporteur be automatically appointed or will the Applicant have to request it following receipt of written confirmation of eligibility to the PRIME scheme? Will the Applicant be allowed to provide wishes for the Rapporteur to be appointed, e.g. at the time of the request for eligibility to PRIME?	We suggest to clarify these aspects in the final EMA guidance documents.
9	134-137	Kick-off meeting Will the kick-off meeting be organized by the EMA immediately following receipt of written confirmation of eligibility to the PRIME scheme? Will the sponsors have an opportunity to request participation from HTA bodies at this stage? Will a guidance document be issued to provide explanations on timelines/format/organization of this meeting and what will be expected from sponsors for this meeting?	We suggest to clarify all these aspects in the final EMA guidance documents.
9	170-171	Will the scientific advice letter provide information on which basis a follow-up SA should be further requested (and milestones) whatever the scope of the SA?	We suggest to clarify this.

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9	175-177	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). It is unclear within which timelines (following confirmation of eligibility to PRIME) the EMA could request an update on development of no SA requests are submitted.	We suggest to clarify this, as well as the format and the content of the update which would be required (e.g. would a format similar to the annual reports for orphan-designated product be requested?).
9	178-183	It is mentioned that the SAWP/CHMP will re-assess whether the criteria for eligibility to PRIME are still met (e.g. based on emerging data) and notify the applicant/sponsor. It is unclear whether this re-assessment will be done on a regular basis, and under which process.	We suggest to clarify these aspects.
9	187-197	Does the Agency have an objective in terms of number of products to be granted PRIME in 2016?	
9	246-253	The Annex 1 suggest that preliminary clinical evidence could be based on relevant clinical outcomes, as well as established surrogate, other intermediate endpoint or PD marker. In some diseases, in particular some rare diseases where there is no consensus on relevant clinical outcomes, could the Agency take into consideration an evidence of substantial improvement of patients quality of life to assess the eligibility to PRIME?	
9	302-304	We understand that the review procedure of eligibility requests will not provide any opportunity for the applicant to answer potential questions that could be raised by the SAWP and could help assessing the eligibility request. The proposed mechanism for the Applicant is to wait for the final CHMP recommendations including the reasons for the decision and if better evidence can be provided, to submit a new request.	We would suggest the Agency to consider the possibility of a clock-stop (with a limited duration) after D30 in case of questions from the SAWP that may be addressed by the Applicant.

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10	General	Eurordis very much welcomes the PRIME procedure which is very much needed. As many developers of new medicines in the field of rare diseases are SMEs or smaller biotech companies, with sometimes limited regulatory experience, to provide them with additional guidance all along their regulatory pathway can only be a positive step. In addition, rare diseases is the world of unmet medical needs, almost by definition: many rare diseases have been neglected for decades, did not benefit from comprehensive clinical research over the years, and developers who take the challenge of developing new medicines to treat these unmet needs are conducting projects in unexplored areas, with little knowledge on the natural disease evolution, little consensus on relevant endpoint selection, and rare EMA evaluation guidelines. The impact of PRIME could be measured in different ways: • From orphan medicinal product designation to marketing authorisation application, there is often a long gap. Sponsors of an orphan designation provide annual reports to the EMA on the development of the designated medicines, and whether or not a PRIME procedure is used could have a positive impact in the timelines between orphan drug designation and completion of the clinical development. Could this gap be reduced, this would represent a major achievement. • Another possible measure could be the reduction of the number of outstanding issues or questions to the applicant when the CHMP/CAT is evaluating a new marketing authorisation application, compared to historical data (orphan products for unmet needs which haven't benefited from PRIME at the time of their evaluation). • The accelerated review itself, with duration of 150 days as opposed to 210,	

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		would represent 60 days less for the evaluation. This is significant; however this would only accelerate access to the medicine if this could also accelerate the Health Technology Assessment phase, and the subsequent pricing/reimbursement decision. For this, in particular for the REA (Relative Effectiveness Assessment), where HTA doers need to exchange information with the CHMP at an early stage to prepare their assessment, i.e. it would be key to make sure this is actually happening. Timelines should be aligned with HTA timelines, e.g. EUnetHTA Rapid Assessments, and this should be part of the Annual Work Plan of the HTA Network 2016-2017, and EUnetHTA Joint Action 3 due to start March 2016. If an impact of the average duration from Marketing Authorisation Application submission to Actual Placing on the Market could be measured, this would also demonstrate the utility of the PRIME scheme Qualitatively, PRIME use by developers could also be associated with more diverse designs for clinical trials, so-called adaptive designs or new designs, as explained in the EMA guidelines for small populations	
10	65	It is extremely important to consider the potential for a compassionate use, as well as its possible timelines, given the manufacturing capacities as early as possible in the development of new medicines for these unmet needs. Therefore the kick-off meeting should also be an opportunity to include discussions on the compassionate use as part of the discussion on the development plans.	to discuss development plans **(including the potential for a compassionate use)**, regulatory pathways and confirmation of eligibility for accelerated assessment
10	82-119	EURORDIS agrees with the proposed eligibility criteria. For orphan medicinal products, one way to verify if the product is for an unmet need is when the orphan designation did not use the significant benefit criteria, as non-applicable (for products which obtained orphan designation before applying for	For products aiming at treating rare diseases and for which an orphan designation can be sought, it would be recommended to submit an orphan designation application prior to

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		the PRIME scheme). For orphan medicines, maybe the reflection paper could address whether the application for a PRIME scheme should follow the orphan designation, or whether both can be made independently in terms of timing.	applying to the PRIME scheme, as the unmet medical need can already be scientifically assessed by the Committee for Orphan Medicinal Products.
10	102-104	In case of a medicine to treat a rare disease, and even more so in case of an orphan medicinal product, the Committee for Orphan Medicinal Products could be involved in the review of requests for eligibility.	to add In case of orphan medicinal products (OMP), the Committee for Orphan Medicinal Products (COMP) will also be involved in the review of requests for eligibility
10	118-119	EURORDIS wonders whether the reference to eligibility to the PRIME scheme could not be made at the same time when the marketing authorisation application is submitted rather than once a marketing authorisation has been granted.	In case of a subsequent centralised marketing authorisation **application submission**, reference to eligibility to the PRIME scheme granted by the CHMP will be mentioned in the ~~European Public Assessment Report~~ **EMA web page on New Medicines Evaluations** (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/document_listing/document_listing_000349.jsp&mid=WC0b01ac05805083eb*)
10	126-127	to be consistent with lines 68-69, this could address situations where the applicant is progressing to proof of concept stage, exceptionally (as “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	In early stages of development, following demonstrated proof of principle, focusing on SMEs and applicants from the academic sector**, and in exceptional cases**

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		products potential public health impact".)	**preceding the demonstration of the proof of principle**:
10	130	to add clinicians	(e.g. Health Technology Assessment (HTA) bodies, patients**, clinicians**).
11	General	The PGEU supports this initiative in the context of increasing access to medicinal products for areas of unmet medical need. The PGEU would like to stress the importance maintaining principles of safety of the medicinal product concerned throughout this process, as with the accelerated assessment procedure. Additionally, the PGEU supports the text in paragraph 178 – 186 (below) in the context of only including medicinal products in this process which genuinely will address unmet medical need.	
11	178-186	PGEU supports this paragraph in the context of need to maintain the safety aspects and clinical benefits to patients.	None.
12	General	Clarification is required on how this scheme might link into FDA/EMA joint initiatives (eg cluster discussions/ joint scientific advice) and whether a breakthrough therapy designation by FDA could influence whether a PRIME designation will be granted or vice versa. When providing update reports on progress during PRIME, would this link up to any reports provided to FDA during Breakthrough designation, and would it be possible to receive consolidated advice from both agencies?	
12	59-61; 70-73	Further clarification and more detailed information would be desirable on the type and level of data required to be accepted into PRIME, particularly recognising that available clinical data could be limited at proof of principle stage.	None

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12	83-85	Clarification is requested on whether there is a limit to the number of PRIME designations annually granted by the EMA.	None
12	89-95	Clarification is required on the situation whereby a single product has multiple indications in development, however only a sub-set of the indications are targeting an indication of unmet medical need, and therefore meeting the eligibility criteria for PRIME.	None
12	132-133	Clarification is requested by the Stakeholder on the process of selecting the rapporteur at an early product development stage. It would be desirable that in order to maximise the utility and quality of input, the Rapporteur choice should be selected upon scientific expertise, rather than resource allocation.	None
12	158-161	If a product maintains its eligibility for PRIME throughout its development up until MAA could it be defined in what circumstances, if any, the product might not receive accelerated assessment designation.	None
12	175-177	Clarification is requested by the Stakeholder on the expectations of the content of development update reports during the monitoring phase (from acceptance into PRIME scheme up to MAA filing). Will templates be prepared (in a similar manner to PIP Annual Reports)?	None
12	178-182	The Stakeholder would appreciate clarification on the situation whereby a product is accepted onto the PRIME scheme and then subsequently rejected after a re-assessment as well as more detail on process of assessment leading up to rejection. Would this mean that the company is precluded from applying for accelerated assessment for this product? Could the Rapporteur be changed so the MAA Rapporteur is different from that involved with PRIME?	None

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13	General	Pfizer welcomes the proposal to introduce PRIME as a further step forward to bringing important medicines to patients in a timely and efficient manner. Given involvement in the scheme will likely result in a greater level of interaction between the sponsor and regulator (which in principle is very welcome), Pfizer would request that clarity is provided on the fee structure for the scheme. In addition, Pfizer would encourage the EMA to find ways to adapt the existing scientific advice processes and information requirements to ensure the interactions are conducted in a timely fashion and the benefits of the scheme are not offset by the administrative burden of preparation for, and conduct of, formal scientific advice meetings.	
13	45	It would be helpful to explicitly state that one of the overall objectives of the scheme is to accelerate development and not just assessment. Acceleration can be achieved by using and encouraging innovative approaches to development (e.g. Adaptive Pathways) and does not imply a lowering of regulatory standards. In any case, the EMA should consider how to publish and defend the PRIME initiative, reassuring the public that safety will not be compromised.	'…a scheme has been developed to reinforce early dialogue and regulatory support to stimulate innovation, optimise **and where possible accelerate** development and enable accelerated assessment of PRIority MEdicines (referred to as PRIME).'
13	68	Earlier access to the scheme should not be exclusively limited to micro-, small- and medium-sized-enterprises (SMEs) and the academic sector but should be (where justified) open to any product development requiring additional early support. It is important these criteria remain flexible given many innovative developments do not always follow the classic development milestones.	
13	83	The key eligibility criteria for entering the PRIME scheme should be based on the potential of the product in development to address a high public health need and	Delete lines 83-85.

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		unmet medical need. This could potentially apply to existing products which are in development for major new indications or combination products; for example where the product is to be used in a completely new patient population and/or full clinical (and possibly some safety and quality) development is required. It is recognised that the EMA has resource constraints, but it is important prioritisation is based on medical need and the need for additional regulatory support rather than where the product is in its lifecycle. This principle is also important for products being developed via Medicines Adaptive Pathways to Patients (MAPPs) / Adaptive Pathways. The product may already be on the market for a small sub-population, but it can be foreseen that enhanced and ongoing regulatory support could be crucial to the expansion of the label given the innovative nature of the use of real world data in this approach (e.g. registries, healthcare databases; lines 205-206). For MAPPs products which remain eligible for PRIME for later indications/label expansion, enhanced support should be available after the initial approval.	
13	96-99	Eligibility is noted as requiring meaningful improvement of efficacy, however often times there are compounds in development that might have meaningful benefit with regards to safety. This is recognized in the annex (lines 254-259) but is not included in the main text.	Include improvement of safety to the definition of major therapeutic advantage to patients.
13	113-119	The document does not mention whether confidential and proprietary information will be omitted from the published data.	Please clarify that confidential and proprietary information will not be included in the published data.
13	132	The early appointment of the CHMP/CAT Rapporteur is a welcome feature of the PRIME scheme. It will be important, however, that the selection criteria for Rapporteurs is highly robust and based on an appropriate level of skill and	Early appointment of CHMP/CAT Rapporteur should be based on objective criteria and methodology and experience of assessment

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		experience not just in the therapeutic area but also in assessment of highly innovative products and developments in areas of high unmet medical need. For example, it would be helpful if the Rapporteurs have prior experience with products authorised via Accelerated Assessment and Conditional Marketing Authorisation. It would also be helpful if the Applicant could express a preference as part of the process. Although this is not normally considered in assigning rapporteurship, the success of PRIME is highly dependent upon the Rapporteur and therefore an applicant may have a justification for a particular preference (e.g. prior national scientific advice).	of products in areas of high public health need. Appointment may also take into account any preferences suggested by the applicant.
13	161	Given the early assignment of CHMP and CAT Rapporteurs, an informal system of 'rolling submission' should be permitted. In such a system, early provision of reviewable modules would be able to be submitted to the Rapporteur and Co-rapporteur when available, even if this is before the critical path element of the application. This will serve the additional purpose of making accelerated assessment more operationally feasible, especially in the case of Advanced Therapies in which Quality and other data may be voluminous and highly complex to review.	A 'rolling review' in which reviewable components of the dossier could be submitted to the CHMP and CAT Rapporteurs early, should be a voluntary element of the new system.
13	201	Although US FDA Breakthrough Therapy Designation (BTD) should not be a requirement for PRIME designation, if a product has already received a BTD, this should be recognised as being useful to support the justification for PRIME eligibility. This would encourage alignment between the two regions.	
14	General	In general, the proposed PRIME scheme is endorsed. The scheme could, through an enhancement of regulatory, scientific and HTA support, lead to better development plans for new medicinal products and improve the quality and content of MAAs ensuring that these meet the regulatory requirements. Ultimately,	

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		this could then result in an earlier approval of new medicinal products that fulfil an unmet medical need and their access to the market. This will be to the benefit of patients and might incentivise the development of new, innovative medicinal products that fulfil an unmet medical need. NOMA has identified the following issues were we would like to make comments to the refection paper.	
14	General	**Early time point for eligibility to PRIME to achieve best results** In the reflection paper it is stated that products eligible for a "PRIME status" should demonstrate the potential to address an unmet medical need. Ideally, both pre-clinical and exploratory clinical data should be presented to substantiate this claim. An exception is, however, foreseen for products developed by SMEs and academia that could be eligible for PRIME-status based on promising non-clinical and very early clinical data. In practice receiving a "PRIME-status" at an early stage of development might be more relevant for all sponsors. Receiving "PRIME-status" during early phases of development of promising medicinal products could lead to increased investments and thus hopefully speed up their development. The potential gains of receiving a "PRIME status" might be during earlier stages of the development program and not during later stages such as after exploratory clinical studies and this could be reflected in the paper. SMEs/academia should thus not be treated differently from other pharmaceutical companies and early eligibility should be an opportunity for all sponsors. If a "PRIME status" is granted during early stages of development, the main emphasis will be on the potential to fulfil an unmet medical need and to a lesser degree on the available non-clinical and/or exploratory clinical data that can show	

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		that the product has potential to bring a major therapeutic advantage to patients. In such cases, the claim to fulfil an unmet medical need should be properly justified by applicants and critically assessed by the SAWP and committees involved in granting a "PRIME status". A consistent definition of "unmet medical need' should be applied, in line with the Guideline for conditional marketing authorisation. In addition a clear, strict and transparent practice for eligibility should be implemented.	
14	General	**Involvement by committees and MS to the eligibility assessing process** A SAWP coordinator and EMA scientific officer will assess eligibility requests for PRIME. CHMP or CAT will thereafter adopt their assessment and conclusion on granting a "PRIME status". From the current paper it is unclear how this assessment by the SAWP coordinator and EMA scientific officer will be performed and followed up. The following points should be further addressed and specified before implementing the PRIME-scheme: o Is there a possibility for other MSs to comment on the joint assessment by the SAWP coordinator and EMA scientific officer? o Will there be an opportunity to ask questions to or request clarifications from PRIME applicants before making a decision on granting a "PRIME status" to a medicinal product? o What will happen when no consensus is reached among the MSs and/or committees on granting a "PRIME status"? Since the ultimate aim of the PRIME scheme is to enable faster access of innovative medicinal products to patients, the inter-committee processes should preferably be as efficient as possible. o All MSs, including those that are not members of SAWP, should be able to comment, both in writing and during subsequent discussions in the relevant committees, on the conclusions reached by the SAWP coordinator and EMA scientific officer. Furthermore, in order to be able to make an informed	

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		decision on the granting of a “PRIME status” all MSs should also have access to the requests for “PRIME-status” submitted by the applicants, including all non-clinical/clinical data that is used to substantiate the claim.	
14	General	**Composition of SAWP - all MSs to be represented** In order to further ensure all MSs are able to participate in the PRIME-scheme and also considering the important role the SAWP will play in this scheme, we suggest that all MSs are represented in the SAWP. This will allow all of the MSs to be actively involved in the granting of a “PRIME-status” and subsequent scientific advices given to applicants, either as one of the SAWP coordinators, or as a commenting MS. We also believe that the involvement of all MSs during the development of “PRIME products” will strengthen the robustness of the scheme and secure impartiality and reduce the perceptions of “biased” assessments.	
14	General	**Clear roles to prevent conflict of interest** A separation of roles between those providing scientific advice and offering support through the PRIME scheme and those evaluating marketing authorisation, i.e. CHMP and CAT, should be carefully considered. This can be taken care of by appointing new Rapporteur teams (Rapporteur and Co-Rapporteur) at the time of MAA.	
14	General	**CAT Rapporteurs for all ATMPs** If EMA decides to implement early appointment of CHMP Rapporteurs in the PRIME scheme, we will propose appointment of only CAT Rapporteurs for all ATMP products eligible for PRIME.	
14	General	**Involvement of PDCO** The paper should reflect on the situations where the condition concerned includes (solely or also) children, as it might impact the already existing early interaction	

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		established through Paediatric Investigation Plans (PIP) and PDCO. Companies will most likely come for agreement on a development plan at early stage (after phase I in adults), meaning that early regulatory interaction is already partly in place through this system (also continuously through later modifications).	
14	General	**Criteria for withdrawal of medicinal products from the PRIME scheme** To secure objectivity and independence, reassessment of eligibility should be done regularly. The paper/procedure should include clear criteria for when emerging data during the development should indicate new assessment of the eligibility for PRIME support.	
14	General	**Importance of offering involvement of HTA** Norway underlines the importance of offering early involvement of integrated HTA support and advice. Such coordinated advice can help develop documentation that can be relevant also for relative effectiveness evaluations and for securing use of relevant comparators, thus promoting earlier access for patients to important medicines.	
15	General	Well written and appears to become a valuable document. I don't have any specific remark.	
16	General	The Alliance for Regenerative Medicine (ARM) warmly welcomes this initiative from EMA/CHMP. The acceleration of development and access to promising new therapies is an important objective that will be beneficial to all stakeholders and in particular patients. Advanced therapies have the potential to address important unmet medical needs by curing or dramatically changing the course of severe diseases and we believe a large number of them could benefit from this new scheme in the coming years. We applaud this initiative and thank the EMA for its commitment and efforts to accelerate patient access to important and transformative new medicines. We appreciate the inclusive approach (multidisciplinary participation and multi-	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		stakeholder involvement) and the encouragement for SMEs and members of the academic sector to apply early. We believe that this new scheme may contribute to increase the pace by which scientific discovery translates into tangible, transformative treatments or cures for those who suffer from chronic and debilitating illnesses. The new scheme could also increase the competitiveness of Europe by allowing some important products to become available earlier.	
16	General	***Recommendations based on experience gained with the US Breakthrough Designation scheme:*** The objectives and eligibility criteria for PRIME and the US breakthrough designation (BTD) scheme are similar though PRIME has some additional advantages as compared to the BTD scheme. For example, PRIME designation can be awarded to products with promising in vivo data and early proof-of-principle data in humans. We believe it would be beneficial to consider the US experience thus far with the BTD program, in particular: 1. The lack of clarity on the eligibility criteria for a BDT resulted in numerous rejections of applications. Although FDA urges applicants to seek early informal consultations to help gauge if a product is eligible for BTD, we believe having clarity from the outset on eligibility criteria would increase the efficiency of the PRIME scheme. 2. It would also be important to clarify, to the extent possible, some of the terms employed by EMA. Specifically, we suggest to provide the definitions and to use in a consistent way terminologies such as exploratory clinical data, proof-of-concept, proof-of-principle, and proof-of-mechanism. 3. Guidance on the appropriate application procedures would be helpful. We would suggest some guidance or possibly a Q&A document for organizations considering applying to the PRIME scheme that addresses the aforementioned items.	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		Furthermore we urge early FDA-EMA interaction to ensure harmonization, convergence or cooperation with regard to the eligibility criteria and requirements. This is important because major divergences in approach between regions could undermine the key objective of PRIME to provide timely patient access to medicines.	
16	General	***Interactions with other existing procedures, expert groups and committees:*** We seek clarification of how PRIME relates to existing procedures such as the scientific advice procedure, as well as the role, scope, and remit of the various committees, offices and task forces representing multiple entry points to engage with EMA. The SME office and the Innovation Task Force are instrumental in facilitating engagement with regulatory authorities in a developing field such as ATMPs. In particular, the role of the existing Innovation Task Force is to provide early support to developers of products based on emerging science, which to a large extent, is similar to the objective sought with the PRIME initiative. It would therefore be beneficial to clarify whether the Innovation Task Force will continue to play a role for promising new therapies and if so, how the different bodies will interplay. Orphan diseases are typically an area of important unmet medical needs and many ATMPs in development are targeting orphan diseases indications. However the Committee for Orphan Medicinal Products (COMP) is not mentioned in the reflection paper and it would be helpful to clarify its role, if any, in the new scheme when relating to the development of orphan drugs. We also note that programs can be inhibited substantially when the paediatric plan and interactions with PDCO do not occur at an early stage. For this reason, the Paediatric Committee (PDCO) should be involved as early as possible in this	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		process.	
16	General	***Involvement of HTA bodies:*** The new scheme plans to involve multiple stakeholders, including HTA bodies and patients and we welcome this proposal which is essential to ensure an effective market access after marketing authorisation. However we believe that many HTA bodies in Europe may be hesitant to engage in discussions on products at an early development stage, particularly when clinical data are missing or very scarce. We therefore believe that early provision of information or support to the HTA bodies is critical to ensure their participation in the scheme and we welcome any initiative that could be taken to this end.	
16	General	***Need to keep the procedure flexible and effective:*** The academic/research community as well as SMEs are a crucial part of the European drug development ecosystem. Many of these organisations have extremely limited resources, both financial and human. We therefore urge the EMA to ensure that procedural requirements allow optimal flexibility and efficiency to ensure that the requirements do not deter such groups from seeking early advice under the PRIME scheme.	
16	General	***Extension of fee reductions to research and non-profit communities:*** As mentioned previously, ARM is a multi-stakeholder organisation which includes members from the research community including universities, translational centres, non-profit and/or charitable foundations, etc. Early development of promising new medicines also takes place in these important settings and the reflection paper states that these institutions could apply under the new scheme (Line 116-117). However fee reductions are only foreseen for SMEs as expressed in Line 128. We propose extending fee reductions to applicants of the academic sector, foundations and research/translational institutes in order to encourage this	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		community to seek scientific advice and stimulate the validation and execution of development plans for discoveries that show highly promising potential. Extending the fee reduction to the academic/research sector would represent an important stimulus for translational research. This in turn would help increase the delivery of therapeutic solutions to patients in need.	
16	General	***Scope of advice provided under PRIME:*** It is not explicitly mentioned whether the support provided through this framework will address all aspects of a MAA (CMC, preclinical and clinical) or whether this will focus on the clinical development only. ARM is in favour of the former as early guidance on manufacturing and quality aspects could be particularly beneficial to academia and SMEs to speed up the clinical development and registration of ATMPs. The scope for the new scheme is limited to promising new medicines that address unmet medical needs. However there are examples where products that have already been approved for one indication show promising results in another indication with an important medical need. The adaptive pathways approach will help increase the number of products in such situation. We believe there is value in opening PRIME scheme to an approved medicinal product for the development of a different indication that addresses unmet medical needs.	
16	General	***Varia:*** We believe that having a PRIME designation could be criteria to be eligible for the Adaptive Pathway programme, once it becomes sustainable.	
16	General	We would welcome more details on the timing of evaluation of PRIME requests, e.g. by providing more details in Annex 2. As with many of the EMA procedures, there is an opportunity for evaluators to outline specific questions and for the	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		applicants to provide the responses prior to a decision. This opportunity should be included in the review process for these PRIME requests.	
16	57-58		"…, but also to enhance the regulatory and scientific support on offer to these products through advice at key milestones in development **well in advance of any filing.**"
16	59-61	Clarify the definition of "exploratory clinical data" e.g. "a trial using an endpoint likely to be predictive of a long term outcome" and provide examples. Confirmatory clinical studies usually designate the pivotal trials that are completed prior to marketing authorization, i.e. at a late stage of development. The mention of confirmation clinical studies in this sentence is therefore confusing.	
16	59-61	Eligibility to the PRIME scheme will depend on the availability of adequate non-clinical and exploratory clinical data. Further insight into what EMA constitutes as "adequate" non-clinical data would be helpful for Sponsors to appreciate the EMA expectations prior to requesting PRIME.	
16	61 & 71	It is unclear what the differences are between "Proof of principle stage" and "Proof of concept stage". Based on the distinction made at line 237 (clinical stages of development – proof of concept) and line 260 (early development – proof of principle/proof of mechanism), these terms seem to be used at different development stages but their exact meaning should be clarified, notwithstanding the fact that flexibility in the scheme should be maintained	Provide definitions with examples to illustrate the different terms.
16	83-85	We believe there is value in opening the scheme to products with an initial marketing authorisation but with important therapeutic innovation in a new indication with unmet medical needs.	"The PRIME scheme is limited to products under development which are innovative and yet to be placed on the EU market **for this indication**, i.e. where there is an intention

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			to apply for an ~~**initial**~~ marketing authorisation".
16	96-99	A major therapeutic advantage can also occur when there is a significant improvement to the safety profile. The sentence on lines 96-99 however limits the therapeutic advantage to improvement of efficacy.	"… through a meaningful improvement of efficacy, such as having an impact on the onset and duration of the condition, **a meaningful improvement of safety, such as avoiding or significantly reducing serious adverse events,** or improving the mortality or morbidity of the disease".
16	102-104	Clarify the role of COMP for products intended for orphan diseases, if any.	
16	108-110	The anticipated composition of the oversight group should be provided. Most notably, will this include participation by EMA only or will external advice also be solicited if warranted?	
16	121-124	Clarify whether the support provided under the PRIME scheme is limited to the clinical development programme or whether it also encompasses the quality/manufacturing and non clinical development aspects.	
16	128-130	Extend the possibility of fee reductions to academic sector, research/translational institutes and foundations	"Scientific advice (with fee reductions for SMEs**, academics, research/translational institutes, foundations and other not for profit institutions…**)…"
16	131	For ultra-rare conditions the ability to conduct multiple clinical trials may not be possible. As a result, EMA should allow for a level of flexibility to the timing of the appointment of the CHMP/CAT Rapporteurs with consideration for acceptance of	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		nonclinical proof of concept data in lieu of clinical proof-of-concept data.	
16	134-137	PDCO should be involved in the kick-off meeting and over the course of development. In addition, the participation of HTA agencies at an early stage should be encouraged and we therefore propose that they be added at the time of the kick-off meeting.	"An initial kick-off meeting with multidisciplinary participation from the EU network (SAWP and relevant committees members and experts), including the CHMP/CAT Rapporteur, **PDCO assessor and HTA bodies**, to understand the proposed development programme, give preliminary guidance on requirements for MAA **and market access**, and to develop ~~of~~ **a** schedule for gaining regulatory and scientific advice.'
16	150-151	In consideration of the concern raised in relation to line 131 the following change is proposed.	"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 **study(-ies)** ~~**studies**~~".
16	178-183	In cases where the landscape of products approved in a particular indication changes, we propose that there be opportunity for the sponsor to defend a product's eligibility to remain in the scheme prior to the withdrawal of PRIME support.	
16	237-259	In the PRIME application at clinical stages of development, an overview of the intended clinical development plan should be provided.	Add a similar paragraph as on lines 287-289 after line 259.

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
16	246	In consideration of the concern raised in relation to the comment on line 131 the following change is proposed.	"**Where feasible**, ~~**P**~~**p**reliminary clinical evidence should indicate substantial improvement in patients.
16	261-262	In consideration of the concern raised in relation to line 131 the following change is proposed.	"Medicinal products in early stages of development could also access the PRIME support scheme based on nonclinical data and, **where feasible,** very early clinical data showing the promising activity of the medicinal product."
16	287-289	If the EMA is in agreement that PRIME would provide added value to the quality as well as the proposed non clinical and clinical development, sponsor companies should provide a brief outline of the future quality plans in Annex 1 as well.	"Furthermore, the application should contain a brief outline on the future plans regarding the **quality**, preclinical and clinical development; future studies should be easily distinguishable from studies already performed or ongoing."
17	General	With the aim to increase the impact of this new procedure on the real timely availability to new beneficial medicinal products for human use for patients and for medical/paramedical staff, some generic comments are reported here below: 1) with reference to Lines 192-193: Relevant procedural documents (including 'question and answer' guidance to applicants, templates) will be published prior to launch. Line 305: Templates will be developed to support the procedure. General Comment: if it is planned in the first trimester 2016 a draft of relevant	

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		procedural documents will be available to stakeholders for comments, proposals, etc… If it will be confirmed the "Briefing Document Template- rev.0" – standard template, or it will be updated with some changes. 2) Line 260: Early stages of development (Proof of principle/proof of mechanism) General Comment: in the first stages of the development, to evaluate an impartial methodology based on a checklist of mandatory requirements, ensuring Proof of principle/proof of mechanism 3) Line 293: Annex 2 – Procedure for review of requests for eligibility General Comment: if this new procedure will be independent and parallel from the "Orphan designation procedure"	
17	215-216	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. **It is essential and priority (compared to other proposals), considered for the therapeutic area and given its importance for the pharmacoeconomics and for the disease to which the medicinal product for human use is aimed.**	
17	241-245	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. **For the product's potential different routes and times of administration (ie: depot system), than standard therapy, are included to improve the**	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		compliance of patient's treatment.	
18	General	Further clarity on whether entry into the PRIME scheme will be indication specific would be welcomed. In the instance that an unlicensed molecule is being developed in more than 1 area of high unmet medical need can the PRIME designation apply to only one indication or can it apply to more indications? What if the indications are not within the same therapeutic area?	
18	General	Will the PRIME scheme be available for molecules being developed for new indications, not just New Molecular Entities (NMEs)? The benefits such as early Rapporteur Involvement as well scientific advice with multiple stakeholders (including HTAs) could also be advantageous in the development of a new Indication.	
18	General	The reflection paper comments on the possibility for multi-stakeholder involvement through scientific advice. It is assumed that PDCO will participate in scientific advice as outlined in 'European Medicines Agency Guidance for applicants seeking scientific advice and protocol assistance'. Further detail on any impact of PRIME designation on the PIP process and PDCO's involvement in PRIME would be welcomed.	
19	General	HollandBIO and its members welcome the new PRIME scheme which offers greater support to developers of priority medicines addressing major public health needs within the exiting EU regulatory framework. HollandBIO welcomes the opportunity to submit these comments and observations on the proposed features of the scheme outlined in the draft reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		medicines (EMA/CHMP/57760/2015).	
19	General	In order to make the scheme truly beneficial and result in timely access to new beneficial and safe medicines for patients, we would like to draw your attention to the following comments: • **Criteria of PRIME eligibility should focus on products for indications with an unmet or urgent medical need.** These products can either be new products or existing products for new indications, and granting PRIME status should be irrespective of company size. In view of the upcoming *In Vitro* diagnostics regulation and the role of the EMA in the autorisation of companion diagnostics, eligibility of these products should be taken into consideration when drawing up the criteria.	
19	General	• **Early appointment of rapporteur is key benefit** For the success of PRIME it will be beneficial when a preference for a CHMP/CAT Rapporteur can be given by the MAH (similar to the process of selection of Rapporteur and Co-Rapporteur).	
19	General	• **Flexible point of entry** Timing for granting PRIME status should be flexible with regard to the development stage of the product.	
19	General	**Confidentiality of business information should be garanteed** Especially at the very early stages confidentially of business information is of utmost importance for companies. Therefore this confidentiality should be garanteed during the whole	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		PRIME programme.	
20	General	Alexion welcomes the proposal for enhance early dialogue to facilitate accelerated assessment of priority medicines. We believe that the proposed framework will be beneficial for new products in development that could potentially address unmet medical need. Consideration of such a mechanism for more detailed engagement during development is very welcome and should be encouraged.	
20	62-67	In addition to the Scientific Advice which remains the primary mechanism for obtaining (endorsement of) advice during the process, and because getting Scientific Advice can be bureaucratically burdensome and not necessarily meet the timelines of development for products to address unmet medical need, additional mechanism to obtain informal feedback all along the development would be welcome. One parameter that is also critical is the rapidity with which the EMA is able to schedule both the informal and formal meetings with the rapporteur.	Consider options for more frequent and potentially informal interactions with the Rapporteur in addition to engagement of SAWP at key points during development.
20	62-67	It would be nice to add that relevant committees to be included in the kick off meeting would include COMP for orphan designated products and PDCO for development that are mainly pediatric.	
20	68-73	The Agency should consider opening this up to sponsors other than SMEs or academic groups. If a product is genuinely likely to result in a significant advance in a therapeutic area, its development could be facilitated by the PRIME scheme whatever the nature of the sponsor company. This could still be granted in exceptional circumstances, i.e. the nonclinical data need to be remarkably positive and convincing for a product to qualify.	
20	83-85	Significant scientific advances are not restricted to products in development; major unmet medical needs can be fulfilled by new indications for approved products, eg.	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		Sildenafil for the treatment of pulmonary hypertension. The scheme should be opened to include marketed products for which applicable indications are in development in the expectation of accelerating to a Type 2 variation to the original MA.	
20	96-99	In the guidelines to be developed, it would be important to have more details on the specific criteria that the Agency will check to confirm eligibility for PRIME.	
20	128-130	Using Scientific Advice more frequently would increase the burden on sponsors, both in terms of resource and financial cost.	Reduced fees for Scientific Advice could be considered to encourage more interaction for PRIME products. Also as mentioned before, more frequent and potentially informal interactions with the Rapporteur in addition to engagement of SAWP at key points during development.
20	132-133	We would recommend the early appointment of EMA Product Lead as well as the Rapporteur, since the EMA Product Lead is expected to facilitate the communication and relationship between the different stakeholders and different committees involved in the development (SAWP, COMP, PDCO). It would be very beneficial for PRIME to get one point of contact that would follow the program from PRIME eligibility to approval. We would also recommend that the EPL would be an experienced and senior EPL in order to leverage the experience on other procedures specifically for PRIME.	
20	134-137	Please clarify if it is expected that the sponsor will be included in the kick-off meeting. If not, sponsor attendance should be included. Per previous comment, we would recommend to include the early appointed EPL in	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		the kick off meeting.	
20	138-140	Consider option for frequent interaction with Rapporteur and MS Agency staff (See previous comments), and with EPL.	
20	141-142	Please provide examples of regulatory aspects of development which might be addressed by coordinated EMA support.	
20	148-149	We would add in the other initiatives proposed joint FDA/EMA advice, because we believe that for this kind of dialogue, interactions between FDA and EMA are key for a successful global development.	
20	165	In order for patients to get access to PRIME products as early as possible, we propose the possibility for “rolling submissions” or “preliminary assessment”. Usually, CMC and nonclinical modules would be available earlier than the clinical modules and could be submitted earlier so that review could be initiated earlier. This could be either in a formal process to be determined, or as informal review by the rapporteur which could then reduce the number of questions for the CMC and nonclinical modules at the time of the official procedure.	
20	165	The intense dialogue should in our view continue until the approval of the new product, and even after the approval of the product, in particular in the case of products approved under conditional approval or exceptional circumstances, or PRIME. We propose to have additional informal meetings with the Rapporteur and the assessors outside of the standard clarification meetings. For example, at Day 80, after receiving the draft assessment report of the rapporteurs, a discussion with the Rapporteur would be important to get prepared to Day 120. It is important that these informal meetings would be scheduled quickly when a need for discussion is identified. We would like to propose that save-the-date are	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		planned in the initial timetable of the MAA to be sure that rapporteur/EMA and corapporteur would have common availabilities for discussion. These slots could be cancelled if they appear to be unnecessary.	
20	209-213	If assessment of unmet medical need includes non-approved products then it may be difficult to establish a consistent standard across all MSs due to possible differences in national standards of care. Consider the option that the definition should predominantly be based on products approved for the proposed indication.	
20	296-197	In order to reduce the number of applications for PRIME eligibility that have no chances to go through, we propose to include the possibility of pre-submission advice that would help the sponsor to understand the likelihood of success of the application. This would be helpful particularly at the beginning of the application of PRIME when both sponsors and EMA will have limited experience on the procedure. The advice would be non-binding and for information only.	
21	General	We welcome the opportunity to respond to this consultation. We welcome this reflection paper as an acknowledgement of the need to explore ways, within the current regulatory framework, to support the development of new medicines addressing unmet needs. One of EGAN's members, Genetic Alliance UK, recently held a multi-stakeholder workshop to investigate how to improve access for patients to advanced therapies medicinal products. We were pleased to have Patrick Celis from the Agency to present an informative explanation of the work of the Committee for Advanced Therapies. The results of this workshop are currently being prepared for dissemination.	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		Many of the perspectives that emerged from this workshop are directly relevant to the PRIME proposals. In particular, the following: First, while early provision of scientific advice is potentially hugely valuable to developers, we are seeing in the UK Advanced Therapy Medicinal Product (ATMP) sector that many developers are not utilising the opportunities to engage with regulatory bodies that already exist. A key challenge is how to encourage developers to communicate with regulators such as the EMA earlier and more often than is common practice. It is not sufficient for the advice and support to be available, its availability needs to be promoted widely. The EMA needs to continue and broaden its initiatives to proactively engage with developers and encourage them to consider their interactions with regulatory bodies as a conversation rather than a single hurdle to be overcome. Second, in determining which products will enter the PRIME program, it is vital that patient perspectives be taken into account. Patients are the best judges of what constitutes an unmet medical need, and their views should be at the centre of this scheme.	
21	68-70	As we are seeing with the ATMP regulation, it is not only SMEs that tend to lack regulatory and medicine development experience. This is also an obstacle to academic and non-profit developers bringing innovative products to market. We welcome the scheme being opened to academic organisations, but believe that in order to function as intended, non-profit organisations should also be included.	There is also value in opening the scheme to SMEs and applicants from the academic **and non-profit** sector**s** 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

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
			development experience.
21	138-140	Parallel EMA/HTA meetings to help ensure developers are fully informed on likely data requirements for MAA and reimbursement decisions are potentially beneficial. We are concerned that member states that have devolved or regional health technology appraisal systems are less well placed to benefit from this growing relationship, as national representatives are not necessarily disseminating the results of European level discussion effectively.	
22	General	The French National Institute of Cancer (Institut National du Cancer, INCa) is a National Health and Scientific Agency for cancer control that reports to the Ministries of Health and Research. It develops an integrated approach to cancer control: from prevention to screening, care and research, including access to medicines and innovations. INCa thanks EMA to give the opportunity to interested parties to comment on the PRIME project. In many types of cancers, there is still an unmet medical need and new drugs are awaited to obtain relevant benefits in terms of Progression Free Survival (PFS) and Overall Survival (OS) with an acceptable safety profile. An early access to promising innovations is wished by patients as well as physicians. From an overall viewpoint, the French National Cancer Institute supports early access to priority medicines, provided that their benefits/risks ratio is highly presumed positive for the patients who really need them. Several tools are currently available or under evaluation to accelerate marketing authorization (MA) of new medicines, *i.e.:* - Conditional Marketing Authorization;	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		- Accelerated assessment of MA. - Adaptive pathways. PRIME is a new scheme proposed by EMA aiming to improve the quality of the development of “priority medicines” in order to obtain high quality clinical data eligible for an accelerated assessment. To reach these goals, PRIME uses two different preexisting tools, *i.e.:* scientific advices and accelerated assessment of MA. Eligible medicines will benefit from a strong support from EMA early in their development. This support is supposed to optimize the level of evidence of generated clinical data (because of better clinical design, use of optimistic comparator and key efficacy criteria) in an efficient timeframe. In principle, the accelerated marketing authorization of “PRIME” should guarantee the generation of clinical data sufficiently reliable, informative and mature to: - ensure the safety of treated patients; - clearly define the target population of the product; - define the place of the product in the therapeutic management of the disease notably compared with other treatment options. The PRIME program answers to an early access need, frequently met in the area of cancer. The PRIME program concurs to authorize priority medicines without reducing the evaluation standards today applied to all medicines. The PRIME scheme may even improve the robustness of the clinical data. Therefore, although 75% of new anticancer drugs approved between 2010 and 2015 in Europe already got a scientific advice from EMA, the French National Cancer Institute (INCa) supports this new approach.	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		In a general view, INCa strongly supports any action in favor of an early access to priority medicines in cancer and France has developed for many years several dedicated tools to promote and secure it, notably : - A national early access program called ATU (Temporary Use Authorization corresponding to the European Compassionate Use or named patients basis use) that permits an early access to new anticancer drugs covering an unmet medical need while they are still under development or under assessment for a marketing authorization in the European Union. This program has been set up 20 years ago and allows not only an early access for patients with serious diseases to new medicines but also a close supervision of treated patients through a therapeutic protocol (defining treatment, information and monitoring of patients, follow-up of patients and data collection). Between January 2010 and August 2015, 20 out of 45 new anticancer drugs that have been authorized by EMA were available before MA in France through the ATU program (44.5%). The duration of pre MA access is around 5 months for anticancer drugs (see table in annex). Thus, the ATU program permits to keep the timeframe of assessment for the marketing authorization reasonable and compatible with a careful review of the benefit risk ratio of the drug and an early access for patients who need the drug reliably. - A new type of National clinical trials access program such as the AcSé program[8] supported by INCa [9] that gathers academic basket trials (phase II trials) allowing patients to benefit in an early and safe manner from therapies targeting a specific anomaly identified in their tumor. This access	

[8] Safe access to innovative target therapies for cancer
[9] http://www.e-cancer.fr/Professionnels-de-la-recherche/Recherche-clinique/Le-programme-AcSe2

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any

is proposed within an open clinical trial available everywhere in France to patients suffering from cancer without therapeutic options.

Overall, the French National Cancer Institute is strongly engaged in the support and promotion of a safe early access to innovative anticancer drugs and proposes new programs to reach this goal. However, INCa believes the robustness of the evaluation and the assessment of the benefit risk ratio of new anticancer drugs should be closely maintained. While awaiting MA, national early access programs as ATU, ACSé or expanded access clinical trials are feasible at a national level.
Any process designed to accelerate the MA assessment of priority medicines is generally supported by INCa but should always be discussed with regards to a compassionate use program.

INCa suggest improvements to the detailed PRIME procedure.

INCa is happy to contribute to the safe early availability of cancer therapies.

Annex / Table: Delays between the French authorization for temporary use (cohort ATU) and MA of new anticancer drugs approved between January 2010 and August 2015 by EMA.

Tradename	INN	Delays ATUc/MA (days
Adcetris	brentuximab vedotin	-113
Arzerra	ofatumumab	
Bosulif	bosutinib	
Caprelsa	vandetanib	
Cometriq	cabozantinib	
Cyramza	ramucirumab	-48

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		Dacogen	decitabine		
		Erivedge	vismodegib		
		Farydak	panobinostat	-23	
		Gazyvaro	obinutuzumab		
		Giotrif	afatinib		
		Halaven	eribulin mesylate		
		Iclusig	ponatinib		
		Imbruvica	ibrutinib	-262	
		Imnovid	pomalidomide	-395	
		Inlyta	axitinib		
		Jakavi	ruxolitinib	-144	
		Jevtana	cabazitaxel	-55	
		Kadcyla	trastuzumab emtansine		
		Keytruda	pembrolizumab	-350	
		Lenvima	lenvatinib	-57	
		Lynparza	olaparib	-123	
		Mekinist	trametinib		
		Odomzo	sonidegib		
		Opdivo	nivolumab	-165	
		Perjeta	pertuzumab		
		Pixuvri	pixantrone dimaleate		
		Provenge	sipuleucel-T		
		Stivarga	regorafenib	-270	
		Tafinlar	dabrafenib		
		Tepadina	thiotepa		
		Teysuno	tegafur / gimeracil /		

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	oteracil	
Unituxin	dinutuximab	
Vargatef	nintedanib	10
Votrient	pazopanib	
Xalkori	crizotinib	-236
Xaluprine (ex Mercapto-purine Nova)	mercaptopurine monohydrate	
Xofigo	radium 223 chloride	
Xtandi	enzalutamide	-123
Yervoy	ipilimumab	-12
Zaltrap	aflibercept	
Zelboraf	vemurafenib	-277
Zydelig	idelalisib	-109
Zykadia	ceritinib	-212
Zytiga	acetate d'abiraterone	-35
	Mean	**-150**
	Median	**-123**

22	112	Considering the major interests of PRIME and the support it could offer notably to micro enterprises and academic researchers, the French National Cancer Institute considers that this support could also be proposed in a proactive way by EMA on the basis of: - EMA knowledge of new products under development (scientific watchfulness, scientific advice); - A suggestion notably from a Member State of the European Union.	EMA can also propose in a proactive way PRIME support, when it or a MS has identified potential Priority medicines.
22	114	EMA should publish the list of the “PRIME medicines” in order to help public researchers, health care professionals, health national agencies and all other stakeholders including patients to identify and learn about new priority innovations	Monthly report **including the name (s) of the substance(s),** the therapeutic area, the type of data on which the eligibility to access the scheme was granted or rejected, its

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		as early as possible.	phase of development,and **the name and** the type of applicant .
23	General	All the partners of the REGenableMED project are aware of the existence of this draft Reflection Paper. We welcome the opportunity to review this Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME). We welcome the support that the EMA is providing for fostering the development of new medicines, notably through assistance regarding the regulatory frameworks. To this end, the PRIME scheme is seen as an interesting new regulatory tool promoting accelerated approval for new medicines addressing major public health needs. However, it seems necessary to clarify how this new scheme will be integrated within the EMA's organisation and how it will be articulated with other existing tools, not only the accelerated assessment. Regarding the EMA's organisation, it appears necessary to clarify what roles the Innovation Task Force and the SME's office will play in this new scheme. Will they just be in charge of orienting applicants towards this new scheme? In any case, such role should be mentioned in this reflection paper. Regarding the other existing tools, it may be relevant to guide the applicants towards the certification procedure (as well as CAT's recommendation on classification) in case of advanced therapy medicinal products and eligibility to PRIME at the early stages of development (proof of principle/proof of mechanism). Finally, it is noted that there is a fee to enter this new scheme. Will this be additional to the one for scientific advice? In any case, this aspect should be	

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		considered in this reflection paper.	
23	19		To add “PRIME: PRIority MEdicines”
23	102-104	It appears the CHMP will 'recommend eligibility to the scheme', but could you please clarify what status this recommendation will have. It looks a bit like a weaker version of ATMP's certification procedure for SMEs - how might it relate to this?	
23	107-110	This paragraph describes useful oversight of the whole process. The later Appendix provides useful details on the range of data and evidence that must be submitted at different stages of product development. Would it be possible to add value to PRIME by building, as a result of all the submissions, a data infrastructure that could capture the results of non-trial based clinical studies (so long as these are not commercially sensitive): this would be a wider resource that could be drawn on over time?	
23	108	Could the Reflection Paper say more about the envisaged 'Oversight group', e.g. its composition, expertise etc.?	
23	111-112	It may be difficult in some cases to “confirm” the eligibility to the centralised procedure depending on the data submitted.	“When access to the scheme is recommended by CHMP, eligibility to the centralised procedure will also be **considered and subsequently** confirmed at the same time.”
23	129-130 139-140	One of the support mechanisms proposed includes early 'potential' ('possible' would be better) involvement of HTA (and patients). It would be good to indicate how such involvement would be decided - on request	“with the ~~potential~~ **possibility** to involve multiple stakeholders”

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		of the applicant? - by negotiation? Could also here say that the process will incorporate lessons from the EMA adaptive pathways pilot.	
23	263-265	Please clarify whether the entry to the PRIME scheme at the early stages of development (Proof of principle/proof of mechanism) will be limited to SMEs and applicants from academic sector, (i.e. a company that is not an SME could not enter the scheme at the early stages).	
23	305	The final line of the appendix 2 refers to to-be-developed 'templates' which will inform judgements about , presumably, how 'convincing' (li 266) or 'compelling' (li 270) the case for PRIME status and support is - how will such templates be developed and by whom, with what expertise?	
24	General	We have developed this response to the EMA's proposal for the PRIME scheme with our Centre for Drug Development (CDD) and our technology transfer arm Cancer Research Technology (CRT). This includes feedback that we have received from our industry partners. In summary: We welcome the European Medicines Agency's (EMA's) proposal for the PRIME scheme. We believe this scheme has the potential to accelerate the development and approval of innovative medicines addressing an unmet medical need so they are able to benefit patients at an earlier stage. • We believe the success of this scheme will depend on member state support and we hope to see the UK's Medicines and Healthcare products Regulatory Agency (MHRA) set out their commitment to promote the scheme and support its implementation. • The EMA should further clarify eligibility criteria to the scheme and set out	

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		their intended processes for selecting products to grant PRIME designation. • The EMA should set out the potential demand for the PRIME scheme, the number of designations it expects to award each year, and the resource it has allocated to support the successful implementation of the scheme.	
24	General	<u>Timely development and access of innovative medicines</u> Cancer Research UK believes that all cancer patients should have access to the best, evidence-based interventions for their disease. This means that while it is imperative to get new treatments to patients as soon as possible, particularly in life-threatening diseases such as cancer, it must be done in a robust and evidence-based way. We welcome the EMA's continued commitment to review the regulatory framework for the timely development and access of innovative medicines. Whilst national schemes, such as the UK's Early Access to Medicines Scheme (EAMS), are being explored, we believe that the real value to accelerating the development pathway will be found in the delivery of an effective adaptive approach that is relevant across all member states. We have therefore been very supportive of the EMA's Adaptive Pathways pilot and welcome its proposal to introduce the PRIME scheme. **For the success of the PRIME scheme, it will be important for member states to lend their full support. We therefore hope to see the MHRA set out their commitment to promote the scheme and support its implementation.**	
24	General	<u>The priority medicines (PRIME) scheme</u> We believe that the PRIME scheme has the potential to accelerate the development	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		and approval of innovative medicines addressing an unmet medical need so they are able to benefit patients at an earlier stage. We welcome that the revised guidance emphasises the importance of early dialogue with the EMA. Such an approach gives organisations developing new treatments more certainty about the approach they take to gathering evidence and how it will be treated during assessment. It is particularly helpful that this scheme will enable SMEs and applicants from the academic sector to get PRIME designation for a medicine at an early stage in its development, on the basis of compelling non-clinical data or tolerability data in initial clinical trials. Through early engagement with regulators, such designation could accelerate the development of medicines in our CDD portfolio. It could also serve to highlight a drug's potential and thereby increase the likelihood of its development being continued in later phase trials by a pharmaceutical company.	
24	General	Although EMA has set out how an applicant should justify eligibility to this scheme, we are still unclear as to whether drugs in our CDD portfolio would be eligible. **We think that the EMA should further clarify eligibility criteria to the scheme and set out their intended processes for selecting products to grant PRIME designation.** We do welcome that the EMA intends to publish a monthly overview of the number of recommendations adopted including broad characteristics on the substance(s), the therapeutic area and the type of data on which the eligibility to access the scheme was granted or rejected. Over time, we believe this information will help clarify the eligibility criteria and EMA's rationale for granting PRIME designation.	
24	General	The **EMA should set out the potential demand for the PRIME scheme, the number of designations it expects to award each year, and the resource it**	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		has allocated to support the scheme. There are strong similarities between the PRIME scheme and the FDA's fast track and breakthrough designation schemes that have proved popular in the US. In the first two years of the breakthrough therapy scheme, nearly 250 applications were received1. 68 of these were successfully granted breakthrough designation, even though its sponsoring legislators intended it to apply to only a handful of drugs each year2 and the FDA predicted that two to four drug candidates each year would be granted designation3. It is important the EMA looks to these schemes as an indicator of the potential demand for PRIME in order to correctly anticipate and allocate sufficient resource to ensure the success of this scheme.	
25	General	Regeneron welcomes the initiative taken by the Agency in developing the PRIME scheme in order to maximise the use of existing regulatory tools to bring innovative medicines to patients in an efficient manner. In particular, the early appointment of a Rapporteur and scope for increased regulatory dialogue are welcomed.	
25	83-85	We recommend expanding the scope of PRIME-eligible applications to include Type II variations for new indications of an existing license that demonstrate the potential to address, to a significant extent, an unmet medical need. In the current reflection paper, access to PRIME is limited to initial marketing authorisation applications (MAAs). We suggest the Agency consider expanding the scope of eligibility to PRIME to all qualifying applications, which may include new indications for already approved medicinal products. Based on this consideration, please see new proposed text following line 83-85 below.	"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 marketing authorisation application through the centralised procedure." (83-85) "In limited circumstances, applicants may request PRIME eligibility for new indications of an existing license. This would facilitate the increased regulatory dialogue in advance

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			of, for example, Type II variations, and would also support situations where a new indication may fall into the mandatory scope of the centralised procedure even when the initial marketing authorisation was granted through other processes".
25	113-119	The current text in Lines 117-119 may be open to multiple interpretations. We believe that this monthly overview of number of recommendation will not disclose the individual decisions adopted by the CHMP. To minimize confusion in interpretation, we recommend that the reflection paper clarify that no other information (e.g., Sponsor name, drug name, data, and CHMP decision) will be published in the CHMP Monthly Report. We also propose it is clarified that the outcome where negative will also not be made public. Please see revised wording for consideration:	Lines 117-118: "The individual outcome adopted by the CHMP **on access to the PRIME scheme** for a given **application, whether positive or negative**, will not be made public."
25	126-130 138-140	The reflection paper identified key supporting features of the PRIME scheme which includes early appointment of a Rapporteur. We anticipate that the Agency will provide additional guidances to assist applicants in both the application process and engagement of Rapporteur/Agency for the PRIME process. It would be helpful to receive further clarification on the levels of formal and informal contact/Scientific Advice meetings anticipated so that applicants are able to prepare and plan for the PRIME application and process. We would also suggest that the introduction of the PRIME scheme may offer the Agency the opportunity to consider the value of implementing a rolling MAA submission concept in the EU.	
25	260-265	For promising medicinal products in early stages of development (proof of principle/mechanism), we do not agree with limiting entry to PRIME to SMEs and	"Entry at this early stage will be **permissible to all applicants**. SMEs and

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		applicants from the academic sector. For promising medicinal products in early stages of development, access to PRIME should be available to all applicants. Using rare disease development programs as an example, if a Sponsor has a therapy showing promising nonclinical data and justification, it should still qualify for the PRIME scheme at the early stage, and would have the opportunity to benefit from tailored assessment and regulatory support/guidance to better inform development plans. If one of the objectives of PRIME is to meet unmet medical need, with the potential of significantly addressing such a need, patient access to this potentially innovative products should not be restricted based on the size or commercial standing of the Sponsor/applicant.	applicants from the academic sector **are encouraged to apply for PRIME at this early stage to gain** advice on tests and trials to support confirmation of eligibility through to later clinical phases of development."(Lines 263-265)
26	General	We recognise that reflection papers are high level. The reflection paper provides a good overview of the proposed accelerated assessment for PRIME.	
26	General	The paper is comprehensive and as such, the proposals outlined are likely to deliver the objectives .The specific objective from the viewpoint of accelerated therapeutic innovation is particularly welcomed.	
26	General	Patient safety is particularly relevant with the accelerated access. Effective and responsive monitoring and escalation systems will be critical, especially in relation to new technologies in the clinical stages following "demonstrated proof of concept ". The paper, in section 5 identifies that products will be monitored at regular checkpoints but there is no mention of escalation processes in the event of a significant clinical adverse event. We consider that the proposal would be strengthened by the inclusion or explicit recognition of the need for an escalation process.	
27	General	ES does not see completely the need to establish a completely new scheme	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		dedicated to monitor closely the development of specific products. The risks associated with the proposed eligibility criteria and the management of the procedure (including the controversial early appointment of the CHMP member) can be anticipated. The potential uncertainties created by this new system could be managed with activities and tools provided by the current framework. In our view, the support of innovation, the development of promising products as well as minor partners (academia, SME, etc) and the other objectives described herein can be achieved with existing tools such as the scientific advice and the innovation network. Consequently, we are of the opinion that, before establishing a new scheme, we must analyze the current situation and to adjust or reconsider the existing system to ensure that all the situations and cases described in this paper are covered, without creating new doubts in the system.	
27	General	ES does not agree with the proposed early designation of CHMP rapporteur. We really believe that the scientific/regulatory support can be given by the system without having to assign a CHMP rapporteur, which will be obviously perceived by the general public as a weakness of the system as this may interfere with the independence of the medicinal product evaluation. See also specific comment on Lines 132-133 & Lines143-149	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
27	General	The level of commitment of the Applicants with a granted PRIME designation should be clarified within this reflection paper. The PRIME scheme will cover a need for supporting the innovation/development of promising products within the EU, by providing early regulatory/scientific support to those developments that may be of the patients benefit. From our view, the responsibility of monitoring the different stages of development assumed by the Health Authorities should be offset by a clear commitment on the part of applicants. The level of commitment required for applicants is unclear within the paper. Assuming that the recommendations given through the scientific advice are not mandatory and the applicant could deviate if properly justified, the procedure should consider this possibility as well. the reflection paper should establish how to manage the support if the applicant does not follow the recommendations and describes potential causes for revoking the PRIME designation granted. In order to achieve the final objectives of the scheme, we should ensure that a bilateral commitment (Health authorities-Prime applicant) is placed. The criteria for granting the PRIME designation is related to (1) the unmet medical need concept and (2) major therapeutic advantage or significant/substantial improvement. Both concepts are extremely similar to the criteria applied for orphan designation.	

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		Considering the above and in order to be consistent, we must ensure that the eligibility criteria, requirements and definitions used for the PRIME scheme are as aligned as possible to those used for orphans. In this regard, topics such as the consideration of existing alternative treatments (the formulated products are considered valid alternatives for PRIME but not for orphans), the need for establish direct comparison versus the existing alternatives to prove the benefit improvement or the potential risk of 'slicing' indications/sub populations should be carefully considered. In this sense, considering issues such as existing alternative treatments (formulated products are considered as valid alternatives for PRIME but not for orphans), the need to establish a direct comparison against existing alternatives to prove the improvement or potential risk of 'Indications/subpopulations slicing' should be carefully considered.	
27	General	The coordination and collaboration of the National Innovation Offices is essential for the identification of the products that can benefit from this scheme, and should be mentioned within the reflection paper.	
27	General	The PRIME scheme should be consider an additional regulatory tool to promote and support the innovation and development of promising products within the EU. The objective should not be having a high number of PRIME designation at the end of the year but identifying all the products that could benefit from this regulatory tool even if the result was a reduced number of applications/designations per year. In this sense we should not actively promote the use of this scheme for specific products/objectives (e.g. intended products for dementia, antimicrobial) but we	

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		should identify any interesting product for any need/therapeutic area even if it is not considered to fall under the society priorities.	
27	53-58	The document should clearly state the objective(s) of the proposed support scheme. It is stated in this paper that *'the PRIME scheme would introduce the possibility not only to identify products fulfilling the criteria for accelerated review early but also to enhance the regulatory and scientific support on offer to these products [...]*' However, from our view, the real objective to be achieved through this scheme, would be **supporting the innovation in EU in the patients benefit**: 1) Identification of the innovation at the earliest possible stage 2) enhancement of the regulatory and scientific support on offer to these products, projects or developments (which is specially relevant in the case of SME/academia, but not exclusive) In this regard, the 'identification of products fulfilling the criteria for accelerated review early' mentioned in this section, should not be considered an objective *per se* but a logical consequence of the identification of the innovation (promising products) and therefore, should not be stated as objective of this scheme.	Do not focus the objective of this reflection paper only on the accelerated assessment and authorisation of products Lines 53-56). Alternatively, please state clearly that this measure is taken to support the innovation in EU in the patients benefit. And that this innovation will be promoted by the early identification of promising projects as well as the advice and close monitoring of such developments.
27	83-85	This sentence is clearly stating that i.e new indications will not have access to this supportive scheme. However, if the objective is the early identification of 'promising' products and the potential cover of unmet needs, the possibility of supporting the investigation of not only completely new products but also new indications of already authorised should be considered in a case by case basis.	Update the paragraph according to our previous comment
27	94 & 97	The meaning of the terms 'significant extent', 'major therapeutic advantage' and	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		'meaningful improvement', included within this section should be further clarified	
27	108	Proposed change (if any): The composition of the proposed 'oversight group' should be further described in this section	
27	123-124 158-161	Is indicated in lines 123-124 that the '*[…]written confirmation of eligibility to the PRIME scheme will include* ***early confirmation of potential of accelerated assessment'.*** On the other hand, lines 158-161 indicate that *'[…]the products designated for prime support are anticipated to benefit from the accelerated assessment procedure,* ***which is to be formally confirmed shortly before submission of the MAA'.*** From our view, and as previously noted, the paper is excessively focused on the accelerated assessment. The objective of PRIME scheme has to be 'support' the innovation/development of promising products and the accelerated assessment should be only considered as a mere consequence/measure of this support, just as the other proposed measures such as the early designation of CHMP rapporteur, etc. In addition, the accelerated assessment could (or could not) be finally obtained depending on the results, the fulfilment of the criteria, etc. (please note that the PRIME designation could be granted even in absence of exploratory studies!) Therefore, it is not clear for us why the written PRIME designation has to include this early confirmation of potential of accelerated assessment.	From our view, there is no need to mention the early confirmation of potential of accelerated assessment within the written confirmation for the PRIME scheme. Moreover, the paper should be reworded to not focus on the accelerated assessment but the support of the innovation/development of promising products.
27	126-130 138	Although is clear that one of the main objectives of this scheme is to provide scientific/regulatory support to both SME and academia as well (as non profit organizations?) in the development of promising products, the fees reduction is	The fees reduction for the academic sector should be considered as well.

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		only considered for SME. In order to be consistent with the proposed objective, the financial support to the academic sector should be also considered. As indicated in this paper, both SME and academia are smaller players with limited regulatory and development experience, and fee reductions for Scientific advice can help to facilitate the access to this support. Therefore, the academia should also be eligible for this fees reduction.	
27	132-133 143-149	(included as general comment as well): ES does not agree with the proposed early designation of CHMP rapporteur. We really believe that the scientific/regulatory support can be given by the system without having to assign a CHMP rapporteur, which will be obviously perceived by the general public as a weakness of the system as this may interfere with the independence of the medicinal product evaluation. Although we could ensure the independence of our evaluation, we must recognize that this measure may impact on the confidence in the system of the general public. It is difficult to understand that the responsible for leading the support during the product development is the same person to lead its critical evaluation. But, what is more important, there is no need to be the same person and of creating this uncertainty in the system as we have alternative mechanisms to perform both functions ensuring consistency throughout the procedure	ES does not agree with the proposed early designation of CHMP rapporteur. The deletion of this measure is proposed, and the paper should be reworded accordingly. However, if this early assignation would be finally accepted, the role of the Rapporteur would have to be further detailed in the reflection paper to ensure that their contribution is well defined and understood.

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		The SAWP is a working group dependent of the CHMP that can take the responsibility to provide support to the development keeping the consistency with the CHMP (as always done). The fact that the SAWP coordinator leading the support is a different person from the final CHMP member responsible for leading the assessment will be perceived better by the general opinion. We could even consider the designation of the same country for both functions at the different stages of the procedure but we believe that this measure would not be necessary as the current system in place already ensure consistency and trust in the system. Moreover, the fact that the CHMP and SAWP members can change each 3-years (if not early due to personal/institutional decisions) has also to be taken into account, as the objective of personalizing the support/evaluation will not be achieved in some cases.	
27	175-176	The text indicates that *'in case no Scientific advice requests are submitted, applicants would be asked to provide an update on the development progress[...] at relevant milestones'* In our opinion, this would be applicable in the case that the development is stopped and the applicant withdraws or waives the Prime designation. On the contrary, if the applicants maintains the prime designation and the development is still ongoing, there should be a mechanism to ensure that the bilateral collaboration is guaranteed (See also our general comment No.2)	
27	188-189	The paper is stating that the proposed scheme *'has been developed in consultation with the Agency's scientific committees, the EC and its expert group STAMP as well*	It is proposed that the text is reworded as follows:

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		as the regulatory network'. However, neither the committees, STAMP nor the general network have been directly involved in the development and design of this scheme. They have only been informed by the Agency about a fixed proposal with very little room for modification. Therefore, it is proposed that the text is reworded to clearly state that the PRIME scheme has only been informed to the network and NOT developed in consultation.	The proposed scheme was ~~**developed in consultation with**~~ **presented for information(or informed) to** the Agency's scientific committees, the EC and its expert group STAMP as well as the regulatory network.
28	General	To increase the impact of this new procedure on the real timely availability to new beneficial medicines for patients, three suggestions are submitted: 1) the main criteria for eligibility should be an expected "significant clinical benefit or a major contribution to patient care", taking into account the great experience of EMA for OMPs 2) the procedure should cover also the extensions of indication 3) an update of the assessment at the time of MA could favour the harmonization and reduce the time of the national procedures for reimbursement	
28	92	a better explanation of the criteria for eligibility is mandatory for the best success of the new procedure. A great experience for OMPs, using the suggested definition reported below, has been already done and should be exploited.	product concerned will be of ~~major therapeutic advantage to those affected~~ **significant clinical benefit or a major contribution to patient care**
28	99	same as for the first comment	Morbidity or mortality of the disease **or a major contribution to patient care**
28	245	same as for the first comment	Advantage for patients **or a major contribution to patient care**
28	88-89	insert a paragraph to expand PRIME for the extension of indication	**The PRIME scheme can be used also for**

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
			an extension of indication with the same criteria of eligibility and procedure as for a new medicine.
28	183	an updated re-assessment, if requested by the sponsor, for the PRIME eligibility criteria at the time of the MA could favour the national procedures for the timely access to new beneficial medicines for patients, as in the main objective of this new procedure.	no longer met. **In addition to this, to favour the national procedures for the timely access to new beneficial medicines for patients, if requested by the sponsor, the eligibility to PRIME is re-assessed at the time of the Marketing Authorization.**
28	305	see the last comment above	add the following paragraph: **Under request by the sponsor, the assessment for eligibility to PRIME can be repeated at the time of the Marketing Authorization. This updated review can be performed to favour the national procedures for the timely access to new beneficial medicines for patients. This re-assessment will be fully reported into the EPAR.**
29	General	**A PRIME example of how EMA is pushing for accelerated market approvals, but at what cost for patients?** **Health Action International, International Society of Drug Bulletins, Mario Negri Institute for Pharmacological Research, Medicines in Europe Forum, Nordic Cochrane Centre and Wemos** are glad to contribute to the EMA public	

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		consultation on the *Draft Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME).*	
29	General	In this joint response, we highlight concerns with current attempts to weaken marketing authorisation requirements in the EU, most notably through the EMA's adaptive pathways project. The PRIME scheme appears to be a complementary move to entrench the provision of confidential, customised advice to pharmaceutical companies in the regulatory system for expedited approval and coverage of new, expensive medicines which as evidence suggests will rarely bring therapeutic advance but often safety concerns.	
29	General	**Expedited approval schemes should guarantee patient safety and better therapy** EU pharmaceutical legislation provides that, as a general rule, before a medicine is authorised it has to undergo ''extensive studies to ensure that it is safe, of high quality and effective for use in the target population''.[10] The requirement for the demonstration of solid evidence about benefits and harms before a medicine is approved protects patients' safety. It contributes to medical innovation by requiring companies to generate meaningful clinical data. Besides the conventional marketing authorisation scheme, the EU has introduced some specific regulatory procedures to allow for early access to new medicines. These include "approval under exceptional circumstances", and "conditional marketing authorisations" and ''accelerated assessment'. Whilst the use of	

[10] Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		expedited approval schemes is justified in the context of truly unmet medical needs, early access to medicines must not jeopardise patient safety or clinically relevant outcomes. After all, people suffering from a rare disease or life-threatening condition also deserve medicines that are approved on the basis of concrete evidence of benefit, not merely hope or interim clinical trial results. Data from the European Commission show that the timelines for drug licensing have dramatically shortened over the last 10-20 years.[11] A major concern is that premature licensing comes at the expense of thorough evaluation, leading to more pharmacovigilance problems later. US researchers found that drugs approved after legislative changes introduced to speed up the approval process were more likely to be withdrawn or receive a new "black box warning" than drugs authorised before the bill's passage.[12] In Canada, 34% of drugs approved through the priority review received a serious safety warning compared with 19% of those approved through the standard pathway.[13] Years of experience also show that manufacturers fail to honour post-marketing commitments to provide missing data (e.g. in the context of conditional marketing authorisations) adding to concerns on patient safety.[14] [15] Evidence also demonstrates that mechanisms for early access fail to guarantee better therapy. An assessment from the independent drug bulletin Prescrire reveals that amongst 22 drugs "approved conditionally" in the EU from 2006-2014: 27% are "not	

[11] European Commission Directorate General Competition. "Final Report of the Pharmaceuticals Sector Enquiry"; 8 July 2009.
[12] Frank C et al "Era of faster FDA Approval has also seen increased blackbox warning and market withdrawals" Health Affairs 2014; 33(8): 1453-1459.
[13] Lexchin J "New drugs and safety: what happened to new active substances approved in Canada between 1995 and 2010?" Archives of Internal Medicine 2012: 172:1680-1.
[14] US Government Accountability Office "Drug safety – Improvement needed in FDA's postmarket decision-making and oversight process" Report GAO-06-402, 2006. www.gao.gov: 63 pages.
[15] Carpentier D "Can expedited FDA drug approval without expedited follow-up be trusted" JAMA Internal Medicine 2014; 174 (1): 95-97.

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		acceptable" (e.g., *"product without evident benefit but with potential or real disadvantages");* 28% have a "judgement reserved" (e.g., *"rating postponed until better data and more thorough evaluation are available"*); 9% are "nothing new", only 18% are "possibly helpful" and only 18% clearly "offer an advantage". A recent study from Banzi and colleagues covering the same period of conditional marketing approvals states that "the benefit-risk profile of medicines conditionally allowed is rarely reassuring and strong enough to make the expected public health advantage outweigh the risk of limited clinical information".[16] Despite the scarcity of clinically superior medicines, pharmaceutical sales more than doubled between 1990 and 2010.[17] Pharmaceutical expenditure is highly concentrated on expensive me-too therapies. According to a 2015 OECD report, the proliferation of high-cost specialty medicines targeting small populations and/or complex conditions will be a major driver of health spending growth in the coming years. The report finds that whilst some of these medicines are of benefit to patients, others provide only marginal improvements.[18] The consolidation of a new business model by the pharmaceutical industry - the "niche buster" model – is contributing to increased pressure on health authorities to reduce evidence requirements for marketing authorisation and price-setting. Clearly, instead of weakening existing mechanisms for medicines' early market entry expedited approval schemes must: • address true unmet medical needs (i.e. a medical condition that significantly affects someone's quality of life or leads to serious morbidity	

[16] Banzi R, et al "Approvals of drugs with uncertain benefit–risk profiles in Europe" *Eur J Intern Med* 2015, http://dx.doi.org/10.1016/ j.ejim.2015.08.008
[17] Naci H, Carter AW, Mossialos E. Why the drug development pipeloine is not deliverign better medicines. *BMJ* 2015; 351: h5542
[18] OECD. Health at a Glance 2015, Chapter 2. Available at http://www.oecd-ilibrary.org/docserver/download/8115071ec005.pdf?expires=1450718870&id=id&accname=guest&checksum=343E98E092BF1B49FA61AFE0FB0A26BF

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		or mortality and for which no adequate medical treatment exists); • allow thorough marketing authorisation assessments by regulators • lead to the (conditional) approval of medicines based on clinical trial data that demonstrate an advance over existing treatment options with respect to outcomes that matter to patients; • be subject to rigorous and proactive pharmacovigilance requirements, including application of dissuasive sanctions in case of non-compliance.	
29	General	**Adaptive pathways: lowering marketing authorisation requirements and shifting even more the burden of proof to post-market** Several attempts have been made, particularly in the last 15 years, to weaken marketing authorisation requirements in the EU. In 2008 the European Commission put forward a legislative proposal to expand ''conditional marketing authorisations'' beyond situations of unmet medical needs, in the context of the review on pharmacovigilance rules. The Commission aimed to reduce R&D costs and give pharmaceutical companies "*a faster return on investment*".[19] Instead of supporting this move, the European Parliament and the Council reiterated the need to ensure that "*a strengthened system of pharmacovigilance does not lead to the premature granting of marketing authorisations*". Ultimately, the Commission's proposal was not part of the new pharmacovigilance legislation adopted in 2010.[20] [21]	

[19] Prescrire Editorial Staff. "European pharmacovigilance: increasingly outsourced to drug companies" *Prescrire Int* 2014; 23 (155): 302-307
[20] Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance". Official Journal of the European Union, 27 October 2012 ; L299/1-L299/4.
[21] Regulation (EU) No 1027/2012 of the European Parliament and of the Council of 25 October 2012 amending Regulation (EC) No 726/2004 as regards pharmacovigilance » Official Journal of the European Union, 27 October 2012 ; L299/1-L299/4

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		The move towards flexible marketing authorisation schemes for medicines in situations other than those covered by existing expedited approval schemes was also envisaged in the EMA's Road map 2015, published in 2010.[22] The EMA referred to a ''progressive licensing'' scheme that should apply to situations ''characterised by a better-defined or more restricted population of good responders, followed by a broadening of the population post-authorisation when more 'real-life' data are available''. Supporting this move, European pharmaceutical industry associations and industry-sponsored patient groups wrote to the European Commission in December 2013 calling for adaptive licensing pilots.[23] In March 2014, the EMA launched the adaptive pathways pilot project (also known as adaptive licensing (AL)).[24] The adaptive pathways scheme aims at bringing drugs to the market earlier by starting with a niche indication in a small population group and then broadening use through additional phases of data gathering. Initial licensing would be based on less comprehensive data, relegating much of the demonstration of evidence about a medicine's effects to the post-marketing phase. Observational studies would also inform decisions about subsequent authorisations. According to supporters of this model, ''a successful AL [adaptive licensing] pathway for any drug will also be dependent on the willingness of patients, health-	

[22] European Medicines Agency. Road map to 2015. The European Medicines Agency's contribution to science, medicines and health
[23] Eurordis Website. "News: Promotion of progressive patient access bears fruit". 11 June 2014. www.eurordis.org/news/promotion-progressive-patient-access-bears-fruit
[24] European Medicines Agency. Pilot project on adaptive licensing. 19 March 2014

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		care providers, payers, and regulators to accept a greater level of uncertainty in the expectation of a drug's improved benefit and/or improved safety''.[25] For this model to be implemented as envisaged, healthcare technology assessment (HTA) bodies need to be willing to accept lower evidence standards: "adaptive licensing would require (...) to reduce the development misalignment between marketing and reimbursement decisions" and should "allow for early approval and coverage of a new compound (...) based on smaller initial clinical studies".[26] [27] To reduce such "misalignment" the EMA and HTA agencies are to provide confidential "scientific advice" to pharmaceutical companies in parallel, at an early stage of the development process. Although the EMA argues that the adaptive pathways approach uses regulatory processes foreseen in the existing legislation, the Agency is currently revising a series of existing guidelines for expedited approval schemes.[28] [29] In addition, it now proposes new schemes such as the Priority Medicines (PRIME), aimed at enhancing the involvement of regulators and HTAs bodies during drug development processes and speeding up market access – key elements of the adaptive pathways model.[30]	

[25] Eichler H-G et al. "Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval" *Clinical Pharmacology & Therapeutics* 2012; **91** (3): 426-437.
[26] Eichler H-G et al. "Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval" *Clinical Pharmacology & Therapeutics* 2012; **91** (3): 426-437.
[27] Eichler H-G et al. ''From Adaptive Licensing to Adaptive Pathways: Delivering a Flexible Life-Span Approach to Bring New Drugs to Patients''. *Clinical Pharmacology & Therapeutics* 2015; **97** (3)
[28] European Medicines Agency. "Guideline on the scientific application and the practical arrangements necessary to implement the procedure for accelerated assessment pursuant to article 14(9) of regulation (EC) No 726/2004" EMA/CHMP/697051/2014-Rev. 1. Public Consultation launched on 23 July 2015.
[29] European Medicines Agency. "Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004" EMA/CHMP/509951/2006,Rev. 1. Public Consultation launched on 23 July 2015.
[30] European Medicines Agency (2015). Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME). Draft. EMA/CHMP/55760/2015

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
29	General	**The EMA's PRIME scheme: an undue rush to market entry** The EMA's Reflection paper on PRIME says that this programme aims at ''strengthening support to medicines that have the potential to benefit patients who presently have no treatment options, or that may offer a major therapeutic advantage over existing treatments''.[31] Through PRIME, the EMA will provide ''early and enhanced scientific advice and regulatory support'' to pharmaceutical companies to facilitate data collection and enable faster assessment. The PRIME scheme is ''limited to products under development which are innovative and yet to be placed on the EU market''. The concept of ''innovative medicines'' has for long been captured by the pharmaceutical industry and is popular in discussions on adaptive pathways. According to the EMA's glossary, an innovative medicine is a ''medicine that contains an active substance or combination of active substances that has not been authorised before''.[32] It is important to emphasise however that from a therapeutic perspective, true drug innovation refers to therapies that bring a meaningful improvement over existing treatment with respect to outcomes that matter to patients. Under the PRIME scheme, eligibility will rely on how far the medicinal product is expected to address an unmet medical need. According to the EMA's Reflection paper, such justification could include a description of the product's observed and predicted [our italics] effects, its clinical relevance and added value and its impact	

[31] European Medicines Agency (2015). Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME). Draft. EMA/CHMP/55760/2015
[32] European Medicines Agency. Glossary. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/document_library/landing/glossary.jsp&mid=&startLetter=I

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		on medical practice. Medicinal products at early stages of the development process may be eligible (based on non-clinical and very early clinical data) in addition to those in clinical stages of development (e.g. exploratory studies). Preliminary clinical evidence should be based on relevant clinical outcomes but also on established surrogate endpoints. It is important to bear in mind that a low regulatory bar gets in the way of genuine therapeutic innovation, leading to the pursuit of marginal outcomes and a me-too mentality.[33] However, regulators are progressively lowering evidence requirements for approval of new medicines, by allowing smaller trials, surrogate endpoints and placebo comparisons.[34] Surrogate endpoints do not guarantee that a drug will affect health status in a clinically meaningful way for patients. Nonetheless, they are commonly used, especially in expedited approval schemes.[35] A study revealed that between 1995-2004 most cancer drugs were approved in Europe on the basis of surrogate endpoints such as ''tumour shrinkage [that] did not translate most of the time into significant survival benefit''.[36] Similarly, a recent US study revealed that the great majority of cancer drugs approved between 2008 and 2012 on the basis of surrogate endpoints (86%) had either unknown effects on overall survival or failed to show gains in survival. The authors concluded that most cancer drug approvals have not been shown to, or do not, improve clinically relevant endpoints.[37]	

[33] Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics - the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity. The John Conley lecture. *JAMA Otolaryngol Head Neck Surg* 2014;140:1225-36
[34] Naci H, Carter AW, Mossialos E. Why the drug development pipeloine is not deliverign better medicines. BMJ 2015; 351: h5542
[35] Light D, Lexchin J "Why do cancer drugs get such an easy ride?" *BMJ* 2015; 350: h2068 doi: 10.1136/bmj.h2068
[36] Apolone G, Joppi R, Bertele V, et al. Ten years of marketing approvals of anticancer drugs in Europe: regulatory policy and guidance documents need to find a balance between different pressures. Br J Cancer 2005;93:504-9.
[37] Kim C, Prasad V, 2015. Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: An analysis of 5 years of US Food and Drug Administration approvals. *JAMA Internal Medicine*.

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		A characteristic element of the adaptive pathways model that the EMA proposes to further promote under the umbrella of PRIME is the active joint involvement of regulators and HTA bodies in drug development. According to the EMA´s Reflection paper on PRIME, by providing scientific advice, the EMA and HTA bodies would guide companies on development plans from the very beginning, with the ultimate goal of enabling expedited approval and coverage. The EMA even proposes an early appointment of the CHMP Rapporteur to *''enable continuity in a life-cycle approach and support the development of important innovative medicines (…)''.* The Reflection paper continues *''the Rapporteur will support the development by directing applicants towards the EMA scientific advice on data requirements for future MAA as well as raising awareness on the use of early access tools where relevant (...).''* The provision of scientific advice by regulators to the regulated raises concerns about conflicts of interest and institutional capture. Such concerns are accentuated when the committee responsible for deciding on marketing authorisation/HTA decision is also giving advice through its involvement in the scientific working party. The lack of transparency associated with these interactions undermines regulatory accountability and the fee-for-service procedure de facto creates a financial dependence on the pharmaceutical industry. The potential bias of regulators involved in providing advice **and** deciding on marketing authorisation/reimbursement are genuine concerns. To incentivise the development of health technologies that genuinely respond to patients and society's needs, address health outcomes and improve public health,	

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		the regulatory environment must send a clear signal to the pharmaceutical and medical devices industries by setting the bar higher and demanding the delivery of relevant, comparative evidence of efficacy and safety. This can be generally achieved by publishing detailed joint guidance (by regulatory agencies and HTA bodies) on requirements for data packages that needed to be supplied, choices of comparators, and preferred trial designs. **The PRIME scheme, however, appears to be another move to entrench the provision of confidential, customised advice to pharmaceutical companies in the regulatory system to facilitate expedited approval and coverage of new, expensive medicines, which as evidence suggests will rarely bring therapeutic advance but often safety concerns.**	
29	General	**Conclusions** Regulatory flexibilities for early market access should be applied only in fully justified circumstances, and must ensure patient safety and an advance as compared to best available treatment. To promote innovation in the pharmaceutical sector, the regulatory environment must send a clear signal to the pharmaceutical industry by setting the bar higher – and not lower as suggested - and demanding the delivery of relevant, comparative evidence of efficacy and safety. For this purpose, the following recommendations should be considered: • Demand a robust evaluation of new drugs before marketing authorisation (introducing the demonstration of added therapeutic value); The requirement for demonstration of solid evidence about benefits and harms before a medicine is approved is of particular importance since it can be	

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		challenging to identify serious adverse drug reactions during the post-marketing phase. • Ensure that expedited approval mechanisms are used only in duly justified circumstances (e.g., when there is a true unmet medical need) and that (conditional) approval of medicines is based on clinical trial data that demonstrate an advance over existing treatment options for patients and clinically-relevant outcomes. • Allow for thorough marketing authorisation assessments by regulators; • Ensure rigorous and proactive pharmacovigilance requirements, including the application of dissuasive sanctions if post-marketing requirements are not complied with. • Reinforce the independence of drug regulatory agencies from corporate influence and funding. • When scientific advice is given, in exceptional circumstances, as a minimum standard: - It should not be provided in exchange for direct fees from individual pharmaceutical companies. Instead, it could be funded through general corporate taxation. - Patient and consumer advocates, and expert clinicians with direct or indirect conflicts of interest should not be involved in scientific assessment procedures.	

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		- A separation of roles should exist between regulators and stakeholders involved in the provision of advice and subsequent discussions on marketing authorization or HTA decisions. - Regulatory procedures shall take into account a sufficient representation of the range of views that may exist between patient advocacy groups, between consumer groups, and between patients with different conditions or different severity of disease. - Public access to documents related to scientific advice shall be ensured. EPARs and national regulatory documents should include an additional section giving comprehensive information about the scientific advice given at each stage of the development process.	
30	General	The International Alliance of Patients' Organizations (IAPO) welcomes this reflection paper and its aim to achieve an objective that, if properly fulfilled, could significantly improve patients' lives. We agree that "timely access to new beneficial and safe medicines" is crucial for patients to effectively deal with "unmet medical needs", as well as supporting progress toward truly towards patient-centred healthcare and universal health coverage. From our experience with our members (250 patients' organizations globally, across disease areas and countries), through regional and global collaboration for example with Innovative Medicines Initiative (IMI) Get Real and PROTECT projects, as well as the EMA and WHO patient involvement initiatives, we know that access is at the heart of patients' concerns. We encourage further careful consideration of potential implications of the process to accelerate access to new medicines. The process is complex, and needs early and genuine collaboration between all stakeholders to try and overcome a number	

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		of challenges and barriers, which should be explicitly identified and understood in order that "patient focused innovation" is credibly pursued and achieved.	
30	38-39	Regarding safety implications of new medicines and accelerated access. In these lines, and in places throughout this section, particular emphasis is placed upon two key issues: 1) To accelerate patient access 2) New beneficial medicines. Particular attention is here paid to new medicines, and we want to highlight that some patients can be reluctant right away to adhere to a new treatment if safety concerns are not communicated and addressed. While safety concerns regarding new medicines are satisfactorily acknowledged and discussed in this paper we feel there is another important aspect regarding safety which should be equally well highlighted. This aspect regards the risks that are involved in "the process of accelerating access". There is clearly an overlap between the risks/implications of launching a new medication and accelerating patients' access to it. However, they are not the same.	In developing the PRIME scheme proposal further, the EMA could improve this section by highlighting and describing the major challenges/barriers of "accelerated access" and how these could be addressed.
30	86-88	Regarding Effectiveness. We were surprised that in Section 3, entitled "Proposed Eligibility Criteria and Procedure", the word effectiveness is not mentioned. According to PRIME, alongside safety, the key criterion to consider in order to determine whether or not a product is eligible for the accelerated procedure is a demonstrated potential to address to a significant extent an unmet medical need. Nevertheless, although a definition of unmet medical need is provided, we are concerned that the document is not as clear as it could be to help people understand what it means (and includes/excludes). While emphasis is certainly placed upon verifying a new medicine's efficacy, an equivalent explanation is not provided as to how its relative effectiveness will be evaluated – while efficacy is at the core of quality and safety of medicines, for patients who are desperate for new treatments, effectiveness in the real world is at least as significant.	**C**oncepts such as unmet medical need, therapeutic advantage, improvement of efficacy, can be further explained in the document to strengthen the link between new medicine access, and access to medicines that work. We consider that relative effectiveness could be taken into consideration and included in the eligibility criteria.

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		As is stated in lines 97-98, data should support the claim that the product can bring a *"major therapeutic advantage to patients, through a meaningful improvement of efficacy"*.	
30	113-116	Regarding Information sharing. The information that is intended to be published and circulated in the monthly report is useful. In addition to that, we think it will be important to produce an overview of how the product has or may impact on patient-related outcomes.	
30	246-251	Regarding outcomes. A final comment regards the process aimed at testing the "clinical benefit" of the new medicine. In the paper it is stated that at the beginning, the evaluation of "the strength of evidence" will be based on clinical response and safety data in patients. Thereafter, in the second phase, "preliminary clinical evidence should indicate substantial improvement in patients". The concept of "improvement" should be better substantiated by shedding light on the outcomes that will be taken into account. In general, while it is fully acknowledged that *"it will be difficult to justify eligibility to the PRIME scheme on the safety aspects alone during the development"*, we consider that it is not sufficiently clarified what criteria will primarily be looked at in order to decide whether the product works well or not.	While we accept that effectiveness data may not be available particularly in the early stages, there are emerging new pathways and research approaches that recognise and seek to take account of effectiveness earlier in new medicine development, so this could be of particular relevance to the PRIME scheme, and therefore reflected in the document. An option is to consider whether proxies for relative effectiveness will be taken into consideration in the process of assessment.
31	General	The Biotechnology Industry Organization (BIO) thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the "*Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME)"* (EMA/CHMP/57760/2015). BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in	

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		the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products. We support the EMA efforts to optimize the development and accelerated assessment of medicines which treat illness of major public health interest, based upon enhanced interaction and early dialogue with medicine developers, with the proposed launch of PRIME in the first quarter of 2016. Flexibility in the scientific advice (SA) process is necessary. The SA process should be tailored for PRIME and sufficiently flexible to allow for timely, informal feedback to sponsors. BIO would welcome the opportunity to provide further ideas on the operational enhancements to better tailor the SA process for PRIME. It is also recommended that SA would potentially cover all aspects of the development, non-clinical, clinical and chemistry, manufacturing and control (CMC). We also applaud the goal of PRIME to provide enhanced scientific and regulatory support to companies developing medicines that may offer new therapeutic options to patients who currently have no treatment options, or a major therapeutic advantage over existing treatments. BIO notes that PRIME reinforces early dialogue and builds on regulatory processes already in place within the European Union (EU) legal framework, including SA to optimize the generation of robust data and the accelerated assessment procedure to improve timely access for patients to priority medicines. We are pleased that the objectives of PRIME are aligned with the proposed EU Medicines Agencies Network Strategy to 2020 in seeking to support patient-focused innovation and timely patient access to new beneficial and safe medicines for patients. BIO believes that a top priority is the need to strengthened scientific and regulatory cooperation at a global level, supporting the argument of permitting all	

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		applicants to apply for PRIME designation earlier in product's development, an approach more aligned with U.S. FDA Breakthrough Designation. The goal should be to develop an optimal global development program for these highly innovative and differentiated medicines and converge scientific thinking among Health Authorities in order to allow achievement of this goal. Eligibility for PRIME should be extended to all indications expected to address an unmet medical need. The principles of PRIME should allow for applicants to engage at an early stage of development for new products or additional uses for existing products where the potential to benefit public health and address an unmet need can be demonstrated. Therefore, PRIME should also apply to existing products in development for new indications or part of a combination product. Allowing all applicants to apply for PRIME after proof of principle will ensure that the applicant has the chance to engage relevant committees as soon as relevant, including early engagement on CMC issues and early agreement on CMC plans, which can be a critical barrier to expedited review and availability of new medicines. This principle is particularly important when considered in the context of products being developed via Medicines Adaptive Pathways to Patients (MAPPs) or Adaptive Pathways. These products may already be on the market for a small population. However, enhanced regulatory support could be crucial to the expansion of the label for indications to address an unmet need in larger populations. For products which remain eligible for PRIME for later indications / label expansion, enhanced support should be available after the initial approval. The PRIME scheme should also encourage innovation related to expanding of	

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		indications (i.e., Type II variations including for re-purposing of a medicine) in areas of unmet medical need. Currently, approval of new/extended indications usually takes >150 days (the standard being an initial 90 day assessment, with a 60 day assessment for Responses to RSI), despite such filings normally containing far less CMC and nonclinical information than an initial Marketing Authorisation Application (MAA) dossier. It is important that eligibility be based upon unmet medical need, rather than solely where the product is in its lifecycle. Should not all applicants be allowed to submit their PRIME application at proof of principle, PRIME may unintentionally evade its purpose by adding an extra step between the availability of early clinical trial data and the start of pivotal clinical studies. Indeed, if some applicants could only apply for PRIME after proof of concept, they would need to prepare, submit and await approval of the PRIME eligibility request, appointment of the Rapporteur and setting-up of the PRIME kick-off meeting prior to submitting their application for SA. This may be in the midst of their clinical trials when delays may impact patients. A key benefit of the scheme is early assignment of the Rapporteur. Timeliness and limited administrative burden of procedures upon the applicant should be maintained. We would encourage the EMA to find ways to adapt the existing scientific advice processes and information requirements to ensure the interactions are conducted in a timely, expedited fashion and the benefits of the scheme are not offset by the administrative burden of preparation and conduct of formal scientific advice meetings. Similar adaptations should also be considered for interactions with other committees within EMA (e.g. PDCO, COMP) for PRIME designated products. Consideration should be given to simplify the application procedure for PRIME for	

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		products already granted Orphan Drug Designation, as these products would have already been assessed by the EMA as providing a significant therapeutic benefit in an area of unmet medical need. We believe that a substantial move towards early patient access to innovative medicines in Europe will not be possible without HTA bodies' early involvement in the discussions. It is important to ensure that adequate support is given to those applicants who chose to engage in joint EMA/HTA scientific advice. It will likewise be important that national HTA bodies assign resources to cooperate in the above schemes and fully contribute to these discussions. Although in many cases the involvement of HTA bodies could make a difference to actual subsequent access discussion, we recommend that it should remain applicant's prerogative to decide whether or not to include HTA bodies as parts of the scheme and at which point in time. Coordination with FDA and other Health Authorities is strongly suggested. We encourage the EMA to consider PRIME in the context of global development as major divergences in approach between the regions could undermine the key objective of PRIME of timely access to medicines in Europe. The global nature of product development should be recognized and therefore the ability to allow for FDA-EMA dialogue, if desired by the applicant, ought to be accommodated within the scheme. Based upon the current global business trends, there should likely be acknowledgement that development of a given product may be transferred between companies. If product ownership is transferred through merger/acquisition, then participation in PRIME should transfer to the new owner.	
31	7	Given the potential positive impact for PRIME, we support expediency in	

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		implementing the final policy and remain readily available should further input be useful.	
31	53-56	As described, designating an MAA to an accelerated timetable occurs just prior to filing. EMA intends for the PRIME scheme to 'identify products fulfilling the criteria for accelerated review earlier'. This is most welcome since early preparations for accelerated review help ensure that timelines for accelerated assessment can be maintained, and allow for early agreement on timelines for provision of data in line with proposals in the EMA revised guideline on accelerated assessment. Many companies must coordinate submissions globally including the timing for Certificate of Pharmaceutical Product (CPP) dependent countries. Companies must also plan for use of their resources (*e.g.*, manufacturing preparations, IT dossier support, and regulatory responses to questions) in advance and the earlier the review procedure timelines are known, the more efficient the planning process becomes.	
31	68-73	As mentioned under 'General Comments', data demonstrate that early advice from regulatory agencies increases the likelihood of a positive result for developing a new medicine. Therefore, we believe that the PRIME scheme should be available to all applicants at the time of proof of principle. There are several other important incentives to motivate SME product development such as a reduction of regulatory fees (Line 128) and availability of dedicated EMA expertise. EMA is offering early advice at reduced fees to SMEs and academia at the clinical proof of principle stage. Others must wait until the clinical proof of concept stage and pay full fees. Mechanisms should be anticipated to deal with this increased work load at the early stage of development without short changing those who	N/A

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		must pay at a later stage of development.	
31	83-85	A significant new indication for an authorized product requiring development of an entire new clinical data package should also be possible to qualify for PRIME, if meeting the criteria for unmet medical need as detailed in the draft guideline.	Proposed to change from "~~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.~~" to "The PRIME scheme is applicable to products under development, but also to authorised products being developed for a new indication, which are innovative, meet the criteria for unmet medical need, and where there is an intention to apply for an initial marketing authorisation or line extension application through the centralised procedure."
31	93-99	EMA describes the eligibility requirements for PRIME as a product "should demonstrate the potential to address to a significant extent the unmet medical need for maintaining and improving the health of the Community; potential to bring a major therapeutic advantage to patients, through a meaningful improvement of efficacy…". Though, there may be cases where it would be possible for a product to be eligible for PRIME through 'meaningful improvement of safety'. There could be a product that is expected to have similar efficacy to one already on the market, but with a significantly improved safety profile. Medicines providing major improvements in	• Alignment and reference with the interpretation of major therapeutic advantage as included in the revised guideline on conditional marketing authorisation. • As experience is gained over time, consider expanding eligibility criteria to include situations of meaningful improvement of patient safety and in certain situations, major

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		patient care should also be eligible in certain cases.	improvement in patient care.
31	113-118	EMA describes the types of information about PRIME applicant requests that it will list in its monthly reports.	EMA should simply make available summary PRIME metrics such as total number of requests, numbers of requests granted/denied and percentage within different general therapeutic areas.
31	126-127		Delete sentence: ~~*In early stages of development, following demonstrated proof of principle, focusing on SMEs and 126 applicants from the academic sector:*~~
31	128-130	EMA notes the need to involve multiple stakeholders including HTA bodies. We support that iterative steps on scientific advice should allow systematic involvement of HTA bodies building upon the current parallel scientific advice established by EMA. This will be key for the ultimate success of the scheme and Member States should ensure HTA bodies will have the resources to contribute to the discussion. Also in terms of stakeholder engagement, as EMA gains experience under PRIME, EMA, FDA and PMDA should develop regular mechanisms for an exchange on scientific discussions and experiences. This will be paramount for global development considerations.	
31	150-157	The major focus of the PRIME support appears to be on clinical development.	It will be necessary for chemistry, manufacturing and control (CMC) and quality aspects to be considered within PRIME along with the clinical development plans, to ensure the CMC development can progress at the same pace as clinical.
31	162-165	EMA describes its encouraging expectation for 'intensive guidance…to lead to better informed development plans…aiming overall to ensure patients access to	We suggest that EMA note the PRIME

Stake-holder no.	General / Line no.	Stakeholder comments	Proposed changes by stakeholder, if any
		these promising medicines in the shortest possible timeframe'. EMA does not mention the types of data that it will collect internally to measure how the program is functioning to realize this goal. BIO suggests that there should be a thorough review and possible adjustments to the PRIME scheme after a period of 5 years of experience. We hope that through its PRIME experience, EMA will discover novel approaches to SA, engagement of stakeholders and regulatory procedures.	experiential data that it will collect, the metrics that will be important, the frequency by which it will analyse the data, and the stakeholder input needed once the program becomes operational.
31	178-183	EMA notes that "PRIME support may be withdrawn if emerging data were to show that the criteria are no longer met." Further, appreciating that the eligibility status of a product may change over time, if EMA considers that an initial PRIME designation no longer applies, there should be a process for the applicant to discuss this with EMA before a final decision is taken. The applicant may have generated new data and/or information since it submitted its initial PRIME application, which could affect EMA's final decision. In addition, some clarification would be welcomed as to how regulatory support would be continued in instances where PRIME designation is withdrawn. For example, will the appointed CHMP Rapporteur still remain with the product through the Marketing Authorisation Application?	A discussion process should be envisaged with the applicant prior to a final decision on withdrawal of a PRIME designation.
31	198	In Annex 1, EMA describes the content to be submitted as a justification by the applicant for inclusion within PRIME. In order to streamline the application process and to reduce unnecessary administrative burden, it should be possible for applicants to refer to existing documents (e.g., Investigator's Brochure, Orphan drug application). The future PRIME application template should mirror as much as possible the structure of these and other existing documents.	

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31	287	A plan for CMC development should be included	Additional text in italics: A new second last bullet to be added: *A plan for CMC development should also be included focusing on critical parameters.*
31	299	Having submitted a PRIME request, a company will receive a response 40 days following the start of the procedure (i.e., SAWP 1 meeting). Efforts should be made to expedite the process and minimize any delays. More details of the procedure for evaluating PRIME eligibility requests would also be welcomed. For example, will the preliminary reports shared with CHMP be made available to sponsors as part of the procedure or will sponsors only receive the final CHMP decision? In addition, please consider building in opportunities for applicants to provide responses to questions for clarification purposes during the review of PRIME eligibility requests. This could help avoid negative outcomes for applicants, as appeals are not foreseen with respect to PRIME eligibility requests and a new request should only be made with new evidence or data.	
32	General	Cell Therapy Catapult welcomes the opportunity to comment on this very interesting and innovative scheme. We believe that PRIME will be of much interest to ATMP developers, many of whom are SMEs or academia-based. The possibility to provide potentially life-changing therapies developed by this community, through the PRIME scheme, to patients at the earliest opportunity is highly appreciated. We expect that the full engagement of all stakeholders will be fundamental to achieving this and are therefore encouraged by, and support, the involvement of HTA bodies and patient groups. Similar developmental pathways are available through the US FDA (e.g. Fast Track/Breakthrough Designation) and	

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		the PRIME scheme presents an opportunity, where appropriate, to coordinate accelerated approval of a product in both the EU and US. We believe this initiative would be strengthened by early FDA-EMA interaction to ensure that similar data packages are required for each territory. In this respect, we would be supportive of interactions between EMA and FDA to support this. We urge the EMA to ensure that procedural requirements are designed to be uncomplicated and allow maximum flexibility to ensure that requirements should not be deterrent to such groups to seek early advice under the PRIME scheme. We strongly encourage the EMA to produce detailed guidance for companies considering applying to the PRIME scheme that makes very clear what the eligibility criteria are, explains the terminology and provides guidance on the appropriate application procedures and the role of the SME office and Innovation Task Force in these various schemes. The strength of the scheme is the early involvement of the HTA bodies and patient bodies. We feel it is crucial that the HTA are adequately supported at an early stage in the implementation of this process to ensure their engagement. Our other general comments are as follows: Is PRIME going to operate on a pilot scale initially, similar to Adaptive Pathways, or is there capacity to support all anticipated applications?	

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		Extending the PRIME scheme to SME and academic applicants at an earlier stage of development (prior to exploratory clinical studies) is welcomed. These applicants will benefit from targeted advice at an early stage. It is however somewhat unclear what level of data is required from these applicants at this early stage to demonstrate 'proof of principle'. For example, in lines 260–291 it is unclear whether there must be at least some clinical data available or whether eligibility to the scheme can be granted on the basis of non-clinical data alone. Further clarity on the need for early clinical data in addition to non-clinical data for SMEs and academics would be therefore welcomed. This is also important because of the need for Scientific Advice to adequately support both non-clinical and clinical study planning. Overall, given the different requirements for applicants at the proof of principle stage compared with those who have achieved clinical proof of concept, it is suggested that the earlier stage might be badged as 'pre-PRIME' with specific guidance and procedures. Clarification is required as to whether Scientific Advice is provided free or at the SME rate to academic applicants? We believe this is an important element of the scheme that should be affordable academic applicants. Many products which may qualify for PRIME may also be eligible for entry to the Adaptive Pathway scheme. It is unclear from the consultation paper who these schemes will interact, if at all, and when developers should choose one scheme over the other. On a similar vein many PRIME-eligible products may be orphan products and it is unclear the role of the COMP in the PRIME scheme.	

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		Clarification is required as to whether PRIME status provides automatic eligibility for Accelerated Assessment unless the PRIME status is rescinded during development, and at which stage this eligibility is confirmed (e.g. is it at the time of a MAA pre-submission meeting?). Is it possible to switch between the PRIME and Adaptive Pathways routes should the need for that become evident during either procedure. It is considered helpful that the guidance should enable potential applicants to understand which scheme is best for their product. Given that eligibility for accelerated assessment may be granted on early nonclinical and clinical data. It is considered important that the procedure should provide support to applicants in addressing any Quality related issues. Annex 2 of the draft reflection paper suggests that the initial review of a request for eligibility to the PRIME scheme is done through the Scientific Advice procedure. We request advice is given on the timeframes for procedures e.g. between submission of a request and start of Scientific Advice, and is a second submission required prior to start of Scientific Advice? Clarification is requested on the eligibility of orphan medicinal products (presumably not yet designated) for PRIME. If they are can information be provided on how the data requirements compare to non-orphan medicinal products? If addition can clarity be provided, appropriate, whether COMP will be involved in the PRIME procedure.	

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		It is noted that some potential applicants may have generated clinical data through schemes which enable the use of unlicensed medicinal products, e.g. Hospitals Exemption, Compassionate Use. Is it possible for data generated through such product use to be considered as early clinical data when considering a product's eligibility for the scheme? There are a number of terms e.g. proof of concept, proof of principle, proof of mechanism, early data which we feel would benefit from greater explanation. A glossary of definitions may be helpful.	
33	General	**EAHP response to EMA reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME)** The European Association of Hospital Pharmacists (EAHP) has read and considered the above referenced reflection paper and makes the below comments in response to the consultation. **General support for the direction of the initiative with 3 risks to be acknowledged** At a broad level, EAHP supports the consideration of the Agency in terms of seeking to create a process of prioritization for new medicines that clearly and reliably promise the potential of addressing major public health needs. However any such process requires careful oversight and monitoring for potential unintended consequences some of which occur to EAHP as including the risks of:	

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		1) regulatory capture and conflicted interest within the agency; **2)** eligibility criteria operating ineffectively; and, **3)** patient safety needs being compromised; These risks can be militated against through first of all having awareness of their presence, and secondly building into the new processes measures targeted at guarding against these risks.	
33	General	**1) The risk of regulatory capture** Regulatory capture - the process by which regulatory agencies come to be dominated by the industries they are charged with regulating – is of course a risk EAHP imagine the EMA is alive to at all times. However, it occurs that such risk could be particularly present within the PRIME proposal whereby staff and actors on behalf of the Agency become more closely involved in facilitation of assessment procedures for industry interests. EAHP would therefore wish to see greater acknowledgement of this potential within the proposal paper, including but not limited to: • further explanation of how rapporteur and co-ordinater independence will be preserved (E.g. via codes of ethics or other guidance material); • greater understanding of the intended makeup of “oversight groups”, with the background of members of high importance in terms of ensuring integrity and independence; • explanation of how the implementation of this policy overall will be	

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		monitored and scrutinised on an ongoing basis; • the standards of public transparency by which this policy process will be implemented to – what will be published, and when? EAHP advocate that appropriately qualified healthcare professionals and patients be involved in the processes, for the expertise and perspective they can bring to both oversight and determinations, but also as a form of independent third party in respect of the agency and industry interaction. It was with concern that EAHP read at line 129-130 for example, that healthcare professionals are not explicitly described as a stakeholder for involvement within Scientific Advice.	
33	General	**2) The risk of eligibility criteria operating ineffectively** In many ways the crux of the success or otherwise of the PRIME proposal rests upon the soundness of the operating definition by which potential new medicines are either included or excluded from the scheme. By exclusion, a potential new medicine can become, de facto, and by implication, “non-priority”. Therefore it is imperative that judgments for inclusion or exclusion are made according robust criteria. EAHP therefore suggest the following amendments to strengthen the criteria provided in Annex 1 of the reflection paper:	
33	203-218		**Unmet medical need** • In general, the justification ~~may be~~ **is** more convincing if based as much as possible on epidemiological data about the disease (e.g., life expectancy, symptoms and duration,

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			health- related quality of life). The claims ~~could~~ **should** be substantiated e.g., from published literature or healthcare databases. • Where relevant, the unmet medical need ~~could~~ **should** 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~~ **should** be included. The effect of available treatments ~~could~~ **should** 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~~ **should** include a

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			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.
33	General	**3) The risk of patient safety needs being compromised** Somewhat related to the above described risks of regulatory capture, potential conflict of interest within the agency, and the robustness of the eligibility criteria, a general pervading risk may be considered within the PRIME proposal of patient safety being compromised from any acceleration of authorisation procedures. The mechanisms for independent oversight and transparency of processes are therefore of high importance. Further elaboration on how this will be achieved would have been welcome in the paper. EAHP trust the above points of feedback will be duly reflected upon as part of the analysis of consultation responses.	
34	General	L'Agence européenne du médicament a publié un document de réflexion et lancé une consultation publique le 26 octobre 2015 sur le futur régime « PRIME » destiné à optimiser le développement des médicaments prioritaires et faciliter l'accès des patients à ces produits. Pour les autorités françaises, ce projet PRIME est l'exemple typique de l'adaptation de mesures déjà existantes au niveau européen permettant de donner une plus grande efficacité au système d'autorisation et doit donc être soutenu. Cependant, PRIME s'inscrivant dans le cadre de la réglementation pharmaceutique actuelle, les mesures/incitations proposées s'avèrent limitées. Les autorités françaises estiment	

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		qu'il serait intéressant de lancer le projet PRIME et d'envisager d'ouvrir les critères d'éligibilité à d'autres produits pour lesquels la recherche est insuffisante/déficiente. Il conviendra également de compléter ce dispositif PRIME par de nouvelles mesures incitatives afin de le rendre encore plus attractif, si besoin en faisant évoluer la réglementation européenne.	
35	General	• IPFA greatly appreciates the EMA initiative of further reinforcing regulatory and scientific support to foster development of new medicines addressing major public health needs. The integration of the processes proposed by the new guidance on accelerated assessment and conditional marketing authorisation would help mutual understanding between health authorities and industry, and therefore efficient acceptance of product developments. When combining the regulatory scientific advices from all CHMPs committees and with the HTA's advices prior to and the MAA assessment, EMA initiative is aiming at prevent, after regulatory approval, HTAs decisions that today can lead to delays in patient access to innovative medicines due to reimbursement and pricing requirements involving clinical data. • However, in order to reach this aim, HTAs have to be definitively involved at the very beginning, and as a full partner, not merely "with the potential to involve multiple stakeholders (e.g. Health Technology Assessment (HTA) bodies, lines 128-129". It would only be when HTAs would be decision makers as well as CHMPs Committees at a very early stage that a real fostering of patients access to priority medicines would occur. • EMA should explain how this new PRIME scheme relates to previous initiatives	

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		as the parallel EMA/HTA advice, between CHMP's committees and HTAs, as well as to the SEED initiative. Has this new scheme been designed from the results of these two pilot initiatives and planned in order to implement such early collaboration? IPFA would highly recommend this is the case.	
35	68-69	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. Please explain if the Scheme is reserved for SMS or would apply to any company, implying that it would comply with the other conditions (lines 59-61: *availability of adequate non-clinical and exploratory clinical data to justify a potential major public health interest prior to the initiation of confirmatory 60 clinical studies at proof of concept stage*; lines 86-87: *major public health interest and in particular from the viewpoint of therapeutic innovation (i.e. those which fulfil the accelerated assessment criteria);* and lines93-94: *potential to address to a significant extent the unmet medical need)*	
35	82	(On link with previous comment) All designated Orphan drugs and medicinal product for rare diseases in development as long as presenting potential access to therapies for unmet medical needs should be included in the scheme eligibility criteria. IPFA members' products are dedicated to patients with rare diseases and not each of IPFA Members is an SME. Therefore, there should be no discrimination fostering product development.	
35	128-129	HTAs have to be definitively involved at the very beginning, and as a full partner	"Scientific advice (with fee reductions for SMEs) on the overall development plan and at major development milestones, ~~with the~~

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			~~potential to involve multiple stakeholders (e.g.~~ **in collaboration with** Health Technology Assessment (HTA) bodies **and** patients~~)~~.
35	131-138	HTAs should be all the way involved systematically, not when thought of being useful	**(Lines 132)** Early appointment of CHMP/CAT Rapporteur (in line with current process, objective criteria and methodologies) **and HTAs.** **(Lines 134)** An initial kick-off meeting with multidisciplinary participation from the EU network (SAWP and relevant committees members and experts), including the CHMP/CAT Rapporteur **and the HTAs**, to understand the proposed development programme, give preliminary guidance on requirements for MAA, and to develop of schedule for giving regulatory and scientific advice. **(Lines 138)** 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.~~ **in collaboration with** Health Technology Assessment (HTA) bodies **and**

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			patients~~)~~.
35	145-148	here again, HTAs should be all the way involved systematically, not when thought of being useful	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.~~ **using** parallel EMA/HTA advice, **or other initiatives (e.g.** adaptive pathways**)** to facilitate timely access to patients.
36	General	The coordination and collaboration of the National Innovation Offices is essential for the identification of the products that can benefit from this PRIME scheme and therefore, the EU Innovation Network should be mentioned within the reflection paper.	