November 15, 2017

Submission of comments on Concept Paper on predictive biomarker-based assay development in the context of drug development and lifecycle (EMA/CHMP/800914/2016)

Comments from:

Name of organisation or individual
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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The Personalized Medicine Coalition (PMC) represents innovators, scientists, patients, providers, and payers, to promote the understanding and adoption of personalized medicine concepts, services, and products for the benefit of patients and the health care system. PMC welcomes and supports the EMA's intention to develop a guideline to replace the 2010 Reflection Paper on co-development of pharmacogenomic biomarkers and assays in the context of drug development (EMA/CHMP/641298/2008). The role of companion diagnostics (CDx) and their co-development with therapeutics have become increasingly relevant for the development of both therapies and *in vitro* diagnostics since the Reflection Paper was published, and there is a need for comprehensive, up-to-date guidance on the subject. Many of PMC's members will present their own responses to the EMA and will actively advocate for those positions. PMC's comments are designed to provide feedback so that the general concept of personalized medicine can advance and are not intended to impact adversely the ability of individual PMC members, alone or in combination to pursue separate comments with respect to the proposed guideline or related issues.	

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	In addition to the specific line revisions below, PMC recommends inclusion of the following important topics in the planned guideline: • An explanation of how competent authorities will collaborate to facilitate co-development of a medicinal product and a CDx and interact with sponsors on medicinal product/CDx co-development programs; • A description of circumstances under which contrived samples may replace sponsor-obtained specimens of a particular marker in analytical validation studies; and • An allowance for diagnostic manufacturers to provide a CDx to laboratories for setup and verification after finalizing design and completing clinical trials but prior to CE marking, so as to help ensure timely patient access to a therapeutic upon approval and/or authorization with an associated test. Finally, the U.S. FDA is also in the process of developing guidance on the same topic as this planned EMA guideline (Principles for Codevelopment of an *In Vitro* Companion Diagnostic Device with a Therapeutic Product	

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	were issued by FDA as draft guidance on 15 July 2016). PMC recognizes that different legislations apply to both *in vitro* diagnostic devices and medicinal products in the EU and USA but, given the increasingly global nature of product development, PMC urges the EMA, wherever possible, to ensure convergence of the planned EU guidance with that of the FDA.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 28-44		Comment: In the problem statement, although Lines 38-39 commendably note that it would be helpful to provide guidance on using a close-knit development program linking drug and IVD development, it is not clear whether the guidance will address the issue of whether the CDx or predictive BM assay will need to be approved simultaneously with the medicinal product to be marketed. Lines 79-81, which indicate that the impact of non-harmonized life cycles of medicinal products and CDx will be considered in the guidance, suggest that there may be circumstances under which such simultaneous approval may not be necessary. Proposed change: Clarify whether simultaneous approval of the medicinal product and the CDx will be required for marketing, and if not required, the circumstances under which subsequent approval of one or the other may occur.	
Lines 33-35		Comment: The concept paper states that "if it is *recommended* in the labelling that a medicinal product *should be* used in conjunction with a predictive BM, any *commercial assay* used for this purpose will be considered a CDx and will require an appropriate conformity certificate (CE mark)." It is important to define *commercial assay* and not to conflate companion diagnostics, which are required for the use of a therapeutic, with complementary diagnostics, which may	

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		provide helpful information in connection with a therapy but is not required for its use. A CDx is a device which is *essential* to the safe and effective use of a corresponding therapy. A complimentary diagnostic may be *recommended* to be used in conjunction with a drug but it is not describing a CDx, and it should not be regulated as such. The predictive BM should only be regulated as a CDx if the drug labelling *requires* that the drug *must only be* used in conjunction with a predictive BM. Proposed changes: Define "commercial assay", "companion Dx", and "complementary Dx" in the glossary. Revise lines 33-35 to read, only if it is "required" in the labelling that a medicinal product must only be used in conjunction with a predictive BM, any commercial assay used for this purpose will be considered a CDx and will require an appropriate conformity certificate (CE mark).	
Line 39		Comment: This line refers to the use of clinical trials to generate evidence required to support validation of the diagnostic. However, methods other than clinical trials may produce valid scientific evidence for purposes of validation of the diagnostic, and should be considered. Proposed change: Revise Line 39 to read, "…the two, and use of clinical trials *or other valid scientific evidence* to support	

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Lines 50-60 Line 64		validation of the diagnostic." Comment: We commend EMA for acknowledging that a CE-marked IVD may not be available to measure potentially predictive BMs during drug development, as this is often the case with novel BMs. While we agree that the assay used in clinical development may itself be co-developed as an eventual CDx, that may not always be the case, and the concept paper does not clearly address whether or under what circumstances an investigational assay used in clinical development would need to obtain a CE mark. Proposed change: Clarify that an assay intended for and labelled as "investigational use only", "for performance evaluation only", or "research use only" should be exempt from CE marking, but that to provide reasonable assurance that the assay has the necessary performance characteristics for the intended use. Comment: The concept paper indicates that when a predictive BM test is recommended for the safe and effective use of an approved drug, the continued evaluation of benefit and risk post-approval will depend in part on the availability of a suitably validated and quality assured assay, "whether CE-marked or 'in-house'." We do not believe it is necessary or appropriate to describe suitably validated and quality assured assays as only falling into the categories of "CE marked" or	

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Lines 84-86		"in-house"; there may be suitably validated and quality assured assays that fall into neither category. Proposed change: Delete "whether CE-marked or 'in-house'". If the term "in-house" is used anywhere in the guidance, it should be very clearly defined in the glossary. Comment: Several terms that will need to be defined are not referenced in the examples given for the glossary. Proposed change: Add "commercial assay", "in-house", "bridging studies", "pivotal trial", and "early explorative study" to the glossary of defined terms. If the concept of a "complementary diagnostic" is addressed in further development of the guidance, that term should be defined in the glossary as well.	