07 November 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
ACRO (Association of Clinical Research Organizations)

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).

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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 Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 130,000 employees engaged in research activities around the world (including 57,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually. ACRO 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 medicinal products have become increasingly important	

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	aspects of both medicinal product and *in vitro* diagnostic development since the Reflection Paper was published, and there is a need for comprehensive, up-to-date guidance on the subject. In addition to the specific comments below, ACRO recommends that guidance on the following important topics should also be included in the planned guideline. Most importantly, in order to ensure that administrative regulatory procedures do not cause undue delay to drug product or assay development, ACRO recommends that the guideline should explain how competent authorities will collaborate to facilitate co-development of a medicinal product and a companion diagnostic, and the opportunities for sponsors to interact with regulators to seek guidance on a medicinal product/CDx co-development programme. Just as Regulation (EU) No. 536/2014 facilitates investigational medicinal product (IMP) clinical trials in multiple member states by establishing a coordinated assessment procedure, Regulation (EU) No. 2017/746 establishes a coordinated assessment procedure for applications for *in vitro diagnostic device* performance studies. However, as a result of the different legislative bases, no link is established between the assessment	

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	and authorisation of clinical trials and performance studies. In the case of a late stage pre-authorisation study of both an IMP and a CDx, the trial will require authorisation under both regulations. The experience of ACRO member companies is that EU member states vary considerably in their ability to coordinate the assessment and authorisation of such studies under current IMP and *in vitro* diagnostic device legislation, frequently resulting in administrative delays in some member states. ACRO therefore recommends strongly that the planned guideline should address arrangements for the coordination between competent authorities responsible for medicinal products and *in vitro* diagnostic devices of assessment of applications and subsequent substantial modifications for a single trial utilising an IMP and a CDx, including the possibility for cross-referencing between the two required applications in order to avoid dossier duplication. Additional issues that ACRO recommends be addressed in the planned guideline are as follows: • In analytical validation studies, there may be cases where multiple markers will be detected/measured by the CDx, and analytical validation of each reported marker may be	

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	required. However, it may not always be possible for a sponsor to obtain specimens containing a particular marker, and so ACRO recommends that the guideline should make clear that validation studies with contrived samples will be permitted under such circumstances. • In some clinical trials of a medicinal product, test results from an investigational *in vitro* diagnostic used in the trial may be generated only for exploratory analyses and not to direct treatment of the trial subjects (which is achieved by other means). In such cases, the *in vitro* diagnostic does not meet the definition of a CDx and therefore such trials should not require approval under the Regulation. ACRO recommends that the planned guideline should include a clear statement to this effect. • Pre-screening of patients during clinical development (especially common in oncology) may result in a biased clinical trial population that does not represent the population that would be selected by the CDx in real-world testing. ACRO therefore recommends that the guideline should specifically include guidance on pre-screening and the avoidance of bias.	

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	• In the post-approval phase, a laboratory will often need time to set up and verify a new CDx before it can be used for routine clinical testing. This could result in significant delay before patients benefit from a CDx that has recently been CE-marked. Such a delay could mean that patients are unable to receive the associated medicinal product during this period of time, even if both products receive contemporaneous approval. To ensure immediate patient access to the medicinal product upon approval, ACRO recommends that the guideline should allow for CDx manufacturers to provide the CDx to laboratories for setup and verification (only), after its design has been finalized and clinical trials have been completed but prior to its CE marking and/or authorisation of the associated medicinal product. Additionally, ACRO notes that the 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 were issued by FDA as draft guidance on 15 July 2016). ACRO recognises that different legislations apply to both *in vitro* diagnostic	

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	devices and medicinal products in the EU and USA but, given the increasingly global nature of product development, ACRO 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 26-27 and Lines 46-47		Comment: The language used is too broad and does not explain what aspects of the "interface between medicinal products and predictive BM assays, including CDx" will be addressed in the proposed guideline, e.g. will the guideline focus on the process or criteria, or both, for qualifying predictive biomarker assays for use in medicinal product development? Proposed change (if any): The intended scope of the proposed guideline should be clearly defined.	
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 biomarker 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 (if any): Clarify whether simultaneous approval of the medicinal product and the CDx will be required	

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		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 biomarker, any *commercial assay* used for this purpose will be considered a CDx and will require an appropriate conformity certificate (CE mark)." This statement is problematic in several respects. First, by definition, a CDx is a device which is *essential* to the safe and effective use of a corresponding medicinal product. Drug labelling *recommending* that the drug *should be* used in conjunction with a predictive biomarker may be describing a complementary diagnostic that may provide helpful information in connection with the use of the drug, but it is not describing a CDx, and it should not be regulated as such. The predictive biomarker assay should only be regulated as a CDx if the drug labelling *requires* that the drug *must only be* used in conjunction with a predictive biomarker. Second, since this requirement only applies to a "commercial assay", that term will need to be very clearly defined in the glossary. Proposed change (if any): Revise lines 33-35 to read, "If it is required in the labelling that a medicinal product must only be used in conjunction with a predictive biomarker, any commercial assay used for this purpose will be considered a CDx and will require an appropriate conformity certificate (CE	

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		mark)." Define "commercial assay" in the glossary.	
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 (if any): Revise Line 39 to read, "…the two, and use of clinical trials or other valid scientific evidence to support validation of the diagnostic."	
Lines 50-60		Comment: We commend EMA for acknowledging that a CE-marked IVD may not be available to measure potentially predictive biomarkers during drug development, as this is often the case with novel biomarkers. 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 (if any): 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	

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		for the intended use, the Member States should require notification of performance of verification and validation prior to use of the assay in the trial.	
Line 64		Comment: The concept paper indicates that when a predictive biomarker 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 "in-house"; there may be suitably validated and quality assured assays that fall into neither category. Proposed change (if any): 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.	
Lines 84-86		Comment: Several terms that will need to be defined are not referenced in the examples given for the glossary. Proposed change (if any): 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	

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		defined in the glossary as well.	
		ACRO thanks the Agency for the opportunity to provide these comments on this Concept Paper on predictive biomarker-based assay development in the context of drug development and lifecycle. Please contact ACRO (knoonan@acrohealth.org) if we can provide any additional details.	

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