31 January 2016

Submission of comments on 'Scientific guidance on post-authorisation efficacy studies' (EMAPDCO/CAT/CMDh/PRAC/CHMP/261500/2015)

Comments from:

Name of organisation or individual
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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)*
	Paving the way to faster approvals but at what cost? 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". 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. During the discussions of the legislative proposals on Pharmacovigilance, 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".* Over the last 2 years, the European Medicines Agency has launched several initiatives that aim to change the interpretation of the current legal framework for market authorisations in the European Union (EU) and to promote faster approvals for "innovative" medicines in the EU. This concerted move is promoted under the guise of increasing access to patients, yet fails to address the underlying shortcomings of accelerated procedures and their over-reliance in post-marketing surveillance.	

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	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. This includes providing scientific guidance that sets appropriate standards for the design, conduction and reporting of high-quality, useful and valid post-authorisation efficacy studies. **Post-authorisation commitments are often not honoured.** Years of experience also show that manufacturers fail to honour post-marketing commitments to provide missing data adding to concerns on patient safety. A frequent reason provided is that participants are too difficult to recruit. [i] [ii] [iii] Patients are less likely to participate in a clinical trial with all its constraints if the medicine is already available on the market. Also pharmaceutical companies have very little incentives to actually conduct post-marketing studies which could reveal that their drug is less effective or more harmful than initially presumed. According to a recent study on conditionally-approved drugs, the median time taken by companies to meet the specific obligations was four years (range 0.2 to 7.7) and there were delays or discrepancies in the fulfilment of obligations in more than one third of the authorisation procedures.[iv] In contrast to the approach proposed by the EMA in its consultation document, concrete measures to dissuade, penalties and sanctions should be applied to those marketing	

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	authorisation holders which do not comply with their obligations. The EMA must closely monitor marketing authorisation holders and apply sanctions in case of non-compliance (i.e. in the form of fines; revoking the conditional approval). Clearly, if a PAES is considered mandatory by the EMA, rigorous and proactive requirements must be ensured. In the EU, the new pharmacovigilance regulation explicitly allows drug regulatory authorities to withdraw marketing authorisations when pharmaceutical companies fail to conduct post-marketing studies. However, despite the results reported by Banzi et al [4], this provision has not been implemented till date. It is much more difficult for regulators to remove a drug from the market once it has been approved than to refuse approval in the first place. In the post-marketing scenario, even in the face of new evidence of higher risks or questionable efficacy, withdrawing drugs can be a lengthy and complicated process, often faced with opposition from patient groups.[v] [vi] According to an example from a US study, "this tension emerged (…) around bevacizumab, which was approved for the treatment of metastatic breast cancer on the basis of surrogate end points under the accelerated-approval pathway. When subsequent studies showed no increase in patient survival, withdrawing the indication took nearly a year and generated substantial opposition. Some insurers even still cover off-label use of the drug for this non–evidence-based purpose".[vii] The pre-market requirements for double-blind randomized controlled trials establish an indispensable level of scientific rigour that is often not present in the post-market period. The use of observational studies exploring national health	

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	services data has limitations and does not provide the required level of proof.[viii] Observational studies are of weaker quality than randomised clinical trials as differences in patient characteristics often affect outcomes; and there are fewer methodological standards. The scientific guidance under consultation suggests that observational studies and registers can be used to estimate the effectiveness of interventions. However, this is rarely true, particularly when the drugs being studies have very small effects. Observational studies are also more prone to confounders and can only be used to demonstrate causality in very limited situations. Randomisation reduces bias, produces a balanced comparison between treatment arms (drug being studies VS comparator) and enables a quantification of errors due to chance. Yet, as is mentioned throughout the document, randomisation can be difficult to achieve after authorisation. Therefore, the greater the evidence gap pre-approval, the greater is the need to rely on data that is less robust and coming from observational studies. In addition, the use of surrogate endpoints in PAES further decreases the reliability and usefulness of post-marketing efficacy data, making the matters worse. **Use of surrogates** 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.[ix]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''.[x] 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	

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	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.[xi] **Transparency and Access to data** The EMA's transparency requirements are enshrined in the EU directive 200/83/EC which regulates pharmaceutical products, as well as in the EU freedom of information Regulation (Regulation 1049/2001)[xii] which governs public access to documents at European Union's institutions and agencies. The accountability and public scrutiny of Health Authorities' decisions are only possible when the public has access to both the body of evidence and the rationale on which decisions are based. However, the guidance document makes no mention to Regulation 1049/2001 and to the fact that under its provisions, European citizens are entitled to access any documents produced or received by European institutions, especially when an overriding public interest is at stake (article 2.3 of EC Regulation 1049/2001). This includes access to information about PAES studies. For more than 15 years, the EMA has failed to comply with a key measure of the European Freedom of Information Regulation (Regulation (EC) N°1049/2001), adopted in 2001: to set up a register of documents that it holds. This makes it very difficult for citizens to determine which document to request, leading to endless exchanges with the EMA before documentation is provided.	

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)*
Line 49		Comment:The text reads "*the demonstration of benefits therefore relies on persuasive and extensive data on the clinical outcome of interest*". The use of adjectives as persuasive and extensive is extremely vague and inappropriate to describe clinical data. Proposed change (if any): Replace persuasive and extensive by reliable and valid data.	
Page 5 (Lines 80-81).		Non-randomized trials are considered of major importance in order to develop the adaptive pathways model. This document seems to be paving the way for the implementation of adaptive pathways, which is, at this stage only a pilot project, not an EMA policy.	
Line 86		Comment: The text reads "*one or more control arms should, as appropriate, be allocated to placebo (perhaps as add-on to standard of care and/**or** an established medicinal product of proven therapeutic value*". Proposed change (if any): This sentence is unclear. There is no ethical or public health rationale to conduct a comparison of the medicine to be studied with placebo when an established medicinal product – standard of care	

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		– is available. The latter allows the assessment of therapeutic progress and should therefore be preferred.	
Line 91		Replace "It may be preferable to compare the medicinal product subject to PAES with that of an established medicinal product of proven therapeutic value", by "The medicinal product subject to PAES should be compared with an established medicinal product of proven therapeutic value ; should this is not possible then it must be justified in detail".	
Line 50 lines 277-290		Comment: The document mentions "validated surrogates" as an established practice to support a positive harm-benefit balance in an indication. In the same way, the paragraph 4.2 (lines 277-290) considers surrogates to be an useful tool when they are considered to be sufficiently informative by the scientific/regulatory community. This is not acceptable. The use of surrogate endpoints warrants extreme caution. Hard outcomes should always be envisaged before licensing and PAES should not be used as a panacea to fix (after marketing) an inappropriate original drug trial design. The study cited by EMA by Svensson and Menkes (JAMA Intern Med, 2013) clearly states that only in very few exceptions (slowly progressing conditions without existing therapy or very rare diseases) the use of surrogate endpoints can be deemed reasonable. This article does not mention other potential examples as suggested by the EMA (such as complex or composite measurements or key secondary outcomes).	

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		Proposed change (if any): Remove the reference to validated surrogates.	
Line 99 108 to 145 page 11 (Lines 329-332).		Comment: Exploratory trials are defined as those where control of systematic errors is enabled through randomisation, blinding and allocation concealment. It seems that pragmatic trials cannot apply these standards, while in fact they can (and should). It is true that external validity of explanatory trials may be limited and pragmatic trials can add useful information in a post-authorisation scenario. But this cannot be a reason to lower standards in the first approval or to base approvals mainly in non-explanatory trials. Proposed change (if any): Correct text to also include that pragmatic trials can and should also be controlled for systematic errors through randomisation, blinding and allocation concealment.	
Page 6 (Line 146).		Observational studies have been widely promoted by drug companies in primary care as a promotional technique to increase prescriptions of new products among physicians (seeding trials). These types of studies should not be contemplated or considered appropriate as PAES.	
Page 8 (Lines 218-220).		This paragraph is very unclear. What types of registries are supposed to be established by marketing authorisation holders, under which circumstances? Taking	

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		into account that observational studies are mostly based on clinical records held by regional or national health services, are pharmaceutical companies to be allowed to have access to such data in order to carry out a particular study? Please clarify and provide specific examples.	
Page 12 (Lines 372-375) and page 13 (lines 397-398).		It is unclear why there should be an agreement between sponsor and regulator to decide the adequate study design to addressing a research question. This should be exclusively defined by the regulator, which should make that decision based on public health priorities. Resorting to scientific advice in this context might jeopardize EMA's independence and also result in studies which do not respond to the agency's needs.	

Please add more rows if needed.

References:

[i] 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.

[ii] Carpentier D "Can expedited FDA drug approval without expedited follow-up be trusted" JAMA Internal Medicine 2014; 174 (1): 95-97.

[iii] Lexchin J “Notice of compliance with conditions: a policy in limbo” Healthcare policy 2007; 2 (4): 114-122 (+ annexes: 5 pages).

[iv] 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

[v] Gibson SG , Lemmens T. Niche Markets and Evidence Assessmetn in Transition: A critical review of proposed drug reforms. Medical Law Review, Vol. 22, No. 2, pp. 200–220 doi: 10.1093/medlaw/fwu005

[vi] Light D, Lexchin J (2015) Why do cancer drugs get such an easy ride? » BMJ 2015;350:h2068 doi: 10.1136/bmj.h2068

[vii] Darrow JJ et al « New FDA Breakthrough-drug category-Implications for patients » N Engl J Med 2014 ; 370 (13) : 1252-1258

[viii] Moore T, Furberg C. “Electronic Health Data for Postmarketing surveillance: a vision not realized” *Drug Saf* 2015; **38**:601–610

[ix] Light D, Lexchin J “Why do cancer drugs get such an easy ride?” *BMJ* 2015; 350: h2068 doi: 10.1136/bmj.h2068

[x] 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.

[xi] 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* 2015;175(12):1992-1994

[xii] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents. Official Journal of the European Communities 31 May 2001: L 145/43-L 145/48.