EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Mrs Paola Testori Coggi
DG Health and Consumers (DG Sanco)
Rue Breydel 4
B232 07/095
1049 Bruxelles
BELGIUM

25 February 2013

Doc. Ref.: EMA/91070/2013

Human Medicines Development and Evaluation

Dear Paola

Subject: PCPAES/12/01 — Public Consultation on PAES

We are pleased to provide you below with the EMA position on each of the items mentioned in the Commission's consultation paper on the delegated act on Post-Authorisation Efficacy Studies (PAES), which was released on 28 November 2012.
These comments further complement our views set-out in the EMA Reflection Paper on PAES of July 2012.

Consultation item No 1, EMA position:
It is in the interest of public health that PAES as a regulatory tool with the purposes depicted in the pharmacovigilance legislation enters rapidly into operation so to allow the EMA to enlarge the regulatory options at its disposal. This would become particularly valuable in those selected circumstances in which it is recognised and predicted that the collection of further information on the efficacy of medicinal products in the post-authorisation phase allows addressing relevant uncertainties in the benefit-risk that can ultimately trigger regulatory actions.

A delegated act illustrating major scenarios for PAES would be warranted in order to clarify what kind of studies would be expected and to guide stakeholders in the legal framing of the studies purposes.

Consultation item No 2, EMA position:
A PAES could be designed as an interventional or a non-interventional study. Controlled clinical trials of health care interventions are either explanatory or pragmatic. Explanatory trials are designed to determine efficacy under ideal conditions of use so to maximise internal validity while pragmatic trials aim at determining efficacy in routine, everyday practice. In the text, however, it does not emerge clearly that pragmatic studies are in essence controlled clinical trials and that belong to the category of interventional trials. The only fundamental characteristic that differentiate pragmatic trials from explanatory clinical trials is that exclusion criteria are kept to a minimum and inclusion criteria are widened so as to reflect as much as possible the full spectrum of real-life patient population that is going to receive the treatment. Also importantly, additional on-trial procedures, such as use of

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

concomitant medications or defined visits and tests, are not always strictly dictated by the protocol but could be left to the decision of the treating physician reflecting so everyday medical practice. These studies are expected to be randomised trials as is the case for explanatory trials. Therefore, the Commission may wish to amend the text to reflect that pragmatic trials are generally considered as controlled clinical trials rather than observational studies. In addition, when it comes to the generalizability of the results, the reference to the use of modelling (between brackets) may need to be clarified as it seems difficult to interpret in this context.

The EMA current thinking is that interventional studies are expected to represent the majority of PAES cases and would be the preferred option in several instances, particularly if the efficacy estimates are expected to be highly affected by confounding factors or biases in the population under evaluation. Nevertheless, carefully- designed and well executed non-interventional studies may allow a measurement of the benefit of a medicinal product in conditions of everyday clinical practice, in a non-selected patient population and without intervention as regards the choice of drugs prescribed, and they could therefore be used in selected circumstances as a tool to demonstrate effectiveness with the potential to bring high regulatory impact. This would be particularly the case if it is evident that the explanatory clinical trials setting introduces trial methods that greatly increase the gap with everyday medical practice to the point that the efficacy estimates in pivotal clinical trials cannot be entirely predictive of the benefits in real-life use. It is in the interest of public health to fully explore the potential added value of observational studies and pragmatic trials in the context of regulatory decisions.

Therefore both efficacy and effectiveness should be considered in scope.

Consultation item No 3, EMA position:
We believe that these scenarios cover the majority of cases based on current experience. It cannot however be excluded that some other situation not covered here could arise in the future. Therefore, openness to any potential new scenario that could be well justified from a regulatory standpoint should be considered.

Consultation item No 4, EMA position:
The Agency is eager to supplement delegated acts with a scientific guideline as deemed appropriate. The guideline may be expected to underpin methodological aspects related mainly to non-interventional and pragmatic studies as with respect to explanatory trials, adequate guidance from EU and/or ICH documents is already available.

We hope you find these comments helpful and remain at your disposal for any additional clarification or input from my services for the further progressing of the delegated act.

Yours sincerely,

Guido Rasi
Executive Director

Cc: DG Sanco Unit D-5 : Sabine Juelicher, Florian Schmidt, Helen Lee