Delegated Act on Post-Authorisation Efficacy Studies (PAES)
Comments from Leem, association of pharmaceutical industry in France
-February 18th, 2013-

General comment: Health Authorities should not expect from the Marketing Authorization holders to provide an answer to all the questions raised during the evaluation of the application.
It is important too, that the Clinical trial Regulation proposal should be attractive enough to allow the setting up of PAES in Europe. The possibility to grant MA under exceptional circumstances or conditional MA should remain feasible.

Consultation item No 1: Do you think that a delegated act on the situations in which a post-authorisation efficacy study may be required will be of added value and that the Commission should consider bringing forward a draft delegated act? Please provide reasons for your opinion.

A delegated act appears a good way to formalize the situations in which such PAES may be required, and to limit the interpretation of other regulatory texts. It should be more precise on the situations related to PAES requirements.

PAES should concern only future approved indications of drugs and not already approved drugs.

Consultation item No 2: Do you have any comments on the above? Do you agree that generally speaking post-authorisation efficacy studies should focus on generating efficacy data?

This question has no global answer as it may depend on the context of the uncertainty leading to the request: to get a marketing authorization or to get a price/ reimbursement.
We agree that all efficacy data are not available when the MA is granted. PAES may be required if the results they will give will help to answer the efficacy concerns.
But, if we consider healthcare management, conditions of reimbursement and market access, these situations can be very different from one country to another, and it will be difficult to draw a conclusion.
Studies based on real life conditions could give information on effectiveness and if we consider that PAES are mainly based on efficacy data, we don't take into account all the other data given by registries for example. Such data could be asked by local authorities for reimbursement process.

<u>Consultation item No 3</u>: Please comment on the seven different situations described above. Do you agree that in these situations, a competent authority may ask for a postauthorisation efficacy study? Are there any other situations not covered by points 5.1 to 5.7 in which it would also be justified to oblige a marketing authorisation holder to conduct an efficacy study? If this is the case, could you please elaborate on these situations and, if possible, give specific examples to underpin the need?

General Comment: This section generalizes situations on the basis of specific example (HIV or Vaccines). This approach seems risky as it may allow to apply the delegated act to a numerous number of situations not always relevant. For this reason, it is recommended to describe preferably the needed PAES in specific guidelines available per disease and not to make them a possible general requirement for all medicines via a delegated act.

1- Studies aimed at determining clinical outcome following initial assessment based on surrogate endpoints

It could be of interest to conduct such studies in this case. Surrogate endpoints are nevertheless not chosen at random and are usually accepted as highly correlated to the clinical outcome they represent, there should be no surprise therefore and specific attention to the study design should be well documented and agreed therefore. And a new surrogate endpoint must only be imposed to new drugs if previous surrogate was not validated or is no more valid on the basis of new scientific data.

Before, it is important to think about what will be happen if the PAES does not confirm the medical outcomes presented with the surrogate endpoints and what will be the impact on the MA ?

2- Studies on combinations with other medicinal products

This should be kept in very particular situation where medicinal product use was not available at the time of development for instance and emerge in the evaluation period. The MA Holder of the last MA granted should not have to perform all these studies alone, a "shared" assessment with all the different MA holders involved should be proposed, with specific Incentives .

And taking into account the different therapeutic strategies in the different member states, it will be very difficult to select the right one. The Pharmacovigilance process gives also answers to this question.

3- Studies in sub-populations

Same as 2-, it is expected that main information may be available in the application dossier and that if a specific population is supposed to be targeted, feasibility should be considered and discussed with the applicant. It should be on an exceptional basis because it is not possible to assess the efficacy of a drug in all the subpopulation.

4- Studies in the context of the European standard of care

Heterogeneity of EU standard of care may prevent form addressing this very important question at a EU level and may transfer this question on a more local level. Such situation may also arise on a limited basis where transferability to the real life is questionable. However, PAES should not be imposed at EU level by regulators to address local or national specificities. It could be possible only if there is a consensus between all European countries on the standard of care.

5- Studies linked to a change in the understanding of the standard of care for the disease and/or the pharmacology of the medicinal product

Network meta-analysis and other types of analysis may be of interest to be considered when new standard of care emerge in order not to ask all drugs to reassess their risk/ benefit balance in this new context. This proposal is possible only for new drugs which have to be compared to the previous standard of care.

6- Studies aimed at determining the long-term efficacy of a medicinal product

This situation is clearly in the same idea as the surrogate endpoint one and has a strong rational where development of a new drug has been conducted on a short or a middle term. It should be envisaged only in case of strong documented suspicion of efficacy; It is important to keep in mind that in chronic disease, the patient is followed by a GP or specialist who has to reevaluate on a regular basis the benefit/risk ratio of the treatment. The evaluation of the long term efficacy is linked to the safety profile of the treatment. This kind of PAES should remain exceptional (ex innovative therapy which change the disease course). The evaluation of the long term B/R ratio is also based on information given by Risk Management Plan and PASS.

7- Studies in everyday medical practice

Is real-life studies the same as everyday medical practice ? Clinical trials are not the best way to evaluate such criteria.

Heterogeneity of everyday medical practices, local recommendations, conditions of access to the treatment (treatment pathway, reimbursement) may certainly lead to a majority of situations where such a question cannot be addressed at the EU level and should be kept on the local stakeholders hand. This is also a situation where transferability is questioned and this may be the real question to address. However, PAES should not be imposed at EU level by regulators to address local or national specificities. This kind of proposal should be included in specific guidelines on diseases.

Consultation item n° 4:

The design should be adapted to the main objective of the study. We cannot choose the same design to demonstrate the efficacy in a specific sub-population and the efficacy in everyday medical practice. The study design is linked to the objective of the study. That is the reason why it is difficult to standardized the design of such PAES.

Non interventional studies design can be appropriate to generate post authorization efficacy data. The inclusion/exclusion criteria are restricted so, a large variety of patient profile can be included in the study. Bias and confounding factors can be identified, anticipated and analyzed and a priori solutions provided in order to manage these bias.

Consultation item n° 5:

In different countries, Post authorization studies impact on reimbursement and price negociations. PAES as well as PASS have to be taken into account by health authorities on their own evaluation and request.

Post authorization studies are mandatory in the context of conditional MA and MA under exceptional circumstances. How these PAES are integrated in this context ?