DELEGATED ACT ON POST-AUTHORISATION EFFICACY STUDIES
(ARTICLE 10B OF REGULATION (EC) NO 726/2004 AND ARTICLE 22B OF DIRECTIVE 2001/83/EC)
Deadline for Public Consultation: 18 February 2013

Comments from La Haute Autorité de Santé (HAS), France

2. THE CONTEXT OF A POST-AUTHORISATION EFFICACY STUDY

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.

Yes, it appears necessary to clearly describe situations in which PAES may be required. Therefore, the general idea of elaborating a delegated act on PAES is supported.

There are broadly 2 possibilities described in the document:

1. PAES required **at initial marketing authorisation** due to concerns relating to **some aspects** of the efficacy of the medicinal product that can be resolved only after the medicinal product has been marketed'.

2. PAES required **after the marketing authorisation** has been granted, 'when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly'.

It is essential that reasons for asking PAES be clearly identified and described in the CHMP assessment report, and the need for a PAES well substantiated; it is even more important to give a clear framework of PAES required after MA has been granted (see comments below).

3. THE REGULATORY PURPOSE OF A POST-AUTHORISATION EFFICACY STUDY

As national Health technology Assessment agency, we would like to stress that robust and adequate data provided in marketing authorisation is essential for an initial assessment for reimbursement purposes. Therefore, post-authorisation efficacy studies, should not lead to the premature granting of marketing authorisations. Instead of facilitating the process, this would considerably slow down access to market for at least some medicines.

4. EFFICACY VERSUS EFFECTIVENESS

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?

It is agreed that PAES should focus on generating efficacy data when adequate. However, the chapter is unnecessarily long and appears partly out of scope for the remit of EMA, especially the discussion on the type of data/evidence needed for reimbursement decisions from national

healthcare systems. The whole context as well as the vocabulary used (e.g. the term "intervention") are considered inappropriate for PAES setting and should be amended.

Post-authorisation efficacy studies are legally binding and are imposed if the results they produce will help to answer in an objective and robust manner the efficacy concerns that led to the imposition of the study in the first place. The robustness of data will enable the marketing authorisation holder and the competent authorities to re-consider whether a marketing authorisation should be maintained, varied or withdrawn. **It should not be forgotten that data coming from PAES are only one among other arguments to take into account while reconsidering B/R of a medicinal product**.

If PAES may sometimes collect data *in everyday medical practice*, the design of such studies should be appropriate (randomised trial design) in order to provide data robust enough. Comparative observational studies or "pragmatic" trials with randomised treatments allocation are some examples. The text should be clear on this point. **The methodology of PAES as compared to RCT phase III trials should be revisited and more clearly explained**.

It is proposed that this chapter be merged with the chapter 3. Here is the proposal for shortened and amended text:

Authorisation decisions for medicinal products are made on the basis of the objective criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations. At the time of granting the marketing authorisation the (therapeutic) efficacy of a product is established on the basis of randomised controlled clinical trials, i.e. clinical trials that are randomised as appropriate versus placebo and/or versus an established medicinal product of proven therapeutic value.

According to the new pharmacovigilance legislation, postauthorisation safety studies and post-authorisation efficacy studies may be requested to collect data for the assessment of safety or efficacy of medicinal products in everyday medical practice. This reference to everyday medical practice by the legislator could be interpreted as building a bridge to the trials outside the scope of a controlled clinical trial setting.
However, in view of the clear regulatory purpose and the need for robust data as the outcome of a PAES, these studies will have a randomised trial design in order to address the efficacy concerns that led to the imposition of the study in the first place.

Indeed, post-authorisation efficacy studies should only be imposed if there is the reasonable assumption that the results they produce will help to answer in an objective and evidence based manner the initially identified efficacy concerns.

5. SITUATIONS IN WHICH A POST-AUTHORISATION EFFICACY STUDY MAY BE REQUIRED

Consultation item No 3: 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?

Even if the scope of PAES requested by HTA bodies is larger (e.g. defining treatment strategy and its added benefit compared to existing treatments), situations listed below cover an important part of requests that HTA bodies may formulate (at least in France) to gather real-life evidence beyond the regulatory information on relative efficacy of a medicinal product available at the time of marketing authorisation in view of making evidence recommendations for reimbursement decisions.

For this reason, and **in order to request PAES fit for purpose for both regulatory and HT assessment**, it is crucial to consider how collaboration between bodies that can request PAES, notably HTA bodies and EMA, can be put in place. If no consultation happens between EMA and HTA bodies concerning the requests for PAES, there is a significant risk that EMA requests do not cover the need for additional studies at the HTA/reimbursement level.

There is an ongoing collaboration of EU HTA bodies on harmonising the requests for additional evidence generation; this is one of specific objectives of EUnetHTA Joint Action 2 Work Package 7, constituted of more than 25 partner institutions and led by HAS. HTA bodies can and should have an important role in this exercise. However, if **HTA bodies input** appears possible in the second situation (PAES required after the marketing authorisation has been granted), it is all but obvious for PAES required at initial MA.

5.1. Studies aimed at determining clinical outcome following initial assessment based on surrogate endpoints
Agreed. Surrogate endpoints for the initial MA should be fully validated and accepted only if clinical outcomes are impossible to obtain at a reasonable time frame.

5.2. Studies on combinations with other medicinal products
It is unclear what and how one can extrapolate existing data on a new combination and what kind of uncertainty PAES should answer. In addition, “mandatory” character of this type of PAES appears inappropriate

5.3. Studies in sub-populations
No particular comment

5.4. Studies in the context of the European standard of care
No particular comment

5.5. Studies linked to a change in the understanding of the standard of care for the disease and/or the pharmacology of the medicinal product
No particular comment, even if this situation appears rare.

5.6. Studies aimed at determining the long-term efficacy of a medicinal product
If there is a well-founded suspicion based on scientific rationale and/or data provided in the submission file that the effects of a medicinal product may wane or change over time (e.g. decrease in efficacy due to neutralising antibodies, resistance or new mutations or very long-term effect of disease-modifying drugs), and MA is given due to unmet medical need, PAES should be requested and their design well described. However, these situations should be more clearly identified in this document.

5.7. Studies in everyday medical practice
As clearly stated in this and other documents, the robust data from PAES should provide regulatory authorities with key information, necessary to either complement initial evidence or to verify whether the marketing authorisation should be maintained as granted.
Everyday practice or "real-life" studies are usually requested by the HTA bodies for example to check if benefits of a medicinal products are affected by the real-life conditions of use and to check transferability of data gathered in RCT to a real-life setting. The reasons given here to ask for everyday medical practice PAES cover the scope and aims of health technology assessment for reimbursement purposes of almost every drug assessed by HTA agencies. Therefore, this chapter appears inappropriate in its current form. If PAES collect data *in everyday medical practice,* their design should be appropriate (randomised trial design) in order to provide data robust enough to question initially given marketing authorisation. The methodology of PAES as compared to RCT phase III trials should be revisited and more clearly explained.

In the case of vaccines, where indeed efficacy studies are not always done or possible, gathering post-MA efficacy data appears necessary. In these cases, prospective studies after MA in order to establish at least putative correlates for short and/or long-term protection are sometimes requested. It is strongly recommended to elaborate on the design of such trials as the current text may lead to a wrong idea that any kind of data on vaccines coming after MA may be acceptable.

As a conclusion, there may be situations where efficacy studies are not done for MA; in these cases, PAES may be requested; randomised trial design will be requested in most cases.
In situations where PAES provide data relevant for HTA of a medicinal product, transparent and well defined collaboration process between EMA and HTA bodies should be put in place.

Consultation item No 3: Please comment on the seven different situations described
Please see above.

6. STUDY DESIGN

Consultation item No 4: Do you have any comments on the above?
Please see comments on points 5.6 and 5.7
The following sentence should be deleted: **"**Nonetheless, in certain specific circumstances, as explained under point 5.7, pragmatic trials or observational trials will be the point of reference for the design of a post-authorisation efficacy study.

Consultation item No 5: Please feel free to raise any other issues or make any comments which have not been addressed in the consultation items above.

There will be situations where PAES requested by EMA (such as studies in specific sub-populations, or studies to show long-term efficacy and on final endpoints) will be of direct interest to HTA bodies. It is essential that collaboration between EMA and HTA bodies of the EUnetHTA network be put in place in a transparent and well defined way to review and discuss such trials, in particular it is essential that the design of these trials cover both EMA and HTA needs. It is recommended to introduce this important aspect of overlap and necessity for collaboration in this document.

Again, not only the scope but also study design of a PAES to request should be reviewed and broadly agreed upon by EMA and HTA bodies.

If **HTA bodies input** appears possible in the second situation (PAES required after the marketing authorisation has been granted), it is all but obvious for PAES required at initial MA.

Paris, February 14th, 2013