20 February 2013
EMA/89579/2013

Response to:

DELEGATED ACT ON POST-AUTHORISATION EFFICACY STUDIES

(ARTICLE 10B OF REGULATION (EC) NO 726/2004 AND ARTICLE 22B OF DIRECTIVE 2001/83/EC)

POST-AUTHORISATION EFFICACY STUDIES

Ref. Ares(2012)1405774 - 28/11/2012

Submitted by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Working Group on Health Technology Assessment.

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Consultation item No. 1

It is agreed that a delegated act on the situations in which a post-authorisation efficacy study may be required will be of added value by providing sponsors with examples of when a post-authorisation efficacy study may be required. A draft delegated act would help provide sponsors with greater clarity to enable long term planning and budgeting as they await the final act.

Most PAES will be conducted in usual care settings and most will be organised as randomised trials. Current experience with PAES is scanty but it is likely that practical, ethical and financial difficulties could arise when randomised trial will be implemented in settings not accustomed to this type of research. Giving a legal format to PAES is likely to facilitate their acceptability by member states' health authorities, health professionals and patients.

This is also a timely measure, because thanks to EUnetHTA[1] , which was established to create an effective and sustainable network for HTA across Europe, a harmonisation of the requests regarding effectiveness studies is under way through its Joint Action 1 (yet finished) and Joint Action 2 (which is started recently and will last until October 2015). Moreover, a permanent network of HTA bodies will be set up in application of the Article 15 of the Cross Border Health Care Directive, so that this cooperation between HTA bodies will be maintained after the end of the Joint Actions. Harmonising the requests (or recommendations) for additional evidence generation, notably on "effectiveness studies" is precisely an objective of the Work Package 7 of the current EUnetHTA Joint Action. This work package gathers more than 25 partner institutions, mainly HTA bodies, across Europe, and is led by HAS (France).

In addition, EMA and EUnetHTA have been in direct contact to discuss areas of cooperation and collaboration. The newly created working group on HTA was presented during the last EMA-EUnetHTA meeting (Copenhagen, November 20, 2012) as a group which can help in exploring methodologies and initiatives to link ENCePP and EUnetHTA. The key element could be for EUnetHTA and EMA to develop and agree on a methodology for observational studies to identify and collect information to fill knowledge gaps in the post licensing phase[2].

A delegated act on the situations in which a PAES may be required will be of added value because the legislation is not clear enough on these situations. It will also allow the marketing authorisation holder to set up studies which would take into accounts both EMA and HTA bodies' needs.

It will be of more added value if:

- It takes into the accounts HTA bodies requirements for post authorisation studies. In case EMA considers that there is need for a study to demonstrate the efficacy of a product in post authorisation period (for example because of non-generalisability of clinical trial results to real world practice), this decision may also be of interest for HTA bodies of European countries. However, HTA bodies may have their own questions on the effectiveness of the product, too. If no consultation happens between EMA and HTA bodies concerning the request of PAES, there is a significant risk that EMA requests do not cover the need for additional studies at the HTA/reimbursement level.

[1] http://www.eunethta.eu/

[2] Meeting notes available at : http://www.eunethta.eu/outputs/ema-eunethta-meeting-summary-report-november-2012

- It provides a common basis of requirements for effectiveness studies among EMA and HTA bodies in a concerted way. This implies that it should use a well-defined terminology and a clear definition of the expected level of quality or evidence which is acceptable both for EMA and HTA bodies.
- It includes the feasibility of PAES into the conditions of its requirement.
- It defines the type of organisations which should be considered "reliable" in the conduct of such studies (MAH? CRO? Academia?...)
- It defines a clear framework for the protocol submission and validation of the results of such studies.
- It requires that the results of such studies should be disseminated, even if they negatively impact the product.

The feasibility and credibility of the study is a very important factor that should be addressed by the delegated act. Indeed, a review of the actual post authorisation study requests conducted by HTA bodies reveals that many of the requested studies are never conducted. Among those which are started, many do not come to an end because of enrollment or other feasibility issues. Among those which come to an end, many are considered "unreliable", because they have been conducted by the MAH.

Consultation item No. 2

The text related to consultation item 2 is not clear. As it stands now, the proposal of PAES for generating efficacy data is not different than asking to authorisation holders to perform additional phase III/pivotal studies. If so, then it would better to wait for additional phase III/pivotal data before granting a market authorisation. PAES cannot be restricted to efficacy because safety and quality will also be considered. The text gives the impression that effectiveness is to be evaluated through observational studies or pragmatic trials and that usual phase III type of protocols do not apply to effectiveness assessment. However, the boundaries between efficacy and effectiveness are vague: one way to read the footnote 14 definition is that an efficacy trial could turn into an effectiveness trial if subject inclusion criteria were different (e.g. more representative of potential users). If so, randomised trials for assessing effectiveness are feasible. The text should thus tell more clearly which methodological differences would exist between phase III/pivotal trials and PAES, and up to which point these differences will not jeopardise unbiased evaluation of efficacy. The text should better define boundaries between efficacy and effectiveness randomised trials, if such difference would be of relevance in the context of randomised trials.

The description of methodologies is unreferenced and inaccurate. It is recommended that the document refers to a published source such as the ENCePP Guide on Methodological Standards[3] to describe study methods.

Instead of "There are two broad methodologies that are used to generate data on real-world practice: observational studies and pragmatic controlled trials….. to end of section"

The following text is proposed:

[3] http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE_2.pdf

"The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)[4] has published a Guide on Methodological Standards in Pharmacoepidemiology that provides a comprehensive overview of observational research methodologies."

It is accepted that post authorisation efficacy studies should focus on efficacy data. Like clinical trials, the expected outcome measures should be defined in advance for each type of therapy.

Also, it is important that the outcomes requested for these studies are selected in such a way that they are less sensitive to the healthcare system of a given country, in order to facilitate pooling or extrapolation of data to entire Europe.

One of other needs in this domain is a common scoring of evidence level based on the type of the study. The definition of the evidence level should also take into account the quality of conduct of a study (through an ENCePP Study Seal[5] or use of the ENCePP Checklist for Study Protocols[6] for example). It should be defined what type of evidence or data source is acceptable for PAES.

Comment on page 8, paragraph 1: "as they basically sacrifice internal validity to achieve generalisability (e.g. through modelling)." The provided example can be replaced by "…(e.g. through collection of information from a large population of heterogeneous individuals with various confounders)".

The last paragraph can be challenged. One of the problems with interventional clinical trials is that they are sometimes impossible, unethical or very expensive to conduct especially among specific populations such as the elderly, children and pregnant women. This is one of the reasons of paucity of relevant efficacy or safety data among the elderly, children and pregnant women. As a result, requesting studies which would face feasibility challenges should be avoided. Instead of emphasising on specific study designs, the delegated act may promote the use of appropriate designs by referring to ENCePP methodological guidelines. The choice of the appropriate design should be guided by the research question, the required level of evidence, and the feasibility of the study in real world. Simple and cost effective study designs and methods should be encouraged to increase the number of studies which come to an end.

Today, large databases of patients allow the conduct of studies which take into the account several confounders in matching of patients and provide high statistical power. In database studies one can get full information on existing data, and there should be no loss to follow-up (the French national database covers 97% of the population, and the same is true in Denmark or Finland. Generalisability is immediate when working on the full database or on a representative sample. Interventional studies in PAES should have no other inclusion or exclusion criteria than the approved SPC. This will not capture use and effects of drugs outside the formally approved indications, and might miss a large part of pragmatic efficacy data. However, recent works (e.g., Bosco et al, J Clin Epid, 2009) and recent experiences (some of which are still to be published) show that some methods (eg propensity scores) are not really able to fully control confounding by indication. The way to perform unbiased analysis of data collected during routine medical practice is challenging and would deserve specific research activities.

In point 4, top of page 8: the presumption of limitations relating to poor data quality or completeness is not built into observational studies, but only in the quality of the study itself. This is a common preconception by persons who do not have direct experience of such studies when they are well done. There is no intrinsic reason for poor data or incompleteness, only poor quality of the study operators.

[4] http://www.encepp.eu/
[5] http://www.encepp.eu/encepp_studies/index.shtml
[6] http://www.encepp.eu/standards_and_guidances/index.shtml

With sufficient effort, data is as good and complete as in clinical trials and there is no reason it should not be.

For instance in one of our studies in 5500 myocardial infarctions we have 95% completeness of information on >6000 events of interest leading to hospital admission including hospital discharge summaries or if necessary hospital documents.

The use of the word randomisation is important since some interventional trials under the EU Clinical Trials Directive definition are non-randomised. It is the randomisation element that provides the rigour that is needed. Such randomised trials could fall anywhere on the explanatory to pragmatic trial continuum.

Instead of:

"However, if it can be considered at all, this would be the exception rather than the rule. In view of the clear regulatory purpose and the need for robust data as the outcome of a PAES, the large majority of studies will have a clinical trial design.",

the following text is proposed:

"However, if it can be considered at all, this would be the exception rather than the rule. In view of the clear regulatory purpose and the need for robust data as the outcome of a PAES, the large majority of studies will have a randomised trial design versus a non-randomised trial design."

Consultation item No. 3

Point 5.1: this chapter speaks only of cancer, and should be extended to all drugs or diseases that rely on proxies. PAES should not rely on proxies but on hard endpoints (though they may also be used to confirm the validity of the proxies).

Point 5.2: agree. However, this seems to be more valid in the context of conditional marketing authorisation.

Combination with medicinal products: this concerns not only HIC therapies but also cancer: when a cancer drug is put on the market, associations with other drugs are mostly not studied, and new drugs and drug combinations are developed every day, on which there is little or no information. These studies could be based on the observation of real-life use of drug combinations and their changes and evolutions: this also pleads for a continuous observation of prescription practices.

Point 5.3: agree.

Point 5.4: agree.

Point 5.5: agree.

Point 5.6: agree. Another example is the development of resistance to antibiotics over time.

Point 5.7: This situation is not clear. This paragraph can be reworded as "...when the results of pivotal clinical trial cannot be transposed to the real world practice because of behavioural, compliance …"

Other situations in which a PAES can be demanded:

- When lack of efficacy exposes the patient to a risk: drugs used in emergency situations, strong antibiotics, vaccines, contraceptives… If these drugs are not efficient in real world, the patient may lose the chance of receiving an efficient alternative.

- When a study which has been conducted in one of EU countries (or another part of the word?) provides evidence that the effectiveness of the drug in real life is below the level for which it was granted authorisation. In such case, a well conducted PAES allows the assessment of the hypothesis in a wider population.
- When the existing evidence on the safety profile of the drug suggests that the benefit-risk balance of the drug is becoming equivocal, so that there is need to define its effectiveness in real practice in order to be able to re-evaluate its benefit-risk balance in real life.
- When the clinical trials which led to the marketing authorisation made use of endpoints that are not common in real practice. For example if the endpoint of clinical trials for an anti-osteoporotic drug was the TS score, if this score is not commonly used by general practitioners who commonly manage osteoporotic patients, a PAES may be required with a more commonly used endpoint such as fracture rates.
- The efficacy in populations not covered in premarketing studies, especially drug combinations, or diseases that are not included in the drug summaries of product characteristics (SPC) but might have been so. For example, if a drug such as an NSAID is authorised in rheumatoid arthritis (RA), it may be necessary to know its effects in other inflammatory diseases requiring long-term therapy such as psoriatic rheumatism or ankylosing spondylitis.

Consultation item No. 4

Some of the terminology used in the Delegated Act is unclear and could be misleading in a regulatory point of view. We refer to the use of “pragmatic clinical trial” and “observational studies”. Example pages 7 and 8: "There are two broad methodologies that are used to generate data on real-world practice: observational studies and pragmatic controlled trials. Observational studies are often based on the analysis of patient registries owned by public or private sector insurers, research and health technology assessment bodies, patients' and healthcare professionals' organisation or pharmaceutical undertakings. Pragmatic trials, on the other hand, observe clinical practice." It’s unclear what the difference is between observational studies and pragmatic clinical trials. “Controlled trials” by definition cannot represent data generated from “real-world practice”. The Clinical Trial Directive (Directive 2001/20/EC) gives clear definitions of clinical trials (art 2a) and non-interventional trials (art 2c). It is also clear that the Clinical Trial Directive does not apply to non-interventional trials (art 1.1). Therefore, in a regulatory point of view, “non-interventional trials" are governed by local regulations or guidelines which have been issued based on the definition provided in art 2c of the Clinical Trial Directive. In a regulatory point of view the distinction between clinical trials and non-interventional trials is essential in order to apply the correct regulatory framework for the study conduct.

Section 3 page 6 gives the definition of the PAES as: "post-authorisation efficacy studies that are covered by the delegated act have a clear regulatory purpose. They are imposed as an obligation on the marketing authorisation holder and are part of the conditions to which a marketing authorisation is made subject. They directly affect the material scope of the authorisation. "Section 4 page 8 mentions that "In view of the clear regulatory purpose and the need for robust data as the outcome of a PAES, the large majority of studies will have a clinical trial design.” If a PAES is a condition to a MA, the "non-interventional / observational" design would be more appropriate as per the definition of clinical trials and non-interventional trials in the Clinical Trial Directive. Indeed, non-interventional trials are design to observe the use of medicinal products as per their marketing authorisation.

It is important that the terminology used here is consistent with the EU Directive definitions of interventional and non-interventional trials. Some interventional trials under the EU directive are non-

randomised and so would not be considered adequate to provide efficacy data in most situations. The EU Directive uses the word trial and not study.

There is a real demand from MAHs for guidance on the acceptable methodology and the level of evidence (design, quality) for the PAES. If the guidance is not provided directly in the delegated act, the text should envisage adoption of ENCePP or other guidelines as the standard which should be followed.

The assertion that observational studies are highly affected by biases and confounders is rather strong. It may be true when looking at relative efficacy as determined in RCT. However if what is needed is absolute efficacy as the drug is used, they are the only methods that do provide generalisability and unbiased measures of actual efficacy or effectiveness, where RCTs are essentially not as useful (for instance the NSAID usage in the VIGOR and CLASS studies represent less than 2% of actual population user patterns: these studies are interesting for relative efficacy, but totally useless to identify the real benefits of the drugs).

Consultation item No. 5

This is an important document that will be very useful to sponsors of biopharmaceutical products. However, greater clarity in the use of terminology is needed to be consistent with existing regulatory material.

In any case, there is a missing item that should be considered: the proposal does not display criteria for evaluating when “certain well-reasoned scientific concern” (page 6) would deserve a PAES. Have such criteria already been discussed and reported somewhere, or will decision for PAES be left to the EMA evaluation panel, depending on the drug and concern at stake?