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Comments

To: European Commission, sanco-pharmaceuticals-D5@ec.europa.eu

From: German Pharmaceutical Industry Association (BPI),
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CC:

Subject: COMMISSION DECISION ON A "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 [PCPAES/12/01 — Public Consultation on PAES']

Date: 18 Feb 2013

Comments of Bundesverband der Pharmazeutischen Industrie e. V. (BPI) - German Pharmaceutical Industry Association Concerning the Draft "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"

02/18/2013

BPI appreciates the opportunity to review and comment on the above mentioned draft paper. In general we agree with the draft, however, we see the need to take into account the following general points:

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Comments

(A) General comments:

It would be highly appreciated to establish clear parameters for the a) definition of PASS and b) for the definition of PAES to ensure clear classification between both (primary endpoints are representative for the character of the study).

(B) Specific comments:

In the following part of this position, the BPI will answer the consultation items the Commission raised in the concept paper.

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 could help to clarify situations in which PAES are required because the given statement of the legislator is vage.

PAES are appropriate and important instruments for evaluating the efficacy of a medicinal product, thus, a delegated act to implement PAES is of added value. Legal certainty and clarity as to the regulatory scope of a PAES is essential to obtain robust and reliable data from such a study.

In general a delegated act on the situation in which a post authorization efficacy study may be required, would be in the interest of public health and regulatory clarity as well as MAH. Article 10b of Regulation (EC) No 726/2004 and Article 22b of Directive 2001/83/EC do not describe sufficient the issue in which situations or under which circumstances a PAES may be required. Moreover in contrast to PASS,

currently no corresponding guideline for PAES exists or is planned. Consequently, more background and clarifications regarding this issue are needed.

One important question in this context is WHY a GVP module concerning PAES is not scheduled and WHY a delegated act should be discussed? The background is that a GVP module has a recommendatory character and a decision of a regulatory authority (RA) on case-to-case basis, which makes sense, is possible. Although Article 22b of the Directive 83/2001 proposes the adoption of delegated acts to determine the situations in which post-authorisation efficacy studies may be required under Articles 21a and 22a of this Directive, it is considered to be more appropriate to set up regulatory guidelines similarly to the GVP modules. A delegated act has a more legally binding character and there is only marginal scope for case-related decisions.

Of particular importance is a more detailed clarification concerning scenarios in which a PAES will be imposed as a requirement to the marketing authorisation. Competent authorities have to balance benefits against risks during the assessment of new medicinal products. Significant uncertainties concerning the efficacy of any new medicinal product can not be accepted by any competent authority if this could burden the benefit risk assessment with unacceptable risks. Therefore it is interesting to understand the scenarios or aspects in which efficacy concerns are acceptable/not acceptable from the commission’s point of view.

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?

Yes, we agree that generally speaking post-authorisation efficacy studies should focus on generating efficacy data, but note that safety related issues will always be part of it und have to interpret separately. Furthermore it should be kept in mind that the main research question of a trial should define the design of a trial. If there is a need to get new causality information, an explanatory trial is necessary (see 5.1). If there is a need to get information about real life conditions and the causality per se is proven (e.g. special populations (see 5.3.), concomitant medication (see 5.4.), compliance etc) pragmatic trials or well-designed non-interventional trials should be performed.

According to consultation paper obviously the EC has the opinion, that a PAES has a clear regulatory purpose and the need for robust data as the outcome of a PAES, the large majority of studies will have a randomized controlled trials design. Indeed, a clinical design most likely in the form of a phase IV study should be the major part of PAES. However, NIS for example active post-marketing surveillance or observational studies (*Anwendungsbeobachtungen* according to §4 German Medicine Act (AMG)) should also have impact since these are structured plans to elicit important data from an administered population. Why these data shouldn't be "robust"?

Efficacy data from NIS or interventional studies will provide substantial information in a long-term sense from daily medical practice. However, also safety and tolerability should be assessed in the course of a PAES as this together with the efficacy information is essential for assessing the benefit-risk profile of a drug (see 5.5).

If the intention of the legislation is to generate robust data on the medical benefit of the product then focusing on efficacy data is clearly favored over the collection of

effectiveness data in a non interventional or pragmatic trial setting. Such effectiveness data is information regarded supplementary to findings from classical RCTs either supporting the initial assessment of the medicinal products with “real life” data or raising questions to be analyzed in further clinical trials. Moreover, effectiveness data is not accepted by certain HTA bodies in the context of reimbursement assessments since it can be highly biased. E.g. during the German early benefit assessment RCT data are regarded as gold standard. However, it would be appreciated if the design of PAES could be aligned between the HTA bodies and the marketing authorisation authorities in order to make the respective data applicable for both, marketing authorisation as well as reimbursement assessment.

In our opinion the pragmatic trial is defined unclear. In the context of the consultation paper it appears, as if the pragmatic trial is considered to belong to non-interventional trials. The pragmatic trial, however, is definded as a randomised controlled trial and therefore it is interventional and not observational (Witt C. Forsch Komplementmed 2009; 16: 292-294).

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 post-authorisation 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?

We agree that the given situations can be reasons for the authorities to ask for PAES. The given different situations demand for different designed trials (see consultation item 2b).

5.1

Confirmation of surrogate data particularly if referring to survival endpoints requires large patient collectives and long observation periods. This can be very time and cost intensive, particularly if the data have to be generated in a clinical trial (GCP) setting. Therefore it should be considered if there is other approaches to decide if surrogate data can be applied or not (e.g. definition of surrogates to be considered validated on indication level; validation studies on important surrogates which are considered not adequately validated yet, which after validation are accepted without further research (financing of such studies with benefits for all applicants in the respective indication to be discussed) etc.).

5.2

In studies on combinations with other medicinal products, not only uncertainty on efficacy could be clarified, but also drug interactions, tolerability of the combination and other safety issues.

5.3

Whenever thinking about the analysis of sub-populations it should be borne in mind that it is difficult to analyse these patients in terms of efficacy if the definition of the sub-population is too narrow. This is since in very small patient collectives only large outcome differences between the treatment arms will be statistically significant. Furthermore, studies in subpopulations are already requested at the time of the initial MA as part of a PIP deferral.

5.4

Studies should not only be conducted in the context of the European standard of care but in addition, of best supportive care, particularly in oncology trials. This is of particular importance for the study design as this type of reference therapy could be relevant for the health technology assessment of a newly developed medicinal product.

On the other hand and in context with the mentioned situations (5.1. to 5.7), in which a PAES may be required by the competent authority, the delegated act explicitly mentions a situation, where a marketing authorisation has been granted based on non-EU clinical data, but complementary data in the context of the European standard of care are requested to allow a more precise evaluation of the efficacy of the medicinal product.

Such an appraisal of evidence from clinical trial data is completely unacceptable, because it would severely violate a basic principle of directive 2001/83/EG, as amended. According to article 26, marketing authorisation of a medicinal product has to be based on evidence of a favourable risk-benefit balance and sufficient substantiation of therapeutic efficacy. To come to this conclusion, the competent authority can either accept or not accept the submitted clinical trial data.

As detailed in article 21 a (f) of 2001/83/EG, conditional marketing authorisation requesting additional PAES can only be granted, if concerns relating to some aspects

of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. This is evidently not the case, where evaluation of efficacy in the context of the European standard of care cannot be sufficiently evaluated based on submitted clinical trial data. In this situation, the competent authority has to request additional European data before granting a marketing authorisation.

Therefore it is necessary to completely delete topic 5.4 from the delegated act.

One general question is why a study in form of a PAES should be repeated in the context of European standard in the case of a license for a medicinal product is granted by RA / EMA on the basis of a study outside the EU.

5.5

Indeed during the life cycle of an authorised medicinal product, it is possible for a significant change to occur in the standard of care for the diagnosis, treatment or prevention of the disease, but not in every case there is a need of a reassessment of benefit-risk balance of a medicinal product. For example there are many medicinal products, which have licenses during decades and have a very established safety profile and an accepted value (also medicinal products with well established use status) within a field of treatment or diagnosis. Such medicinal products should not have to prove in every case whenever a new auspicious active substance in the respective field of treatment will be released into the market.

Based on the Guideline on Good Pharmacovigilance Practices (GVP), Module VII, for a number of active substances, referred to in Articles 10(1), 10a, 14, 16a of directive 2001/83/EC as amended, Periodic Safety Update Reports (PSURs) are no longer required. These active substances are listed in the “List of Union reference dates and frequency of submission of periodic safety update reports” (EMA/630645/2012 Rev.4). A PSUR comprises the cumulative assessment of available data on an active substance’s safety and risk-benefit balance. The active decision that PSURs are no

longer required implies that a compound's risk-benefit balance has been sufficiently demonstrated and no further data are required.

Active substances listed in EMA/630645/2012 Rev.4 as exempt from the PSUR requirement are typically compounds that have been extensively used and scientifically studied over decades and have become basic treatment principles in many therapeutic areas. Due to the long-standing use, these products are no longer patent protected and usually marketed by multiple generic companies. Their use is driven by established clinical standards.

For example, diuretics used to treat arterial hypertension had been developed and received original marketing authorisation based on scientific and clinical standards valid at the time of their development decades ago. Although scientific and clinical standards have been considerably advanced since, the value of diuretics for the treatment of arterial hypertension is still generally accepted. Requesting PAES for this class of compounds would pose major and partly insurmountable ethical and logistical problems, such as receiving IEC/IRB favourable opinion or motivating patients and investigators to participate. In addition, these products are typically low-price goods in a generic market environment with very small profit margins. It is unclear how PAES for such products could ever be funded and who should serve as sponsor. Therefore requesting PAES for these for formal reasons on a routine basis with the rationale that "an improved understanding of the disease and/or the pharmacology of a medicinal product has brought into question the criteria used to establish the efficacy of the product at the time of approval" would jeopardize the availability of important basic treatment principles for prevalent medical conditions.

To avoid such a deterioration of medical care due to routine regulatory processes, active substances listed in EMA/630645/2012 Rev.4 as exempt from the PSUR requirement need to be explicitly exempt from any requirements of PAES by the delegated act.

Furthermore, the goal of the above mentioned articles (10(1), 10a, 14, 16a of directive 2001/83/EC as amended) was to protect the regulatory status of these active substances. The aim of the delegated act on PAES is therefore contradictory to the goals laid down in these articles. To maintain the spirit of the directive these substances must stay exempt from the delegated act on PAES.

5.6

PAES will probably be requested from those manufacturers of tissue-engineered products, which had previously been on the market and now have to undergo a MAA according to the ATMP regulation EC 1394/2007. Since coming into force in 2009, the applicants started their clinical development programs and thus can only provide short-term data from controlled clinical trials, which do not give information about long-term (5 and more years) efficacy and safety of these TEPs.

Consultation item No 4: Do you have any comments on the above?

The choice of study design should adequately reflect the purpose and question addressed in the objective of the study. Yes, we agree that in specific circumstances – especially those explained under point 5.7 – the design of a PAES as an observational or pragmatic trial may be the most appropriate. The delegated act should point out that various trial designs are possible for a PAES covering both the design of a RCT but also the design of an observational study. The design in detail should not be covered.
In that context we would like to raise the questions how “robust data” are defined and what is accepted with regard to evidence-based medicine levels? Is it possible to get a scientific advice for the design of a PAES?

Basically we absolutely agree with the opinion that the design of a PAES shouldn’t necessarily be covered in detail by the future delegated act since there are too many different possible situations that require PAES.

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We would like to note, that the view of the authorities may not be that of the decision makers for reimbursement in the respective country.

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.

Non-prescription medicinal products

According to article 71(1) of 2001/83/EG as amended, medicinal products that contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation, shall be subject to medical prescription.

By inference, granting non-prescription status to a medicinal product after careful evaluation of available clinical trial data and post-marketing experience implies the position of the competent authority that no further investigations are required.

Therefore, non-prescription medicinal products should be explicitly exempt from any requirements of PAES by the delegated act.