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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"

Comments of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) represents via national member associations, including EUCOPE (Germany), EMIG (UK), SwedenBio (Sweden) and the US Biotechnology Industry Organization (BIO) more than 900 mid-sized innovative - often family owned - pharmaceutical and biotech companies. In addition, many innovative companies from Austria, Bulgaria, France, Germany, Greece, Italy, the Netherlands, Sweden, and the UK are represented on the board of the association. EUCOPE membership includes innovative family owned companies such as B.Braun, Sigma-Tau, Ferring, Miltenyi or Vianex as well as innovative companies active in the field of biotechnology and rare diseases such as Alexion, Celgene, InterMune, Otsuka or Grifols (www.eucope.org).

EUCOPE highly appreciates the opportunity to review and comment on the above mentioned draft paper. Please find some General Findings (I) and comments on the specific Consultation Items (II) below.

(I) General comments:

The obligation to conduct post authorization efficacy studies (PAES) is laid down in Articles 22a and 22b of Directive 2001/83/EC and Articles 9 IV and 10a of Regulation 726/2004. While these provisions contain references to scenarios in which post-authorization studies are necessary, clear parameters for the definition of PAES would be appreciated.

(II) Comments on specific Consultation Items:

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.

EUCOPE appreciates the effort of the European Commission to clarify the regulatory scope of PAES via a delegated act. Legal certainty and clarity as to the regulatory scope of a PAES is essential to obtain robust and reliable data from such a study.

We agree with the statement in the Concept Paper that the respective Articles of Regulation (EC) No 726/2004 and Directive 2001/83/EC call for a further clarification to sufficiently describe in which situations or under which circumstances a PAES may be required. Moreover in contrast to PASS currently no corresponding guideline for PAES exists.

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?

EUCOPE shares the views stated in section 4 of the Concept Paper in general. However, it should be clear that safety related issues have to be interpreted 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 obtain new causality information, an explanatory trial is necessary (see 5.1). If there is a need to obtain 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.

The Consultation Paper states that the large majority of studies will have a randomized controlled trials design. We expect that a clinical design most likely in the form of a phase IV study should be the major part of PAES. However, also non interventional studies (NIS) for example active post-marketing surveillance or observational studies should have an impact as well since these are structured plans to obtain relevant data from the treated patients.

Efficacy data from NIS or interventional studies can provide substantial information 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 randomized controlled trials (RCT) 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.

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?

EUCOPE regards the situations described in points 5.1 to 5.7 as mostly adequate reasons for the authorities to ask for PAES. The different situations may demand trials with a different design (see comments above on Consultation item No 2).

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

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 primarily whether there are other options to decide if surrogate data can be applied or not (e.g. definition of surrogates to be considered validated on indication level or validation studies on important surrogates which are considered not adequately validated yet, which after validation are accepted without further research).

5.2 Studies on combinations with other medicinal products

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 Studies in sub-populations

Regarding the analysis of sub-populations it should be borne in mind that it is difficult to analyze these patients in terms of efficacy if the definition of the sub-population is too narrow. This is due to the fact that 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 in the context of the European standard of care

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 the context of the situations set out in points 5.1. to 5.7, in which a PAES may be required by the competent authority, the Concept Paper refers to a situation, where a marketing authorization 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.

EUCOPE regards such an appraisal of evidence from clinical trial data as unacceptable as it would not be in line with a basic principle of Directive 2001/83/EC. According to Article 26, a marketing authorization of a medicinal product has to be based on evidence of a favorable risk-benefit balance and sufficient substantiation of therapeutic efficacy.

According to Article 21a (f) of Directive 2001/83/EC, conditional marketing authorizations requesting additional PAES can only be granted, if concerns regarding the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. This is 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 authorization.

We regard it therefore as necessary to leave the situation set out under point 5.4 out of the delegated act.

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

During the life cycle of an authorized 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. However, not in every case there is a need for a reassessment of benefit-risk balance of a medicinal product. For example, there are many medicinal products, which have been on the market for decades and have a soundly established safety profile and an accepted benefit (also medicinal products with well established use status) within a field of treatment or diagnosis. Such medicinal products should not have to prove efficacy in every case whenever a new active substance in the respective field of treatment is released to the market.

Based on the Guideline on Good Pharmacovigilance Practices (GVP), Module VII, for a number of active substances, referred to in Articles 10 I, 10a, 14, 16a of Directive 2001/83/EC, 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 standard 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.

Often, such medicinal 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.

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

In this context, the specificities of Advanced Therapy Medicinal Products (ATMP) would have to be taken into account regarding a PAES, especially regarding manufacturers of tissue-engineered products, which had previously been on the market and now have to undergo a MAA according to the ATMP Regulation 1394/2007. Since the Regulation came into force in 2009, the applicants started their clinical development programs and can thus 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. EUCOPE agrees 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.

We regard it as adequate 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.

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 I of Directive 2001/83/EC, 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.

It follows, that the granting of a 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.

In case of any comments or questions please don't hesitate to contact us (+32.475.202622).

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