PPTA
Plasma Protein Therapeutics Association

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European Commission
Directorate General for Health and
Consumers (SANCO)
B-1049 BRUSSELS

SUBJECT:Public Consultation on post-authorisation efficacy studies

Dear Madame/Sir,

PPTA is the international trade association and standards-setting organization for the world's major producers of plasma derived products and recombinant analogues, collectively referred to as plasma protein therapies. The therapies are used in the treatment of a number of rare diseases. The diseases are often genetic, chronic, life threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. The therapies include clotting factor therapies for individuals with haemophilia A and B and other bleeding disorders; immunoglobulins to treat a complex of diseases in individuals with immune deficiencies; therapies for individuals who have alpha-1 anti-trypsin deficiency, and albumin, which is used in emergency-room settings to treat individuals with shock, trauma, burns, and other conditions.

PPTA welcomes the Commission's initiative to consult with stakeholders on the possibility of a delegated act laying down the situations in which post-authorisation efficacy studies may be required and the added value of the act.

1. A DELEGATED ACT —WHAT IS THE ADDED VALUE?

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.

No, in our opinion a delegated act on situations in which post-authorisation efficacy studies are requested by regulatory Authorities will not facilitate post-authorisation life cycle requirements (except for orphan indications) for the following reasons:

1. Additional legislation is not necessary as the critical needs for PAES are appropriately covered under existing boundaries including conditional and exceptional marketing authorization provisions as well as in the context of a serious PV signal.

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2. For biological medicinal products including plasma derived medicinal products and their recombinant analogues current guidelines already recommend post-licensure (long-term efficacy) studies in order to collect additional data to ensure consistency in long-term treatment compared to pre-licensure clinical studies. As examples may serve *The Guideline on the clinical investigation of human plasma-derived von Willebrand factor products (CPMP/BPWG/220/02), Guideline on clinical investigation of recombinant and plasma derived factor VIII products* (*EMA/CHMP/BPWP/144533/2009), Guideline on clinical investigation of recombinant and plasma derived factor IX products* (*EMA/CHMP/BPWP/144552/2009)* and other product specific guidelines. Consequently there is no need for a particular delegated act on post-authorisation efficacy studies for plasma derived medicinal products and their recombinant analogues.
3. Expansion beyond the current PAES boundaries has the potential for adding significantly to the cost of product development and may have a detrimental impact on bringing new products to market as well as the ability to maintain current licenses. For example, the commercial drivers for a company to conduct additional efficacy studies as new therapies come to market should be sufficient to drive conduct of such studies if financially advantageous. The determination that additional costly efficacy studies may be required *in certain cases*, to *complement* existing data opens the door for potential expansion of MAA holder responsibility in the absence of a clear safety signal warranting such information.
4. There is no clear requirement that the Authority provide a “burden of proof” to justify the requirement for additional efficacy studies. A requirement to merely “compliment” existing data would be unduly burdensome to MAA holder.
5. Current legislation requires the proof of efficacy prior to licensure. As mentioned in the EC public consultation letter and referring to *Recital 10 of Directive 2010/84/EU,* a strengthened pharmacovigilance system may not lead to the premature granting of marketing authorizations, but <u>some</u> medicinal products (including new active substances, biological products and biosimilars) are authorized subject to additional monitoring. Post-authorisation efficacy studies cannot be used to compromise the initial level of evidence that is required to grant a standard marketing authorisation. Consequently PAES do not represent a help, but rather a burden to developers of new treatments.
6. For orphan and ultra orphan indications, post-authorisation efficacy studies under real life conditions or patient registries might be an option in order to facilitate earlier (conditional) Marketing authorization and availability of treatment for patients.

<u>Conclusion/recommendation</u>:

1. It is acknowledged that a delegated act might increase legal certainty and clarity regarding requests from Authorities to conduct post-licensure clinical studies.
2. However, *Recital 10 of Directive 2010/84/*EC clearly states that <u>some</u> medicinal products are subjects to additional monitoring, on the other hand, in

practice, it is highly probably that Authorities might favor interpretation as obligatory requirement for all new MAs to become effective, and not as supplementary clinical data for some medicinal products.

3. According to *Article 290 of the Treaty on the Functioning of the European Union* delegated acts are non-legislative. Although a delegated act is not a legally binding document, if EC defines situations in which post-authorisation efficacy studies are required, on short or long-term it is likely that it will become an obligatory requirement. As a result the burden and costs for applicants/sponsors of any new active substance and/or biological medicinal products including biosimilars will increase with negative impact on developmental programs for new medicinal products.
4. We recommend, especially for the development of biological products in orphan and ultra-orphan indications, an increase of the possibility to conduct post-licensure studies (under real-life conditions) and allow licensure with a limited clinical dataset. This would speed up the availability of new treatments for a particular vulnerable population when no treatment is available. However a delegated act is not necessary.

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

2. 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?

No, in our opinion post-authorisation efficacy studies should not be requested for the purpose of generating efficacy data, since these data have already been generated in (placebo) controlled clinical studies prior to licensure. As mentioned in *Recital 10 of Directive 2010/84/EU* a strengthened system of pharmacovigilance may not lead to the premature granting of marketing authorisations. The purpose of the additional monitoring and the PV system is to compile safety data rather than efficacy data.

1. The difficulty in designing an appropriate study, with adequate controls and sample size could require a substantial financial commitment to the MA holder. The feasibility to conduct an efficacy study post approval needs to be carefully considered as the efficacy of the product has already been demonstrated. The requirement to demonstrate additional efficacy in response to a requirement to conduct a study to “compliment” the existing data does not seem justified unless there is a clear signal that implicates a change in efficacy of the marketed product.
2. Ability to monitor post-approval effectiveness should be considered acceptable since efficacy has already been demonstrated in controlled clinical studies prior to traditional licensure. Assessment of effectiveness is more reflective of “real world” use and should be considered a valid approach to determine if there has been an impact on the performance of the product once introduced into the market. Developing enhanced PV methods to allow for robust effectiveness studies would be an area that could benefit the MA holder.

3. The requirement for additional PAES should not be associated with the desire to generate data to support recommendations and decisions on the initial uptake by pricing and reimbursement authorities. The MA holder should be responsible for determining whether additional studies could be funded to support their commercial competitiveness in these areas.
4. For indications in treatment of infections, the effectiveness of treatments might only be detectable by national surveillance programmes. This is in particular the case for epidemical or nosomial cases.
5. The *Note for guidance on evaluation of vaccines (CHMP/VWP/164653/2005)* "Vaccine effectiveness reflects direct (vaccine induced) and indirect (population related) protection during routine use. Thus, the assessment of vaccine effectiveness can provide useful information in addition to any pre-authorisation estimates of protective efficacy. Even if it was not feasible to estimate the protective efficacy of a vaccine pre-authorisation it may be possible and highly desirable to assess vaccine effectiveness during the post-authorisation period." However, for licensure of vaccines Authorities require placebo-controlled, randomized studies pre-Authorisation. Consequently post-licensure effectiveness studies would be requested in addition to pre-authorisation efficacy studies and might be an obligation in the context of the risk management plan. However, since vaccine effectiveness studies in the European population do not only apply to one single vaccine, but need to be assessed across vaccines. As stated in the above mentioned guideline "It may not be possible or appropriate for applicants to conduct studies to estimate vaccine effectiveness since coordinated regional or national networks may be necessary to ensure that cases are reliably detected".

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

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

1.2. Studies on combinations with other medicinal products

1.3. Studies in sub-populations

1.4. Studies in the context of the European standard of care

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

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

1.7. Studies in everyday medical practice

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?

Handling of missing data in special situations is a challenge to all marketing authorization holders. At the time of initial MA a limited number of subjects have been studied in clinical trials – often in global clinical trials in various regions of the world. However, current legislation requires renewal applications and assessments with the aim to re-evaluate the risk/benefit after a certain point of time after marketing. PSURs and PV system play important roles in this process. Studies should focus on those complementary areas, e.g. age subsets, where the largest differences to the source population are expected. An extrapolation concept as proposed in EMA *Concept paper on extrapolation of efficacy and safety in medicine development (EMA/129698/2012)* would be helpful to reduce costs and unnecessary trials in specific target population. Post-authorisation data in some of the proposed areas might be collected through post-authorisation patient registries.

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

1. We agree that PAES would be appropriate for item 5.1. determining clinical outcome for therapeutic situations where surrogate endpoints support the generation of efficacy data prior to availability of clinical endpoints e.g. severe disability, amputation, mortality etc. These surrogate endpoints help the assessment of new treatments in severe conditions and might facilitate the availability of medicinal products in life-threatening, severe disabilitating and orphan and ultra-orphan indications.
2. Not in all situations a placebo-controlled study prior to licensure is feasible and ethically justifiable (intensive care and emergency products).

1.2. Studies on combinations with other medicinal products

1. We do not agree with the PAES as a requirement since the ability to execute such studies would provide an undue burden to the MA holder. The frequently changing landscape of new approved therapies would create regulatory uncertainty as to when and who would decide that there is a need for MA holder to study these therapies. The commercial need to assess the use of the product in these situations should be the driver for decision to conduct such studies for differentiation of a product.
2. Effects on safety of vaccines need to be considered when two vaccines are administered concomitantly (separate limbs). This applies in particular for administration in infants. While it might be feasible to perform a formal assessment on immunogenicity interference in adults, this might not be feasible for infants since parents might not provide consent to clinical studies. As vaccines safety aspects are sufficiently discussed in the *Note for guidance on evaluation of vaccines (CHMP/VWP/164653/2005)* there is no need to cover vaccines in a delegated act.

1.3. Studies in sub-populations

1. As a rule, prior to MA, large (double-blind, placebo-controlled) studies are conducted to prove efficacy and safety of a new treatment. It is not feasible to design a clinical study including participants reflecting all sub-groups of the population regarding ethnicity, co-morbidity, age-groups, gender etc.
2. In our opinion, a requirement to conduct studies in sub-populations after MA is too open ended and can result in a financial burden that is not clearly justified based on evidence that the particular subpopulation responds differently to the product and will have a high rate of uptake in this population. The requirement for conduct of a study in subpopulations may result in a regulatory burden to design and execute studies that are not feasible or require considerable product development costs to the MA holder as has been seen with the expansion of the requirements for pediatric formulations and studies beyond those originally studied and licensed for use in the intended adult population. It should be acceptable to state in the SmPC when data are not available in relevant subpopulations.
3. Sponsors of new medicinal products might decide to exclude certain subpopulations from the label when they were not included in the clinical trial.
4. In most clinical concepts for new medicinal products under development pregnant women are excluded which leads to warnings and contraindication information in the SmPC. How shall pregnant women be handled in the context of post-authorisation efficacy studies?
5. For biosimilar medicinal products the Guideline on similar biological medicinal products containing monoclonal antibodies; non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010) clearly state that “Clinical studies in special populations like the paediatric population or the elderly are normally not required since the overall objective of the development programme is to establish comparability”. Since the efficacy of the medicinal product has been shown by the reference product (meaning a biological product licensed in the European Union) there is no need for biosimilars to conduct post-licensure efficacy studies in subpopulations. Consequently biosimilars can be exempted from these studies in a delegated act.
6. As discussed in the “concept paper on the need for a guideline on subgroup analysis in randomized clinical trials” (EMA/CHMP/EWP/117211/2010), a guidance document on methodological issues relating to subgroup analyses would be appreciated. However regulatory authorities need to be wary about the over interpretation of subgroups.
7. An extrapolation concept as proposed in EMA Concept paper on extrapolation of efficacy and safety in medicine development (EMA/129698/2012) might help reduce clinical studies to the amount really needed to fill scientific gaps especially for biological medicinal products.

See response to consultation item 5.

1.4. Studies in the context of the European standard of care

1. The *ICH E5 guideline (ethnic factors in the acceptability of foreign clinical data CPMP/ICH/289/95)* was adopted with the purpose to facilitate the registration of medicinal products among different geographic regions by recommending a framework for evaluating the impact of ethnic factors upon the efficacy or safety of a product. Appendix D of ICH E5 summarizes factors that might make a medicine sensitive to ethnic factors e.g. pharmacological class, gender, age. In case of a linear pharmacokinetic, little potential for drug-drug interactions or drug-diet interaction studies in the context of European standard of care are not expected.
2. The *Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population (EMEA/CHMP/EWP/692702/2008)* summarizes background research on a number of medicinal products and concludes that extrapolation of data from global clinical studies to the European population might be difficult due to a number of extrinsic factors e.g. medical practice (differences in co-medication), disease definition (medical conditions differ across the world) and study population (severity and clinical stage of the disease in question). Additionally life style, social and economic environment, genetic factors and genotype pathogen strain might impact the outcome.

Consequently for global clinical studies, subgroup analysis including only European subjects might be an option pre-licensure (e.g. for orphan indications).

3. For Biosimilars, the "*Guideline on similar biological medical products containing monoclonal antibodies – non-clinical and clinical issues*" *(EMA/CHMP/BMWP/403543/2010)* states for pre-licensure studies "The inclusion of patients from non-European countries is generally possible if there are no intrinsic differences, but it may increase heterogeneity. Knowledge of efficacy and safety of the reference mAb in a particular region may be necessary in order to prospectively define an equivalence margin. Stratification and appropriate subgroup analyses are normally expected if patients from different global regions are included in order to demonstrate consistency with the overall effect. Diagnostic and treatment strategies should be comparable in order to prevent the influence of extrinsic factors."
4. Studies in the context of the European standard of care should not be the burden of an individual company, but should rather be a joint effort of pharmaceutical companies, healthcare professionals, health authorities etc. It would be an option that the European centre for disease prevention and control (ECDC) collects and evaluates relevant scientific and technical data and coordinates the European networking of bodies.

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

1. In our opinion Marketing Authorisation holders are obliged to continuously

keep their dossiers updated. Consequently an obligation for additional studies linked to a change in the understanding of the standard of care for the disease is not deemed necessary.

2. The assessment of the benefit and risk assessment of a licensed product shall be primarily based on the safety and efficacy of a medicinal product. Thus, it is suggested to focus on considerations to conduct additional clinical studies to support the benefit-risk assessment or effectiveness of licensed products as recommended by the CIOMS Working Group IV, 1998 (Report on the Balance for marketed-drugs: evaluating safety signals.)

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

1. The Regulation on Advanced Therapy Medicinal products (Regulation (EC) No 1394/2007) and the Paediatric Regulation (Regulation (EC) No 1901/2006) already refer to the potential need for long-term follow-up.
2. Long-term efficacy studies after initial Marketing Authorisation should not be required. PAES as PV surveillance should be adequate to identify changes in product performance. Long-term efficacy and safety is collected through the PV system and is an increasing request for inclusion in the risk management plan of new active substances, biological products and biosimilars.
3. The Note for guidance on evaluation of vaccines (CHMP/VWP/164653/2005) recommends “As appropriate to the vaccine and its anticipated mode of use, the potential long-term impact of vaccination on the epidemiology of the vaccine preventable infection(s) should also be addressed in the post-authorisation period”. However these observational studies or subject registries have high probability of bias. Consequently long-term efficacy or effectiveness studies in the view of epidemiology should be a cross-company, cross-national, cross-European effort coordinated by ECDC.
4. There are already a number of guidelines for the development of biological medicinal products that recommend post-licensure efficacy studies. For example, The Guideline on the clinical investigation of human plasma-derived von Willebrand factor products (CPMP/BPWG/220/02). “To ensure consistency in the long-term between data from the clinical studies and from routine use, a post-marketing study should be undertaken and a protocol submitted with the dossier”.

Consequently, for biological medicinal products there is no need for an additional delegated act requesting this kind of studies.

1.7. Studies in everyday medical practice

Studies in everyday medical practice should not be required PAES as PV surveillance should be adequate to identify changes in product performance. A clear signal that a change in product performance has occurred would warrant a request for PAES. Market needs for differentiation of the product should be considered as the key driver in a MAA holder determining the need to conduct additional studies to

address these situations (inclusion in the SmPC/PIL as to long term efficacy and use with changes in SOC during medical practice occurring over time)

Conclusion/recommendation

Post-authorisation efficacy studies might be an option in life-threatening, severe-disabilitating or orphan indications especially if, at time of initial MA, only limited clinical data are available. In these conditions Authorities should increasingly allow for conditional approval or under exceptional circumstances with an obligation to conduct PAES. Supplementary information on safety issues evolving in everyday medical practice, in the context of European standard of care or in long-term use will be collected through a strengthened PV system and measures need to be defined in the RMP which is a legal requirement at initial MAA.

4. STUDY DESIGN

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

1. As discussed in the "*Concept paper on the need for a guideline on subgroup analysis in randomized clinical trials" (EMA/CHMP/EWP/117211/2010*), a guidance document on methodological issues relating to subgroup analyses would be appreciated.
2. Design and Sample size considerations and pre-specification of statistical analysis are of particular importance for a valid statistical inference, also in the context of post-authorisation studies (in everyday medical practice).
3. Particular considerations should be made for vaccines. As laid out in the *Note for guidance on evaluation of vaccines (CHMP/VWP/164653/2005)* it might be highly desirable to assess vaccine effectiveness after authorization. However, if vaccine effectiveness is estimated from observational studies, there is no randomization step and a high potential to introduce bias. Consequently secondary attack rate studies might be an option. In these circumstances efficacy estimates are expected to be highly affected by confounding factors and therefore biased in the population under evaluation. While Non-interventional studies for the purpose of collecting efficacy data might be of interest for Healthcare professionals, they might not be accepted by licensing Authorities for update of the SmPC.
4. Sponsors / MAHs need to carefully choose the efficacy endpoint(s) and timelines as mistakes in assumptions or the design of post-authorisation studies risk a suspension of the Marketing authorization if interpreted as lack of efficacy.

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.

Issues:

1. It should be clarified in which situations regulatory authorities should require to see subgroup analyses that companies have not otherwise submitted.
2. What are the criteria for "old" or well-established medicinal products when the benefit was assessed with different criteria?

3. Are there special requirements for the conduct of PAES?
4. What are the procedures and requirements for PAES for products with the same active ingredient and different brand names?
5. What are the specific requirements for Biosimilars?
6. What are the efficacy requirements for pregnant women given the fact that most PVs aim to collect safety information only for non-pregnant women?

Further comments:

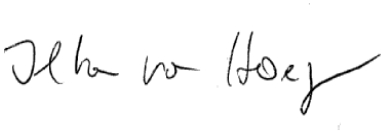
1. A specific guideline for the conduct of PAES or alternatively a clarification in the RMP requirements would be appreciated.
2. There might be a need to have studies covering multiple products with the same active ingredient and compare to comparators, establish registries collecting data on co-morbidities and co-medication etc. These registries might best be handled by ECDC.
3. We support the *EMA Concept paper on extrapolation of efficacy and safety in medicine development (EMA/129698/2012)* in order to avoid unnecessary studies in target populations. It is recommended to develop an extrapolation concept using a systemic analysis of the available data (in-vitro, preclinical, clinical) in order to develop a hypothesis regarding the similarity of the disease and the similarity of response to intervention between source and target populations. The EMA Extrapolation working group proposes the development of an algorithm for extrapolation in all areas of medicine development. In the context of a biological medicinal product development a checklist could be development to assess source and target population: (1) Similarity of disease (subtypes based on aetiology, pathophysiology, clinical manifestation, progression (indicators)). (2) Similarity of medicine disposition & effect (mode of action, PK, PD). (3) Similarity and applicability of clinical efficacy and safety endpoints. The resulting rationale should help select the extrapolation strategy:
    - No extrapolation: full study program in the target population
    - Partial extrapolation: reduced program in target population depending on the magnitude of expected differences and certainty of assumptions
    - Full extrapolation: some supportive data to validate the extrapolation concept
4. It is acknowledged that compilation of data in the context of European standard of care, everyday medical practice and interaction with other medicines would make sense given the fact that clinical development for licensure of medicinal products is conducted globally including clinical sites outside of Europe. However this should be a joint effort between companies and Authorities and should not be an obligation for an individual pharmaceutical company. These aspects need to be evaluated for classes of pharmaceuticals / active ingredients. Consequently, a proposal would be that the European centre for disease prevention and control (ECDC) collects and evaluates relevant scientific and technical data and coordinates the European

networking of bodies. The results should be summarized in a publicly available report and be used for developing Core SmPCs. This approach would especially be helpful for biological medicinal products (both plasma and recombinant origin).

Medicinal products for orphan indications where only limited number of patients are eligible for the treatment should be handled individually since the development is extremely expensive and requires substantial efforts in scientific basis research as well. For pharmaceutical products in orphan indications it might be an option to establish patient registries post-licensure and collect data in the context of daily life. These registries could be proposed as post-licensure measure in the risk management plan which is a legal requirement in the context of initial MAA.

We hope that you will find our comments constructive and helpful. We remain at your disposal, should you have any questions or need further clarification.

Sincerely Yours,



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