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Response to the consultation paper 'Delegated Act on Post-Authorisation Efficacy Studies' PCPAES/12/01 — Public Consultation on PAES

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The European Scientific Cooperative on Anthroposophic Medicinal Products (ESCAMP, www.escamp.org) is an independent scientific cooperative. The aim of ESCAMP is to develop the scientific basis for a permanent regulatory framework for anthroposophic medicinal products in Europe. The issues raised in the consultation paper 'Delegated Act on Post-Authorisation Efficacy Studies [PAES] from the European Commission' (PCPAES/12/01, henceforth abbreviated PCPAES) concern ESCAMP. See also the Conflict of interest statement, below.

Introduction

The **legal context** for the proposed Delegated Act is the adoption of a new EU pharmacovigilance legislation in 2010, referring to the *"possibility of requesting the marketing authorisation holder to conduct [PAES] complementing efficacy data that are available at the time of the initial authorization."* (DA, p.3) This is further elaborated: *"It is set out in the legislation that, in the case of an initial marketing authorisation, PAESs may be required where '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'. Following the granting of the marketing authorisation, they may be imposed 'when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly'."* (PCPAES, p.6)

PAES are currently used *"in the framework of conditional and exceptional marketing authorisations or as a follow-up to a serious pharmacovigilance signal or efficacy concern"* (PCPAES, p.6). Thus, PAES "*have a clear regulatory purpose".* (PCPAES, p.6)

Two **possible changes to the present framework for PAES use** are:

- Extension: *"the new provisions in the 2010 legislation seem to imply that the boundaries for these studies have been expanded beyond their existing use"* (PCPAES, p.5)
- Clarification: *"determine the situations in which post-authorisation efficacy studies may be required"* (PCPAES, p.3) and *"a more global and systematic approach to post-authorisation efficacy studies… Instead of referring to postmarketing studies in different pieces of legislation or hinting at their existence in several articles…"* (PCPAES, p.5)

The PCPAES does not present any explicit scientific evidence or elaborated arguments for an **extension** of the present framework for PAES use but rather aims at a **clarification** of the framework, by describing seven *"situations in which a post-authorisation efficacy study may be required"* (PCPAES, Chapter 5. pp.8-11). These situations are defined by particular properties of the patient groups, the medicinal products in question, the standards of care for the disease, or the clinical studies submitted to regulatory authorities for initial market authorisation.

Comments on the PCPAES in general and on Consultation item No 1 (Delegated act on the situations in which a PAES may be required)

The PCPAES concerns the legal boundaries for a regulatory decision to require PAES – as a result of new concerns about the efficacy of a medicinal product on the market. Such decisions will not only take the efficacy of the product into consideration, but also possible risks. Accordingly, the PCPAES issue can be seen in the context of benefit-risk assessments and their use to inform regulatory decision making, in this case the decision to act by requiring PAES or not to act. This is also clear from the context of the new pharmacovigilance as background for the PCPAES (see above).

As a general principle, the criteria for such **regulatory action** should be **appropriate to the concerns** raised about the benefit-risk profile of the product; in other words: they should neither be too lax (risking regulatory inactivity where action would be necessary), nor too strict (leading to regulatory requirements of many unnecessary PAES, which would be unethical from a research ethics perspective, and also uneconomic). In addition, regulatory decision making should as far as possible be based on objective criteria, leading to a consistent, transparent practice, in order to prevent inequity and unpredictable situations for marketing authorisation holders, doctors, and patients.

In this context, the contribution of the PCPAES document is to list and describe different situations where PAES may be required. Although of value, we do not think this alone is sufficient to assure appropriateness, objectivity, consistency, and transparency of regulatory practice towards PAES.

As the PCPAES demonstrates (Chapter 5), the different situations for which PAES may be considered are very disparate in regard to patient characteristics, effects and risks of the products and in regard to several features of the clinical studies required for market authorisation (e.g. outcome measures, follow-up periods, or even study design). Accordingly, the nature and seriousness of concerns leading regulatory authorities to consider PAES, the impacts of such PAES, and consequently the threshold for the authorities to require PAES may vary substantially across different situations and medicinal products. Any delegated act on PAES would therefore have to include a framework in order to tackle this variability of settings for PAES. Since regulatory decisions an PAES will be based on benefit-risk assessments (see above), such a framework can and should be constructed with due consideration to the principles, methods and tools for benefit-risk assessment of medicinal products [1].

It is therefore highly surprising that the PCPAES document, although mentioning benefit-risk assessments repeatedly, does not comment on the available methodologies and tools for benefit-risk assessment and associated decision making – especially since the European Medicines Agency recently carried out a large, comprehensive Benefit-risk Methodology Project with the main objective to *"improve the current practice of benefit-risk assessment for medicinal products, with an aim to increase the consistency and transparency of the regulatory process"* (EMA/213482/2010, Human Medicines Development and Evaluation, 30 March 2010).

In order to construct a satisfactory legal framework for PAES, appropriate methodology and tools for risk-benefit assessment should be incorporated and adapted for the specific PAES situation (concerns vs. impact of PAES). The framework might for example include specific tools for the assessment of the concerns raised:

- seriousness of the concerns (e.g. severity of newly identified potential risk, quantification of potential reduction of efficacy, number of patients affected)
- quality of evidence for concerns (e.g. clinical studies, case reports and case series, extrapolation from animal or in-vitro experiments, pathophysiological speculation)
- admitted sources for concerns (e.g. peer-review publications, research or pharmacovigilance reports)

Conclusions on the PCPAES in general

A delegated act on PAES should not aim to **extend** of the present framework for PAES use, but should focus on the **clarification** of the present framework. Reason: No explicit scientific evidence or elaborated arguments for such an extension have been presented in the PCPAES.

Conclusions on Consultation Item 1

We do not think that a delegated act which is based solely on a description of the situations in which a PAES may be required will be of added value. Before the Commission considers bringing forward a draft delegated act, the use of available benefit-risk assessment methodologies and tools in order to increase the consistency and transparency of regulatory practice towards PAES must be addressed. Reasons are stated above.

Comments on Consultation items No 2 and 6 (Efficacy vs. effectiveness + Study designs)

The PCPAES rightly refers to an ambiguity in current EU legislation, which refers to *"[PAES] … aimed at collecting data to enable the assessment of … efficacy of medicinal products for human use in everyday medical practice"* (PCPAES, p.8). The assessment of treatment effects *"in everyday medical practice"* would clearly be understood as 'effectiveness assessment' according to current terminology, while the concept of 'effectiveness' itself is not defined in the relevant EU legislation.

Effectiveness in everyday medical practice is commonly evaluated in pragmatic trials, a pragmatic trial being defined as *"a randomised controlled trial whose purpose is to inform decisions about practice"* [2]. Accordingly, pragmatic trials, like their counterpart 'explanatory trials' (roughly equivalent to the term 'controlled clinical trial' used in medicinal product regulation and in the PCPAES) are both interventional studies, incorporating the key design feature of random assignment of patients to intervention or control groups [3]. The two designs differ in terms of research question, setting, patients, intervention, outcome measures, and relevance to practice (Table 1).

Some descriptions of pragmatic trials in the PCPAES are unclear (*"pragmatic trials outside the scope of a controlled clinical trial setting"* (PCPAES, p.8)) or incorrect (*"non-randomised design of the study or [pragmatic] trial"* (PCPAES, p.8), *"non-interventional studies, including pragmatic trials"* (PCPAES, p.11)) and need to be amended.

Table 1, copied from [2]: Key differences between trials with explanatory and pragmatic attitudes, adapted from a table presented at the 2008 Society for Clinical Trials meeting by Marion Campbell, University of Aberdeen

Question	Efficacy—can the intervention work?	Effectiveness—does the intervention work when used in normal practice?
Setting	Well resourced, "ideal" setting	Normal practice
Participants	Highly selected. Poorly adherent participants and those with conditions which might dilute the effect are often excluded	Little or no selection beyond the clinical indication of interest
Intervention	Strictly enforced and adherence is monitored closely	Applied flexibly as it would be in normal practice
Outcomes	Often short term surrogates or process measures	Directly relevant to participants, funders, communities, and healthcare practitioners
Relevance to practice	Indirect—little effort made to match design of trial to decision making needs of those in usual setting in which intervention will be implemented	Direct—trial is designed to meet needs of those making decisions about treatment options in setting in which intervention will be implemented

Among observational study designs, *"analysis of patient registries"* are mentioned (PCPAES, p.7). Such registry or database analyses are often retrospective and rely on data collected for another purpose than scientific research (e.g. cost reimbursement or quality assurance). Prospective controlled observational studies (also called non-randomised controlled trials or cohort studies) on the other hand, share with randomised trials the prospective collection of data collected for study purposes. This observational study design is relevant (e.g. see below on vaccines) and should also be explicitly mentioned.

To sum up, the designs available for PAES include one design tailored to evaluate efficacy (explanatory randomised trials / controlled clinical trials) and several designs that can be used to evaluate effectiveness (pragmatic randomised trials, observational designs such as cohort studies or database analyses). In this context, the PCPAES holds explanatory trials to be the generally preferred design: "*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"* and *"generally speaking [PAES] should focus on generating efficacy data"*. However, according to the description in Table 1, pragmatic randomised trials would be better suited than exploratory randomised trials to assess

effects of medicinal products in everyday medical practice – which is one of the applications of PAES explicitly mentioned in the legislation (PCPAES, p.8). Furthermore, this and other specific properties of pragmatic trials (Table 1) are prominently featured in the PCPAES, Chapter 5: *"Situations in which PAES may be required"*:

- need for more relevant, long-term outcomes (Chapters 5.1 and 5.6)
- flexible intervention [which may include co-medications], (Chapter 5.2)
- broader range of patient characteristics (Chapter 5.3)
- and studies in normal, everyday practice (Chapter 5.7)

Accordingly, pragmatic randomised trials are at least highly relevant– or perhaps even the preferred study design – for many PAES situations.

The use of observational designs for PAES are implied in the PCPAES (p. 11) with a reference to a Note for guidance on the clinical evaluation of vaccines, issued by the European Medicines Agency (EMEA/CHMP/VWP/164653/2005), according to which "*pre-authorisation studies of protective efficacy are not always necessary or feasible*" (EMEA Note, p.10), while PAES (the assessment of *"vaccine effectiveness during the post-authorisation period",* EMEA Note, p.14) can be conducted using randomised trials or "*observational cohort studies*" (EMEA Note, p.14). Thus, PAES are not a priori restricted to randomised trials. This is not against the principles of scientific or evidence based medicine: The relative merits of randomised trials and observational studies have been subject to a long [4-8] and still ongoing scientific debate [9;10]. Randomised trials have a number of limitations, including generalisability problems as discussed in the PCPAES, but also various threats to internal validity, against which randomisation does not protect (e.g. unmasking of blinding, attrition bias, non-compliance with prescribed medication intake in intervention group, use of study medication in control group) [5;11]. Accordingly, the GRADE system, the current state-of-the-art system for grading the quality of evidence from clinical studies [12], whilst starting with randomised trials placed 'above' observational studies, allows for 'upgrading' and 'downgrading' of both types of studies according to specific study features [13].

Conclusions on Consultation Items No 2 and 6

The descriptions of pragmatic trials and observational studies need some correction and expansion, as described above.

We do not agree that *"generally speaking [PAES] should focus on generating efficacy data"*. When planning a PAES, the study design should be suited to the main research question, with due consideration of study feasibility. If the research question is centred on efficacy in an “ideal” setting, explanatory randomised trials (roughly equivalent to 'controlled clinical trials') would be the preferred design. If effectiveness under everyday practice is more important, pragmatic randomised trials (see Table 1 above) and, for some situations, also well-designed observational studies or analyses, are the preferred candidates.

Comments on Consultation item No 3 (Section 5.4: Studies in the context of the European standard of care)

In this section different standards of care in two regions (EU vs. the rest of the world), and possible effects of such differences on the generalisability of study results are discussed. The general argumentation is clear, but the exact phrasing should be re-written to improve clarity, since both regions (EU and the rest of the world) include countries with very different standards of care.

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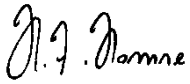

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Conflict of interest statement

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