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HEALTH AND CONSUMERS DIRECTORATE-GENERAL

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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

Deadline for Public Consultation: 18 February 2013

This document does not represent an official position of the European Commission. It is a tool for exploring the views of interested parties. The statements and conclusions contained in this document do not prejudge the content of the future report by the European Commission.

Contact:

Responses should be sent preferably by e-mail to sanco-pharmaceuticals-D5@ec.europa.eu, or by post to the Directorate-General for Health and Consumers, Unit SANCO/D/5, BE-1049 Brussels.
The subject of the letter/e-mail should refer to 'PCPAES/12/01 — Public Consultation on PAES'.

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I. ABOUT THE CONSULTATION

A. INTRODUCTION

The EU pharmacovigilance system is now one of the most advanced and comprehensive systems in the world, and represents a robust and transparent instrument to ensure a high level of public health protection throughout the Union. Pharmacovigilance rules are a key element in the life-cycle management of medicinal products. They are necessary for the protection of public health in order to prevent, detect and assess adverse reactions to medicinal products for human use placed on the Union market.

The EU pharmacovigilance legislation has recently been subject to a major review that led to the adoption of new legislation in 2010, namely Directive 2010/84/EU[1] and Regulation (EU) No 1235/2010[2]. While the main focus of pharmacovigilance is the safety of the product, any new information received or new pharmacovigilance signals detected may have a potential impact on the overall product assessment and more particularly on its benefit-risk balance.

In order to streamline and clarify the regulatory tools of competent authorities for imposing certain obligations on marketing authorisation holders, Directive 2001/83/EC and Regulation (EC) No 726/2004 summarise the conditions, restrictions and obligations under which a marketing authorisation may be granted or which may be requested following the granting of the initial marketing authorisation.

In this context, the new pharmacovigilance legislation refers to the possibility of requesting the marketing authorisation holder to conduct post-authorisation efficacy studies (PAESs), complementing efficacy data that are available at the time of the initial authorisation.[3] In order to determine the situations in which post-authorisation efficacy studies may be required, the Commission is mandated to adopt, by means of a delegated act, measures supplementing the provisions of Directive 2001/83/EC and Regulation (EC) No 726/2004[4].

The purpose of this consultation paper is to support the Commission in further exploring the application of such a delegated act to post-authorisation efficacy studies and to seek views and feedback from stakeholders.

The consultation paper is now being put out for public consultation. Replies or comments should be submitted by 18 February 2013 at the latest.

B. CONSULTATION TOPICS

The consultation text is supplemented by a number of specific consultation items in boxed text raising questions to which the Commission seeks input from interested parties.

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1 Directive 2010/84/EU of 15 December 2010 amending, as regards pharmacovigilance Directive 2001/83/EC, OJ L 348, 31.12.2010, p. 74.

2 Regulation (EU) No 1235/2010 amending, as regards pharmacovigilance Regulation (EC) No 726/2004, OJ L 348, 31.12.2010, p. 1.

3 Articles 9(4)(cc) and 10a(1) of Regulation (EC) No 726/2004 and Articles 21a and 22a(1) of Directive 2001/83/EC.

4 Article 10b of Regulation (EC) No 726/2004 and Article 22b of Directive 2001/83/EC.

Respondents are invited to address those points specifically. Moreover, comments on any other part or aspect are welcome.

C. HOW CAN I CONTRIBUTE?

Stakeholders are invited to comment on this consultation paper, and on the boxed text in particular, by 18 February 2013 at the latest. Responses should be sent (preferably by e-mail) to sanco-pharmaceuticals-D5@ec.europa.eu, or by post to the Directorate-General for Health and Consumers, Unit SANCO/D/5, BE-1049 Brussels. The subject line of the letter or e-mail should refer to 'PCPAES/12/01 — Public Consultation on PAES'.

When you submit your comments and responses, please state whether you are a stakeholder association or a private individual. If you represent an association, please indicate clearly what type of association it is (patients, health professionals, manufacturers, marketing authorisation holders, etc.). If you represent a company, please state whether it falls within the EU definition of a small and medium-sized enterprise (i.e. less than €50 million annual turnover and fewer than 250 employees).

An acknowledgement of receipt will be issued for each contribution received.

The contributions received and the identity of the contributors will be made publicly available on the 'Public health' website[5], unless the contributor objects to the publication of his or her personal data on the grounds that it would harm his or her legitimate interests. In this case the contribution may be published in anonymous form. Otherwise the contribution will not be published nor, in principle, will its content be taken into account. For more information on the processing of your personal data in the context of this consultation, you should read the specific Privacy Statement available on the Public health website.

Professional organisations are invited to register in the Union's Register of Interest Representatives (http://europa.eu/transparency-register/index_en.htm) set up as part of the European Transparency Initiative to provide the Commission and the public at large with information about the objectives, funding and structure of interest representatives.

D. WHAT WILL HAPPEN NEXT?

All contributions will be carefully analysed. Any subsequent Commission proposal will build on the consultation.

[5] http://ec.europa.eu/health/human-use/index_en.htm.

II. THE CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

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

Post-authorisation efficacy studies are not a new feature in the European Union's regulatory framework for human medicinal products but have been around for quite some time, especially in the context of conditional marketing authorisations and marketing authorisations under exceptional circumstances[6]. Likewise, the Paediatric Regulation[7] and the Regulation on advanced therapy medicinal products[8] refer to the possibility of making the performance of specific post-marketing studies a condition of the marketing authorisation in cases of particular concern.

The added value that the 2010 pharmacovigilance legislation brings is a more global and systematic approach to post-authorisation efficacy studies. Instead of referring to post-marketing studies in different pieces of legislation or hinting at their existence in several articles, the new provisions bring the instrument to the forefront, listing it together with other conditions to which a marketing authorisation for human medicinal products could be made subject.

In this context, the Commission is invited to provide more clarity on the scope of this condition by adopting supplementary measures determining the situations in which post-authorisation efficacy studies may be required by means of a delegated act. The Commission has been given some discretion as to whether it should adopt such an act: in accordance with Article 10b of Regulation (EC) No 726/2004 and Article 22b of Directive 2001/83/EC the Commission *may* adopt a delegated act. On the other hand, it is acknowledged that other provisions of Regulation (EC) No 726/2004 and Directive 2001/83/EC seem to encourage the Commission to make use of this empowerment, given that from a public health perspective it may be necessary, in certain cases, to complement the data available at the time of authorisation with additional data about the efficacy of a medicinal product.

A delegated act may prove particularly valuable in providing legal certainty and clarity as to the regulatory scope of a PAES. However, the competent authorities will still need to justify the imposition of such an obligation on a case-by-case basis, taking into account the characteristics of the product concerned.

It is recognised that the new provisions in the 2010 legislation seem to imply that the boundaries for these studies have been expanded beyond their existing use in the framework of conditional and exceptional marketing authorisations or as a follow-up to a serious pharmacovigilance signal or efficacy concern.

Against this background, it could be argued that a delegated act would be in the interest of public health and regulatory clarity.

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6 Article 14 of Regulation (EC) No 726/2004 and Article 22 of Directive 2001/83/EC.

7 Article 34 of Regulation (EC) No 1901/2006.

8 Article 14 of Regulation (EC) No 1394/2007.

Arguably, the disadvantage of any kind of regulatory setting, once established, is the difficulty to react quickly to emerging situations which have not already been addressed in the act concerned, as such reactions may first require an amendment to cover the new situation.

2. THE CONTEXT OF A POST-AUTHORISATION EFFICACY STUDY

In accordance with Article 290 of the Treaty on the Functioning of the European Union, delegated acts are non-legislative acts of general application to supplement or amend certain non-essential elements of a regulation or a directive. The recitals to the 2010 legislation state that the delegated act on post-authorisation efficacy studies should be seen as a *supplementary measure* laying down the situations in which post-authorisation efficacy studies may be required[9]. Interestingly, despite this mandate to the Commission, the legislator has already decided to frame the imposition of an obligation on marketing authorisation holders to conduct a PAES by providing reference points for potential scenarios.

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'[10]. 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'[11].

Any delegated act would have to respect this pre-determination as stipulated by the EU legislator.

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.

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

It should be stressed from the outset that post-authorisation efficacy studies, like any other element of the strengthened system of pharmacovigilance, should not lead to the premature granting of marketing authorisations[12]. They cannot be used to compromise the initial level of evidence that is required to grant a standard marketing authorisation.

Moreover, 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.

The obligation to conduct a post-authorisation efficacy study addresses certain well-reasoned scientific concerns, which could have a direct impact on the maintenance of the marketing authorisation. The study is meant to provide the competent authorities and the marketing

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9 Recital 36 of Directive 2010/84/EU.

10 Article 9(4)(cc) of Regulation (EC) No 726/2004 and point (f) of Article 21a of Directive 2001/83/EC.

11 Article 10a(1)(b) of Regulation (EC) No 726/2004 and Article 22a(1)(b) of Directive 2001/83/EC.

12 Recital 10 of Directive 2010/84/EU.

authorisation holder with key information, in order to either complement initial evidence or to verify whether the marketing authorisation should be maintained as granted, varied or even withdrawn on the basis of the new data resulting from the study.

4. EFFICACY VERSUS EFFECTIVENESS

Authorisation decisions for medicinal products should be made on the basis of the objective criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations[13]. At the time of granting the marketing authorisation the (therapeutic) efficacy of a product is normally established on the basis of (randomised) 'controlled clinical trials', i.e. clinical trials that are randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value.

In the past decade the value of the evaluation criteria has been subject to some debate. This is partly due to an increased focus on real-market access of new medicinal products, which means that new products not only have to satisfy the regulatory requirements of quality, safety and efficacy, but also have to obtain positive reimbursement decisions from national health-care systems; otherwise access to the medicinal product will effectively exclude most patients.

In this context new, but similar, criteria have emerged such as effectiveness and relative efficacy as well as relative effectiveness. The debate has often been complicated by the inconsistent use of terminology. Moreover, effectiveness is not directly referred to in the EU pharmaceutical legislation, at least not in the context of the evaluation of the benefits of a medicinal product. However, when talking in terms of efficacy versus effectiveness, effectiveness is normally used to describe the benefits of a treatment under real-life conditions, as opposed to efficacy, which measures the benefit of an intervention in clinical trials or other controlled studies[14]. Relative efficacy is often referred to as 'the extent to which an intervention does more good than harm, under ideal circumstances, compared to one or more alternative interventions'[15].

In view of making evidence recommendations and decisions on the initial uptake of a medicinal product, health technology assessment bodies and pricing and reimbursement authorities need to gather evidence beyond the regulatory information available at the time of marketing authorisation. This is information on relative efficacy. After some time, some of these bodies are bound to review their initial recommendation by providing new evidence on real-life effectiveness, to measure the effectiveness of a product in comparison to one or more intervention alternatives.

Obviously, real-life information is usually not available at the time of the initial scientific evaluation by the competent authorities. Therefore there have been calls to use post-authorisation studies to gather such data.

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

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13 Recital 13 of Regulation (EC) No 726/2004.

14 In 2008 the EU High Level Pharmaceutical Forum defined effectiveness as 'the extent to which an intervention does more good than harm when provided under the usual circumstances of health care practice'.

15 Definition used by the EU High Level Pharmaceutical Forum.

health technology assessment bodies, patients' and healthcare professionals' organisation or pharmaceutical undertakings. Pragmatic trials, on the other hand, observe clinical practice. Both these methodologies however have limitations; they represent 'less perfect' experiments than efficacy trials, as they basically sacrifice internal validity to achieve generalizability (e.g. through modelling). These limitations include issues concerning data quality and completeness, as well as the non-randomised design of the study or trial. One can therefore begin to question to what extent such pragmatic trials or observational studies would be capable of achieving the regulatory needs described above, for reasons of their respective design. Could such data provide sufficient and sound grounds for acting on a marketing authorisation?

Post-authorisation efficacy studies should only be imposed if there is the reasonable assumption that the results they produce will help to answer in an objective and evidence based manner the efficacy concerns that led to the imposition of the study in the first place.

On the other hand according to the recitals of the new pharmacovigilance legislation, post-authorisation safety studies and post-authorisation efficacy studies may be aimed at collecting data to enable the assessment of safety or efficacy of medicinal products for human use *in everyday medical practice*[16]. This reference to everyday medical practice by the legislator could be interpreted as building a bridge to the more pragmatic trials outside the scope of a controlled clinical trial setting.

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.

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?

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

The following situations may be considered possible PAES scenarios. They build on current regulatory experience.

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

Surrogate endpoints, such as biomarkers or tumour shrinkage, or effect on tumour progression in the area of oncology, have been used in different therapeutic areas as a tool to define the efficacy of medicinal products in exploratory or confirmatory clinical studies. Relevant surrogate endpoint data have the potential advantage of providing clinical evidence of efficacy before data are available from endpoints based on clinical outcome, e.g. mortality data for life threatening diseases, which could require a long period of time. These surrogate endpoints may allow conclusions to be drawn on the benefit-risk balance and the authorisation of new medicinal products, either in the context of a conditional marketing authorisation or under exceptional circumstances. Even in the context of a full marketing authorisation, it

[16] Recital 16 of Regulation (EU) No 1235/2010.

might be considered relevant to generate further efficacy data in the post-authorisation phase in order to monitor the impact of the intervention on clinical outcome or disease progression. Likewise, in the area of oncology it may be considered necessary to verify whether the overall survival data in the post-authorisation phase is discordant with or confirmative of the outcome of the surrogate endpoint.

Given that the generation of such data in many instances is expected to require a large sample size and/or long term follow-up, a post-authorisation efficacy study may be considered appropriate to alleviate any concerns relating to the efficacy of the medicinal product.

5.2. Studies on combinations with other medicinal products

Some medicinal products may be used regularly in combination with other products. While the applicant is expected to address the effects of such combinations in the pivotal clinical studies, it would be unreasonable to expect that all possible combinations are exhaustively studied pre-authorisation. Instead, the scientific assessment could be based partly on extrapolation of existing data. In this context, it might be envisaged that studies on certain treatment combinations could take the form of a PAES. For example, in the context of medicinal products for the treatment of HIV, it might be relevant in very selected cases to gain further clinical evidence post-authorisation from some specific combinations if it is felt that such studies could clarify an uncertainty that has not already been addressed, particularly if such combinations are expected to be used in everyday medical practice.

5.3. Studies in sub-populations

In the pivotal clinical studies conducted pre-approval it might be difficult to gather robust representation of all the different sub-populations of the medication. For some specific sub-populations for which uncertainties with respect to the benefits have been raised, and although not precluding an overall positive benefit-risk balance at the time of opinion, it might be justified to request further substantiation of the evidence of benefit by conducting specifically targeted clinical studies in the post-approval phase. It is assumed that most of these studies would probably be requested at the time of the initial marketing authorisation, but there might be situations in which the request could arise later in the product life cycle based on availability of new data.

A wide range of special populations can be envisaged as potentially applicable, ranging from populations defined by baseline demographic criteria (e.g. age), to populations defined by specific factors affecting disease prognosis or drug pharmacokinetic/pharmacodynamic profile (e.g. pharmacogenomic markers affecting treatment response).

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

There might be situations in which a conclusion on a positive benefit-risk is achieved based on a comprehensive clinical development, including studies conducted outside of the EU. Studies conducted outside the European Union, despite being accepted as demonstration of efficacy, may leave room for uncertainties about the possibility of fully extrapolating the results in the EU context. Consequently, complementary data in the context of the European standard of care would allow a more precise evaluation of the efficacy of the medicinal product. In particular, comparison to relevant active controls that adequately represent the European standard of care would be expected in such trials.

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 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, leading to the potential need to again discuss the established benefit-risk balance of the medicinal product. In its jurisprudence, the European Court of Justice recognised that a modified consensus within the medical community regarding the appropriate assessment criteria of the therapeutic efficacy may constitute new concrete and objective factors capable of negatively affecting the benefit-risk assessment of a medicinal product[17]. In these circumstances, it could be necessary to provide new evidence on the efficacy of the medicinal product in order to maintain a positive benefit-risk assessment.

Likewise, if 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, additional studies may be considered.

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

The long term follow-up of efficacy as part of post-authorisation surveillance does not constitute a mandatory requirement for medicinal products, even for products authorised for chronic conditions. In fact it is acknowledged that in many instances the effects of a medicinal product wane over time requiring a redefinition of a therapy. However, such events do not necessarily compromise the benefit-risk balance of the medicinal product and the appraisal of the beneficial effect exerted up to that point in time.

This being said, in exceptional cases it might be reasonable from a scientific point to request post-authorisation studies where a potential lack of efficacy in the long-term could raise concerns with respect to the maintenance of a positive benefit-risk balance of the intervention and it would be unreasonable to wait for such data before granting the marketing authorisation[18]. This may, for example, be the case for innovative therapies where interventions are supposed to modify the course of the disease. Data on the durability of the effect may affect the overall benefit-risk assessment.

5.7. Studies in everyday medical practice

Studies of everyday medical practice are expected to be requested mainly in those circumstances where there is clear evidence that the benefits of the medicinal product under discussion as shown by randomised controlled clinical trials might be significantly affected by the real-life conditions of use.

This could be the case, for example, where there is a non-negligible impact of behavioural and compliance aspects on health outcomes. Another scenario might be a situation where, despite

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17 European Court of Justice, Case C-221/10P, paragraphs 100-103.

18 It can be noted that 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: 'Efficacy in the paediatric population may also need additional study following authorisation. Therefore, an additional requirement for applying for a marketing authorisation (…) should be an obligation to indicate how he proposes to ensure the long-term follow-up of possible adverse reactions to the use of the medicinal product and efficacy in the paediatric population.' (recital 24 of the Paediatric Regulation).

a high degree of internal validity of the results from pivotal clinical trials, the external validity of the data presents clear uncertainties that warrant further evaluation in the post-approval setting, e.g. impact of co-morbidities and polypharmacy on the effect of a specific intervention in a geriatric context.

Moreover, the current guideline on clinical evaluation of vaccines adopted by EMA's Committee for Medicinal Products for Human Use already notes the importance of effectiveness studies in the particular case of vaccines[19]: 'efficacy studies will not always be feasible. For some antigens, a possible alternative may be to use estimates of effectiveness from prospective studies conducted during vaccination campaigns after authorisation in order to establish at least putative correlates for short and/or long-term protection'. Hence, in the case of vaccines the need for post-authorisation studies, which focus on everyday medicinal practice, mirrors an existing consensus in the medical community.

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?

6. STUDY DESIGN

Aspects concerning the specific design of a post-authorisation efficacy study may not necessarily be covered in detail by the future delegated act. This being said, it is essential that a post-authorisation efficacy study provides robust data to enable the marketing authorisation holder and the competent authorities to consider the results in order to verify whether a marketing authorisation should be maintained, varied or withdrawn.

Interventional studies are expected to represent the majority of cases and would be the preferred option, particularly if the efficacy estimates are expected to be highly affected by confounding factors or biases in the population under evaluation.

Non-interventional studies, including pragmatic trials, have so far rarely been used as a source of primary evidence for determining the size of the benefits of a medicinal product. They have often been considered inappropriate for the measurement of efficacy.

Some recent advances in statistical and pharmacoepidemiological methods (such as propensity score methods and instrumental variables for the control of confounding by indication) have however triggered new discussion around the possibility of performing unbiased analysis of data coming from everyday medical practice.

Nonetheless, in certain specific circumstances, as explained under point 5.7, pragmatic trials or observational trials will be the point of reference for the design of a post-authorisation efficacy study.

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

[19] EMEA/CHMP/VWP/164653/2005.

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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.