



## **Response of the Drug Commission of the German Medical Association**

regarding the reflection paper of the European Commission on the delegated act on post-authorisation efficacy studies (PAES) (Article 10b of Regulation (EC) No 726/2004 and Article 22b of Directive 2001/83/EC)

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## **General remarks**

1) The Drug Commission of the German Medical Association (DCGMA) strongly supports the European Commission statement (cf. Section 3 of the Reflection Paper) that post-authorisation efficacy studies (PAES) must not substitute for insufficient scientific evidence of efficacy of a medicinal product at the time of marketing authorisation. We appreciate the option to answer open questions about the therapeutic value of a new medicine by later studies. However, the option for later studies should not undermine the requirement to prove the efficacy, safety and quality of a medicinal substance before marketing approval is given. Therefore, PAES should be reserved for exceptional, precisely and narrowly defined situations.

2) It seems important, in every single situation where a PAES is envisaged as being made a prerequisite for the initial marketing authorisation of a new drug, due to 'concerns relating to some aspects of the efficacy of the medicinal product' (Art. 21a, No f of Directive 2001/83/EC), that thorough judgment be made about whether or not the required additional information could not have been obtained by appropriate phase III studies, i.e., whether the criterion that these concerns 'can be resolved only after the medicinal product has been marketed' (second part of Art. 21a, No f) really is fulfilled.

Section 5 presents scenarios in which it could be considered to solve open questions by a PAES:

- a) surrogate endpoints may not be sufficiently relevant,
- b) typical and frequently used co-medications were not tested concomitantly with the new drug,
- c) therapeutic effects in typical relevant sub-populations were not investigated,
- d) active controls had not been appropriate in relation to the European standard of care.

From the DCGMA's point of view the scenarios (a-d) do not by any means constitute questions that can be answered in a PAES. This is particularly true for a) and for c). In our opinion these points should have been studied during drug development. Hence, we think that the respective data had to be requested by EMA as part of the application dossier.

3) The two situations in which PAES may be imposed, i.e., a) at the time of initial marketing authorisation (Art. 21a of Directive 2010/83/EC) and b) when a drug is already marketed (Art. 22a), should be clearly and explicitly differentiated – in particular in the description of different medical scenarios.

4) The second criterion mentioned above under No 2) that 'concerns ... can be resolved only after the medicinal product has been marketed' can only be made subject to PAES obligations as a prerequisite for the initial authorisation (Art. 21a) may be considered as absurd. Nevertheless, it should be respected in the Reflection Paper that the Directive does not allow PAES to be requested due to similar concerns if they arise during the time of marketing (when appropriate PAES are actually feasible). The only permitted criterion in this latter situation is that 'the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly' (Art. 22a). This restriction should be observed in the situations outlined under Section 5 (in particular 5.7, but probably also 5.3, 5.1).

5) The term 'effectiveness' relates to the use of a medicine in 'real life' situations, i.e., just what should be examined in a PAES. This term is not (yet) used in EU-legislation and seems to have been largely avoided in the Reflection Paper (Sections 5 and 6). Therefore, we propose to eliminate this source of confusion by clarifying in which specific situation a PAES should take the form of a classical phase III efficacy study or an 'effectiveness' study.

6) In the relevant Directive 2001/83/EC as well as in the Regulation (EC) 726/2004 the term 'benefit' is frequently used as something that should be considered, improved and kept in a favourable relation to harm or risk. It should be clearly defined in the Reflection Paper, how the benefit is addressed by PAES.

It is also unfortunate that the terms 'phase III' and 'phase IV' and the terms for the respective studies which are established and relevant in this context are not used in the Reflection Paper.

7) An explicit statement whether any groups of medicinal products (e.g. homeopathic or anthroposophic medicines) should be exempted from PAES requests would be helpful.

### **Specific remarks**

#### **Consultation item 1:**

*Do you think that a delegated act on the situation 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.*

The intention to provide guidance for stakeholders who might be involved in decision making on PAES is appreciated. A 'Delegated Act' may have the advantage of being easier to amend than EU-Directives or -Regulations. It should, however, clearly mention the responsible parties, i.e., Marketing Authorisation Holders (MAH), competent authorities, advisory groups etc. and their respective roles and responsibilities.

#### **Consultation item 2:**

*Do you have any comments on the above [efficacy vs. effectiveness]? Do you agree that generally speaking post-authorisation efficacy studies should focus on generating efficacy data?*

If, after marketing, e.g., a specific and extremely informative new test is developed which is judged by experts to be the only relevant parameter for measuring the progression of the disease for which the drug is indicated, then a narrow randomized well-controlled trial focusing on efficacy rather than effectiveness data (!) should be carried out (see Situation 5, Section 5 of the Reflection Paper).

Another situation would be a drug indicated for a slow-progressing or chronic disease with data from pivotal clinical trials showing good treatment effects on relevant chemical surrogate markers but only limited preliminary benefit on patient relevant outcomes. In such a case, the request for a long-term PAES designed as an effectiveness study could be justified (see Situation 6, Section 5 of the Reflection Paper).

### **Consultation item 3 I:**

*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?*

#### **Situation 1:**

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

As example it is outlined that the initial marketing authorisation of an antineoplastic medicine was based on data showing a reduction of tumour size (endpoint: e.g. objective response rate) only and suggested that PAES should demonstrate that this also is reflected in final patient relevant outcomes (e.g., overall survival, patient-reported outcomes).

#### Comment:

This example is not suitable because the response rate or reduction of tumour size has a role in evaluating the antitumour activity of new drugs in phase I and II studies, but is not recognized as an endpoint showing patient benefit in all tumours.

We would like to comment on the fundamental concept of authorising new drugs on the basis of a combination of surrogate endpoints on the one hand and the requirement of PAES on patient-relevant clinical endpoints on the other:

Conditional marketing authorisation using surrogate endpoints with 'unclear' clinical relevance as substitutes for final patient relevant outcomes would provide an opportunity to companies and regulatory authorities to avoid the necessary decision making by postponing it till the time when the PAES are completed. If the clinical relevance of the surrogate endpoint is uncertain there is the clear risk that many patients will be treated with a clinically ineffective drug.

Obviously, the clinical relevance and choice of the endpoint investigated in pre-authorisation studies is crucial. A dichotomous decision has to be taken both by the drug developing company and the licensing authority:

Is/was the efficacy endpoint clinically relevant or not?

If not, further pre-authorisation studies on endpoints with sufficient clinical relevance are inevitable.

If yes (as in the example of tumour shrinkage which 'may allow conclusions to be drawn on the benefit-risk balance') the marketing authorisation could be, but does not necessarily need to be, made subject to the precondition that PAES with trial endpoints showing patient-relevant clinical benefit will be conducted later.

Considering the situation that information on medium- or long-term clinical endpoints could be readily obtainable from existing registries, see Comment 3 II a.

## **Situation 2: Studies on combinations with other medicinal products**

In the example given, it is stated that the applicant would have to test the effects of his new drug if combined regularly with other drugs, but that it would be 'unreasonable to expect that all possible combinations are exhaustively studied pre-authorisation'. In the following sentences the idea is outlined that 'studies on certain treatment combinations could take the form of PAES' and that 'such studies could clarify an uncertainty ... particularly if such combinations are expected to be used in everyday medical practice'.

### Comment:

Considering the time of initial marketing authorisation, we agree, of course, that not 'all possible combinations' could have 'exhaustively be studied pre-authorisation'.

Should it turn out, during the post-authorisation phase, that - contrary to what could have been expected pre-marketing - there is ample and clinically relevant concomitant use of a specific drug or group of drugs bearing a reasonable risk of compromising the effectiveness of the drug under consideration, it would seem desirable that the effectiveness of this medicinal product in the presence of those other drugs will be investigated.

## **Situation 3: Studies in sub-populations**

Here, the scenario is outlined that 'it might be difficult to gather robust representation of all the different sub-populations of the medication'.

### Comment:

We do agree that it may emerge, during the post-authorisation period and practical use of a medicinal product, that more patient groups than those for which it was originally authorised might benefit from it. In this situation, the procedure of choice to make the drug formally available to them should be new phase III studies with the respective new subgroups initiated by the MAH at his discretion, followed by an application for extension of the indication.

Likewise, if it is recognized already before or at the time of authorisation that a new drug might work in more patient groups than those fitting the originally envisaged indication, it will be up to the company to decide upon the scope of its clinical trials, in particular whether it needs additional data on those other subgroups to include in its initial application.

In some situations, doctors may consider a medicinal product as beneficial in other than the authorised indications and have already started to use it 'off-label'.

This scenario will be addressed in our proposal 3 II c.

#### **Situation 4: Studies in the context of the European standard of care**

The scenario is outlined that the regulatory authority realises, either at the time of marketing authorisation or post-authorisation, that efficacy studies on which the application for licensing was based and which were conducted outside the EU did not meet the European standard of care, including the issue of appropriate active controls.

##### Comment

In our view, there is no reason that, in case of relevant doubts pertaining to the keeping of European-level standards of care in phase III efficacy studies, these problems couldn't be realised and solved by appropriate pre-authorisation studies. Otherwise, patients could be put at risk, at the time of marketing authorisation already, of being treated by a medicinal product with uncertain or insufficient efficacy.

This issue should be addressed by a scientific advisory meeting far in advance of the application for marketing authorisation.

Additionally, it should be noted that the so-called 'European standard of care' is frequently not well-defined as the Reflection Paper seems to imply: Actually, there may be considerable differences in this respect also between EU member states.

Should the shortcomings only be realised after the authorisation has been granted already (i.e., that they had been overlooked at the review of the MA application), new PAES in the form of appropriate randomised controlled trials would be desirable. However, Art. 22a of the Directive can hardly be used to oblige the MAH accordingly.

#### **Situation 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**

Here, the Reflection Paper presents a situation in which, due to scientific progress after the authorisation of a specific new medicine, new aspects and tests for the efficacy assessment of this drug have been developed.

##### Comment

We believe that in such a scenario it may in fact be appropriate to request new efficacy studies as PAES using the new criteria. These new criteria – including the correct up-to-date choice of active controls – must be established by the scientific community.

#### **Situation 6: Studies aimed at determining the long-term efficacy of a medicinal product**

The scenario is outlined that there may be uncertainty concerning the long-term beneficial effects of a medicine which is meant to be used over years in order to improve chronic conditions or to exert long-term effects, e.g., in paediatrics.

##### Comment

In our view those concerns should be raised at the time of initial marketing authorisation and it may be sensible to link the MA to the prerequisite that appropriate long-term PAES will be conducted.

In this event there are typically poor alternative therapeutic options, the medium-term studies have already shown promising therapeutic results and a sensible design of the study/studies can be developed. Typically, randomised controlled efficacy studies will not be feasible in those situations and the prospect of obtaining any meaningful results at all should be carefully examined. In some cases, registries may be helpful. Guidance pertaining to the appropriate methodology for PAES in these cases should be provided.

In case the doubt as to the long-term (net) benefit are less based on concerns about the effectiveness than on possible long-term adverse drug reactions, the request of PAES (rather than PASS) does not seem appropriate (see also comment to Situation 1).

### **Situation 7: Studies in everyday medical practice**

The scenario is outlined that significant indicators emerge during the post-marketing period that a medicine actually is used quite differently from its terms of authorisation and, therefore, may be less effective than it should be. It is proposed that PAES investigating efficacy (with the meaning of 'effectiveness') under real life conditions and providing a higher degree of 'external validity' than pivotal clinical trials are requested. Methods proposed for PAES in these situations seem to be pharmacoepidemiological studies and pragmatic trials (Reflection Paper Section 6).

#### Comment

We agree that the presented scenario, indeed, raises the question of how to obtain scientifically valid information about the true effectiveness of the medicinal product under actual real life conditions.

We doubt, however, i) the legal justification and ii) the methodological feasibility of PAES in these situations:

i) Art. 22a of the Directive does not seem to provide a hold to oblige the MAH to conduct a PAES, because 'the understanding of the disease' did not change and it could hardly be argued that it is the 'understanding of the clinical methodology' causing doubts as to previous efficacy assessments.

ii) The prospects of getting valid and strong results from such a study seem unfavourable for two reasons:

a) Both patients and healthcare professionals will not act and behave as in everyday life if, and as long as, they participate in a study.

b) Non-interventional studies like epidemiological studies and so-called "pragmatic trials" are notoriously suffering from uncertainties due to bias and confounding. While it is true that they may provide more 'external validity' than randomised controlled efficacy studies and can answer the questions "Did the treatment work?" or "Was treatment A better than treatment B?" they cannot answer the questions "Was it the intrinsic pharmacological property of the new drug A which caused the improvement of the patient?" or "Was it the intrinsic pharmacological property of drug A which was superior to that of drug B?". In other words: A positive effect may well be found in epidemiological or pragmatic studies, but nobody will know with sufficient certainty whether or not it was due to the drug under investigation at all.

### **Consultation item 3 II:**

*Are there any other situations not covered by points 5.1 – 5.7 in which it would be justified to oblige an MAH to conduct a PAES?*

#### a) Availability of easy-access registries with valuable data

In the event that registries providing valuable information about long-term outcome of certain diseases or options for record linkage are readily available (e.g. cancer registries) the MAH could be obliged, at the time of initial marketing authorisation, to later make use of those sources by conducting appropriately designed PAES. The overriding reason for this would not be doubts as to the information quality of the pre-authorisation studies but rather the availability of relevant data during the post-authorisation period. (See also comment to Situation 1).

#### b) Second-line 'escape' situations

There may occur situations where several medicines are available for an important disease, where one or some of them is/are considered as the 'new gold standard', where a medical ranking is established with regard to first, second etc. choice, and where, however, according to new clinical experience some patients unexpectedly do not respond to, or do not tolerate, one or several of the first choice standard options. In such situations the hope may be justified that a specific medicine of a 'lower rank' could still be used as second, third or last choice, i.e. as an escape medicine.

However, it may also be (and is, indeed, likely) that no data are available yet to demonstrate that this 'reserve' drug actually works or is tolerated when the first choice medicine or medicines cannot be used.

In these instances PAES with the candidate reserve medicine administered to patients in whom actually first choice medicines had been tried but had to be stopped may be imposed on the MAH.

Examples could be situations where first choice antibiotics or antineoplastic medicines can no longer be used in some patients, due to development of bacterial or tumour resistance or patient allergy.

One could argue that the criteria for such an obligation as outlined in Art 22a of the Directive are fulfilled, because the understanding of the disease (i.e., bacterial or tumour susceptibility to the new drugs but non-responsiveness in some cases or after some time) and the methodology (i.e., investigation of patients in the second- or third-line scenario) have significantly changed.

### **Consultation item 5:**

*Please feel free to raise any other issue or make any comments which have not been addressed in the consultation items above.*

There is currently no procedure laid down in the new legislation to establish and clarify responsibilities when a PAES is requested by the Agency or a national regulatory authority. This concerns particularly the reviewing of the study objective, design and time frame as well as any recommendation for actions in consequence of the outcome. We would like to suggest that the PRAC should play a leading role, comparable to its responsibility in the approval of PASS, as laid down in the new legislation.