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MINUTES OF THE MEETING OF AN EXPERT GROUP TO DISCUSS THE DELEGATED ACT ON POST-AUTHORISATION EFFICACY STUDIES – HUMAN MEDICINAL PRODUCTS HELD IN BRUSSELS ON TUESDAY 4 JUNE 2013

Attendees: Commission (DG SANCO), Member States' experts, European Medicines Agency (see annexed list of participants)

1. Introduction

The meeting had been convened in order to discuss with experts from Member States the concept paper on the delegated act on post-authorisation efficacy studies (PAES).

After reminding its legal mandate, the Commission explained how the scope of the PAES is defined in the EU legislation. The task the Commission has to fulfil is to identify the situations in which a PAES is required, taking into account the general legal framework. However, it has to be pointed out that the decision of imposing a PAES will still remain case by case.

2. Situations in which a PAES is required

The Commission representative (COM) presented the concept paper submitted for consultation.

- First situation: studies aimed at determining clinical outcome following initial assessment based on surrogate endpoints.

The example EMA suggested where these studies could be useful was in the field of oncology. Some Member States argued that precise examples and clarifications should be provided in the delegated act. Others expressed their difficulties to draw a clear line between conditional marketing authorisation and PAES. The Commission reminded that the decision should be made case by case and that PAES are not intended to replace conditional marketing authorisation but rather to enrich the toolbox of the regulatory authorities.

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- Second situation: studies on combinations with other medicinal products.

The different experts and the EMA agreed that these studies will only be needed in rare situations. They could be useful as regard HIV treatment in selected circumstances, as it would be impossible for companies to conduct studies on combinations with all medicinal products which could potentially be involved. The need for a PAES has to be justified. In case of efficacy issues with a new medicinal product used in combination with an old product, the study should be conducted by the new product marketing authorisation applicant or holder.

- Third situation: studies in sub-populations.

The EMA explained that this scenario covers a broad range of situations and would be quite important. These studies could be carried out in different age groups depending on the need, e.g. elderly people or adolescents, or according to different baseline patient characteristics, e.g. pharmacogenomics markers. Questions were raised on the difference between a PAES and the requirements of the risk management plan or the Paediatric investigation plan. One Member State stressed that PAES could be useful for lifting the suspension of a marketing authorisation. The Commission replied that this new tool will be primarily used for situations when the marketing authorisation is maintained.

- Fourth situation: studies in the context of the European standard of care.

The EMA explained that more and more studies are conducted outside of the European Union, and therefore do not always fully apply to the situation in Europe. One Member State argued that if uncertainties about the possibility of fully extrapolating results of those studies exist, they should be addressed pre-approval. The EMA agreed that this should generally apply, however, pointed out that it cannot be excluded that in some cases PAES could be applicable if the uncertainties are not such to preclude a MA upfront. For example in the field of oncology, where third country efficacy studies are carried out, the results might not be fully applicable in the European Union, as comparators or underlining medical care that have been used may not be fully reflective of the situation in the EU. One Member State expressed its concern as regards the difficulties to come up with a common definition of European standard of care to be applied to clinical trial and valid comparators. The EMA replied that it should be possible to agree on certain key elements, and that it should be normally possible to define a reasonably acceptable European standard of care to be used in clinical studies design case by case.

- Fifth situation: studies linked to a change in the understanding of the standard of care for the disease and/or the pharmacology of the medicinal products.

Some Member States expressed their fear that such studies would lead to a systematic re-evaluation of the products, which regulatory authorities would not be able to undertake in terms of resources, especially in small Member States. One Member State considered that such studies would equal asking for treatment guidelines to regulatory authorities. As for most of PAES, there is consensus that it is a tool that should be used only in limited cases for which there is really a need based on B/R uncertainties.

- Sixth situation: studies aimed at determining the long-term efficacy of a medicinal product.

The EMA considered that these studies, which could be important, would not be required for all chronic medicinal products but in selective situations, such as in the case of cartilage replacement, where it would be unreasonable to ask companies to conduct these studies pre-approval. One Member State argued that regarding advanced therapies, the issue is already covered by legislation. The Commission replied that when such studies are already specified in existing legislation, it will be taken on board in the delegated act.

- Seventh situation: studies in everyday medical practice.

The EMA explained that this point raises the issue of effectiveness. Effectiveness studies are hardly used, except in the case of vaccines, but they could be of relevance in other areas where behavioural aspects could have a major impact on outcome; also in other areas such as in the field of geriatrics could be of value. The methodologies used are pragmatic trials and observational studies. One Member State added that the results of these studies could also be used by public health authorities or HTA bodies. The Commission replied that the delegated act should focus on data required in support of B/R assessment.

Finally, the Commission asked the experts whether the delegated act should cover any additional situation.

The Commission took note of the following points:

- MS mostly supported the situations presented in the concept paper;
- MS mostly considered that no important situation is missing, but that the drafting of the act should allow for additional situations to be covered by PAES without the need to amend the act (e.g. non-exhaustive list).
- MS agreed that a PAES should not be used to lower standards as regards the level of evidence required for the initial marketing authorisation.

3. Efficacy versus effectiveness

The Commission asked the experts whether they agreed on the assumption that PAES should be seen more within the context of efficacy than within the context of effectiveness. Some MS supported the idea that effectiveness studies should be used, since clinical trials do not always reflect real life practice. Besides, methodologies for effectiveness studies have improved. Other MS argued that if these studies are admitted, it would imply to accept that the results are able to challenge data collected with controlled clinical trials. This could be considered as "changing the goalposts" for maintaining the marketing authorisation.

MS mostly agreed that the purpose of a PAES is to come up with strong, robust efficacy data. Effectiveness should be considered when the particular problem leading to the need for a PAES can only be addressed with effectiveness studies.

4. Structure of the delegated act

The Commission presented the structure of the delegated act, which will focus on the situations in which PAES are required. MS mostly supported the suggested structure as outlined in the concept paper.

5. Next step

The Commission informed the group that it will further reflect on the input received during the meeting. In view of the comprehensive discussion no further physical meeting of the expert group may be necessary, however, the Commission will update Member States on the delegated act during the next Pharmaceutical Committee meeting in October.

6. Update on the falsified medicines legislation (Directive 2011/62/EU)

The Commission explained that, as of 2 July, all importations of active substances need to be accompanied by a written confirmation certifying they have been manufactured according to EU-equivalent GMP standards. With regards to atypical active substances, Member States could decide to adopt a pragmatic approach based on risk. The Commission also requested that the scope of the legislation is transposed correctly.

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Annex – list of participants

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BE	Mrs Kholmanskikh - Federal Agency for Medicines and Health Products
BG	/
CY	/
CZ	Mr. Boran - State Institute for Drug Control
DE	Mrs Keller-Stanislawski - Paul-Ehrlich-Institut
	Dr. Weiergräber - Federal Institute for Drugs and Medical Devices
DK	Ms Aaboe Hansen - Danish Health and Medicines Authority
EE	Mrs Kiisk - Estonian State Agency of Medicines
EL	Mr. Klironomos - National Organisation for Medicines
EMA	Mr. Cavaleri - EMA
ES	Mr. De la Fuente Honrubia - Spanish Agency of Medicines and Medical Devices (AEMPS)
FI	Mr. Lapveteläinen - The Finish Medecines Agency, FIMEA
FR	Mrs Perillat - French Ministry of Social Affairs and Health
HR	Mr. Banovac - Agency for Medicinal Products and Medical Devices
HU	Mrs Pallos - National Institute of Pharmacy - GYEMSZI
IE	Mr. Dunleavy - Irish Permanent Representation to the EU
IT	Ms Sottosanti - Agenzia Italiana del Farmaco (AIFA)
LT	Mrs Markuviene - Ministry of Health of the Republic of Lithuania
LU	/
LV	Mrs Studere - State Agency of Medicines of Latvia
MT	Mr. Borg - Medicines Authority
NL	Mrs van Elk - Medicines Evaluation Board (MEB)
PL	Mr. Kolakowski - The Office for Registration of Medicinal Products
PT	Ms Guimaraes - National Authority of Mediciines and Health Products INFARMED
RO	/
SE	Mr. Ljungberg - Swedish Medical Products Agency (MPA)
SI	/
SK	Mr. Gibala - State Institute for Drug Control
UK	Mr. Thomson - MHRA