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Submission of Comments on European Commission Consultation Paper on Delegated Act on Post Authorisation Efficacy Studies -Ares (2012)1405774

Comments from:

Name of organisation or individual
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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

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Consultation Item 1: A DELEGATED ACT — WHAT IS THE ADDED VALUE?

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.

J&J Response

General comment: As part of the consultation process we have contributed to the EFPIA response but we would like to take this opportunity to reinforce certain points and to add specific comments of our own.

- We believe that a delegated act would be of benefit by providing a legal definition of post authorisation efficacy studies (PAESs), since this is lacking in the current legislation, and to set out broad based key principles to be applied in the decision-making process for PAESs. We consider that a public consultation on such a delegated act will be necessary.
- The delegated act should not specify particular scenarios, study details or address efficacy versus effectiveness. We believe it would be more appropriate to include these aspects in guidance in order to achieve the correct balance between the need for legal certainty whilst ensuring flexibility, according to individual circumstances. There is a danger that including this important information in a delegated act will be overly restrictive and will not be reflective of evolving scientific and regulatory developments.

Consultation Item 2: EFFICACY VERSUS EFFECTIVENESS

Do you have comments on the above?

Do you agree that generally speaking post-authorisation efficacy studies should focus on generating efficacy data?

J&J Response

- We consider that there should be flexibility to generate data via the most appropriate study design. Therefore, design of PAESs (and whether effectiveness versus efficacy studies should be used) should be on a case by case basis depending upon the individual circumstances of the PAES request. This could include explanatory randomised clinical trials, pragmatic randomised clinical trials, or observational studies, as appropriate, (Thorpe et al[1]) in light of the importance of the study accurately reflecting actual clinical practice. However, we also consider that randomised clinical trials may be required depending upon the circumstances and do not agree that their use should be restricted necessarily.
- The decision on the trial design will also depend on the regulatory purpose of the study and the capability of the trial to inform regulatory decision-making, as well as the therapy areas and the circumstances of the particular medicinal product involved. As an example, please refer to the additional comments below concerning vaccines.
- The imposition of a PAES study must be driven by regulatory consideration and not by non-regulatory decision-makers.
- We consider that the question of efficacy versus effectiveness should not be addressed in a delegated act. This is an evolving area and so we do not support its inclusion in a delegated act.

[1]Thorpe, K. E., M. Zwarenstein, et al. (2009). "A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers." J Clin Epidemiol 62(5): 464-75. A copy of the article is attached.

In the case of vaccines, efficacy studies may not be appropriate because of: low incidence of disease in specific populations (i.e. influenza in elderly), changes of incidence rate from season to season making the sample size unpredictable, possible mismatch of vaccine and circulating strains. In situations with existing vaccines used in a population, efficacy testing would be ethically questionable and relying on established correlates of protection is generally sufficient for licensing. Therefore, where PAESs are requested for vaccines we believe effectiveness studies rather than efficacy are more realistic and appropriate, though also challenging.

Consultation Item 3: SITUATIONS IN WHICH A POST-AUTHORISATION EFFICACY STUDY MAY BE REQUIRED

Please comment on the seven different situations described in the consultation. 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 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?

J&J Response

We agree that some of the Commission's proposals presented in sections 5.1 – 5.7 may be appropriate circumstances for a competent authority to request a PAES but we do not agree with all seven of them. In particular we do not agree with:

- 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;
- 5.7 studies in everyday medicinal practice

We believe that it is not appropriate to include the situations outlined in this consultation in a delegated act. As decisions about requests for PAES should be made on a case-by-case basis taking into consideration aspects such as the therapeutic area, then formulating the principles as guidelines, not as regulation, is more appropriate. Identifying the criteria to be used, for example in the form of a checklist or decision tree, would help to define the more clearly the circumstances in which a PAES may be imposed. We also consider that the competent authorities should be looking into alternative approaches such as imposition of a cohort study.

In all instances we consider that the need for a PAES will be the exception and will be based on sound and transparent criteria following discussion with the marketing authorisation holder and other stakeholders as appropriate.

Consultation Item 4: STUDY DESIGN

Do you have any comments on the statements outlined in the Consultation?

J&J Response

As outlined earlier we consider that the detail of study design should not be considered in a delegated act and can only be established on a case by case basis depending upon the question that needs to be addressed.

The section of the document cited in item #2 above grapples with the role of interventional vs. non-interventional studies and with the role of tight control of study conditions (as in clinical trials) vs. the need for PAES's to capture information on real-world use. To improve clarity about these difficult trade-offs, and about the difference between efficacy studies and effectiveness studies, it may be useful to address separately the role of design choices, e.g.,

- whether the study should be randomized,
- whether the intent is to learn more about real-world conditions.

The notion of pragmatic vs. explanatory studies as described in, e.g., Thorpe et al. may also be helpful. These authors describe 10 domains of clinical trial design (assuming randomization) that define how pragmatic or explanatory a trial might be. Their Table 1, in particular, succinctly describes the considerations that should routinely be made.

Consultation Item 5:

Please feel free to raise any other issues or make any comments which have not been addressed in the consultation items

J&J Response