<18 February 2013>

Submission of comments on EC Consultation Paper on delegated Act on Post Authorisation Efficacy Studies -Ares (2012)1405774

Comments from:

Name of organisation or individual
EFPIA (European Federation of Pharmaceutical Industries and Associations)

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.

Response
EFPIA believes that a legal definition of post-authorisation efficacy studies (PAES) is required to provide clarity on purpose and scope as the "reference points" in the legislation[1] could be interpreted quite broadly. Obtaining clarity and predictability on expectations for when PAES may be required and ensuring that PAES are not imposed unnecessarily or inappropriately is highly desirable. This could be achieved through the adoption of a delegated act. A delegated act could also provide an explicit and clear legal mandate to EU regulators to accept data from studies other than randomised controlled trials (RCT). However, EFPIA believes that detailed recommendations and design issues for studies should be dealt with in an additional scientific guidance rather than in the delegated act. The combination of a delegated act and a scientific guidance should minimise the risk for arbitrary or unpredictable PAES decisions. This should limit to the extent possible subjectivity in imposing PAES. Additionally a delegated act could be used to outline certain key principles to ensure that PAES are only requested when further data are required and where there is a scientific, evidence-based justification for the request. Some key principles include: • PAES should only be imposed under limited circumstances where needed and within a product's approved indication • Requests for PAES should be supported by a sound reasoning from regulators; PAES should only be considered where there is scientific justification that there are concerns about the efficacy determination at the time of approval that requires further evidence generation. The intent of the request for PAES should not be to generate information on the economic impact of a pharmaceutical product on a healthcare system's budget • PAES should only be imposed where the proposed study is ethically, technically and practically feasible and can be conducted within a reasonable and meaningful timeframe. • Before any PAES are imposed on an MAH, there should be dialogue between stakeholders to ensure there is a reasonable assumption that the data a PAES will produce will help to answer the identified concerns that led to the imposition of the study in the first place and that the study is feasible. The dialogue should also allow the MAH to challenge the basis for a PAES requirement with either additional data or an alternative proposal • The study design for a PAES should be set on a case-by-case basis, and could also consider novel trial designs including pragmatic trial designs, to respond to the research question at hand and in agreement with the MAH. EFPIA recognizes that in these cases, PAES may also be useful for obtaining data, which could also respond to evidentiary requests from other decision-makers (such as payers and HTA bodies). However, whilst EFPIA fully supports the process of facilitating the mutual understanding and alignment of methodologies and realistic expectations of evidence requirements through early and regular dialogue involving multiple decision-makers, EFPIA underlines that requests from non-regulatory decision-makers (such as payers or HTA bodies) should not be the driver for the imposition of a PAES

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

Response

- PAES could be used to underpin accelerated development and approval of products that demonstrate compelling early evidence of efficacy; in such circumstances PAES could be used to confirm the evidence on which the approval is based.

A Delegated Act could also add some value if it helps reduce some of the administrative burden of conducting PAES. A suggested approach is to accelerate and encourage the adoption of the concept of "low intervention" clinical trials as outlined in the European Commission "Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use" within the delegated act.

Whether a delegated act is prepared or not, additional guidance from EMA/HMA will also be necessary. The guidance should ensure there are clear, transparent criteria among industry, the Commission, competent authorities and other stakeholders on the situations in which PAESs should be conducted. EFPIA believes the delegated act should not dictate the type of study that should be conducted; neither in the general terms used in this consultation item, nor in more specific terms for particular scenarios. The additional guidance on PAES is a more appropriate place to discuss (but not necessarily define) possible study types and expectation (e.g., in terms of methods) for effectiveness studies. The reasons for this opinion are:

- There is a danger that early imposition of a delegated act containing such details could be overly restrictive and burdensome compared to guidance. For example, we do not agree with some of the possible scenarios presented in sections 5.1 – 5.7 of the consultation document. The scenarios are better suited for inclusion in a guideline, which can more readily accommodate the case by case nature of regulatory science;
- It will be challenging to maintain a legal text so that it reflects the pace of scientific and regulatory developments.
- Regardless of whether a delegated act is implemented, Competent Authorities will still need to justify the imposition of PAESs.

Should a delegated act be decided upon, it is our expectation that a public consultation would be undertaken, thereby giving stakeholders the opportunity to provide input on the text.

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?

Response
EFPIA believes that the collection of post-approval evidence of efficacy should be to focus on the benefits of a treatment under real-life conditions i.e. effectiveness; the initial regulatory approval of a product is normally based on efficacy data, thus any meaningful re-assessment of benefit should be based on real-life data. A delegated act could add value in clarifying the concepts of efficacy vs. effectiveness; EFPIA does not believe that the differences in post-authorisation efficacy and effectiveness are clearly defined. As outlined in the principles above, EFPIA believes that study design should be discussed on a case-by-case basis depending on the facts of the case. This should ensure that the study to be conducted can be expected to answer the "efficacy question" that led to its imposition. EFPIA also considers the notion that PAES should always equal randomized clinical trials (RCT) is outdated and does not correspond to current expectations. RCTs to evaluate effectiveness in real world settings are challenging to perform and running RCTs post-approval would not take away the criticism that such trials lack external validity. They should be limited in scope and not duplicate the phase III program. Thus, when giving consideration to the need for a PAES, trial designs other than RCT such as pragmatic trial designs should also be considered. EFPIA would also welcome a broader discussion around novel options for the design, management, monitoring and analysis of post-approval clinical studies. Input into evidentiary requests from non-regulatory decision-makers (such as payers and HTA bodies) could be voluntarily sought. However, whilst EFPIA fully supports the process of facilitating the mutual understanding and alignment of methodologies and realistic expectations of evidence requirements through early and regular dialogue involving multiple decision-makers, EFPIA underlines that requests from non-regulatory decision-makers (such as payers or HTA bodies) should not be the driver for the imposition of PAES.

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?

Response
EFPIA agrees in part that a request for PAES may be appropriate in some situations described in the consultation paper provided that the key principles proposed above are followed. However, as decisions about requests are expected to be made on a case-by-case basis, then formulating these situations as guidelines, not as a 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 more clearly the circumstances in which a PAES may be imposed. The position and justification of EFPIA for each of the seven situations described in the Consultation is outlined in the table below. In addition, there are a number of situations where EFPIA believes that PAES should not be requested. These include: - Following guideline revision that could require more Phase III studies or require a change in the primary endpoint of the pivotal studies. The introduction of new guidelines should not lead to Phase III studies having to be repeated or new Phase III studies having to be performed. The re-assessment of an already approved product following introduction of new GLs or change in accepted primary endpoints should not be imposed on MA holders - To study indications outside the approved indication. A new development for indications outside those already approved should always remain the choice of the MAH. Off label use should not be used as the basis for requiring a PAES or to compel the MAH to seek authorization for that use. - It would not be appropriate for regulatory authorities to require studies comparing an approved product versus specific comparator drugs for the purposes of facilitating reimbursement decision making. - To compare the approved product with other products on the market or newer products that enter the market. - Where the results of the registration studies have the potential to change medical practice and therefore the generation of data including sub-optimal control/comparator arms would be unethical.

Response

- When the benefit/risk profile of another product in the same class changes, due to lower than expected benefit determination (for example a negative outcome of a confirmatory study required to support a conditional approval obligation). This should not automatically trigger regulators to request additional studies for other products in the same class

In all situations where competent authorities want the MAH to conduct a PAES, EFPIA expects dialogue between the MAH and the competent authorities to agree the purpose for the PAES and to take into account the practical feasibility of conducting studies within a reasonable time frame to achieve the desired outcomes, before agreement of the need for a PAES.

Situation	**Agree / Disagree**	**Justification / Additional Information**
5.1: Studies aimed at determining clinical outcome following initial assessment based on surrogate endpoints	Partially Agree (See additional information)	It should be recognized that where an indication has been obtained based on "surrogate endpoints", it is because these surrogates are considered as clinically relevant by the medical community. Consequently, an MA based on surrogate endpoints should not be dismissed. Obtaining further data on "hard" endpoints should not usually be required unless evidence exists that raises doubts about the validity of the surrogate endpoint; there are some surrogates that are already widely accepted as representing final endpoints and that in some situations surrogate endpoints are used for ethical reasons. In these cases, PAES should be used to confirm the approved indication, and the data generated from these studies should not automatically be used to challenge the previously demonstrated efficacy data. Where there is evidence that challenges the validity of the surrogate, such an assessment may affect a range of products. In such cases it would not be appropriate to impose a PAES on one single MAH.
5.2: Studies on combinations with other medicinal products	Conditionally Agree (See additional information)	EFPIA recognizes the concept that the Commission is trying to address in this situation and agrees that in some justified cases it is reasonable for competent authorities to request a PAES to conduct a study on certain treatment combinations. However, as clinically meaningful drug combinations are evaluated pre-approval it should be clear that there is not an expectation that all possible combinations should be studied as a PAES; more clarity (including examples) should be provided on the criteria used to identify a drug combination resulting in the need for a PAES. In any request for a PAES, EFPIA would expect the competent authorities to provide a clear justification as to why a particular combination should be considered for a PAES and also to discuss with concerned MA holders the actual possibility to demonstrate improved efficacy and

		the feasibility of the studies. Furthermore, potential alternatives to PAES should be encouraged.
5.3: Studies in sub-populations	Conditionally agree (See additional information)	EFPIA agrees that it may be justifiable for regulators to request PAES in special populations or enriched populations for the indication(s) in which the drug is approved. However, such requests should be limited to where there is strong scientific justification and sound reasoning that the population will derive benefit that is different from that observed in the general population studied in the pre-registration clinical trials; it is not always justifiable or ethical to request PAES where uncertainty exists but there is no scientific reasoning to believe the population will derive differential benefit. In addition, it should be explicitly clear that requests for PAES in sub-populations are restricted only to studies in the approved indications. EFPIA expects that requests for studies in sub-populations will take into account the feasibility of conducting the study(ies) within a reasonable time frame, given the more limited patient pool suitable for such trials. It should also be recognised that studies of subpopulations have major statistical implications. Results from subpopulations are often over interpreted and can provide misleading results; any data needs to be interpreted with caution. This has also been discussed in the CHMP "Concept paper on the need for a guideline on subgroup analysis in randomized clinical trials"[2]. As a general principle, EFPIA would advocate consideration being given to approaches to collect real-life data from electronic health records, registries and biobanks. This is as opposed to RCTs that, as previously discussed, have the potential to be burdensome and lack external validity. EFPIA considers that studies in paediatric populations should be outside the scope of PAES as these types of studies are handled specifically through PIPs.
5.4: Studies in the context of the European standard of care	Conditionally agree (See additional information)	EFPIA agrees that it may be justifiable to request additional studies where the pivotal studies leave uncertainties about the possibility of fully extrapolating the results in the EU context (specifically in the context of European standard of care of the medicinal product). However, EFPIA believes that the circumstances under which PAES can be used to address any significant uncertainty in efficacy brought about by variations in clinical practice among the Member States is very limited. Additionally, it should be recognized that in many cases there is not a consensus between Member States as to what constitutes the standard of care. Thus, EFPIA requests that prior to any request for a PAES in the context of the European standard of care, the competent authorities, taking into account the views of a wide range of stakeholders including patients, the medical community as well as other healthcare decision-makers, agree what is to be considered the European standard of care and that a justification on the basis of quantitative data is

[2] EMA/CHMP/EWP/117211/2010

		provided. Before requesting a PAES, modelling and simulation should also be considered as a relevant alternative. Furthermore, it would be unfeasible for Member State competent authorities to request multiple PAES due to national differences in standard of care between Member States. With globally conducted pivotal trials, it is neither possible, nor reasonable, to expect statistically powered comparative data on every regions' 'preferred' product amongst products that are similar.
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	Disagree	EFPIA disagrees with the Commission's thinking that a significant change in the standard of care for a condition can impact the established benefit/risk of a particular product such that a PAES for a well-established product is justified. The imposition of a PAES should therefore be reserved only for those exceptional cases where strong and significant evidence calls into question previous regulatory efficacy evaluations in the context of the benefit-risk of the product. As such EFPIA requests that the Commission provides examples to demonstrate its thinking. EFPIA believes that for a competent authority to request the MAH to conduct PAES following a significant change in the standard of care, the competent authority must clearly demonstrate how the consensus of opinion within the European medical community has been modified and how this modification impacts the B/R evaluation of the product(s) concerned; a change in opinion from a small minority of the relevant medical community should not be sufficient justification to request a PAES. Well recognised and accepted international scientific guidelines could be considered as a reliable source of evidence of the changing standard of care. Even when a benefit/risk impact can be demonstrated, alternative approaches to PAES should be considered (e.g. changes in standard of care can be managed through treatment guidelines or in revisions to product information, so allowing the physician to make the choice appropriate to individual patients).
5.6: Studies aimed at determining the long-term efficacy of a medicinal product	Partially Agree	EFPIA acknowledges that there may be exceptional cases where loss of efficacy long-term needs further elucidation and agrees with the Commission's view that it would be unreasonable to wait for data to demonstrate the long-term efficacy of a medicinal product before granting a MA. In general, long-term efficacy should be part of the primary efficacy endpoints assessed in pivotal phase III trials used to support regulatory approval. In cases where duration of effect is of interest, the expectation would be that this is pre-planned as a question prior to approval as much as possible. Thus, EFPIA considers that it would be appropriate for competent authorities to request PAES at the time of granting the MA where there is scientific evidence that a change in efficacy in the long term may be clinically relevant, in order not to delay the access of medicines to patients. However, it should be recognised that RCTs may not be feasible. Thus, alternate methodologies,

		such as registries and/or observational studies may be the only reasonable methodologies to use. In addition, for many products, the evaluation of the long term benefit/risk ratio is based also on information given by the Risk Management Plan and included in PASS.
5.7: Studies in everyday medical practice	Disagree	EFPIA understands the Commission's position that real-life use of a medicinal product is often different to use of the product in a controlled clinical trial. EFPIA also understands the position that this may have a subsequent impact on the overall benefit-risk balance of the product. However, EFPIA does not agree with the hypothesis that data generated during clinical development in general are not able to model what will be the benefit of the drug in the 'real world'. The explanation of the Commission's position in the consultation does not provide the clarity and predictability needed to ensure that PAES are not imposed unnecessarily or inappropriately; the result could be that competent authorities request PAES to demonstrate everyday use of the product for every approval they grant. The Commission should better define the situations under which a competent authority may request PAES to demonstrate the B/R of a product under everyday use and to what extent the data generated in this context may impact the terms of the initial MA. EFPIA expects that studies in everyday medical practice are to be requested only exceptionally; there has to be scientific evidence that there is a difference between effectiveness and efficacy with clinical consequences that justify characterisation of the difference, to determine whether there need to be changes to the authorisation. These proposed studies could be adequately replaced by epidemiological studies based on large existing medical databases, including response to treatments, where available on concerned diseases (e.g. databases on HIV patients).

Consultation Item 4: STUDY DESIGN

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

Response
Study design should be part of the discussion between the MAH and the Regulator with a view to establishing the best way of generating the required data to address the identified concerns. Thus, study design needs to be considered on a case-by-case basis. As outlined in our response to Consultation item #1, study design should therefore not be addressed in detail in a delegated act and it is better discussed in a scientific guidance. Some additional key issues that a guidance could clarify include: • How efficacy criteria for "old" or well-established medicinal products can be defined when the original benefit was assessed with different criteria. • The specific requirements for products with the same active ingredient but different brand names? • If orphan drugs could be in scope for PAES and if so how study size and efficacy measures should be reliably established. • Since the conditions required for a properly designed RCT as a post-marketing study may raise ethical issues, this concern should also be discussed Additionally, instead of focusing on the limitations of methodologies utilized by observational studies and pragmatic controlled studies, there could be greater emphasis on how the quality of data collected from these approaches might be improved to allow greater confidence in the conclusions of real world practice. This would then address outstanding questions from both a strict regulatory perspective (precision of result in 'ideal' situation) and one from a reimbursement perspective (is the benefit reproducible in 'real life'). We noted the following statement included the Commission Consultation: "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." It should be acknowledged that there are existing limitations of propensity score analyses which should be further explored The CHMP Concept paper on extrapolation of efficacy and safety in medicine development could help to avoid unnecessary studies in target populations. It should allow conclusions to be reached on the need/acceptability for extrapolation, thus ensuring that target populations are not exposed to unnecessary trials. Throughout the Commission Consultation and in our response, there is a discussion on the role of interventional vs. non-interventional studies and with

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the role of tight control of study conditions (as in RCT) vs. the need for PAES 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 discuss (but not dictate) the role of design choices, e.g.,

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

EFPIA understands "pragmatic trials" to be clinical trials that allow a broader inclusion of patients - reflecting normal clinical practice, such as in terms of co-morbidities and concomitant treatments[3]. However, EFPIA considers that the discussion of "pragmatic trials" is overly simplified and confusing throughout the document:

- RCT designs, especially in post-marketing settings, can contain "explanatory" elements (the effects of an intervention under ideal circumstances) and "pragmatic" elements (the effects of an intervention under the usual conditions in which it will be applied), depending on eligibility criteria, blinding, follow-up interventions, etc. The notion of pragmatic vs. explanatory studies as described in, e.g., Thorpe et al. may also be helpful.[4] These authors describe 10 domains of clinical trial design (assuming randomization) that define how pragmatic or explanatory a trial might be. They in particular, succinctly describe the considerations that should routinely be made.
- Pragmatic clinical trials can also be conducted using initial randomization to alternative treatments, either at a patient or provider level (e.g. "cluster randomization"). In this case their internal validity is increased.
- It is accepted that 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. Exceptions have occurred however, particularly in the case of vaccines.

[3] An IMI project entitled GetReal is aiming, inter alia, to discuss conducting pragmatic clinical trial designs pre-launch
[4] See Thorpe KE, A pragmatic-explanatory continuum indicator summary (PRECIS): A tool to help trial designers. Journal of Clinical Epidemiology 2009;62:464-475.

Consultation Item 5:

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

Draft Response
EFPIA welcomes a more positive attitude towards studies that aim to mimic real-life conditions that is implicit within the Commission Consultation. On occasion, HTA agencies and payer organisations may request additional studies to accompany a reimbursement or pricing recommendation or outcome. In such situations the MAH should have the flexibility to combine studies where it may be efficient to do so and deliver data to address both requests (PAES and post-HTA). Similarly, in cases where in addition to a PAES a post-approval safety study (PASS) is also required for the same product, the MA holder should be allowed to combine the 2 studies whenever possible. This would help optimizing resources and timelines. The text of the Commission consultation seems to only use MAH in singular form. The legislation refers to the possibility of requesting the MAH to conduct PAES at any time following approval and therefore PAES could potentially be requested for multi-source products. In that case, it should be considered how to best conduct the PAES involving all MAHs.