ACRP Regulatory Affairs Committee Review of EMA Draft Guidance

Scientific guidance on post-authorisation efficacy studies

What is the guidance?
This EMA draft guidance helps address questions and decision-making with respect to post-authorisation efficacy studies (PAES). The ultimate goal of PAES is to obtain and maintain benefit-risk information throughout the life-cycle of the product to achieve better labelling and better use of medicines by patients in a clinical setting. The guidance document is separated into distinct sections and offers specific examples and suggested guidance on the following key topics:

- Methods of obtaining desired information for PAES including clinical trials, observational studies, and data sources such as registries and when each method would be appropriate for use
- Scientific guidance on many specific situations such as long-term use, concomitant use with other products, etc.
- Study-conduct guidance such as development of the study protocol and report, data protection, quality control and quality assurance

Who does it impact & how?
This guidance document impacts marketing authorization holders in the European Union that have either been mandated by the competent authority(ies) to complete PAES or who voluntarily choose to complete PAES.

What did ACRP RAC have to say about it?
In general, ACRP's RAC supports the guidance document. Two recommendations were made:

1) Add clarification regarding applicability to clinical trials conducted within the jurisdiction of the EMA but which may fall outside regulatory requirements, such as Investigator-Initiated or Academic studies.
2) Add clarification as to the applicability for Independent Ethics Committees during their evaluation of the proposed research.

When were the RAC's comments sent to the agency?
January 29, 2016

Where can I access this document?
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/11/WC500196379.pdf

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29 January 2016

Submission of comments on 'Scientific guidance on post-authorisation efficacy studies' (EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015)

Comments from:

Name of organisation or individual
Association of Clinical Research Professionals (ACRP)

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

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	ACRP Appreciates the opportunity to provide EMA our comments regarding the Scientific Guidance on Post-market Authorization Efficacy Studies. Overall we find the document clarifies situations under which such a study would be anticipated/expected and provides useful information to help support adequate study design should such studies be conducted. However, we also recognize that in many jurisdictions globally certain types of post marketing trials do not require Regulatory Authority authorization and will not be submitted to the regulator. For example in Canada, Health Canada doesn't need to be notified of clinical drug trials within approved label, although they must be done according to GCP. In the interest of global harmonization efforts, we request that clarification be added regarding applicability to clinical trials conducted within the jurisdiction of the EMA but which may fall outside regulatory requirements, particularly Investigator Initiated or Academic studies. We would also like to suggest that clarification be added as to the applicability for Independent Ethics Committees (Institutional Review Boards, Research Ethics Boards, etc.) during their evaluation of the proposed research.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Comment: See general comments in section 1 Proposed change (if any): See general comments in section 1	

Please add more rows if needed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

06 November 2015
EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015
Paediatric Committee (PDCO)
Committee for Advanced Therapies (CAT)
Pharmacovigilance Risk Assessment Committee (PRAC)
Committee for Medicinal Products for Human Use (CHMP)
Coordination Group for Mutual Recognition and Decentralised Procedures (CMDh)

Scientific guidance on post-authorisation efficacy studies

Draft

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Date for coming into effect	<DD Month YYYY>[1]

Comments should be submitted using this template. The completed comments form should be sent to PAESconsultation@ema.europa.eu

Keywords	***Post-authorisation, Efficacy, Observational, Randomised, Trials Pragmatic, Explanatory, Historical controls, PAES***

[1] First day of the 7th month.

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Scientific guidance on post-authorisation efficacy studies

Draft guidance

1. Introduction

1.1. Legal basis and purpose

Post-authorisation efficacy studies (PAES) of medicinal products are studies conducted within the authorised therapeutic indication to complement available efficacy data in the light of well-reasoned scientific uncertainties on aspects of the evidence of benefits that should be, or can only be, addressed post-authorisation.

A PAES may be initiated, managed or financed by a marketing authorisation holder (MAH) voluntarily, or pursuant to an obligation imposed by a competent authority as follows:

- Within the scope of Delegated Regulation (EU) No 357/2014[2], PAES may be imposed for centrally (CAPs) and nationally authorised medicinal products (NAPs) either:
  - at the time of granting the initial marketing authorisation (MA) 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 [Art 9(4)(cc) of REG / Art 21a(f) of DIR]; or
  - after granting of a MA where the understanding of the disease or the clinical methodology or the use of the medicinal product under real-life conditions indicate that previous efficacy evaluations might have to be revised significantly [Art 10a(1)(b) of REG / Art 22a(1)(b) of DIR].
- Outside of the scope of Delegated Regulation (EU) No 357/2014, PAES may be imposed in the following specific situations:
  - a conditional MA granted in accordance with Article 14(7) of Regulation (EC) No 726/2004;
  - a MA granted in exceptional circumstances and subject to certain conditions in accordance with Article 14(8) of Regulation (EC) No 726/2004 or Article 22 of Directive 2001/83/EC;
  - a MA granted to an advanced therapy medicinal product in accordance with Article 14 of Regulation (EC) No 1394/2007;
  - the paediatric use of a medicinal product in accordance with Article 34(2) of Regulation (EC) No 1901/2006;
  - a referral procedure such as initiated in accordance with Articles 31 or 107i of Directive 2001/83/EC or Article 20 of Regulation (EC) No 726/2004.

This guidance has been developed in accordance with Article 108a of Directive 2001/83/EC which provides a mandate for European Medicines Agency (EMA) in cooperation with competent authorities and other interested parties to draw up scientific guidance on PAES.

1.2. Scope

This guidance is intended to provide scientific guidance for MAHs and for Competent Authorities on PAES in the context of EU regulatory decision-making with regard to: the general need for such studies, general methodological considerations, specific situations and study conduct. It is not restricted to the situations falling within the scope of the Delegated Regulation (EU) No 357/2014.

[2] Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required (OJ L 107, 10/04/2014, p. 1).

This guidance is not intended to replace or reproduce methods available in textbooks on various study designs but to highlight regulators' particular considerations and the potential role of mentioned study designs for the PAES setting. For the specific scenarios where PAES may be considered, additional clarifications are given together with study designs which may be considered useful.

This guidance should be read in conjunction with Delegated Regulation (EU) No 357/2014, Regulation (EC) No 726/2004, Regulation (EC) No 1901/2006, Directive 2001/83/EC and Directive 2001/20/EC[3]. See Annex 1 for other relevant guidance.

2. General guidance on the need for PAES

The granting and maintenance of a MA is dependent on data generated to that point in time from relevant tests and trials supporting a positive benefit risk balance within the authorised therapeutic indication and target population as laid out in the Summary of Product Characteristics (SmPC).

General practice is that to support a positive risk benefit in an indication, demonstration of benefit is required from pivotal, almost invariably randomised, trials that are appropriately designed and conducted in accordance with applicable guidance[4]. The demonstration of benefits therefore relies on persuasive and extensive data on the clinical outcome of interest or a validated surrogate in the patient population of interest. A PAES within the authorised indication may nevertheless be needed where there is a well-reasoned scientific uncertainty the resolution of which is important for understanding therapeutic efficacy and benefit-risk that is to be addressed post-authorisation and for which a study can be designed and conducted that will give interpretable results with the potential to impact on the licensing status or product labelling. This is in keeping with the concept of life-cycle product benefit-risk profiling through targeted post-authorisation research that translates into better labelling and better use of medicines by patients and prescribers in clinical practice.

3. General methodological considerations for PAES

The choice of study design will be based on the scientific uncertainty to be addressed. In designing and conducting a PAES, consideration should be given to ensuring that the requested study will be feasible, ethically acceptable and of a design known to return reliable and interpretable results in relation to its primary objectives. The design should take particular account of the post-authorisation setting and be feasible to complete within a reasonable timeframe.

There may be circumstances in which a PAES imposed in accordance with Delegated Regulation (EU) No 357/2014 could also include additional investigational arms as proposed by the MAH and/or supported by the competent authorities e.g. data for health technology assessment purposes, provided this would not impact on the study integrity and the primary objectives of the study as defined in the condition of the MA.

A PAES may be conducted as a randomised or non-randomised study. Note, as this is a scientific guidance, terms such as randomised, non-randomised and observational are used without prejudice to the definitions pertaining to clinical trials that may be applied in European Union and national legislation, and related regulatory guidance.

Studies involving randomisation may be the preferred design in the PAES setting. Without randomisation, estimates of effects (purporting to reflect only a difference in intervention) can be

[3] To be repealed by Regulation (EU) No 536/2014 in accordance with Articles 96 and 99 thereof.
[4] Exceptions to replication of scientific results are highlighted in CHMP/EWP/83561/05 and CPMP/2330/99.

expected to be affected by confounding factors or biases in the population under evaluation. This is because non-randomised studies, especially those comparing treatment with no treatment, may have a strong relationship between the decision to allocate a particular treatment and prognosis. It is widely acknowledged that results from non-randomised studies of efficacy are generally more difficult to interpret than those from similar studies of safety where confounding is likely to be less. Nevertheless, in certain situations (see section 3.2) the conduct of non-randomised studies, where measures are included to minimise limitations/ biases, could be justifiable in the PAES setting.

All PAES should conform to applicable legislation and recognised international methodological and ethical standards for research.

3.1. Clinical trials

As far as is possible, the methods applicable for preauthorisation clinical trials should also be adopted in the PAES setting. One or more control arms should, as appropriate, be allocated to placebo (perhaps as 'add-on' to standard of care) and / or an established medicinal product of proven therapeutic value and any other design should be justified.

Trial designs, e.g. choice of control arm(s), objective (e.g. superiority or non-inferiority) will be determined by the uncertainty to be addressed, the nature of the intervention and the condition under treatment. It may be preferable to compare the medicinal product subject to PAES with that of an established medicinal product of proven therapeutic value. (See also the specific situations regarding real-life use (Section 4.5) for further discussion on where submission of a PAES with an active comparator may be considered or required).

Clinical trial design options for the design of PAES could include explanatory and pragmatic trials.

3.1.1. Explanatory Trials

Such trials are expected to have a high degree of internal validity and to be tightly designed to reflect the intended indication and treatment regimen, so that the errors and biases will influence the results as little as possible. This will control for sources of bias (systematic errors) by means of randomisation, blinding, and allocation concealment and will have a clearly defined participant population.

These trials play an important role in providing knowledge concerning the effects of precisely defined interventions applied to selected groups under controlled conditions. However, depending on the detail of the protocol, external validity may be limited in applicability. Thus in a PAES setting, these designs are best targeted at uncertainties where a need for tight control of heterogeneity is foreseen. Such an experiment will also need to be feasible post-authorisation and ethical considerations around the choice of control arm must be taken into account.

3.1.2. Pragmatic Trials

Pragmatic trials examine interventions under circumstances that approach real-world practice, with more heterogeneous patient populations, possibly less-standardised treatment protocols, and delivery in routine clinical settings as opposed to a research environment. Minimal restrictions may be placed on modifying dose, dosing regimens, co-therapies or co-morbidities or treatment switching.

The distinction between pragmatic and explanatory clinical trials may be considered as a continuum[5] rather than dichotomous hence the distinction is less important than the design features in respect of trial objectives. For example, some elements (inclusion of a broad patient population or those with higher baseline risks) of explanatory trials could be made more pragmatic without relaxing all of the design parameters associated with the most explanatory type of trials. Pragmatic trials may be more amenable to trial designs not commonly employed for explanatory clinical trials e.g. cluster-randomised or stepped-wedge designs.

From a regulatory perspective, a number of methodological issues are highlighted given that these designs have been less commonly encountered for regulatory purposes: robust randomisation processes with allocation concealment should be used as per explanatory trials. The length of follow up should be sufficient and the events of interest should be detectable. Consideration should be given to the level of bias introduced if the outcome assessment is not masked to the treatment allocation. Consequently, outcomes that can be established to be accurate independent of the investigator or patients are useful.

The analysis plan should consider how to measure the effect of the treatment of interest in the event of discontinuation of study drug or use of rescue medications consistent with the objective of the experiment. Where the objective is to establish evidence for absence of a difference between interventions, the interpretation of findings should take account the level of noise and variability. Specifically it should be justified that the trial is sensitive to detect differences if they exist.

Investigators should therefore report quality metrics i.e. measures quantifying the control mechanisms and the extent to which they were relaxed. Clinical trials conducted for regulatory purposes should be reported in line with applicable legislation but from a scientific perspective pragmatic adaptation in the trial design should be clearly identified in the report as described in the CONSORT[6] statement extension for pragmatic trials.

Consideration should be given to whether or not the pragmatic diagnostic approaches to indications or outcomes are reliable, as pragmatic trials tend not to do confirmatory tests, and whether the results are generalizable in different healthcare settings. However, populations may still be self-selecting and it may be worth checking the demographic characteristics of the enrolled patients.

For the PAES setting, pragmatic trials may be used in situations where there is a need to explore whether the intervention is used in the same way in the real-world setting as in the pivotal trials or where there are concerns about whether trial results translate into this setting or where non-adherence to treatment could be an issue.

Such trials may also be used if the comparator is usual care (if not, an explanatory trial is needed) or if randomisation (as opposed to non-randomisation) is needed to answer a particular question or if strong modifying effects are anticipated.

3.2. Observational studies

Non-randomised studies may be considered for investigating benefits where one or more of the following situations apply: randomisation is unethical or unfeasible, outcomes are infrequent or are far in the future, the generalisability of randomised trials is limited, outcomes are highly predictable, or

[5] Treweek S, Zwarenstein M. Making trials matter: pragmatic and explanatory trials and the problem of applicability. Trials 2009 10:37.
[6] Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, Oxman AD, Moher D for the CONSORT and Pragmatic Trials in Healthcare (Practihc) group. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008;337;a2390.

effect sizes are very large[7]. Observational PAES may additionally be useful to investigate effect modifiers, namely factors that describe important differences between patients within the licensed indication that may influence the level of efficacy of the drug and may not have been fully explored prior to authorisation. Examples of effect modifiers are patient sub-groups defined by factors such as age, co-morbidities and use of concomitant drugs, disease severity, disease duration, treatment history and factors related to a defined country or health care system.

Observational studies to measure benefits require exposures and outcomes which can be measured with a high degree of accuracy(i.e. minimised risk of misclassification bias); objective criteria are preferred. The degree to which relevant confounding factors and effect modifiers can be correctly measured will greatly impact on the confidence with which the results can be interpreted. This will, in general, be easier when comparing with another active treatment rather than no treatment.

Post-marketing observational studies involving secondary use of existing data (see Section 3.3) could be considered in situations where a rapid exploration of an efficacy question is needed.

3.2.1. Studies with concurrent controls

In general, the preferred comparison within an observational study will be to a concurrent set of patients who have not or who are not currently receiving the treatment of interest.

In observational studies of drug effects, confounding by indication and channelling of treatments are amongst the main sources of bias when evaluating benefit endpoints. These need to be addressed. For well-measured confounders, there is little difference in results between different methods used to address confounding, although the impact of unknown, unmeasured or poorly measured confounders remains a source of bias. When it is possible to identify a subset of the observational study population that is broadly similar to that included in the explanatory randomised clinical trials, confidence in the overall study results may be increased if similar results are found in this sub-population. The importance of sensitivity analyses to test the robustness of study results is therefore emphasised.

Observational studies can also be more challenging to interpret due to time-varying confounders in chronic conditions, adherence to treatment guidelines resulting in highly selective patient populations receiving treatment, and temporal changes in prescribing trends, particularly in the early stages of marketing. The ENCePP Guide on Methodological Standards in Pharmacoepidemiology[8] and the ISPE Guidelines for Good Pharmacoepidemiology Practices[9] provides a further discussion of methods that go towards addressing these issues.

3.2.2. Studies with historical comparison data

Comparison of currently treated patients with historically treated controls is difficult for two reasons. The decision to treat applies only to a selected patient group that may differ from the historical controls and the clinical background may have changed over time.

However, comparison to historical datasets may have a role in the PAES setting where obtaining prospective data is infeasible or unnecessary because the historical data are well-characterised and relevant and a large effect size is anticipated. These datasets are most likely to come from formal

[7] Why we need observational studies to evaluate the effectiveness of health care. Black N. BMJ. May 11, 1996; 312(7040): 1215–1218.
[8] The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 3). EMA/95098/2010. http://www.encepp.eu/standards_and_guidances
[9] The International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practices (Revision 2). https://www.pharmacoepi.org/resources/guidelines_08027.cfm

clinical trials for which the selection criteria were well documented and strictly applied and in which the known, important prognostic variables were recorded and can be matched to the treated patient data. A major consideration is whether the selection criteria in the original trials have been applied in the subsequent observational study. Historically treated controls may sometimes be considered when there is insufficient information for more established methods. For example, when a new medicine is used, there may be too little exposure to calculate propensity score models and disease risk score methods for rare outcomes may not work well unless they can be developed with more extensive historical data. If the new drug takes a lot of the market then again historical controls may need to be used.

3.3. Data sources

There are two main approaches for data collection. One is primary collection of data specifically for a study. The other is to use data already collected for another purpose, e.g. as part of electronic records of patient health care ("secondary data collection").

Clinical trials in general will rely on primary data collection. In contrast, using electronic routinely collected clinical healthcare record databases to facilitate the conduct of clinical trials is relatively new and some challenges are likely to need regulatory dialogue if the results of these trials are to be used to support regulatory decision-making. Potential value of using such databases may be realised when outcomes are clinically important acute events (e.g. death and onset of new disease) that are likely to be well recorded. Long-term low-cost follow-up could be possible and studying rare disease outcomes might be facilitated. Any application to treatments in orphan diseases is limited unless extremely large population coverage is available. The quality and completeness of data in the database must be sufficient to conduct a credible study. Important variations exist between individual databases and consequently it should be assured that clinical trial processes can be implemented in a consistent way . Database screening or record linkage can be used to detect and measure outcomes of interest otherwise assessed through the normal process of care. Patient recruitment, informed consent, confidentiality, assuring of patient anonymity, and proper documentation of patient information are areas that still need to be addressed in accordance with the applicable (local) legal and ethical requirements for RCTs. Administrative requirements, coding conventions, quality of data, the ability to link to additional data sources and the ability to provide further clinical details on request are all likely to be specific to a database.

The use of primary and secondary data collection sources for observational studies are well described elsewhere.

Regulators can require marketing authorisation holders (MAHs) to establish post-authorisation registries[10] to support collection of data on effectiveness and safety of medicinal products in the routine treatment of diseases, in particular in cases of paediatric use and orphan products.

The design of a registry (including the definition of the patient population and the outcomes to be measured) should be primarily based on the objectives and the planned analyses as described in a protocol and not on an *a priori* decision on how patients will be recruited. Disease registries will facilitate treatment comparisons within them. Registries based on a single medicinal product alone provide little avenues for treatment comparisons.

[10] The term registry is used in this document to indicate an organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.

Established registries may provide an opportunity to assess patient outcomes including effectiveness particularly where supplementary data collection or linkage are feasible. It is always important to consider the potential utility of existing registries before starting new ones.

Registries allow for a wide variety of observational study design options including prospective cohort studies with nested case-control analysis, inception cohorts, retrospective cohorts for events with short induction times, natural history studies, and cohort studies with internal comparators, linkage and/or supplementary data collection. A common set of variables and procedures (e.g. inclusion criteria, clinical and socio-demographic characteristics, major outcomes, follow-up schedules) can allow extraction of data in a standardised form and facilitate such observational studies. As for any other epidemiological source of data, data quality is crucial. Measures to improve the quality of data, the validity of studies and the usefulness of results from registries include using common terminologies and data dictionaries/definitions, quality control of laboratory and measurements data and standards for collection of patient-reported information.

Registries with large numbers of subjects may allow for heterogeneity of efficacy by different patient characteristics to be studied. Amongst the limitations are those applicable to observational studies and situations where the disease or exposure classification is not specific enough or where follow-up is not possible or available, or where appropriate controls cannot be identified. In terms of data interpretability, it is important to describe the representativeness and generalisability of a registry, and whether it covers the relevant patients and periods of interest. Moreover, the use of registry data is limited by selection bias as with other observational datasets.

3.4. Safety aspects

Safety reporting from PAES which are clinical trials falls under the scope of Directive 2001/20/EC. The provisions set out in Directive 2001/83/EC and Regulation (EC) No 726/2004 apply for studies falling outside the scope of Directive 2001/20/EC. For the latter, detailed guidance is provided in Module VI of the Good Pharmacovigilance Practice.

4. Scientific guidance on specific situations

The following guidance expands on the detail of the situations where PAES may be imposed in the context of Delegated Regulation (EU) No 357/2014. As referred to in Section 1.1 there may be other legal frameworks where such situations might also arise. There may also be a wide range of scenarios arising from change in understanding or the identification of new scientific factors that require a PAES to be imposed. It is, however, emphasised that these studies will be rare rather than routine and that to impose a PAES there should be a well-reasoned scientific uncertainty that is important for understanding therapeutic efficacy and benefit-risk but can be addressed post-authorisation and for which a study can be designed and conducted that will give interpretable results with the potential to impact on the licensing status or product labelling. The clinical relevance of the scientific uncertainty should also be considered.

4.1. Uncertainties concerning benefits stemming from (sub)-populations

An important well-reasoned scientific uncertainty may exist regarding aspects of the target population in the therapeutic indication and a PAES aimed at reducing such uncertainty may be required.

A wide range of potentially applicable sub-populations can be envisaged. These sub-populations may be defined by baseline demographic criteria or specific factors affecting disease prognosis or a drug's

pharmacokinetic/pharmacodynamic profile, e.g. pharmacogenomic markers affecting treatment response. Uncertainty may arise when the target population changes during the course of a development programme (including where new biomarkers are identified), or due to a poor general existing evidence base for authorised products, lack of patient numbers in a given sub-population or unduly restrictive inclusion / exclusion criteria and the consequent reliance on extrapolation rather than clinical trial data to support a broader indication statement. Further study may be aimed at establishing whether an effect exists or whether an effect is modified in a given sub-population.

Both randomised clinical trials and observational studies could be considered. The choice of design will need careful justification taking account of the precise question for which an answer is wanted, the available evidence and the uncertainty.

4.2. Uncertainties concerning benefits stemming from endpoints

The clinical relevance of the outcome measures in assessments of efficacy is essential to support a positive risk benefit. Thus the use of intermediate endpoints that are not the final clinical outcomes at the time of a MA application should only be the basis for a MA when agreed to be surrogates or to be sufficiently informative by the scientific/regulatory community. However, there may be varying degrees of uncertainty in the strength of relation between the intermediate endpoints and the final clinical outcomes[11]. PAES may therefore be required where supplementary data are needed to support the established positive benefit risk balance. Examples include in the case of slowly progressive conditions necessitating extended follow up, or where there are complex composite or intermediate or key secondary endpoints that are important to establishing therapeutic efficacy and benefit-risk but cannot be fully understood on the basis of the clinical trial data presented. In the case of a requirement for long term follow up, observational designs may be necessary.

Another scenario is when additional complementary endpoints are identified for further assessment to provide additional meaningful information.

4.3. Uncertainties in benefits regarding treatment over time

For treatments given on a continuous basis, the benefit risk balance assumes that benefits established in the timeframe of pivotal studies persist. This assumption also applies for intermittent or repeated treatments e.g. where neutralising antibodies, which may abolish treatment effects, develop over time. Where uncertainty arises that a decreased response takes place over time, a PAES may be required. Randomised clinical trials or observational studies could be used to address this uncertainty. The design will be dependent on the degree of uncertainty taking account of the clinical pharmacology of the medicinal product and the possibility of generating interpretable data. Randomised withdrawal designs could be considered and justified taking into account the timeframe of the effects.

4.4. Uncertainties in benefits regarding co-treatment with other products

At the time of its licensing, the use of a medicinal substance in anticipated combination with other treatments must be substantiated in terms of the safety and efficacy of the combination.

PAES may be required for additional potential combinations (simultaneous or sequential) for which uncertainties remain based on the accumulated scientific knowledge or for which theoretical uncertainties arise about a specific combination. The study design will be dependent on the

[11] Svensson S, Menkes DB, Lexchin J. Surrogate Outcomes in Clinical Trials: A Cautionary Tale. JAMA Intern Med. 2013; 173(8):611-612.

uncertainty, in particular whether the aim is to establish efficacy of the new combination per se, or to compare one potential combination with another, and the potential variability.

In the post-marketing setting, treatment paradigms may change over time resulting in treatment combinations that are different to those that were originally studied for the marketing authorisation and PAES may therefore be required if an uncertainty over the use of a particular combination arises.

Observational designs may suffice if justified.

4.5. Uncertainties stemming from benefits of the medicinal product in real life use

A PAES may be required where the benefits of a medicinal product demonstrated in clinical trials may be significantly affected by the use of the medicinal product under real-life conditions, e.g. where the efficacy demonstrated might not translate into a clinical benefit if the use of the drug provokes an effect on the behaviour of the recipients (risk compensation) or impacts negatively on other measures considered as important to prevent the disease. The results of such studies would allow determination of benefit in everyday medical practice and regulatory action if necessary.

A related scenario would be where the choice of control or background treatment is sub-optimal or where a comparison to a particular standard-of-care, usually another medicinal product, is considered necessary even though positive benefit-risk has been established relative to a particular clinical trial control arm. The difficulties in defining standard of care are acknowledged including in the context of appropriate comparator arms, local definitions and the idea of multiple studies defining a number of 'standards of care'. For medical products where a major advancement in care has taken place whilst pivotal trials were ongoing and which also constituted a scenario where an active control would be needed to further inform on the benefit-risk of the product, consideration may be given to requiring a PAES with a relevant active comparator.

Another scenario where the need for PAES might be considered is where a specific scientific rationale questions the external validity of the data across various populations and settings despite a high degree of internal validity of the results from pivotal clinical trials e.g. impact of co-morbidities and polypharmacy on effectiveness of a specific intervention in a geriatric population.

With recognition that the assessment of the risk of a medicinal product is most meaningful when considered in light of its benefits, post marketing evaluation of medicinal products is increasingly based on a benefit-risk management model encompassing evaluation of emerging evidence relevant to both risks and benefits. For example, a formal evaluation of benefit is a feature of Periodic Safety Update Reports. There may be circumstances where important uncertainties concerning a product's benefits become relevant in the context of a post marketing benefit-risk evaluation particularly where knowledge of the safety or benefit-risk profile has changed significantly since first authorisation. In such circumstances the need for a PAES may be considered.

A PAES may also be required in the case of vaccines where protective efficacy studies have not been feasible or to further determine the impact of microbial epidemiology and herd immunity on efficacy. PAES may also be used to estimate vaccine effectiveness using study designs different to those that supported the initial MA. The information gained from assessment of vaccine effectiveness may also be particularly important to add knowledge on the most appropriate mode of use of a vaccine (e.g. need for booster doses in at least some segments of the population to maintain adequate protection over time).

4.6. Change in the understanding of the disease or drug

Knowledge of the mechanism of action of a medicinal product develops throughout the product lifecycle. Investigation of dose-response is a critical aspect of the drug development process. The initial understanding of a positive benefit risk balance may be improved through further investigation of posology. In the case where a change in the understanding of the standard of care for a disease or of the pharmacology of the drug has put into question the criteria used to establish the efficacy of the product at the time of authorisation, a PAES may be imposed.

4.7. Change in scientific factors for previous efficacy evaluations

If new concrete and objective scientific factors (including regulatory or clinical guidance) emerge which significantly bring into question the criteria used to establish the efficacy of a medicinal product at the time the MA was granted, a requirement for a PAES may be considered.

5. Conduct of post-authorisation efficacy studies

Marketing authorisation holders and investigators should follow all relevant EU requirements and the national legislation and guidance of those Member States where the study is being conducted.

5.1. Study protocol and report

Study protocols for PAES should take into account relevant scientific guidance applicable to the issue to be investigated and the study design to be applied. Agreement on the protocol between sponsor and regulator needs to be reached for an imposed PAES. Any amendment to the protocol should be discussed and agreed in advance with the competent authorities.

The time frame for the final study report to be submitted and for any interim report should be agreed by the competent authorities at the time of study request or further refined at time of protocol finalisation. If the study is discontinued, a final report should be submitted and the reasons for stopping the study should be explained. The format of study report should follow the conventional format as per ICH guidance.

It is recommended that agreement be sought as early as possible between sponsor and regulator that the proposed study design is adequate to address the uncertainty in question. Scientific advice on the study protocol between sponsor and regulator with respect to the proposed study design is also recommended.

5.2. Data protection and transparency requirements

The collection, use and trans-border transfer of personal data relating to patients enrolled in a PAES has to comply at all times with the requirements of the Data Protection Rules[12].

To support transparency on PAES that are outside the scope of Directive 2001/20/EC and which are conducted pursuant to a condition of the MA or voluntarily, study information (including for studies conducted outside the EU) should be made available in the EU electronic register of post-authorisation

[12] Data Protection Rules includes Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, the national laws, the laws of the European Union Member States transposing this Directive, the Opinions and guidance developed by Article 29 Working Party and the guidance developed by the competent data protection authorities of the European Union Member States.

studies (EU PAS Register) maintained by the Agency[13]. This recommendation is without prejudice to national transparency requirements.

5.3. Quality control and quality assurance

The MAH should ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified. For PAES imposed as an obligation, the MAH should ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection and adhere to CONSORT or STROBE reporting guidelines. This provision should also be applied to PAES voluntarily initiated, managed or financed by the MAH.

6. Conclusions

To impose a PAES, there should be a well-reasoned scientific uncertainty to be addressed post-authorisation to enhance understanding of therapeutic efficacy and benefit-risk with implications for better use of the medicine in clinical practice. In addition, it should be ethical and feasible for a study to be designed with a suitable methodology and conducted in a manner to give reliable and interpretable answers to the question at hand. Agreement should be sought as early as possible between the regulator and sponsor on the appropriateness of a study design to achieve this and to this end, scientific advice is recommended.

[13] http://www.encepp.eu/encepp_studies/indexRegister.shtml

Annex 1: Relevant guidance

- The extent of population exposure to assess clinical safety for drugs (ICH E1A).
- Dose response information to support drug registration (ICH E4).
- General considerations for clinical trials (ICH E8).
- Statistical principles for clinical trials (ICH E9).
- Choice of control group in clinical trials (ICH E10).
- Clinical investigation of medicinal products in the paediatric population (ICH E11).
- Accelerated evaluation of products indicated for serious diseases (Life Threatening or Heavily Disabling Diseases) (CPMP/495/96 rev. 1).
- Points to consider on applications with 1.) Meta-analyses and 2.) One pivotal study (CPMP/2330/99).
- Points to consider on switching between Superiority and Non-inferiority (CPMP/EWP/482/99)
- Reflection paper on methodological issues in confirmatory clinical trials with flexible design and analysis plans (CHMP/2459/02).
- Guideline on Data Monitoring Committees (CHMP/EWP/5872/03 Corr)
- Clinical trials in small populations (CHMP/EWP/83561/05)
- Qualification of novel methodologies for drug development: guidance to applicants (EMEA/CHMP/SAWP/72894/2008)
- ENCePP Guide on methodological standards in pharmacoepidemiology
- International Society for Pharmacoepidemiology (ISPE) guidelines for good pharmacoepidemiology practices