EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guidance on Post-Authorisation Efficacy Studies

(NB: under development)

Industry Stakeholder Platform on the implementation of the Pharmacovigiliance legislation
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Post Authorisation Efficacy Studies (PAES) not a new concept

Prior to Delegated Regulation (EU) 357/2014 separate legal frameworks existed for PAES in the context of

- Conditional Marketing Authorisation (MA)
- MA in exceptional circumstances
- MA for ATMPs
- The paediatric use of a medicinal product
- Referral procedures

PAES Delegated Regulation (EU) 357/2014

May be required for centrally or nationally authorised products either:

- **At the time of granting the marketing authorisation**: 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

- **After granting the marketing authorisation**: 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

Legal basis for PAES scientific guidance

DIR 2001/83/EC as amended with regard to *Article 108a*

…the Agency shall, in cooperation with competent authorities and other interested parties….draw up scientific guidance on post-authorisation efficacy studies.

Rapporteur Planning Group

- Agency (Jane Moseley, Kevin Blake)
- CHMP (Pierre Demolis, Robert Hemmings)
- PRAC (Stephen Evans, Almath Spooner)
- CMDh (Peter Bachmann, Jascha Hoernisch)

➢ *Regulatory & procedural guidance/Q & A being developed in parallel (Christelle Bouygues)*

Scientific guidance: context and considerations

- Core-elements: relevant legislation
- Building on existing methodological guidance including
  - Clinical Trials methodologies,
  - relevant GVP (e.g. module VIII on PASS)
  - October 2013 PAES Workshop http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/11/WC500155692.pdf
- Other sources: e.g. literature on pragmatic trials, registry guidelines

Considerations for PAES guidance

- Principles based approach – not detailed methods for specific designs
- High-level scope - performance of PAES in situations inside and outside the delegated regulation (DR)
- Expand around situations in DR + high level on methodologies
- Covering imposed only but also mindful of voluntary PAES
- Aim is to bring predictability/consistency to requests

Current proposed draft outline

I. Scope (audience: industry and regulators)

II. General guidance on need for PAES

III. General methodological considerations for PAES

IV. Scientific guidance on specific situations

Current thinking on general guidance on need for PAES

- Situations where well reasoned specific scientific uncertainty with respect to the evidence on benefits of a medicinal product expected
- Not intended to replicate the studies already conducted prior to authorisation or to act as confirmatory trials.
- Note PAES could include additional investigational arms/secondary objectives provided the study addresses the uncertainty in question
- Safety data always important

Uncertainty issues needing PAES

- Population studied
- Endpoints /long term
- Combinations
- Real life
- New information on disease, drug, other scientific factors/standards of efficacy

Current general methodological considerations

- Requested study will be feasible, ethical and interpretable in relation to its primary objectives taking account of the post-authorisation setting.
- Within authorised indication
- A PAES may be conducted as a randomised or non-randomised study
- Studies involving randomisation are the preferred design in assessing benefits
- Without randomisation, estimates of benefit are expected to be affected to an important degree by confounding factors or biases in the population under evaluation.

General methodological considerations

Agreement recommended between sponsor and regulator

- the proposed study design
- interpretable and useable results
- sufficiently address the uncertainty in question.
  - *Early proactive planning vs reactive later in MAA*
  - *Role of Scientific Advice*
  - *Interacting with other stakeholders*

General methodological considerations

Study designs (e.g. Randomisation, choice of control arm, objective) determined by the uncertainty to be addressed the nature of the intervention and condition under treatment

- may be preferable in certain cases to compare the medicinal product subject to PAES with that of an established medicinal product.

Recognise that there may be situations where alternative designs other than randomised controlled trials could be justifiable in the PAES setting and where measures are taken to minimise limitations/ biases in such designs

Further notes:

- Recognise that primary and secondary data sources possible for PAES
- Distinguish between data source aspects (electronic health records, registries, etc.) and study design
- Quality and completeness of data in a database are essential
- All applicable legal, ethical and regulatory requirements should be fulfilled
- Relevant scientific standards should be applied

Indicative timing

- ✓ July 2014: Planning Group finalised with Committee leads
- ✓ July 2014: setting up drafting group
- ✓ Q3/4 2014 preparation and drafting relevant parties

- ❑ Q2/3 2015: Committees/CMD(h) adopt draft for public consultation
- ❑ 3 month public consultation

Thank You

If any queries/suggestions:

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