EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Update on Post-Authorisation Efficacy Studies

Eighth Stakeholders forum on the implementation of the Pharmacovigilance legislation
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Kevin Blake, Jane Moseley, Christelle Bouygues
Human Medicines Research & Development Support Division

PAES: not an entirely new concept

Prior to Delegated Regulation (EU) 357/2014 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

Delegated Regulation (EU) No 357/2014

- Public consultation (Nov. 2012 – Feb. 2013) ✓
- Expert group meeting/consultation (March – Oct 2013) ✓
- Adoption of delegated act by the Commission (Feb. 2014) ✓
- Submission to EP and Council – right to object (Feb- April '14)✓
- Publication and entering into force (April 2014)

➢ *Expand framework for PAES imposition beyond existing legal frameworks*

PAES Delegated Regulation

May be required for Centrally/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

PAES must not be used as a justification for premature granting of MA or to cure absence of any data required to establish the efficacy of the medicinal product

The specific situations within DR

	Delegated Regulation
Initial assessment based on surrogate endpoints	"An initial efficacy assessment that is based on **surrogate endpoints**, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions"
Combination with other products	"In case of medicinal products that are **used in combination** with other medicinal products, the need for further efficacy data to clarify uncertainties that had not been addressed when the medicinal product was authorised"
Sub-populations	"Uncertainties with respect to the efficacy of a medicinal product in certain **sub-populations** that could not be resolved prior to marketing authorisation and require further clinical evidence"
Long term efficacy	"The potential lack of **efficacy in the long term** that raises concerns with respect to the maintenance of a positive benefit-risk balance of the medicinal product"

The specific situations – cont'd

	Delegated Regulation
Change in the under-standing of the standard of care/pharmacology	"A change in the understanding of the **standard of care** for a disease or the **pharmacology** of a medicinal product that requires additional evidence on its efficacy"
Everyday medicinal practice (exceptionally)	"Benefits of a medicinal product demonstrated in clinical trials are significantly affected by the use of the medicinal product under **real-life conditions**, or, in the case of vaccines, protective efficacy studies have not been feasible"
'Other' situations	"**New concrete and objective scientific factors** that may constitute a basis for finding that previous efficacy evaluations might have to be revised significantly"

Imposed PAES – direction of travel

- **Exceptional**
- **Context**: efficacy evaluation
- **Identified concern** – well-reasoned scientific uncertainty
- **Justified** on a case-by-case basis taking into account the properties of the product and the available data
- **Feasible** to conduct including in the post-marketing setting
- **Goal**: address concerns with tangible results with direct impact on the maintenance of the marketing authorisation
- **Design**: appropriate to answer the scientific question – focal point: supplementing efficacy data

Legal basis for PAES scientific guidance

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

In order to facilitate the performance of pharmacovigilance activities within the Union, the Agency shall**, in cooperation with competent authorities and other interested parties,** draw up:

(a) guidance on good pharmacovigilance practices for both competent authorities and marketing authorisation holders;

(b) **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 will be developed/updated in parallel (Christelle Bouygues)*

Scientific guidance: context and considerations

- Core-elements: relevant legislation
- Building on existing methodological guidance including
  - Clinical Trials methodologies,
  - relevant GVP (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 guidance

- Principles based approach vs detailed methods for specific designs
- High-level scope - performance of PAES in situations inside and outside the delegated regulation
- Why around situations vs How on methodologies
- Covering imposed only but also mindful of voluntary PAES
- Bringing predictability/consistency to requests
- Not increasing hurdles/unintentionally increasing numbers of studies being conducted

Further considerations

- Clinical trial or non-interventional study
- Clinical trials expected to represent the majority
- Studies to measure in real life conditions – possible designs
- HTA outcomes
- Early proactive planning vs reactive later in MAA
- Role of Scientific Advice

Possible outline

I. Scope (audience: industry and regulators)

II. Existing guidances

III. General guidance on need for PAES

IV. General methodological considerations for PAES

V. Scientific guidance on specific situations

VI. Conduct of PAES (protocol development, reporting of results, transparency requirements, potential for Scientific Advice)

Indicative timing (to be confirmed)

- ✓ 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
- ❑ Finalise late 2015

Thank You

If any queries/suggestions:

kevin.blake@ema.europa.eu

jane.moseley@ema.europa.eu

christelle.bouygues@ema.europa.eu