EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Scientific Advice delivers planning throughout development

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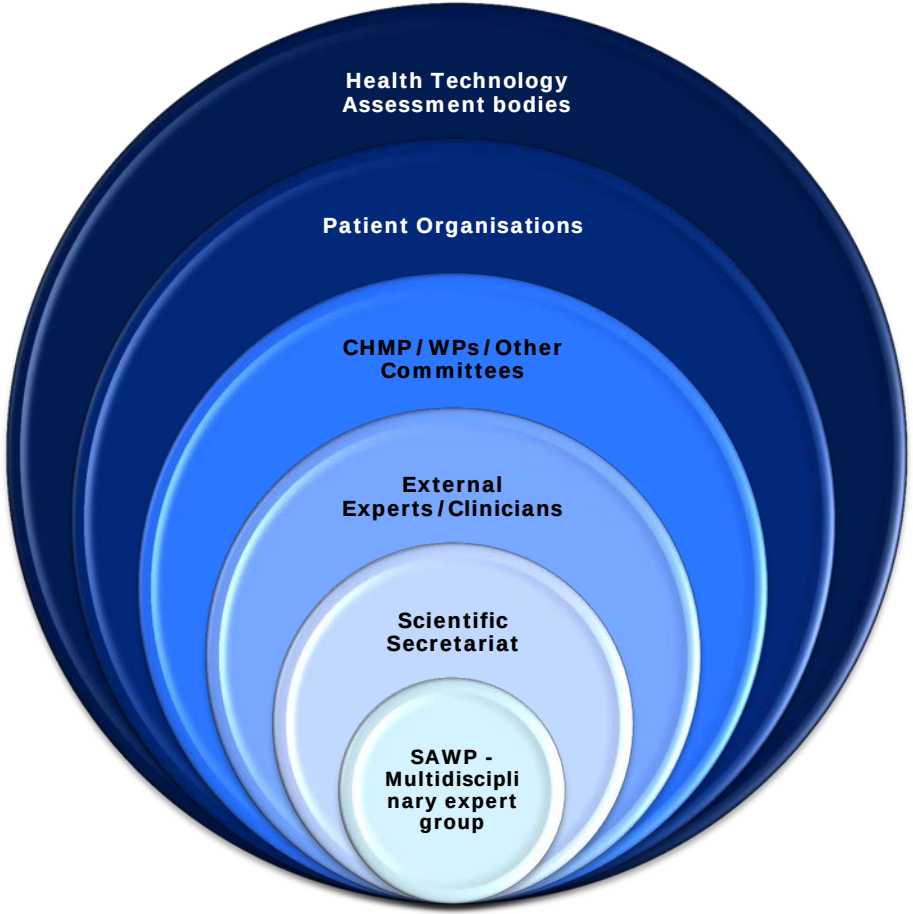
EMA – Scientific Advice

Scientific Advice Network

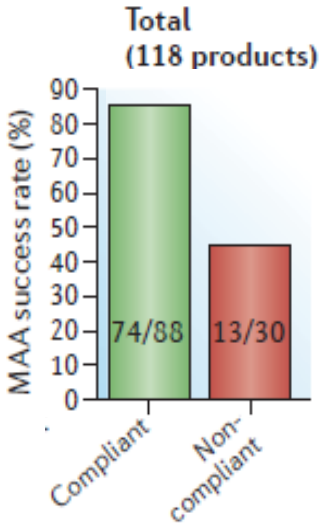
Advising on the scientific requirements for regulatory decision making throughout life-cycle:

- Before the first marketing authorisation (MA):
  questions on manufacturing,
  non-clinical and clinical trials,
  risk-management plans,
  ways to develop generics and biosimilars;
  significant benefit for orphan medicines;
  development in children.
- Post-MA:
  extension of indication to different age groups and stages of the disease;
  different conditions; safety aspects.



Positive impact of SA adherence on MAA procedure and outcome

MAA success



MAA procedural aspects

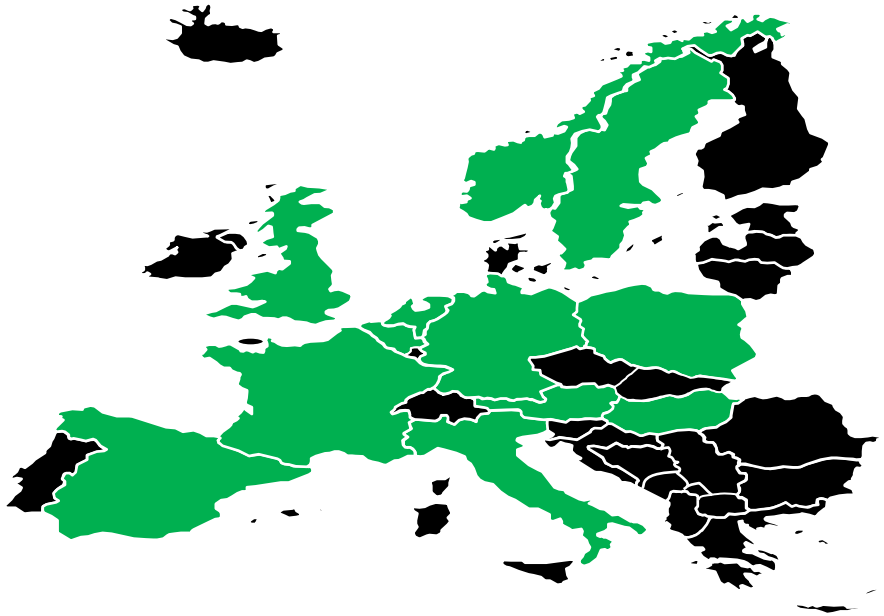
	MAA procedure	Total MO*			
	average days	Quality/Pre-Clinical	Clin. Efficacy	Clin. Safety	Total
Compliance	367	1.64	2.66	0.86	5.16
Non- Compliance	428	4.25	3.91	1.42	9.58

SA/PA submitted in 2008–2012, Hofer et al. Nat Rev Drug Discov. 2015

EMA HTA Parallel SA: Experience to date

- **87 parallel EMA – HTA SA procedures** with EU HTA bodies from UK, Italy, Germany, Sweden, France, Netherlands, Spain, Belgium, Austria, Poland, Norway, Hungary

- **Broad range of indications**: Lung cancer, Breast cancer, Pancreas cancer, Melanoma, Asthma, COPD, Diabetes, Heart Failure, RA, Depression, Alzheimer's, Migraine, Infections, Rare diseases, M. Gravis, Ophthalmology



Parallel HTA/EMA SA - Experience so far

Common discussions: Elements which are necessary for the benefit/risk assessment (Regulators) and added value (HTAs)

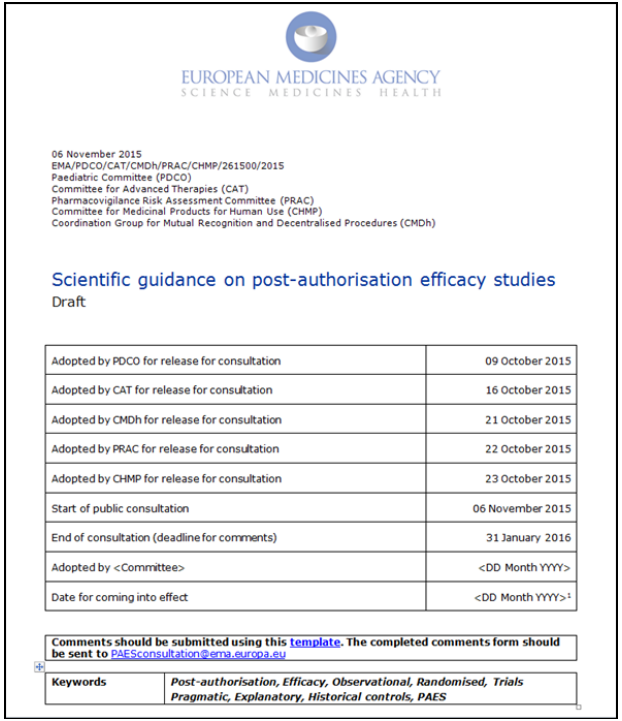
- Comparator: placebo, active comparator
- Clinical endpoints: Survival, quality of life
- Duration of the trial
- Patient population to be included pre marketing / post marketing
- New: registries use , Qualification of novel endpoints
- Tafuri et al. 2016 provide overview of experience up to now

“Late dialogues, including HTA bodies”

- To be developed: collaboration on post-launch data generation
- Aim: one (set of) studies for regulators and HTA bodies (payers); including real-world evidence, which is currently an underutilised resource; to enable refined and extended benefit-risk assessment as well as value assessment and pay-for-performance schemes
- Door now open for (parallel) scientific advice on post-authorisation studies, risk management planning, etc.

PAES definition in draft scientific guidance

"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".



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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

Adopted by PDCO for release for consultation	09 October 2015
Adopted by CAT for release for consultation	16 October 2015
Adopted by CMDh for release for consultation	21 October 2015
Adopted by PRAC for release for consultation	22 October 2015
Adopted by CHMP for release for consultation	23 October 2015
Start of public consultation	06 November 2015
End of consultation (deadline for comments)	31 January 2016
Adopted by <Committee>	<DD Month YYYY>
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***

Extension of the legal framework

- Prior to Delegated Regulation (EU) 357/2014, PAES could be requested in the context of certain MAs (conditional, exceptional circumstances, ATMPs), paediatric use and referral procedures.
- PAES can now be required for medicines with a standard MA:

  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.

When will a PAES be required?

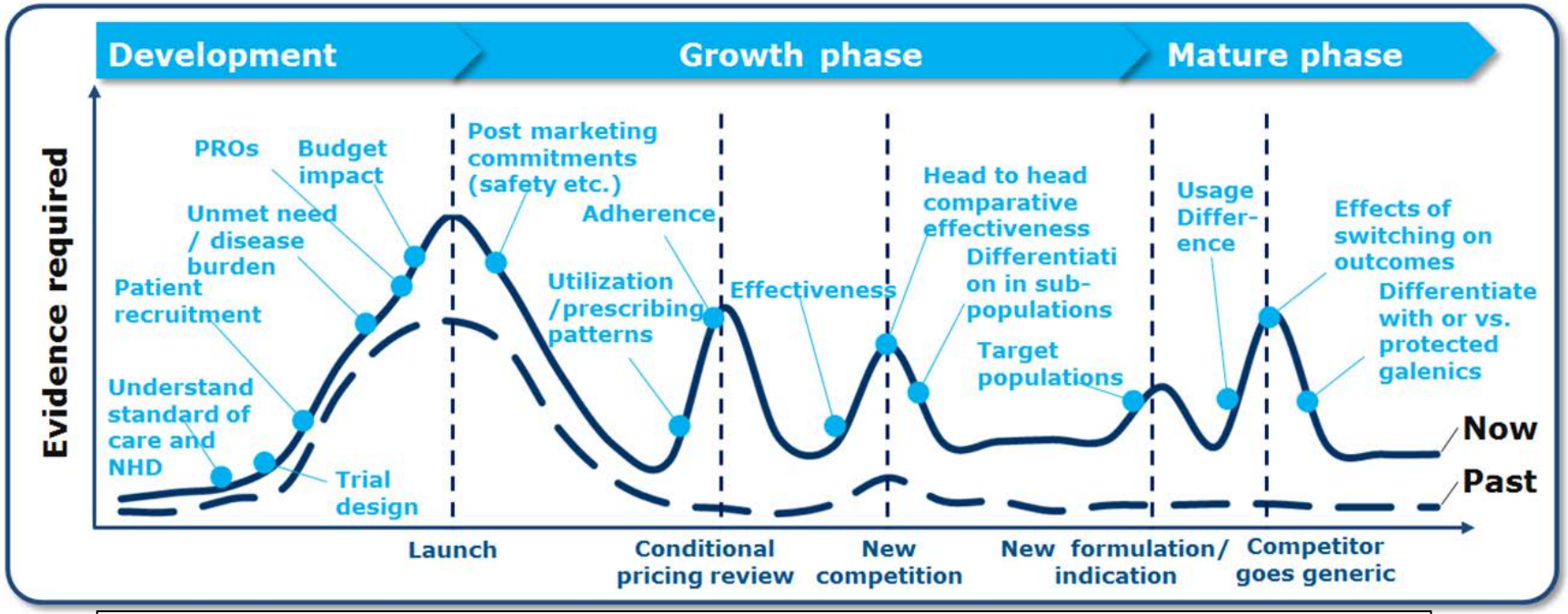
Uncertainties regarding:

- (Sub-)populations studied
- Endpoints
- Long term (treatment over time)
- Co-treatment with other products
- Real life use
- Change in the understanding of a disease or drug
- Change in scientific factors for previous efficacy evaluations

Choice of the study design

- Choice of study design will ultimately be determined by the scientific uncertainty to be addressed;
- A PAES may be conducted as a **randomised** or **non-randomised** study (without randomisation, estimates of effects expected to be affected by confounding factors or biases);
- Clinical trial design options include **explanatory trials** and **pragmatic trials**.
- **Observational studies** (concurrent controls/historical comparisons)
- Interaction with Health Technology Assessment bodies (possibility to include additional investigational arms provided there is no impact on study integrity and study primary objectives; collaboration on electronic health records and registry data)

RWE through the lifecycle



Registries

Hospital data / EHR

PAES/PASS

Health insurance data

RWE – potential applications - SA discussion helpful

- Use of existing disease registries to identify natural history of the disease, current Standard of Care, resource utilisation, adherence to treatment;
- Single arm studies for rare diseases compared with outcomes inferred from disease registries;
- Collection of efficacy and safety data from early access/compassionate use programs to supplement RCTs in small populations;
- Post-authorisation drug registries for effectiveness, long-term outcomes, drug utilisation, PROs, time to treatment failure, diagnosis confirmation;
- Expansion of the indication based on a mixture of disease registries and compassionate use data (e.g. for rare, severe diseases, where RCT data were available for less severe forms of the disease);
- Post authorisation studies to investigate biomarker status of an all-comer population (or other subpopulation selection criterion);

SAWP / PRAC interaction

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Rationale

- Facilitating life-cycle advice on medicines
- Fostering inter-disciplinary / committee thinking

Bring in PRAC expertise - outputs richer and better advice

Ongoing activities

PASS pilot

➢ Requests for EMA scientific advice to Post Authorisation Safety Studies (PASS) protocols, with focus on non-imposed studies.

Scientific advice requests with PRAC consultation

➢ Proactive pharmacovigilance planning, e.g. pre-authorisation advice on Risk Management Plans.

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Scientific advice on PASS protocols / PRAC endorsement

Examples of changes to study designs to better address safety concerns

- *Change from registry to open label extension study of a planned randomised clinical trial.*
- *Change from long term prospective cohort study with historical controls to long term, active controlled RCT.*

✓ **Enhanced dialogue between PRAC and SAWP results in improved study designs.**

Conclusions

- ✓ Prospective planning of data collection is crucial throughout the drug lifecycle.
- ✓ Planning of appropriate evidence generation is a multi-stakeholder effort; Scientific Advice provides a platform to discuss and agree on the appropriateness of a strategy for overall evidence collection, allowing also parallel discussions with HTA bodies
- ✓ Collaboration on RWE among different stakeholders needed to address quality and methodological issues related to data collection and to realise the full potential of real world evidence in supporting product development.

Thank you for your attention

Further information

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