EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Strengthening the prospective discussions on post-licensing evidence generation

Industry stakeholder platform on research and development support

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An agency of the European Union

Overview

Expectation of regulators: role of PLEG, guidance

Regulatory Experience

- At MAA: what PLEG have been requested
- PLEGs in SA, examples, why/how to engage

Conclusions and way forward

Regulators' expectations

Primary concern: benefit risk assessment through out product lifecycle

For scientific question on safety / efficacy – right study - high quality timely data and methods (control of chance, bias and confounding)

- PLEG and scope of data sources
- To address remaining uncertainties that we cannot answer in pivotal data at MAA and to facilitate a strengthened life cycle approach

Regulatory guidances on PLEG

1) Scientific guidance on Post-Authorisation Efficacy Studies PAES

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/12/WC500219040.pdf

Categories of uncertainties

RCT and NonRCT, distinguish data source (primary /secondary) from study design

e.g. Registries can allow wide variety of observational study design options

Data quality is crucial. Measures include common terminologies, quality control and standards

Limitations acknowledged

PLEG in regulatory guidance

2) Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 2) EMA/813938/2011 Rev 2* Corr**

- Registries most suitable - rare disease, rare exposure or special population. Not normally be used to demonstrate efficacy. For: post Marketing Authorisation study effectiveness in heterogeneous populations, effect modifiers, compare risks different groups

  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf

3) Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products EMA/CHMP/65416/2016 rev.1:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000297.jsp&mid=WC0b01ac05800862be

4) Guideline On The Exposure To Medicinal Products During Pregnancy: Need For Post-authorisation Data EMEA/CHMP/313666/2005

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011303.pdf

Regulatory experience - Post MA data requirements

Full MAA

- Annex II:
- PAES delegated act:
- (a) surrogate endpoints
- (b) combination
- (c) sub populations
- (d) long term efficacy
- (e) real –life conditions
- (f) change of standard of care
- (g) new scientific factors

- PASS

Exceptional circumstances

- Specific obligations
- Comprehensive data cannot be provided based on rarity
- Based on scientific grounds)
- Ethics

- B/R positive
- Comprehensive data will never be provided

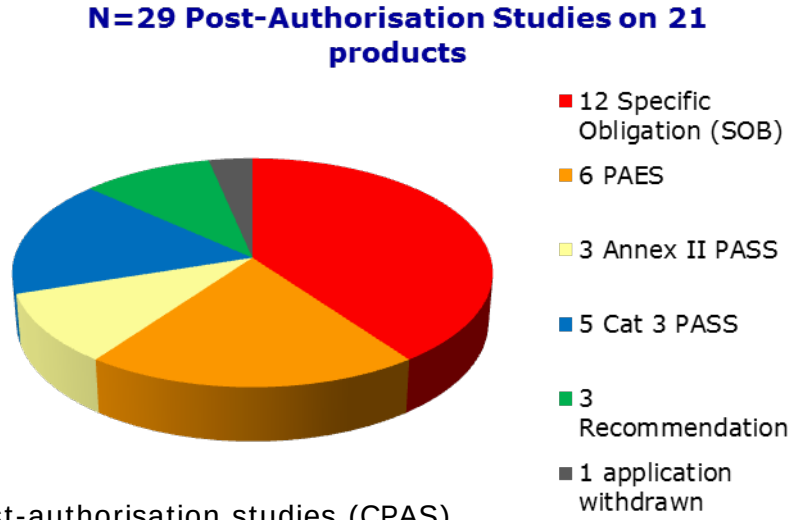
Conditional MA

- Specific Obligations:
- Seriously debilitating diseases or life threatening disease
- Emergency situations
- Orphans

- B/R positive;
- Comprehensive data will be provided;
- Unmet medical need
- Public health benefit outweighs the risks due to need for further data.

Sample of Post-Authorisation Studies (PAS)

- Most Post-authorisation studies for initials MAAs and in Oncology
- 12 Specific Obligations:
  - All Orphans except 1 pandemic
  - Usually ongoing interventional comparative efficacy studies, also PASS
- 6 PAES:
  - All Delegated act(a) all ongoing, 1 Biomarker
  - 5 in Oncology
- 3 Annex II PASS
  - All Registries, 2/3 ATMPs
- 5 Category 3 PASS
  - 3 ongoing studies
- 3 Recommendations
  - 2 Biomarkers, 1 interventional efficacy



Volt-girolt 02 to 10/16 Advisory group on classification of post-authorisation studies (CPAS)

Conditional Marketing Authorisation 10 year EMA report

Figure 22. Status of the imposed studies time of CHMP opinion (N=77)

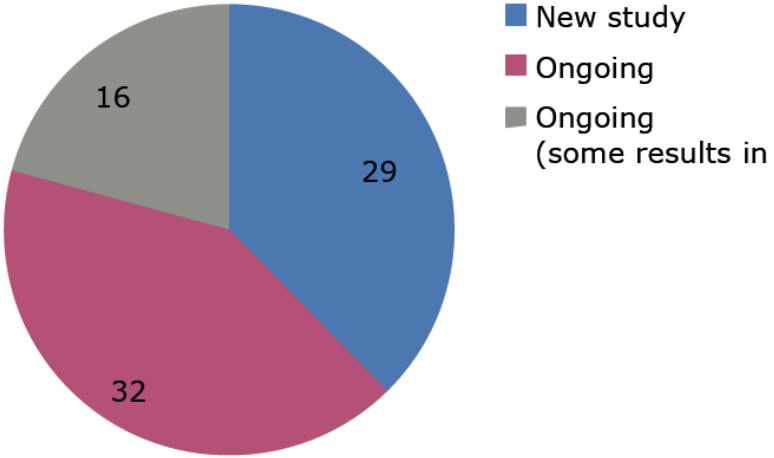
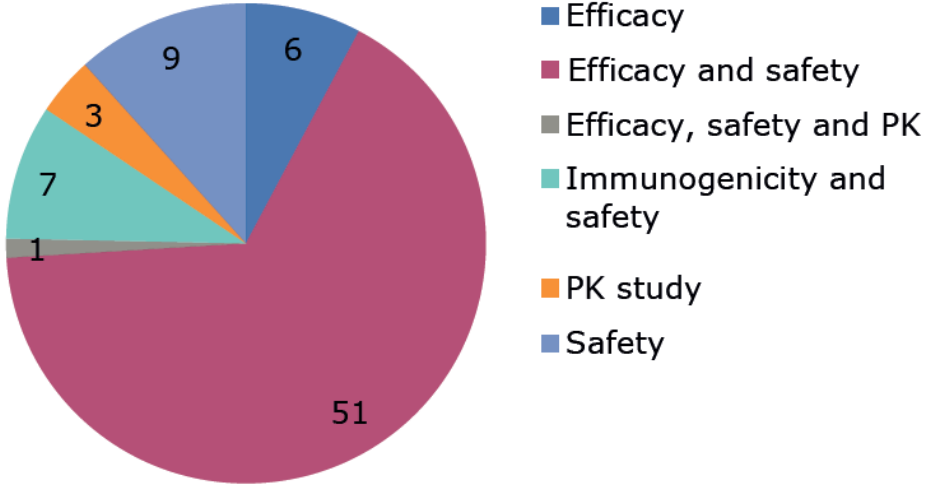
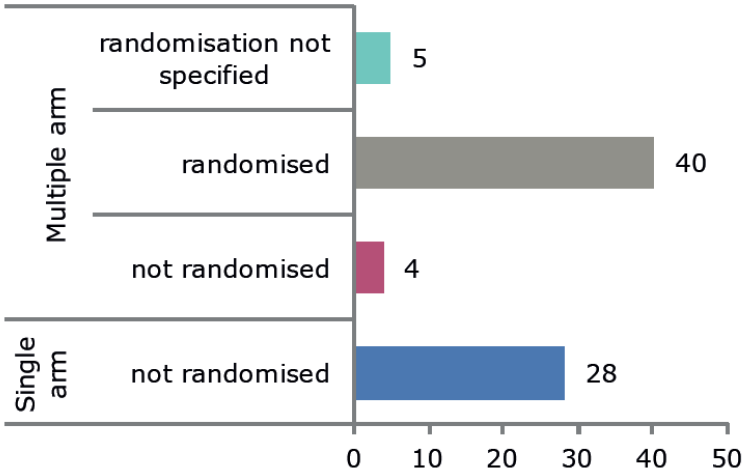


Figure 23. Objectives of the studies imposed as SOs (N=77)



Conditional Marketing Authorisation 10 year EMA report

Figure 26. Study designs of imposed studies (N=77



Regulatory experience at Marketing Authorisation - Registries

Registries as a legally binding requirement for a registry was included as a condition of the marketing authorisation (Annex II) centrally approved products, 2005–2013.

Pharmacoepidemiol Drug Saf, doi: 10.1002/pds.4196

- Issues: Delayed completion, Delayed start, Slow accrual, Low data quality or missing data, Disease registries preferred

Data on Annex II & required registries;

- 53% of 73 registries primary for safety issues , 10% safety outcome & real-world effectiveness; Products 2007 and 2010

Pharmacoepidemiol Drug Saf. 2017 Oct 6. doi: 10.1002/pds.4332.

Review PASS protocol 2012 to 2015

189 PASS, slightly more involved primary data capture (58%).

Majority no comparator (65%)

- 35% assessed clinical effectiveness endpoints. Patient reported outcome (PRO) in 14%
- “Protocol content review ..related to methodological issues and feasibility concerns should raise awareness among PASS stakeholders to design more thoughtful studies according to pharmacoepidemiological principles and existing guidelines”

Br J Clin Pharmacol. 2017 Apr;83(4):884-893.

See also *F1000Research* 2017, **6** :1447 (doi: 10.12688/f1000research.12198.2)

Regulatory experience: scientific advice (SA) on PLEG

- Quite infrequent either as PreMAA or Post MAA advices on PLEG
- **Pre-Marketing** Authorisation Application (MAA) discussions:
  - Common condition; registry for post authorisation safety and effectiveness;
  - Pragmatic trial in cancer indication – primarily effectiveness vs alternative SOC
  - Rare condition; ATMP: on nature of registry (drug vs product) for post authorisation data collection safety and effectiveness

Regulatory experience- scientific advice (SA) on PLEG

- Neurological condition: potential use of registries/cohorts post authorisation for longer term outcomes
- Rare condition, imposed registry for Post Authorisation Safety Study (PASS) for preparatory advice prior to PRAC submission - **Post MAA** discussion

SA presents opportunities for parallel consultations involving other stakeholders in planning Post Launch Evidence Generation

- PRAC interaction established
  - PASS protocols N=4 Category 1, 3, PRAC consultation N=13
- Parallel consultation established
- (Parallel) qualification procedure

Engage early Standard Scientific Advice

Why apply for SA to PLEG

- Conceptual/protocol agreement before implementation and investment in study protocols
- Before MAA, peri MAA, early post MAA
- Registry holders as (part of) consortium
- Demonstrate proactive engagement before MAA
- **Some examples as per SA**

Parallel Consultation with other stakeholders

Product Specific advice

Applicant questions for stakeholder e.g. “will the proposed study meet the stakeholder needs in post licensing evidence generation”

Develop applicant’s position

- e.g. effectiveness objective and how this is sufficient for different stakeholders’ needs post licensing.
- how a product is/will be used locally, registry only? health care expenditure/organisation of care

Need to understand how PLEG data will be used in decision making by stakeholders in subsequent evaluations

- When is the best timing?

Qualification Procedure for novel methods
Registries (Parallel)

Not product specific ; 2 way or 3 way engagement with registry holders, industry, both, Can be in parallel with HTAs

Why apply?

- Definitive regulators advice /answers on specific questions, on what to improve or opinion on the suitability of the data source/method for regulatory purposes, with committee engagement (Safety, efficacy, advanced therapies..)
- Supports harmonisation, quality, interoperability, usability, managing risks, across lifecycle
- Efficient data collection for different stakeholders

Example **disease registry X**: Target population for post-approval Registry, which countries, and outcomes, Which variables, data retrieval frequency, summary data vs patient level raw-data

Other tools relevant to PLEG

EMA registries Initiative: better use of registry data, communication, awareness raising, harmonisation tools and tasks, qualifications

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500227793.pdf

Workshops : general MS and CF registries and reports

Forthcoming workshops:

- A Common Data Model for Europe? – Why? Which? How? 11-12 December 2017
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2017/10/event_detail_001524.jsp&mid=WC0b01ac058004d5c3
- The Role of Observational Data in Assessing the Benefits and Risks of Drugs 1st Dec 2017
  http://www.ema.europa.eu/docs/en_GB/document_library/Agenda/2017/09/WC500235087.pdf

Regulatory use of PLEG: Conclusions 1

- Existing regulatory guidance on strengths, limitations and role of PLEG
- Complements Pivotal RCT data; some remaining uncertainties
- Imposed studies for evidence generation safety and effectiveness and other objectives (RCT and NonRCT) following MAA
- Gap in workability of registries, and scope for improvement in quality and timeliness for post authorisation evidence generation

Conclusions 2

Need for optimisation of PLEG data quality, timeliness, and access

- To progress - Need for PLEG (inc RWE / registries) based discussions on products and proposals/methods for specific uses in SA
  - (scientific question, study design, data source) in scientific advice/parallel consultation/ qualification procedure
  - Best way to obtain regulatory acceptability of particular proposal/RWE for a particular purpose
- Need to understand perceived barriers for stakeholders

Thank you for your attention

Further information

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