EMA - Early Access

PEARRL Annual Meeting 2017-Regulatory Science Symposium

University College Cork, Ireland

Presented by Evangelos Kotzagiorgis
Scientific Administrator, Quality of Medicines Office
Specialised Scientific Disciplines Department
Agenda

Early access tools

- Conditional marketing authorisation
  - What is it?
  - Experience

- EMA Adaptive Pathways
  - Why do we need to be adaptive? - the concept
  - Critical issues
  - Conclusions

- EMA PRIME: priority medicines
  - What is it?
  - The concept - key points
  - Conclusions
Early access tools: Overview

**PRIME**
- Major public health interest, unmet medical need.
- Dedicated and reinforced support.
- Enable accelerated assessment.
- Better use of existing regulatory & procedural tools.

**Adaptive Pathways**
- Scientific concept of development and data generation.
- Iterative development with use of real-life data.
- Engagement with other healthcare-decision makers.

**Accelerated Assessment**
- Major public health interest, unmet medical need.
- Reduce assessment time to 150 days.

**Conditional MA**
- Unmet medical need, seriously debilitating or life-threatening disease, a rare disease or use in emergency situations.
- Early approval of a medicine on the basis of less complete clinical data.

**Parallel advice**
- Other...Compassionate Use, Marketing Authorisation (MA) under exceptional circumstances, etc.
Conditional marketing authorisation

Eligibility for products in at least one of these categories:

✓ aimed at treating, preventing or diagnosing seriously debilitating or life-threatening diseases;

✓ intended for use in emergency situations (also less comprehensive pharmaceutical and non-clinical data may be accepted for such products);

✓ designated as orphan medicines.

CMA may be granted if all the following requirements are met:

✓ the benefit-risk (B/R) balance of the product is positive;

✓ it is likely that the applicant will be able to provide comprehensive data;

✓ unmet medical needs will be fulfilled;

✓ the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data.
Conditional marketing authorisation

CMA valid for one year - renewed annually.

required to complete specific obligations (ongoing or new studies, and in some cases additional activities)

objective to provide comprehensive data confirming that the B/R balance is positive.

Once comprehensive data obtained, the marketing authorisation may be converted into a standard marketing authorisation
Conditional marketing authorisation

Authorisation **before comprehensive data** are available in order to address **unmet medical needs**, when **benefits** of **early access outweigh** the **risks** due to limited data.

*CMA ≠ exceptional circumstances (comprehensive data cannot be obtained even after authorisation).*

A key tool for early access:
- Product can be authorised several years earlier
- Comprehensive data are still generated after authorisation
Conditional Marketing Authorisations

Apart from 2016, there is no clear trend in number of CMAs, which remain an ‘exceptional’ authorisation route.

On average within 4 years a conditional MA is converted into a standard MA.

Data updated on Dec 2016
Key findings of 10 year analysis

- Apart from 2016, there is **no clear trend in overall number**
- On average **within 4 years** a conditional MA is converted into a standard MA
- **Reluctance** in pro-active use by industry – room for improvement in prospective planning
- CMAs successful only in **few therapeutic areas**
- Most specific obligations did not have any **change**
Agenda

Early access tools

- Conditional marketing authorisation

- EMA Adaptive Pathways
  - Why do we need to be adaptive? - the concept
  - Critical issues
  - Conclusions

- EMA PRIME: priority medicines
Please, allow me to introduce you to…

Jane, late fifties, recent diagnosis of advanced cancer, life expectancy: ~2 years

John, late fifties, in good health, family history of cancer, life expectancy: ~20 years

“There is a promising treatment out there; but it’s still early days …”

Should our healthcare systems* cater for the needs of ...
A: only Jane?
B: only John?
C: Jane and John?

An iterative, life-span approach to learning and on-market access, a.k.a. Adaptive Pathways

‘Access vs evidence’: an ethical and scientific conundrum

Need to reduce (unavoidable) uncertainties – fast

Development of non-conventional products (e.g. ATMPs)

Adaptive Pathways a solution to inevitable problems?

Sustainability of costs

Need to enlarge the toolbox for evidence generation (where RCTs cannot answer the questions)
Adaptive Pathways - component parts

- Focus on high unmet need (sub-)population first, and on products likely to have major impact for patients
- Reduce uncertainty as fast as possible; react to incoming data (iterative development; rapid cycle analysis)
- Pre-plan, across entire life span (incl. post-marketing)
- Use entire tool box for knowledge generation
- Leverage multi-stakeholder collaboration
- Manage on-market utilisation
Adaptive Pathways – harnessing existing tools

- Conditional marketing authorisation (in EU legislation)
- Post-marketing commitments; Risk Management Plans (in PharmacoVigilance Regulation)
- Multi-stakeholder scientific advice
- Registries, other data sources
- Adaptive pricing/reimbursement (managed entry agreements)
Agenda

Early access tools

- Conditional marketing authorisation

- **EMA Adaptive Pathways**
  - Why do we need to be adaptive? - the concept
  - Critical issues
    - Need and unmet need?
    - Lowering the standards?
    - Randomised Controlled Trials (RCT) vs Real World Data (RWD)
    - Promises, compliance, “exits"
    - On-market utilisation
  - Conclusions

- **EMA PRIME: priority medicines**
Need and unmet need

Early access
- *is it worth it?*

Addressing ‘unmet need’;
focus on:

- Conditions with major impact on quality of life / life-shortening / debilitating
- Credible promise of relevant improvements in patient-relevant outcome(s) → an acceptably high probability of a relevant effect size
Lowering the standards?

Access vs evidence conundrum has always been acknowledged:

... where, “the **benefit** to public health of the immediate availability on the market [...] **outweighs the risk** inherent in the fact **that additional data are still required**”

[Regulation (EC) No 507/2006]
Lowering the standards?

**Benefit-Risk** (B/R) must be **positive** for treatment-eligible population.

**Same standards for the evaluation** of B/R or the requirement to **demonstrate a positive B/R balance** to obtain marketing authorisation.

Challenges regarding some particular aspects, e.g. sufficient stability data? Manage uncertainty.
Randomised Controlled Trials (RCTs) and Real World Data (RWD)

1. RCTs are the methodology with the highest internal validity (≠ ‘gold standard’, not black & white)

2. For efficient increase of knowledge of benefits and risks: embrace the full evidence spectrum (RCTs, pragmatic trials, observational studies)

3. RWD complements rather than replaces RCTs. The right study type for the right question – where feasible

4. Pre and post-licensing evidence generation are not two different lives, it’s one continuous life
Promises, compliance, exits

Promised data may not be forthcoming, “post marketing commitments might not be honoured”

Compliance with legally binding post marketing studies generally good (but start of studies slow). Regulatory system is robust*; supported by recent experience (post 2012)

Promises, compliance, exits

For regulators, not a new scenario

For payers, plan ‘exit’ (or ‘adaptive disengagement’) scenarios upfront

Payers can get incentives right: limited initial label with prospect of widening, flexible conditions of reimbursement

Subsequent data may not confirm initial promise of high effect size
On-market utilisation

Regulators can provide some (!) steer on appropriate prescribing (Risk Management Plans)

Payer action will be helpful but heterogeneity across EU member states is acknowledged

Access to local healthcare data / drug utilisation review will facilitate appropriate utilisation – where feasible

Right incentives (for companies) will help
Conclusion

Adaptive Pathways is an attempt to solve inevitable problems and challenges in an imperfect world.

These can be successfully addressed by way of adequate pre-planning, and collaboration of stakeholders.

EMA will continue to explore the potential of the Adaptive Pathways concept.

Scientific concept of development and data generation.
Agenda

Early access tools

- Conditional marketing authorisation
- EMA Adaptive Pathways
  - Why do we need to be adaptive? - the concept
  - Critical issues
  - Conclusions
- EMA PRIME: priority medicines
  - What is it?
  - The scheme- key points
  - Conclusions
Features of the PRIME scheme

Early access tool, supporting patient access to innovative medicines

- **LAUNCHED** in March 2016
- **Written confirmation of PRIME eligibility** and potential for accelerated assessment;
- **Early CHMP Rapporteur appointment** during development;
- **Kick off meeting** with multidisciplinary expertise from EU network;
- **Enhanced scientific advice** at key development milestones/decision points;
- **EMA dedicated contact point**;
- **Fee incentives** for SMEs and academics on Scientific Advice requests.
To foster the development of medicines with major public health interest.

**Enable accelerated assessment**
- Promote generation of high quality data
- Facilitated by knowledge gained throughout development

**Reinforce scientific and regulatory advice**
- Foster and facilitate early interaction
- Raise awareness of requirements earlier in development

**Optimise development for robust data generation**
- Focus efficient development
- Promote generation of robust and high quality data

Building on existing framework; Eligibility according to existing ‘Accelerated Assessment criteria’
Eligibility to PRIME scheme

Based on Accelerated Assessment criteria

Medicinal products of major public health interest and in particular from the viewpoint of therapeutic innovation.

- Potential to address to a significant extent an unmet medical need
- Scientific justification, based on data and evidence available from nonclinical and clinical development

- No satisfactory method or if method exists, bring a major therapeutic advantage
- Introducing new methods or improving existing ones
- Meaningful improvement of efficacy (impact on onset, duration, improving morbidity, mortality)
What do we expect to grant eligibility?

**Unmet medical need**
No treatment or clear limitations of existing therapies

**Nonclinical data** supporting pharmacological rationale (e.g. gene therapy)

Clinical exploratory data on **relevant endpoint**

If uncontrolled, use **comparable historical control** i.e. need sufficient information on baseline characteristics

**Magnitude of the effect size** supporting major therapeutic advantage
Entry points PRIME eligibility and required evidence

- **Nonclinical**
- **Phase I**
- **Exploratory**
- **Confirmatory**

**Proof of concept**
- Sound pharmacological rationale
- Clinical response efficacy and safety data in patients (exploratory trials)
- Substantial improvement
- Magnitude, duration, relevance of outcomes to be judged on a case by case basis

**Proof of principle** (For SMEs and academia only)
- Sound pharmacological rationale, convincing scientific concept
- Relevant nonclinical effects of sufficiently large magnitude and duration
- Tolerability in first in man trials

Any sponsor

SMEs
Academia
Kick-off meeting

- Multi disciplinary meeting with relevant experts from SAWP and CHMP and other committees;
- Introduction of product and development status by applicant;
- To take place shortly after eligibility confirmation, at EMA
- Facilitate initial interaction between applicant and EU regulatory network;
- Discuss the overall development plan and regulatory strategy;
- Provide recommendation on milestones and topics for scientific advice.
Early Rapporteur appointment

Opportunity for **knowledge gain** on the product
Identification of **relevant expertise** and build adequate team
Opportunity to **influence** development

Very positive views on the **kick-off meeting**
- Importance of preparation and tailored agenda
- Facilitate interactions across committees and with EMA

**Timing** of PRIME eligibility is critical for fruitful engagement
Involvement in follow-up **scientific advice** and workload
**Need to improve follow-up communications/updates**
Enhanced scientific advice

- 7 products
- 11 SA requests following kick-off meetings

Multi-stakeholder
1 EMA/HTA parallel advice
2 with patients involved

Rapporteur involvement
through one of SAWP coordinator

All aspects covered
Quality, nonclinical, clinical

Scientific advice

Flexibility
Shorter pre-submission
3 adopted in 40 days

Presented at the PEARRL Regulatory symposium 2017 – for personal use only
Requests covering wide range of therapeutic areas and product type

- Oncology: 7
- Haematology-haemostaseology: 6
- Infectious diseases: 1
- Neurology: 2
- Cardiovascular diseases: 6
- Immunology-rheumatology-transplantation: 2
- Gastroenterology-Hepatology: 2
- Pneumology-allergology: 4
- Vaccines: 1
- Endocrinology-Gynaecology-Fertility-Metabolism: 2
- Ophthalmology: 3
- Dermatology: 2
- Psychiatry: 2
- Diagnostic: 1
- Musculo-skeletal system: 1
- Neonatology-paediatric intensive care: 1
- Uro-nephrology: 1

- SME: 11
- Other: 14
- Academic: 2

70% in oncology/haematology
34% of requests for ATMPs
In summary,

Eligibility review: robust, short time, in writing

Majority of PRIME products in rare diseases

Iterative scientific advices with opportunity for multi-stakeholders involvement, including patients
Acknowledgements

Hans-Georg Eichler - Senior Medical Officer

Zahra Hanaizi - Scientific officer, PRIME coordinator

Jordi Llinares - Head of Scientific and Regulatory Management Department

Zigmars Sebris - Scientific Officer Regulatory Affairs
Thank you for your attention

Further information
European Medicines Agency
30 Churchill Place
London E14 5EU

www.ema.europa.eu
info@ema.europa.eu

Follow us on @EMA_News

presented at the PEARRL Regulatory symposium 2017 – for personal use only