EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Adaptive Pathways: concept and critical issues

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Agenda

- Adaptive Pathways; the concept
- Critical Issues
  - Need and unmet need?
  - Lowering the standards?
  - RCT and RWD
  - Promises, compliance, exits
  - On-market utilisation
- Conclusion

Adaptive Pathways, a solution to inevitable problems?

- 'Access versus evidence'; an ethical and scientific conundrum
- Need to reduce (unavoidable) uncertainties - fast
- Development of non-conventional products (e.g. ATMPs)
- Need to enlarge the toolbox for evidence generation (where RCTs cannot answer the Questions)
- Sustainability of costs

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-market)
- Use entire tool box for knowledge generation
- Manage on-market utilisation
- Leverage multi-stakeholder collaboration

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)

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Need and unmet need (1/2)

- Early access – is it worth it?
- Not for all drugs, not for all patients - but for some patients (within a disease entity, with high unmet need) time to access is important

Need and unmet need (2/2)

- 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?

- Benefit-Risk must be positive for treatment-eligible population
- Access versus evidence conundrum has always been acknowledged, see regulation on Conditional Marketing Authorisation: … 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].

RCTs and Real World Data (RWD)

- RCTs are the methodology with the highest internal validity (≠ 'gold standard', not black & white)
- For efficient increase of knowledge of benefits and risks: embrace the full evidence spectrum (RCTs, pragmatic trials, observational studies)
- RWD complements rather than replaces RCTs. The right study type for the right question – where feasible
- Pre and post licensing are not two different lives, it's one continuous life

Promises, compliance, exits (1/2)

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

* http://ec.europa.eu/health/files/pharmacovigilance/pharmacovigilance-report-2012-2014_en.pdf

Promises, compliance, exits (2/2)

- Subsequent data may not confirm initial promise of high effect size
- For regulators, not a new scenario
- For payers, plan ‘exit’ scenarios (or ‘adaptive disengagement’) upfront

On-market utilisation

- Regulators can provide some (!) steer on appropriate prescribing (Risk Management Plans)
- Right incentives (for companies) will help
- Access to local healthcare data / drug utilisation review will facilitate appropriate utilisation – where feasible
- Regulator-Payer collaboration can be leveraged but heterogeneity across EU member states is acknowledged

Conclusion (1/2)

- We have always acknowledged the critical issues of Adaptive Pathways
- We believe that these can be successfully addressed by way of adequate pre-planning, and collaboration of stakeholders
- Much change already happening. Better to plan than “laissez faire”
- Adaptive Pathways is an attempt to solve inevitable problems and conundrums in an imperfect world

Conclusion (2/2)

"Criticism Comes Easier Than Craftsmanship“

Zeuxis (Greek painter, ~400 BC)

- Criticism should always come with alternative (better) ideas
- We welcome any solution to the problems at hand that is **better** than Adaptive Pathways

Thank you

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