EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The EMA adaptive pathways approach to improve timely access for patients to new medicines

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Presentation disclaimer: The views presented are personal

DISCLOSURE

- Nothing to disclose

How it all started

Realisation of competing objectives

• Allow timely access for patients to address urgent medical need	⟷	• Allow only well-studied drugs on the market
• Enable precision medicine, 'difficult' indications	⟷	• Rely on robust study methodology and end points
• Ensure sustainability of the innovation engine	⟷	• Ensure sustainability of health care systems

Evolution of thinking and terminology

- Adaptive licensing, progressive approval, staggered approval →
- Licensing is necessary but not sufficient →
- Adaptive pathways, MAPPs

What do we hope to achieve?

- MAPPs seeks to **foster** access to **beneficial** treatments for the **right patient groups** at the **earliest appropriate time** in the product life-span in a **sustainable fashion**.

Who stands to benefit? 1/2

- **Patients and Providers**
- Earlier access to promising new medicinal products
- Lower *realised* harm

- **Pharma**
- Earlier revenue stream; staggered development costs
- Decrease risks of (costly) late stage failures and post-market withdrawals

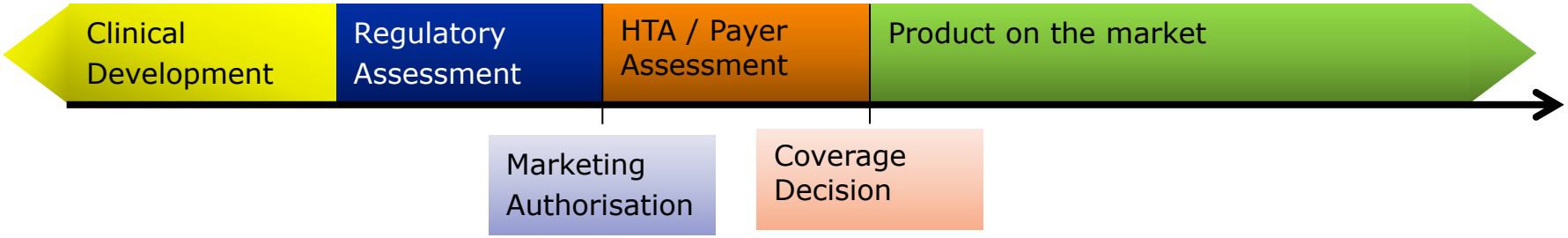
Who stands to benefit? 2/2

- **Regulators**
- Continuous reduction of uncertainty throughout the lifetime of the product
- New risk management paradigm that may restore public confidence

- **Payers**
- Adaptive reimbursement plan to align value with price and utilisation
- Continuous risk/benefit information flow to better support (follow-on) coverage decisions

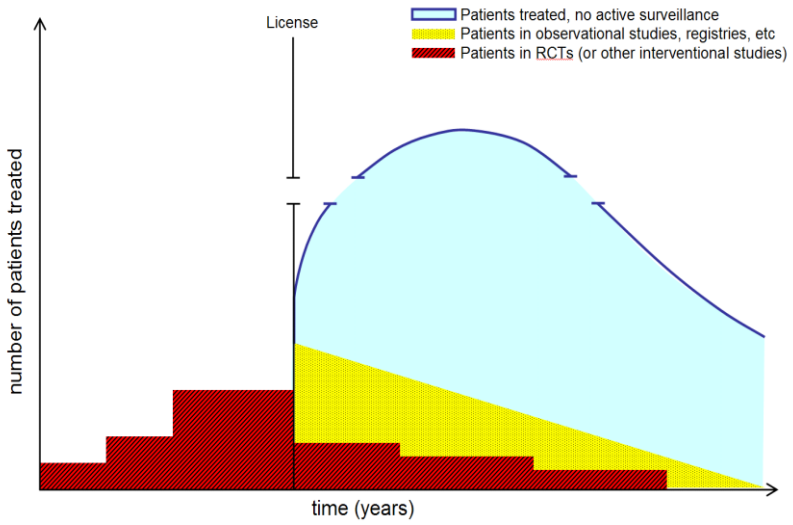
A systems approach – to realise the benefits

- Comprises the entire product life-span:
- Development → licensing → coverage → utilization → monitoring



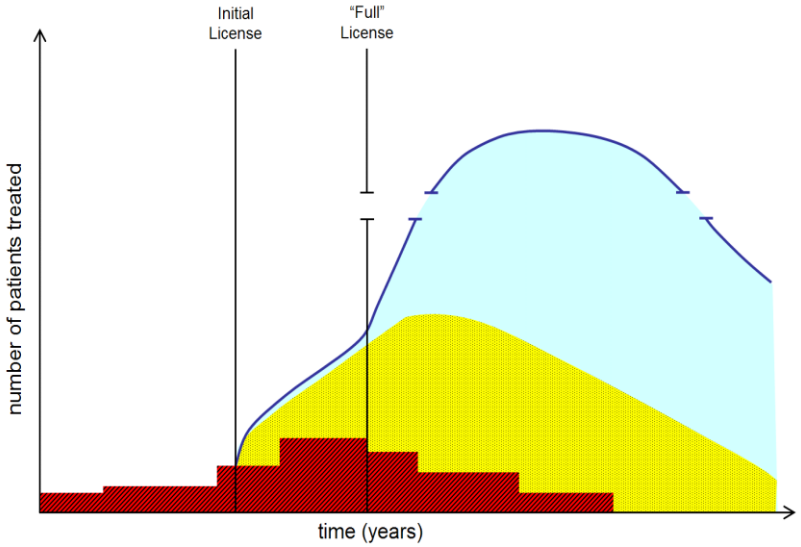
Adaptive Pathways:

Adaptive Licensing & Managed Entry Agreements



Current scenario:

Post-licensing, treatment population grows rapidly; treatment experience does not contribute to evidence generation



Adaptive Licensing:

after initial license, number of treated patients grows more slowly, due to restrictions; patient experience is captured to contribute to real-world information

Eichler HG et al. Clin Pharmacol Ther. 2012

What will change with adaptive pathways?

- Transition from …

• Magic moment	→	Life-span management
• Prediction	→	Monitoring
• RCT only	→	Toolkit for evidence generation
• Big populations	→	Small populations
• Focus on licensing	→	Focus on patient access
• Open utilisation	→	Managed utilisation

Regulatory framework for AL

- Regulatory processes within the existing EU legal framework, e.g.:
- Scientific advice (with participation of HTA bodies and/or payers and/or other stakeholders)
- Conditional marketing authorisation, marketing authorisation under exceptional circumstances, variations
- Risk management plans
- Post-marketing efficacy studies, patient registries, observational studies

EMA's initiatives to enable timely access for patients

- **Operational**: Procedural support for major public health needs
- **Case learnings**: Adaptive (Licensing →) Pathways pilots
- **Conceptual**: IMI Medicines Adaptive Pathways to Patients (MAPPs)

European Medicines Agency launches adaptive licensing pilot project

Press release

19/03/2014

European Medicines Agency launches adaptive licensing pilot project

Improving timely access for patients to new medicines: pilot explores adaptive licensing approach with real medicines in development

The European Medicines Agency (EMA) is inviting companies to participate in its adaptive licensing pilot project. Companies who are interested in participating in the pilot are requested to submit ongoing medicine development programmes for consideration as prospective pilot cases.

A framework to guide discussions of individual pilot studies has been published.

The adaptive licensing approach, sometimes called staggered approval or progressive licensing, is part of the Agency's efforts to improve timely access for patients to new medicines. It is a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorisation to expand access to the medicine to broader patient populations.

As a holistic approach, adaptive licensing requires the involvement of all stakeholders who have a role in determining patient access, including the EMA, the industry, health technology assessment (HTA) bodies, organisations issuing clinical treatment guidelines and patient organisations. All discussions will take place in a 'safe harbour' environment to allow free exploration of the strengths and weaknesses of all options for development, assessment, licensing, reimbursement, monitoring, and utilisation pathways in a confidential manner and without commitment from either side.

Related information

- Research projects
- Adaptive licensing: taking the next step in the evolution of drug approval
- Pilot project on adaptive licensing (19/03/2014)
- Pilot project on adaptive licensing Annex I – Framework for individual pilot studies (19/03/2014)

Contact point:

To initiate a pilot case:
adaptivelicensing@ema.europa.eu

For media enquiries:
Monika Benstetter or Martin Harvey
Tel. +44 (0)20 7418 8427
E-mail: press@ema.europa.eu

Rules of the game

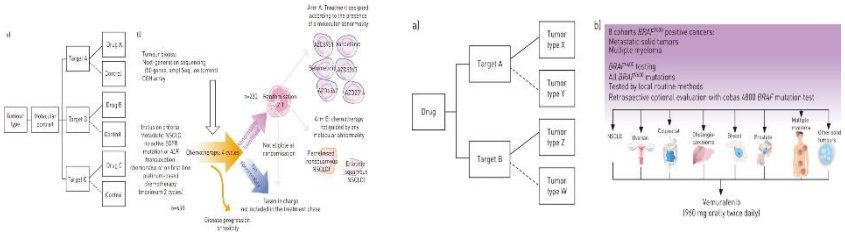
- The discussion is non binding, safe-harbour brainstorming.
- Involve all stakeholders to discuss how to optimise development path and satisfy stakeholder requirements.
- Demonstration of positive Benefit/Risk is –as usual- required for approval – but more initial uncertainty acceptable.
- Only existing regulatory tools to be used.
- AP is flexible.
- Acceptance/rejection in the AP pilot bears no inference about approval potential.

Initial experience

- 58 products submitted as candidates (7 still to be assessed)
- 16 selected for in-depth discussion with company (Stage I)
- Of the selected products:
  - 5 are Orphan drugs
  - 2 are ATMPs (Advanced Therapy Medicinal Products)
  - 5 are Anticancer drugs
- 8 products selected for Stage II (in-depth meetings)

Initial experience

- "Creative intelligence"?
  - Move to higher level of complexity
  - What if scenarios?
- Preparedness?
  - EMA and EORTC are setting up collaborations on how to build molecular knowledge into regulatory science: E.g., IBCD meeting and SPECTA programme
- What acceptable level of uncertainty?
  - A difficult issue, particularly for payers. Whose views? Need patient engagement and tools to gather patient values and views in a reproducible and transparent way.
- Data generation
  - Use of registries/observational studies;
  - Real World Evidence? Challenge to link data from tertiary to primary care.



Menis, Hasan and Besse, 2014.

Real World Evidence

- Opportunities – electronic tools in place
- Optimal use of registries
  - Encourage common protocols, scientific methods and data structures
  - Encourage data sharing and transparency
  - Ensure sustainability and co-ordination.
- Needs to be underpinned by strong methodology
- Can support licensing across the drug life-cycle

"BIG data: Is size the next big thing in epidemiology?"

- More variables has been the main focus so far
- What about more observations (more rows)?
- All this does is increase precision, leading to smaller p-values. All the old problems do not go away
- "Without the right analytical methods, more data just gives a more precise estimate of the wrong thing" – Susan Ellenberg
- Need to be underpinned by strong methodology

Access to fully anonymised data sets from clinical trials will benefit the industry

- Improvements in the design and analysis of subsequent trials
- Comprehensive, quality-controlled databases that may inform future projects and research questions
- Explore heterogeneity of treatment effects
- Comparative-effectiveness information
- Avoid repetition

H. G. Eichler, *et al.*, N Engl J Med 2013; 369:1577-1579

Data Sharing, Year 1 (GlaxoSmithKline)—Access to Data from Industry-Sponsored Clinical Trials.

- A productive and successful first step:
- Studies of risk factors or biomarkers (6)
- Methodologic studies (5)
- Studies comparing treatment regimens (3)
- Studies aimed at optimizing treatments (3)
- Patient-stratification efforts (3)

Strom BL et al. N Engl J Med 2014;371:2052-2054.

Data Sharing Initiatives

- *Project Data Sphere* initiative addressed prior obstacles to clinical trial data sharing and worked with leading legal and privacy experts, as well as clinicians, commercial institutions and patient representatives to build an optimal framework to share data

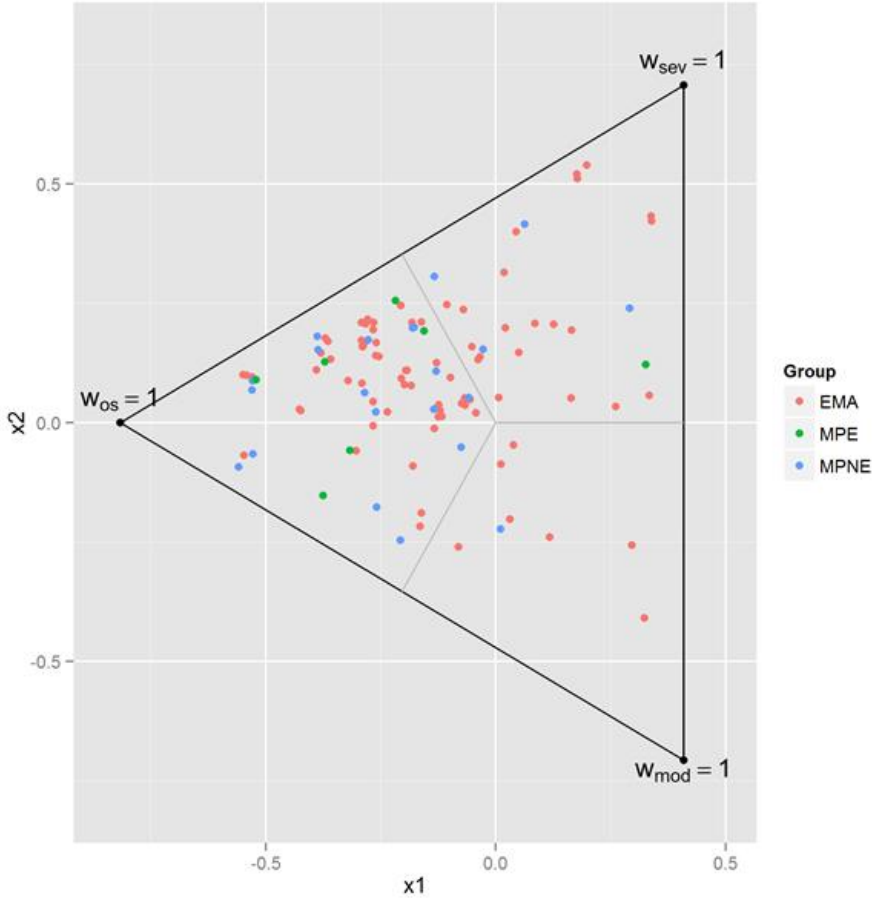
Comparative Effectiveness of Mitoxantrone Plus Prednisone Versus Prednisone Alone in Metastatic Castrate-Resistant Prostate Cancer After Docetaxel Failure
Green A. et al., *The Oncologist* ***2015;*** *20****:516***

Why collect patient values?

- Some patients may be willing to take on higher risks to potentially achieve a small benefit; others may be more risk-averse.
- Evaluations of patient-centric variations in tolerance to risks and perspective on benefits may inform benefit-risk assessment *for a device*.
- If a significant number of reasonable and well-informed patients would accept the probable benefits despite the probable risks, this may help support a favourable benefit-risk profile.

FDA CDRH Draft Guidance (2015)
http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm446680.pdf

Individual preferences: joint and marginal distributions



EMA pilot study to collect patient values (work in progress)

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Conclusions

- Shift the focus from approval to access (systems approach)
- Plenty of opportunities to be seized - but plenty of obstacles to overcome.
- Many decision-makers aligned (in the EU - for now).
- The time is right to collaborate to pro-actively facilitate and accelerate the availability of MAPPs.

Acknowledgments: Hans-Georg Eichler and Andrew Thomson (EMA)

Thank you for your attention

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Further information

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