EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Drug development and drug approval in Europe
An update on the 'Adaptive Pathways' initiative

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Disclosure and disclaimer

Hans-Georg Eichler is a member of staff at the European Medicines Agency and has no conflicts of interest to declare.

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The basis of medicines ("drugs") regulation

Marketing authorisation requires demonstration of:

- Quality, Safety, Efficacy ("QSE")

Companies seeking marketing authorisation submit "dossier":

- Pharmaceutical
- Non-clinical part
- Clinical module

How much data and information is enough to conclude:
"The benefits outweigh the risks"
and
"The uncertainty around both are acceptably small"

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

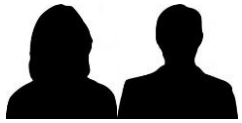
"There is a promising treatment out there; but it's still early days …"

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

*Healthcare systems in EU = regulators, HTAs, payers, policy makers, prescribers, …

Why do we need adaptive pathways?

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

'Difficult' indications?

Smaller treatment-eligible populations ('orphanisation')

1989: one disease: 'Cystic Fibrosis'

- all patients randomised in same study

2015: multiple CF subgroups defined by mutations

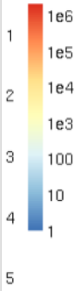
- homozygous F508del-CFTR mutation → **RCT**, **parallel group***
- F508del-CFTR heterozygous with residual function mutation on the second allele → **RCT**, **cross-over***
- Other, less frequent mutations → **n-of-1 or uncontrolled**?

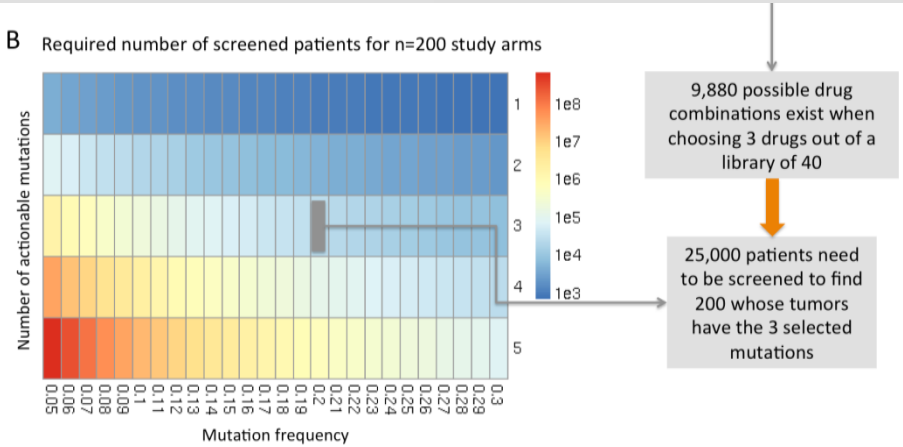
*Source: EMA website: Paediatric Investigation Plan VX-661/Ivacaftor

Is there a future for single drug interventions?

combinatorial complexity of personalised Rx combinations:

9,880 possible drug combinations exist when choosing 3 drugs out of a library of 40





25,000 patients need to be screened to find 200 whose tumors have the 3 selected mutations

Klauschen F et al. The combinatorial complexity of cancer precision medicine. Oncoscience 2014, 1(7): 504

Precision medicine (combinations)

A different set of research question

From:

"Is A better than B in a group of patients?"

To:

"If A truly modulates target X, i.e. has pharmaco-dynamic activity, (how) can we identify patients who benefit, combinations that work?"

Adaptive Pathways: a definition

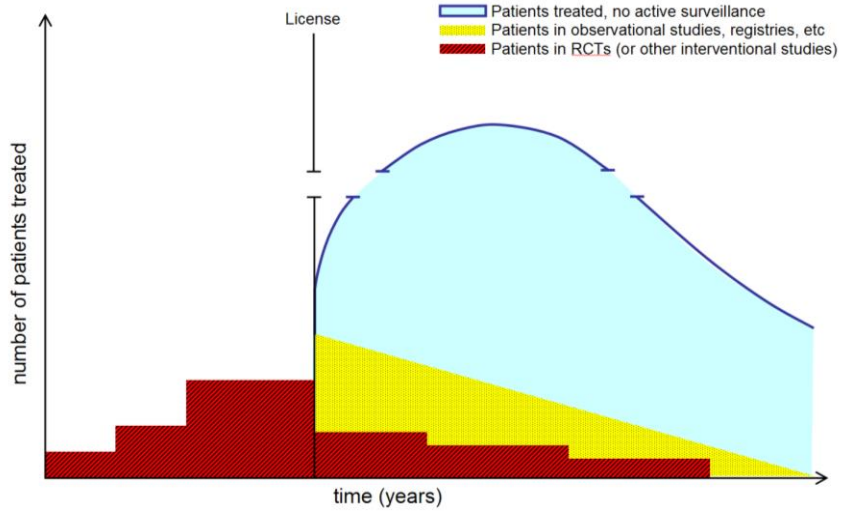
AL is a prospectively planned, adaptive approach to regulation and reimbursement of drugs.

Through iterative phases of evidence gathering followed by evaluation and license/reimbursement adaptation,

AL seeks to maximize the positive impact of new drugs on public health

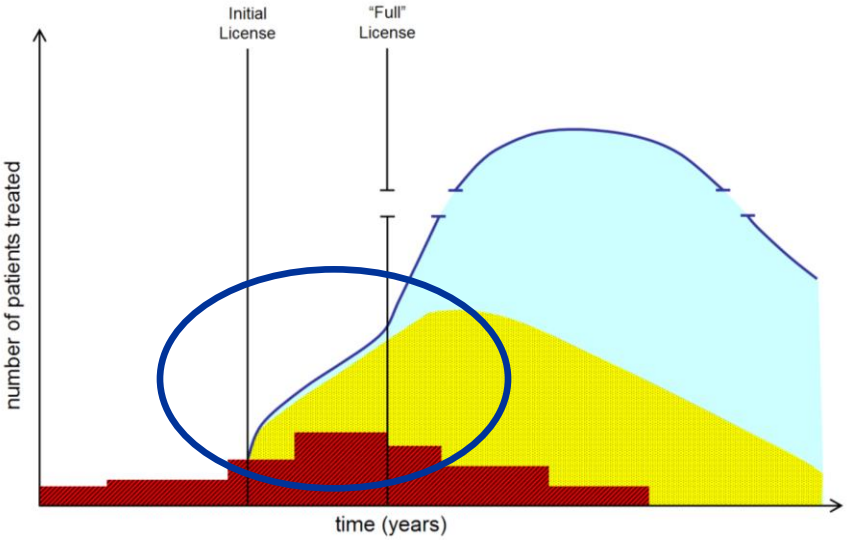
by balancing timely access for patients with the need to provide adequate evolving information on benefits and harms.

Adaptive Pathways in a nutshell



Current scenario:

Post-licensing, treatment population grows rapidly;



Adaptive Licensing:

After initial license, number of treated patients grows more slowly due to restrictions

Eichler et al. Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval. Clin Pharm & Ther 2012, Vol 91 (3), 426-437

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

What does EMA do to promote early access?

- 'Front end': Pilot programs to elicit patient preferences. Early dialogues with Health Technology Assessment (HTA) bodies: ample experience with parallel scientific advice
- 'Back end': Risk management plans, data infrastructure/analysis projects, interaction with HTAs (starting)
- Adaptive Licensing Pilot Project

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:
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Conclusions (1/2)

- A life-span approach (a.k.a. AP, MAPPs) is needed to enable translation of helpful innovation to current *and* future patients
- Dichotomy between research setting and clinical practice setting will be blurred
- Collaboration across and within decision-maker groups is a sine qua non

Conclusions (2/2)

- Evidence will be based on a diverse family of data sources and methodologies complementing (not replacing) RCTs.
- Evidence will see a shift from population focus to patient focus.
- Uncertainty cannot be eliminated but …
- Adaptive Pathways seeks to progressively reduce uncertainty – *increasing* the evidence standard over the product life-span

Thank you

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