



# EU adaptive pathways: deregulation by another name?

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## Who are we?

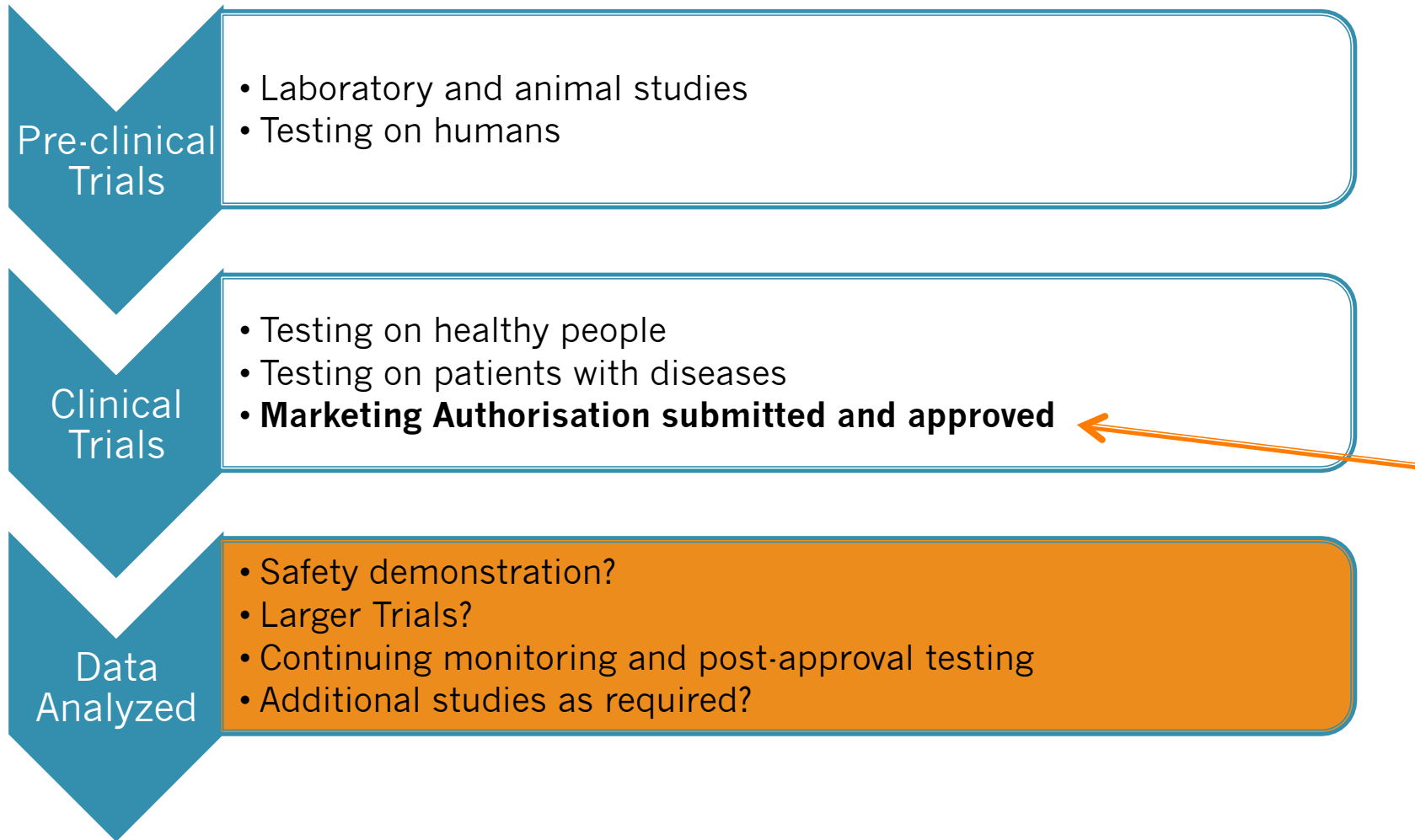
- Prescrire provides reliable and independent information about drugs and therapeutic & diagnostic strategies.
- Our mission: *"To work, in all independence, in favour of quality healthcare, first and foremost in the interest of patients (...)."*
- We publish a monthly journal (French and English editions) and an annual supplement on drug interactions in French.
- We provide several online training modules.
- Prescrire is a fully accredited continuing education organisation.
- Established in 1981, with its main office in Paris, France.
- Member of the International Society of Drug Bulletins, the Medicines in Europe Forum and Health Action International Europe.

*“The adaptive-licensing approach is based on a prospectively-planned process. It starts with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence-gathering and the adaptation of the marketing authorisation to allow broader patient populations to access the medicine.” (1)*

*“...“accelerated access to innovative medicines for patients in need” (1)*

# Drug development & approval with adaptive pathways

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# Disentangling adaptive licensing

## Niche buster model



*“In recent years, the trend in drug development has moved from blockbuster drugs towards pharmaceutical products that meet the needs of patient populations with particular conditions.*

*These “niche” populations are smaller and have a more urgent need for treatment. This has led to increasing pressure on regulatory agencies to accelerate drug approval”*

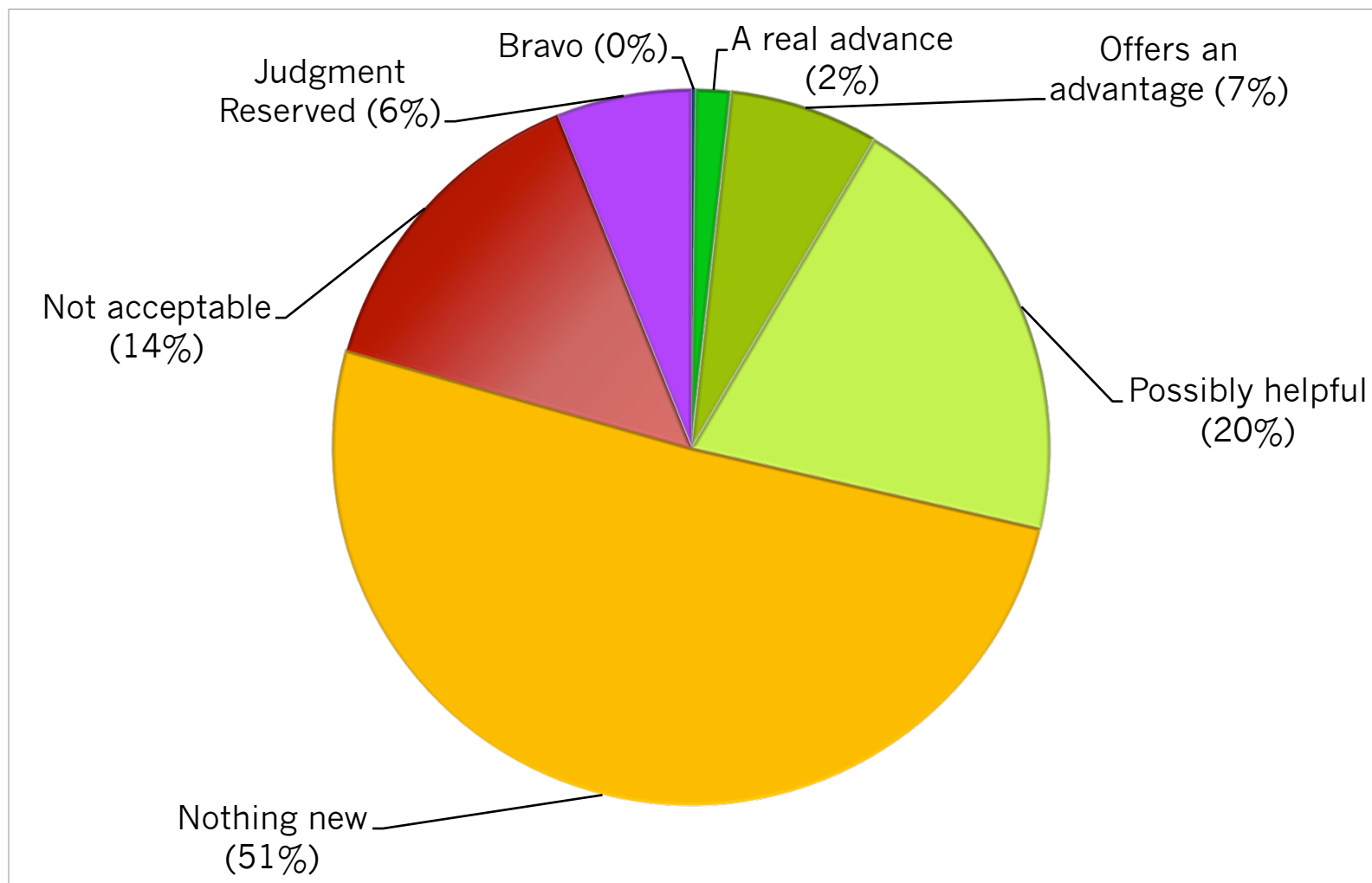
1- Fleming TR. Surrogate endpoints and FDA’s accelerated approval process. *Health Affairs* 2005 ; **24** (January (1)) : 67 :68

## Underlying myths of adaptive pathways

- Marketing Approval = “innovation”
- The number of new drugs entering the market is too small, due to regulatory hindrances.
- “Innovative” medicines are not quickly available and approval procedures are not sufficiently flexible.
- Adaptive licensing allows for “*lifespan management*” of new drugs
- R&D costs are too high

# Marketing Authorisation is not the same as innovation : Prescrire's ratings from 2000 to 2014

Percentages per category, N=1432



“Année du médicament” *Rev Prescrire* 2015; **35** (376) : 132-136.



## In reality...

- Most new drugs are “me-too” drugs
- Timelines for drug licensing have halved over the last 20 years posing threats to patient safety. (1)
- Modalities are available to provide faster patient access to new medicines when there is unmet health need such as conditional approvals, compassionate use.
- The pharmaceutical industry generated higher profit margins than any other industrial sector in 2013. It is likely to have remained the most profitable sector in 2014. Profits are not reinvested in R&D but mainly redistributed to shareholders. (2)
- For orphan drugs, cancer treatments and recently Hep C, the major limiting factor to patient access is price.

1 - European Commission Directorate General Competition. "Final Report of the Pharmaceuticals Sector Enquiry"; 8 July 2009. ec.europa.eu :426 pages.

2 - Gagnon MA "New drug pricing: does it make sense?" *Prescrire Int* 2015; 24 .(162): 192-195.

## Who benefits from adaptive pathways?

*“... the potential benefits for companies would be an **earlier revenue stream** than under a conventional licensing pathway and **less expensive and shorter clinical trials**” (1)*

At a recent EMA event, an industry official admitted that adaptive pathways will lead to **earlier approvals** and will allow companies to enjoy **longer patent protection** (2).

1- H-G Eichler et al «Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval» *Clinical Pharmacology & Therapeutics* 2012 ; 91 (3) :426-437

2- Personal communication by Elias Zerhouni, Head of R&D at Sanofi , during EMA's 20<sup>th</sup> Anniversary Seminar.



Should we be  
worried?

# 1. Accepting adaptive pathways means lowering the bar

- Accepting lower evidence requirements: no tangible evidence of a favourable benefit/harm balance
  - Adopt surrogate markers
  - Allow methodological shortcuts
  - Accept shorter and smaller trials
- Premature evaluations to become the rule, rather than exception

## 2. Shifting the burden of evidence from pre-marketing to post-marketing means shifting health risks and financial burden to society

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- Plan is to delink *"the populations in which the fundamental efficacy hypothesis and the overall safety hypothesis are tested"*.
- *De facto*, EU Citizens are to become guinea-pigs
- *"A prohibition on product liability suits during the initial marketing period"* will apply.
  - Blanket prohibition on legal action by injured patients or payers
  - Achieved by *"communicating the higher than usual level of uncertainty to patients and providers"*

## 2. Shifting the burden of evidence from pre-marketing to post-marketing means shifting health and financial risks to society (2)

- This means that injured patients will be unable to apply for compensation.
- Responsibility rests on the shoulders of patients and healthcare professionals
- Potential for drug induced harm, likely to lead to:
  - Increased Adverse Drug Reactions
  - Increased morbidity and mortality
  - Increased hospitalisations, increased costs

**= greater burden to society!**

### 3. There is no public health rationale to support such a move

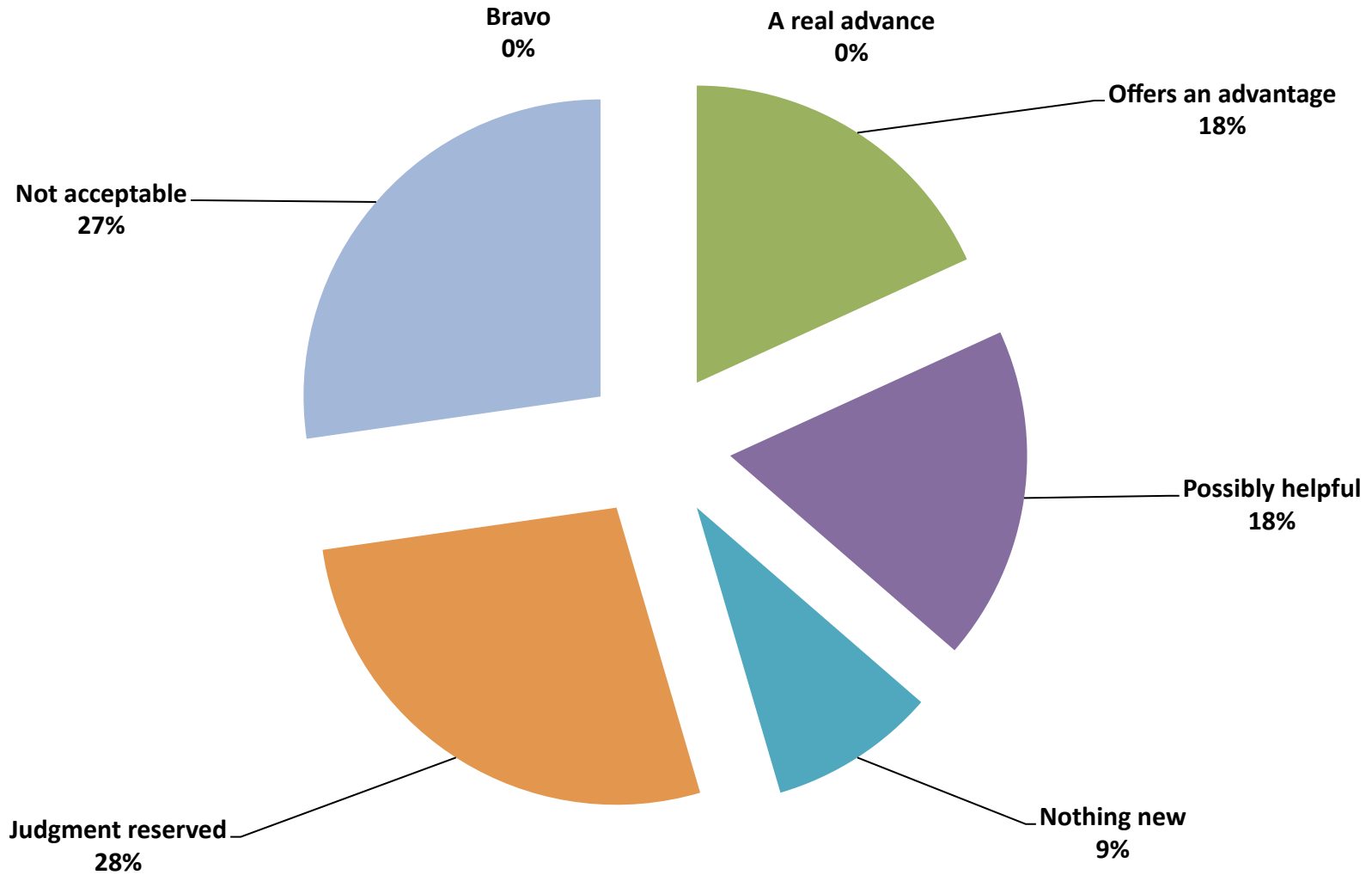
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- 2010 - move to apply conditional marketing authorisations to all new medicines in the EU was rejected.

*“It is essential that a strengthened system of pharmacovigilance not lead to the premature granting of marketing authorisations”*

- Pharmaceutical companies do not honour post-marketing commitments
- Why would patients enrol in a clinical trial if the drug is already on the market?
- Lack of incentive for pharmaceutical companies: study could reveal that drug is less effective or more harmful than initially presumed
- Regulators will have no legal means to demand additional research.
- Use of “*Real world data*”: Limitations of observational studies
- Public authorities will face patients’ opposition if they finally decide to stop reimbursing a drug or to withdraw its marketing authorisation.

# EMA Conditional Approvals (2006-2014) and their Prescrire ratings (per indication)



Note: 24 medicines have been granted conditional approval by the EMA between 2006 and 2014. From these, Prescrire has assessed 22 indications till date.



## 4. Increased control by industry over other stakeholders

### Health Technology Assessment Bodies

- Priority targets for lobbying by pharma, but usually not accessible. That would change with adaptive pathways, since they will be sitting at the table:

*“To be successful, adaptive licensing would require (...) to reduce the development misalignment between marketing and reimbursement decisions” and should “allow for early approval and coverage of a new compound (...) based on smaller initial clinical studies” (1)*

**= approval + reimbursement**

- EMA and HTA bodies are to provide confidential “scientific advice” to pharmaceutical companies in parallel, at an early stage of development  
**= risk of institutional capture**
- Managed entry agreements

1- Eichler H-G et al «Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval » *Clinical Pharmacology & Therapeutics* 2012 ; **91** (3) :426-437

## 4. Increased control by industry over other stakeholders (2)

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### Healthcare Professionals

- First authorization for niche indication
- Presented as tool to prevent “off-label use”.
- *“Greater emphasis [on physicians] by regulators, payers and industry on targeted drug utilization”*: physicians to become responsible if patients suffer harm (1).

### Patients

- *“Access to patients’ electronic medical records and direct contact with patients”*
- Access to patients’ personal data, ability to contact patients directly and further promote products under the guise of better treatment compliance or “education” programmes = **information to patients all over again?**

1 - Eichler H-G et al. “From Adaptive Licensing to Adaptive Pathways: Delivering a Flexible Life-Span Approach to Bring New Drugs to Patients” *Clinical Pharmacology & Therapeutics* 2015; **97** (3): 234–246

## A pilot to circumvent democratic process?

- March 2014: EMA launched publicly an “adaptive licensing” pilot project with “*discussions conducted in a safe harbour environment and all submissions strictly confidential*”
- An exploratory initiative, it “*builds on existing regulatory processes and intends to extend the use of elements that are already in place , including scientific advice*”.
- December 2014 to 28 February 2015
- 58 applications » 17 candidates » 9 pharmaceutical products selected.
- There has been no public consultation from the EMA on this issue. No discussions at EU Parliament or Council.
- Brief report (6 pages) published: little transparency.
- Evaluation due at the end of the procedures: late 2015, early 2016
- Once fully implemented = weakened marketing approval procedures?

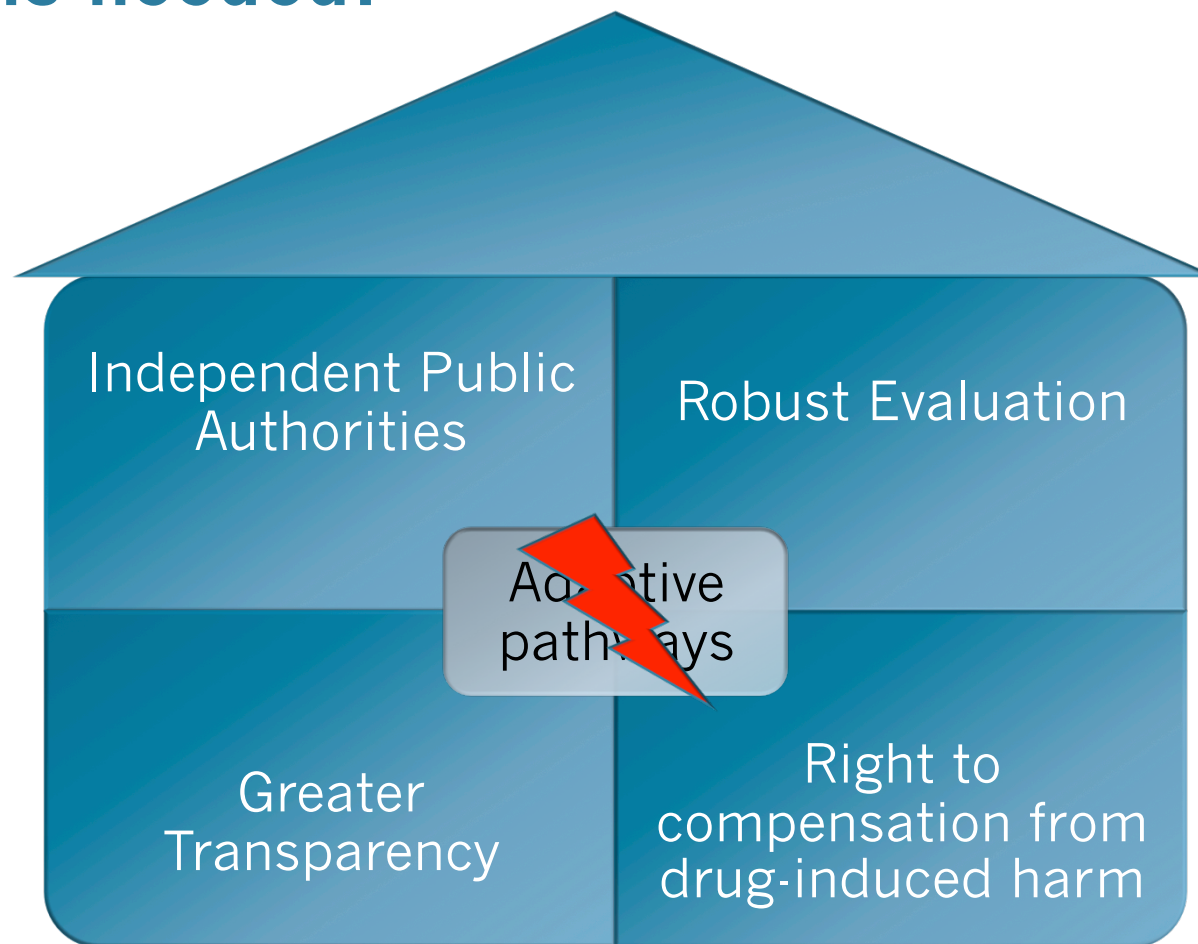
## Spill-over effect: a clear and present danger

- *“Adaptive licensing is envisioned as the ultimate replacement for the current development and authorisation model and as such should be applicable to most new products” (1)*
  
- Other supporters are already asking: *“(...) what would it take to establish this mindset for many or all other therapies?” (2)*

1- Eichler H-G et al «Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval » *Clinical Pharmacology & Therapeutics* 2012 ; **91** (3) :426-437

2-Vermilion Life Sciences Blog “Adapt to Breakthrough” 5 December 2014. <http://blog.vermilion-lifesciences.co.uk/?p=90>

## What is needed?



Remember...

*“Patients need knowledge—answers about the drugs they put in their bodies—not just access”.*

Gonsalves G, Zuckerman D “Will 20th century patient safeguards be reversed in the 21st century?” BMJ 2015;350:h1500.

## The facts...

*“At present, MAPPs may seem to offer more questions than answers, and no-one can predict what it may be able to deliver” (1)*

1- European Voice “Fast-tracking medicines innovation: a question of uncertainties” Report sponsored by Roche and EFPIA.



# Thank you

More information?  
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