EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

"Health, Growth and Finance" Brescia 17th June 2016

Role of drug regulation (if any…)

Presented by Guido Rasi
Executive Director, European Medicines Agency

Mandate of EMA

To evaluate

Quality, Safety and Efficacy of medicine….

….without any reference to economic aspect in the assessment of Benefit/Risk….

…however we are not keen to approve medicines nobody can access…

Access to innovation

Obstacles:

High R&D costs?

Uncertainty? Additional uncertainty (HTA/pricing)?

Prices?

The NEW ENGLAND JOURNAL of MEDICINE

Drug Regulation and Pricing — Can Regulators Influence Affordability?

H.-G. Eichler, H. Hurts, K. Broich, and G. Rasi | N Engl J Med 2016;374:1807-1809

Free Full Text

Traditional Medicine Development and Patient Access Model

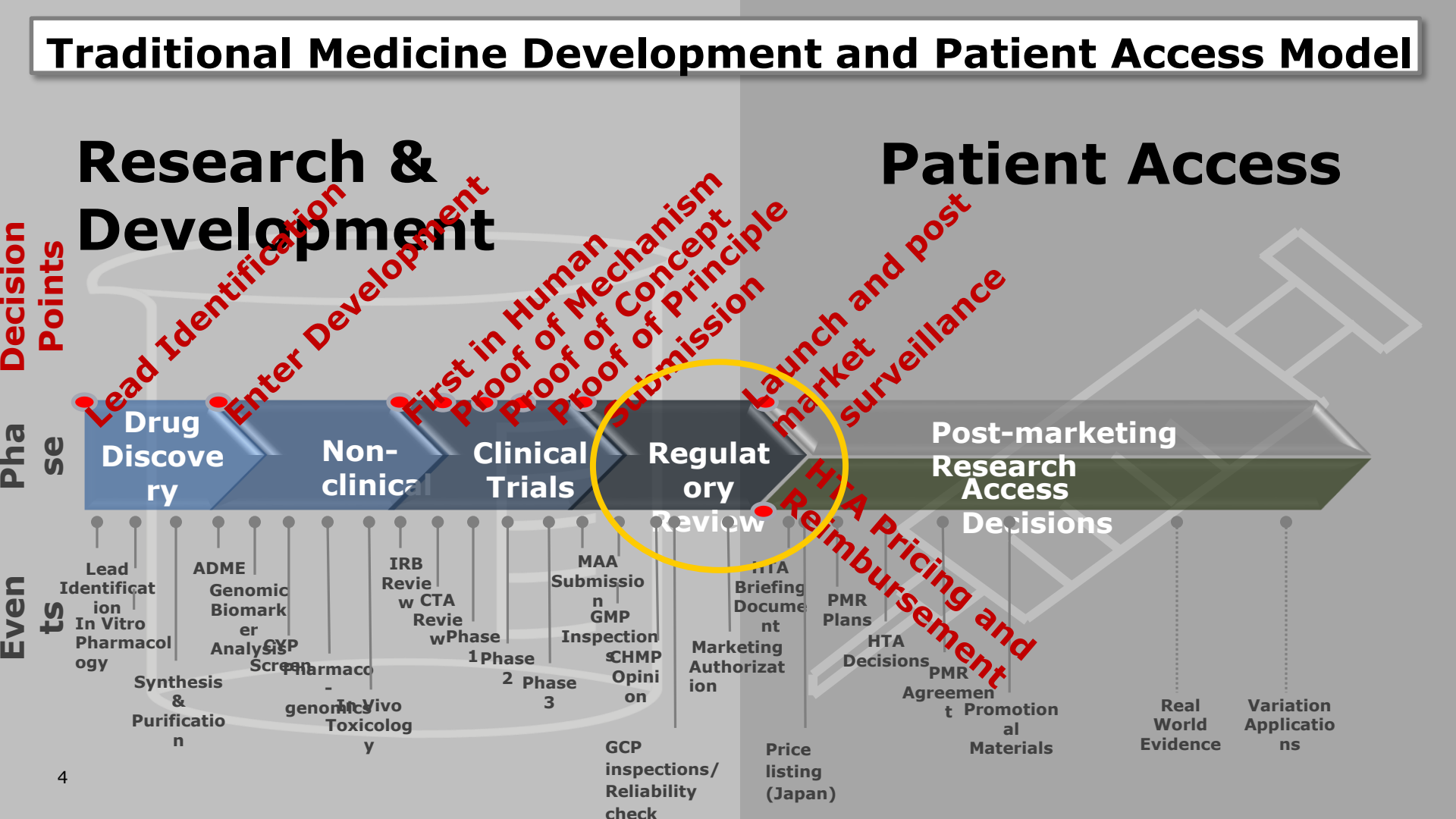
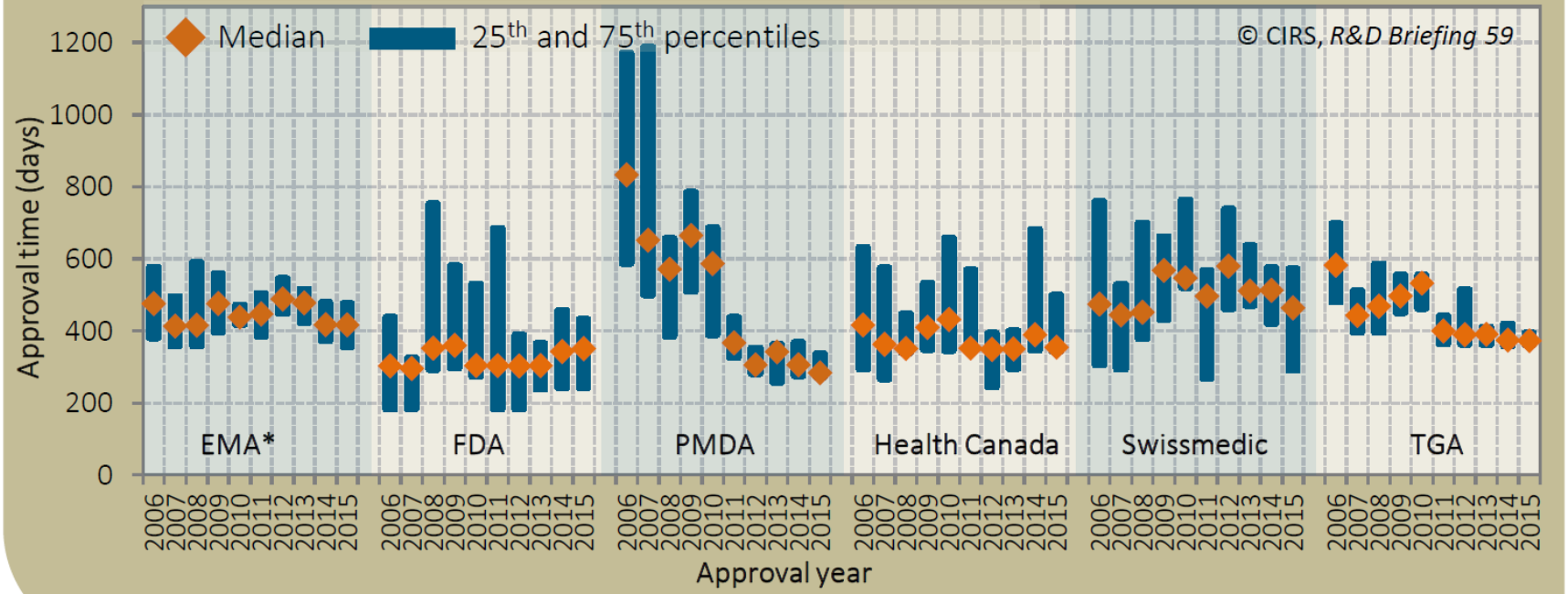


Figure 2: NAS approval time for six regulatory authorities in 2006-2015



*The EMA approval time includes the EU Commission time.

Regulators' incentives for pharma innovation

Direct Financial

- Orphan exclusivity
- Other types of market exclusivity (paed, EU)
- Extra 1 year market protection (sign clin benefit; EU)
- Voucher (FDA; can be sold)

Attracting Investment

Designation of "promising status"

- e.g. Breakthrough Pathway designation (FDA)
- PRIME (EMA)

Process Facilitators

- ITF
- SME office
- Protocol Assistance
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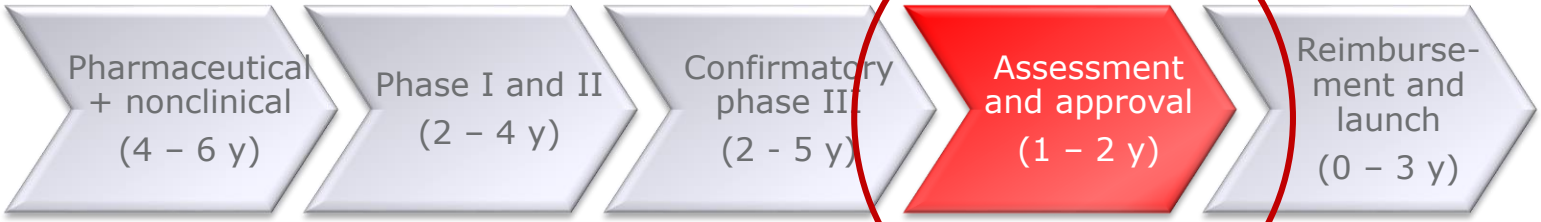
- Rapid assessment, Cond. Approval etc.
- Parallel SA with HTAs

The typical long route of medicines to patients

Development phase:



Chance of reaching access for a product entering the development phase:

0.01-0.1% 5-10% 50-60% 75-90%

Regulatory provisions primarily targeting the risk of development failure:

- Scientific advice
- Support to SMEs …

Regulatory provisions primarily targeting the time to access:

- Conditional MA,
- Accelerated Assessment,
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Why do drug development programs fail (or get delayed)?

A) "if further development proves initial hypotheses wrong." **Often inevitable**

B) Inappropriate development program, wrong studies **Usually preventable**

Who takes the risk?

Companies, investors, **and trial patients**

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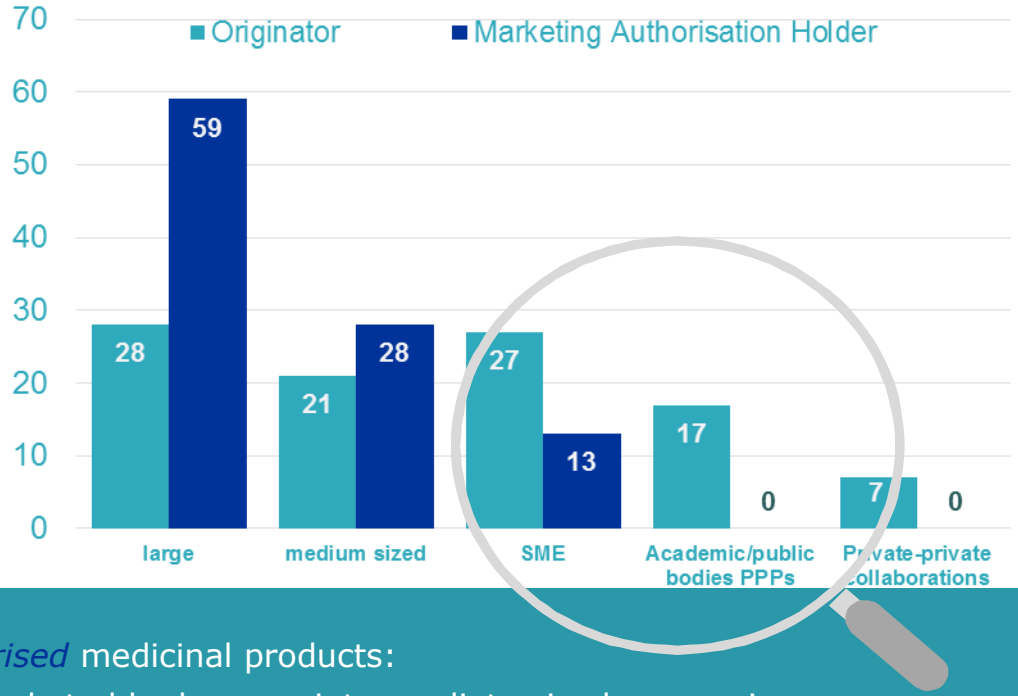
Origins of new medicines

EU 2010-2012

*



*

Of 94 novel *authorised* medicinal products:

- Large majority marketed by large or intermediate sized companies.
- SMEs and academia at the origin of innovation.

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ITF recent trends analysis (2013-2015)

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- **Borderline products and Novel and technologies**
  - Cosmetic / Food
  - Biomaterials
  - Demarcation towards cell, tissue and blood regulation
  - Combination products
  - Nanotechnology
- **Regulatory framework** for "really" **Personalised Medicines**
  - N=1 trials
  - treatment algorithms
  - Modelling and Simulation / Extrapolation
- **eHealth**
  - Health Apps,
  - electronic data collection / processing in CTs / e-consent
- **Bedside manufacturing**
  - bring the (individualised) product to the patient,
  - technical integration / cont. manufacturing / QbD

Regulatory challenges of 'innovative products', examples

Precision medicine: stratification criterion often incompletely understood; small patient numbers

Advanced therapies (gene, cell, tissue based); radio-theranostics: some truly 'personalised'; benefit-risk context dependent; single intervention – long-term outcome

Early disease interception: extremely long observation periods for benefit-risk assessment

Personalised treatment combinations: combinatorial complexity; small patient numbers; clinical indication difficult to define

Cystic Fibrosis - one condition or more?

1989: one disease: "Cystic Fibrosis"

- all patients randomised in same study

2015: multiple CF subgroups defined by mutations

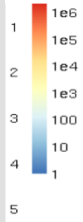
Example: Ivacaftor

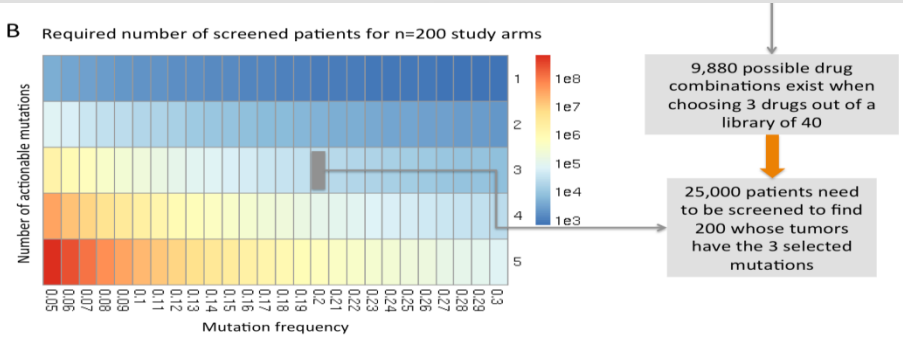
- homozygous F508del-CFTR mutation → **RCT**, **parallel group***
- F508del-CFTR heterozygous with residual function mutation on the second allele → **RCT**, **cross-over***
- Other, less frequent mutations → **n-of-1 or uncontrolled**?

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

The challenge of personalised Rx combinations: combinatorial complexity

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

Choice of endpoints

- The choice of clinical efficacy endpoints remains a controversial topic
  - New intermediate endpoints being discussed (pCR and MRD)
- "Clinical relevance" of endpoints lacks formal regulatory definition (generally OS>PFS)
- Assessment of benefit-risk balance is more complex than simply observing statistically significant effects
  - Based on expert judgment of the totality of evidence (not just *P*-value for primary endpoint comparison)

Pignatti, F., Jonsson, B., Blumenthal, G., & Justice, R. (2014). Assessment of benefits and risks in development of targeted therapies for cancer - The view of regulatory authorities. [Review]. *Mol Oncol*. doi: 10.1016/j.molonc.2014.10.003

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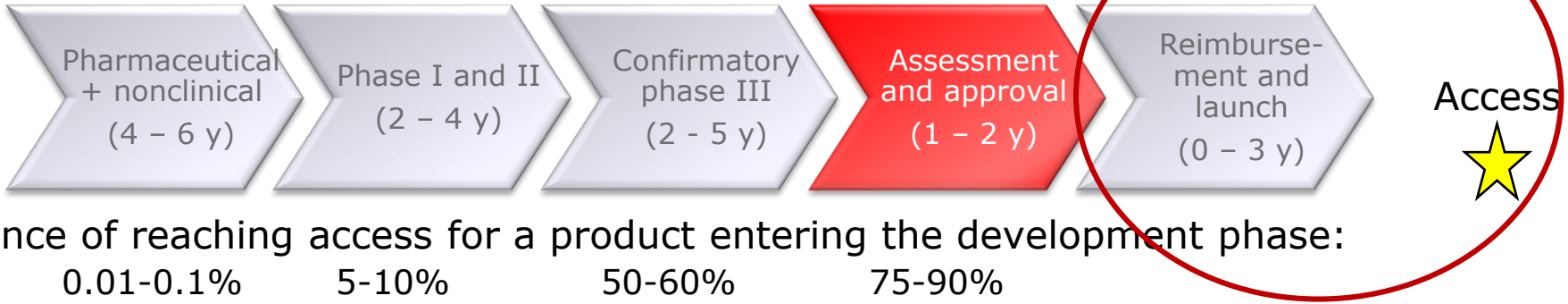

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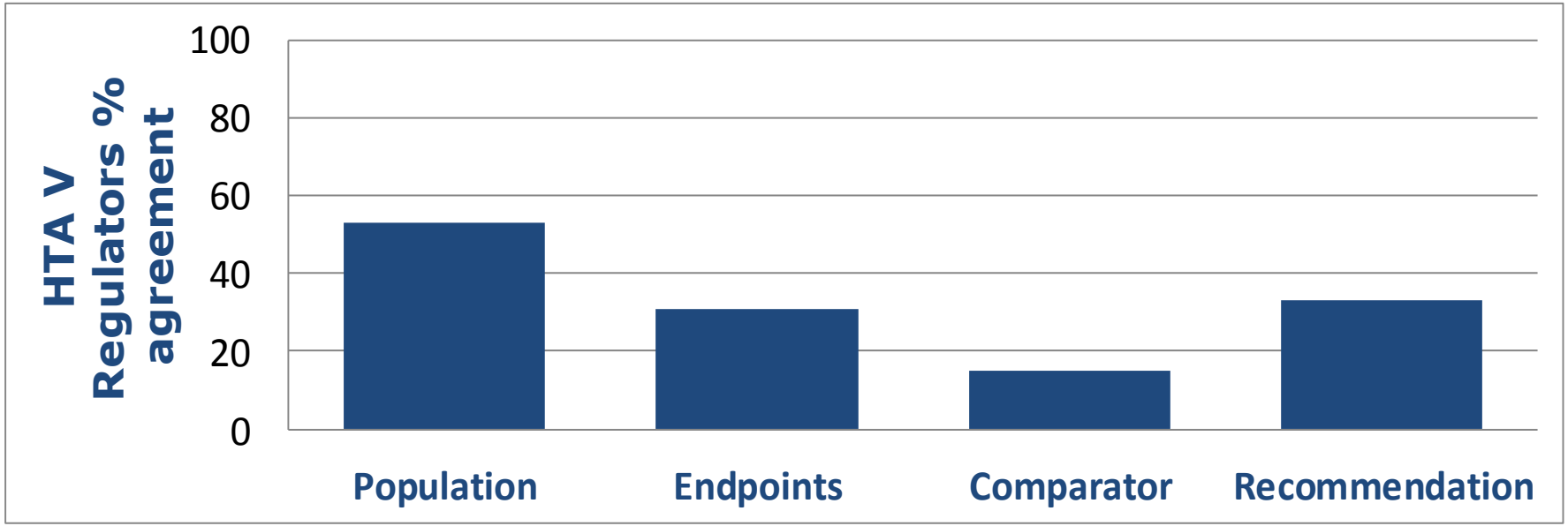
Can Parallel Advice Help?

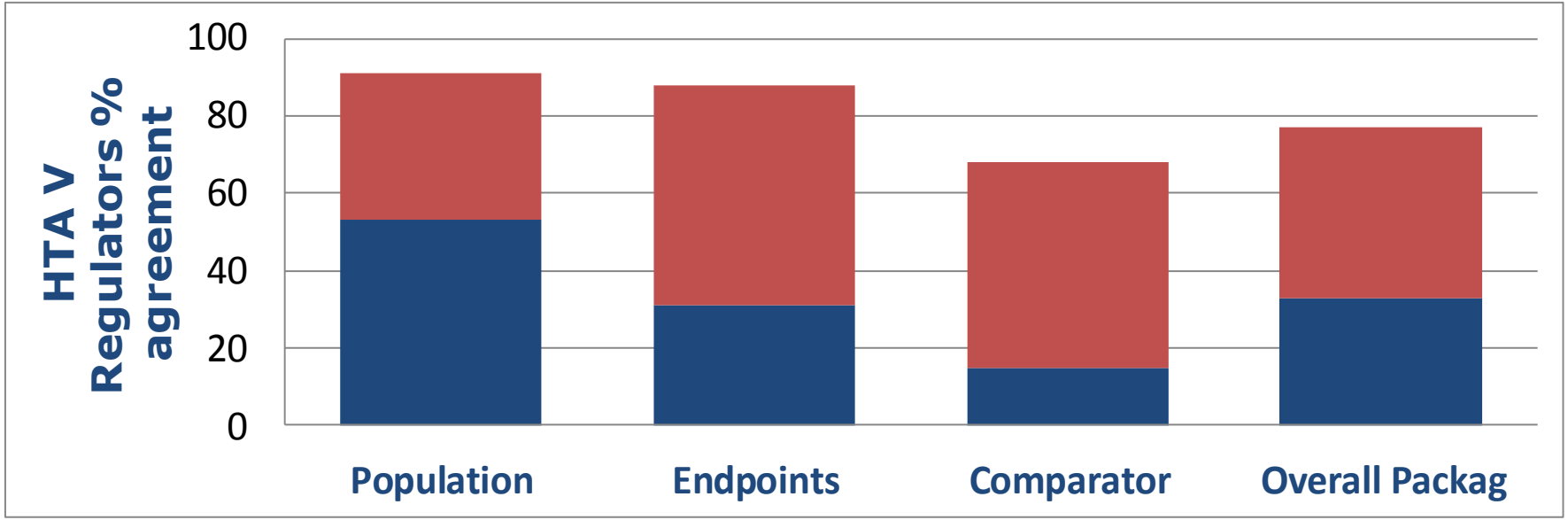
56 products



http://www.efpia.eu/documents/189/61/HTA-Accelerator-In-Depth-Analysis-Final-report

Can Parallel Advice Help?

Commonality?



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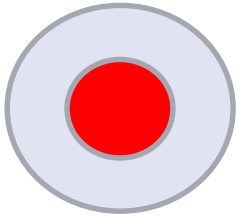
Developers : Time! 4-5yrs?! (*RWE/BMs/SEPs)*

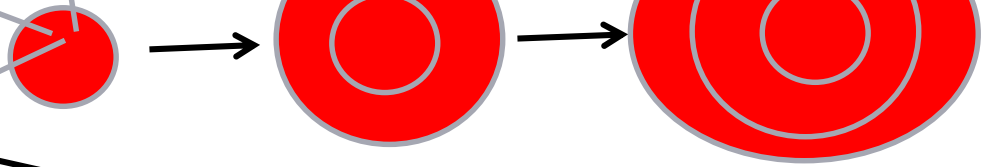
(widening of the indication)

Patients/Regulators: increased B/R

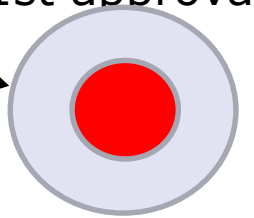
Final target indication in blue, patient group with highest need in red



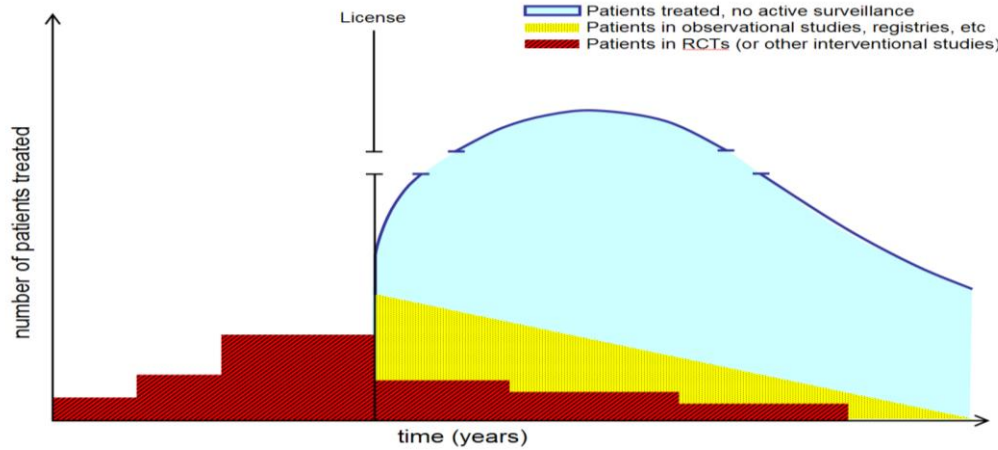
The sponsor could follow 2 strategies

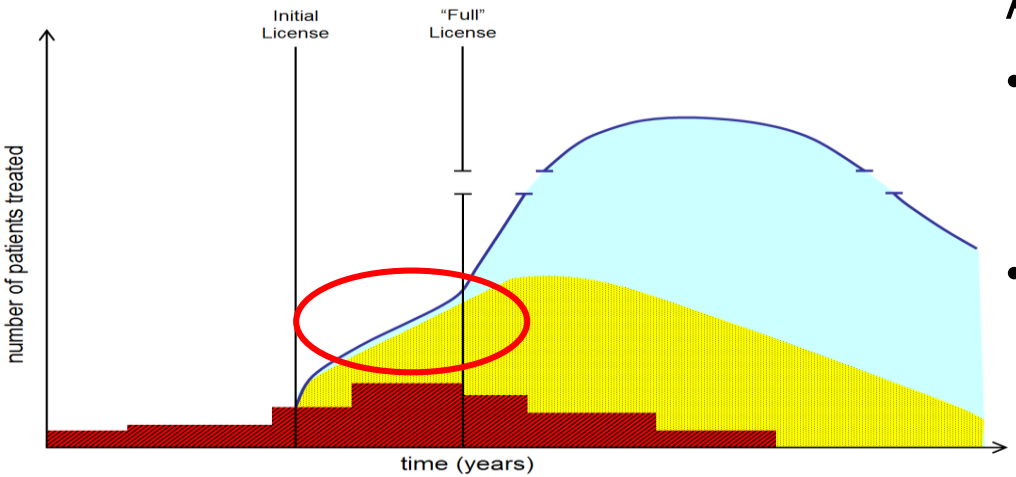


1st approval



Payers: *price, …prescriptions*





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

From prediction to monitoring

Realised versus inherent risk

- 1950/60s: thalidomide (phocomelia; 10.000 cases) high-visibility, low background event!
- 2005: natalizumab (PML; 3 cases)
- 2009: Pandemrix (narcolepsy; 6 cases), *but…*

What type of products are suitable?

1. Strong pharmacological rationale/proof of concept
2. An iterative development plan (start in a well-defined subpopulation and expand, or have a Conditional Marketing Authorisation, maybe surrogate endpoints and confirm)
3. Real World Data (safety and efficacy) can be acquired to supplement Clinical Trials and reflect real life populations
4. Input of all stakeholders, HTAs and patients, is fundamental
5. Unmet medical need

Evolution of the "disease" (condition) concept

19th/20th century: Hematologic malignancies

"Cancer of the blood" → better understanding of pathology → growing number of subpopulations → 90+ "diseases" → disease specific treatment regimens → greatly improved patient well-being and survival

21st century: Type 2 diabetes?

Hypertension?

Colon cancer?

…?

What is a condition (disease)?
A playground for lumpers versus splitters

"There is a compelling case for reforming the taxonomy of human disease by moving away from traditional diagnostic criteria alone to ones that incorporate the scientific advances in molecular and genetic medicine.."

"Failure to do so perpetuates ineffective treatment in medicine…"

Nature Reviews Drug Discovery **10**, 641-642 (September 2011) | doi:10.1038/nrd3534

A call to reform the taxonomy of human disease

Ismail Kola[1] & John Bell[2]

Cost of R&D versus drug prices

The cost of bio-pharma R&D is huge and keeps growing, challenging the sustainability of bio-pharma innovation.

Assume the challenge can be addressed and R&D costs reduced or staggered, will this *per se* result in lower drug prices?

NO. Companies will charge what the market will bear to maximise shareholder returns.

Problem is, the market no longer bears the premium prices and there are now cracks even in the US market with payers pushing back (exhibit: Sovaldi, some cancer drugs)

When prices are pushed down, cost of R&D becomes more relevant and the opportunity cost of regulatory requirements is being questioned ➔ New pathways to market are needed.

Conditions versus treatment-eligible populations

"……..At least 9% of orphan drugs have reached blockbuster status. An additional 25 orphan drugs had sales exceeding US$ 100 million in 2008 alone."

O Wellman-Labadiex,Y Zhou. Health Policy 2010; 95: 216

The bigger picture: what does EMA do to promote timely access?

- 'Front end': PRIME; pilot programs to elicit patient preferences; early dialogues with HTA bodies (ample experience with early parallel scientific advice
- 'Back end': Adaptive Pathways pilots, data infrastructure/analysis development (registries project), interaction with HTAs (starting)

Conclusions (1/2)

- Further fragmentation of treatment-eligible populations is expected to have a positive effect for public health (=precision medicine)
- A new taxonomy of diseases may be needed to support this welcome development (to enable better clinical trials, regulatory and reimbursement decisions, steering of on-market utilisation)
- Regulation (and reimbursement rules) should follow science – not the other way round

Conclusion

Who is in charge to foster a new business model?