EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Les défis du système européen au sujet de l'évaluation et supervision des médicaments

ORDEM DOS FARMACÊUTICOS

Académie nationale de Pharmacie

Presented by Bruno Sepodes
Chair of the Committee of Orphan Medicinal Products

Disclaimer

The views and opinions expressed in the following presentation are those of the individual presenter and should not be attributed to any organization with which the presenter is employed or affiliated with.

EMA/EURN (global?) regulatory challenges

Sustainability

- Health systems (medicines prices)
- R & D (patient access to innovation, Europe competitiveness)

Quality

- Medicines (safety, efficacy, availability)
- Scientific opinions (complexity)

ITF trends analysis from recent years

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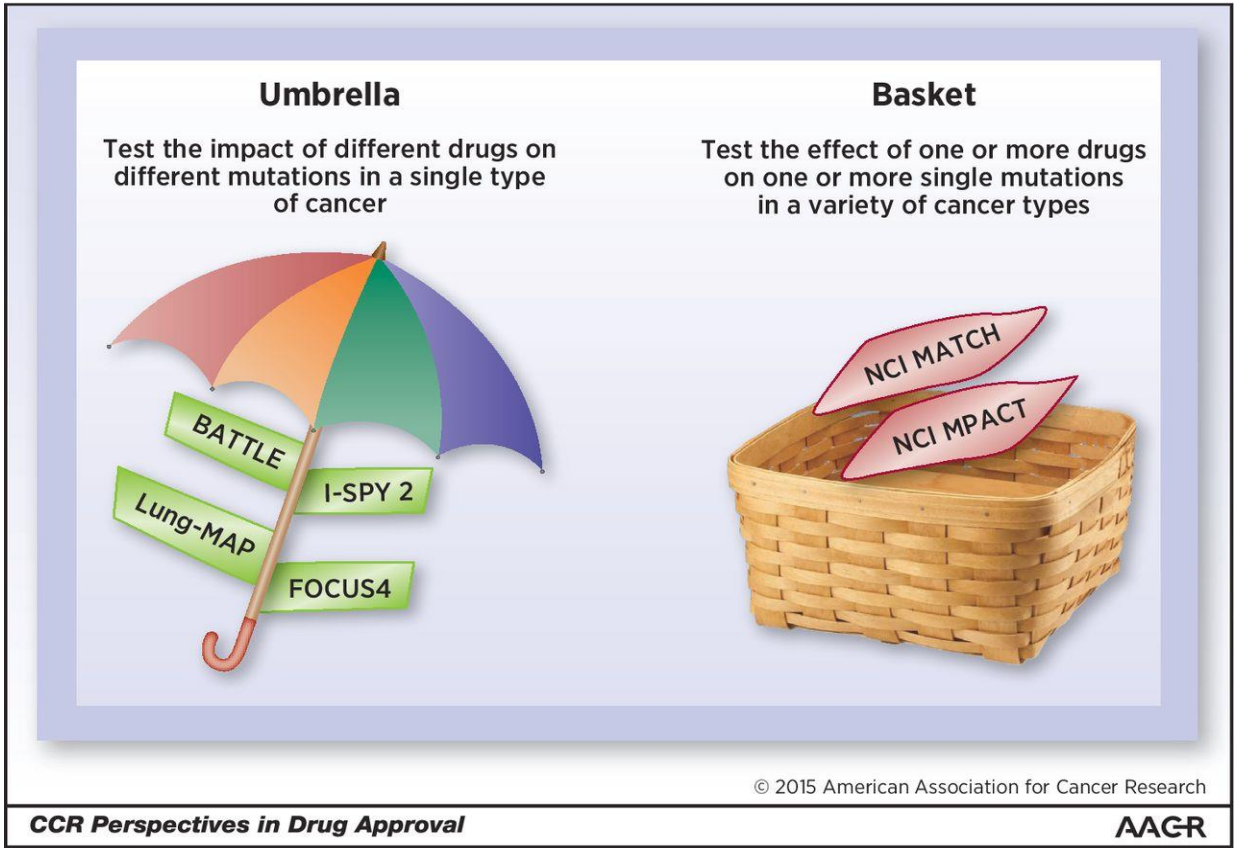
Borderline products and Novel and technologies

- Cosmetic / Food
- Biomaterials
- Demarcation towards cell, tissue and blood regulation
- Combination products
- Nanotechnology

Regulatory framework for "really" **Personalised Medicines**

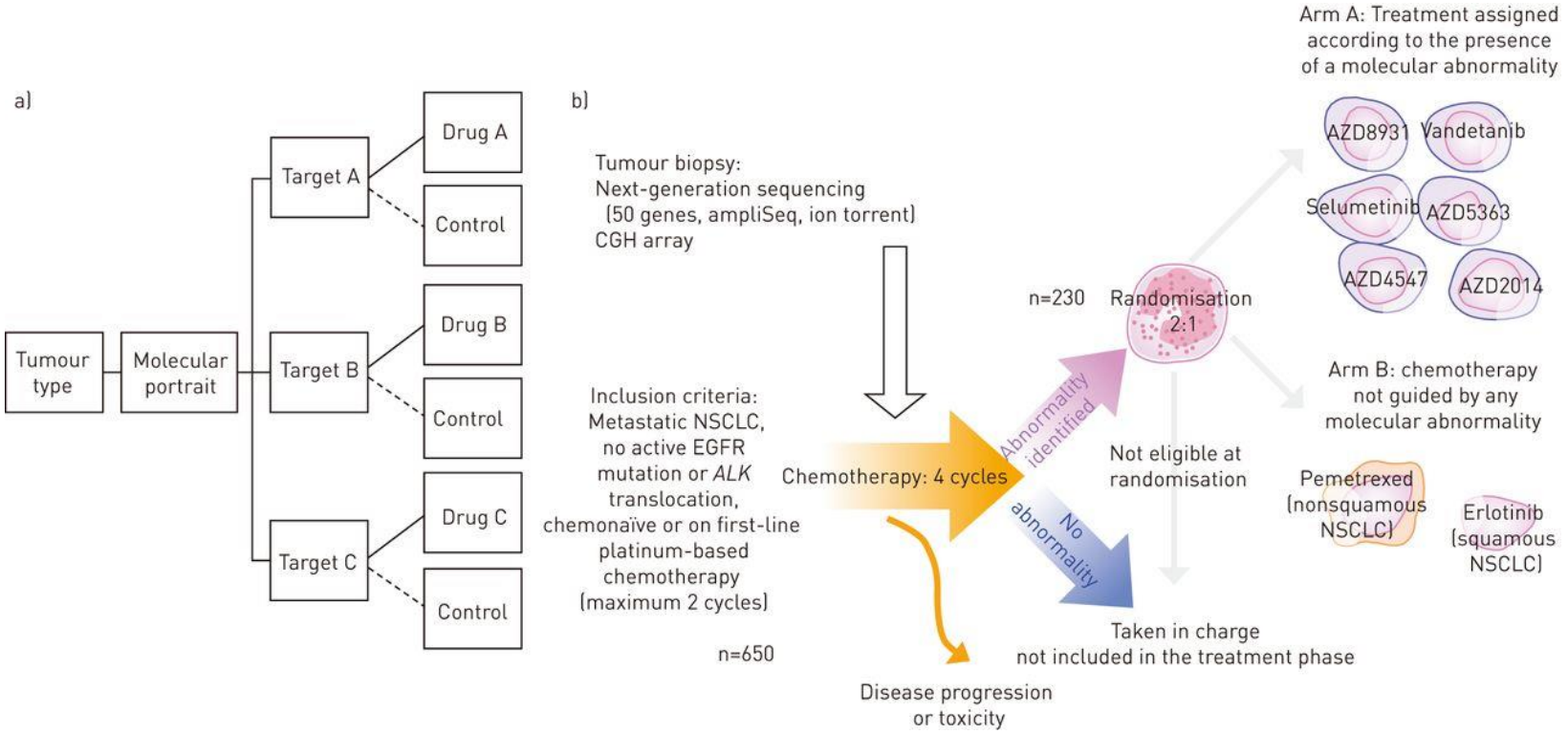
- *n*=1 clinical trials
- Treatment algorithms
- Modelling and Simulation / Extrapolation
- **eHealth**
- Health apps
- Electronic data collection / Processing in CTs / e-consent
- **Bedside manufacturing**
- bring the (individualised) product to the patient,
- technical integration / cont. manufacturing / QbD

Trials are too……



Herbst et al, Clin Cancer Res 2015

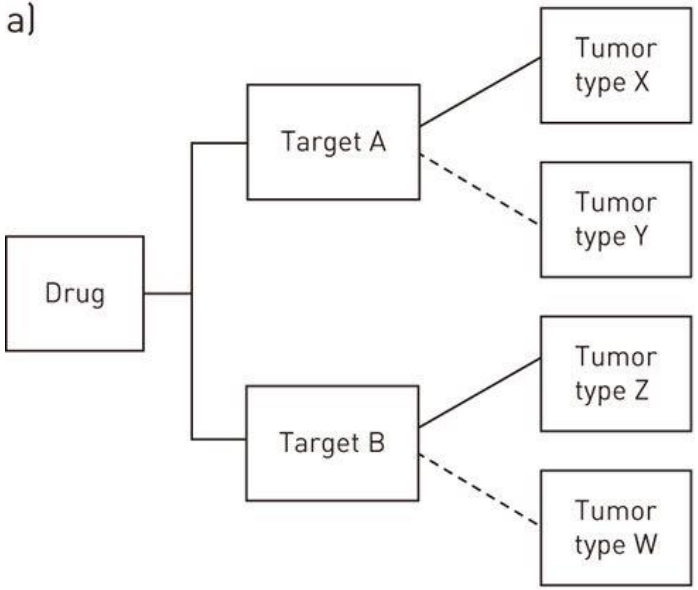
Umbrella design



Menis et al, Eur Respir Rev 2014

Basket design

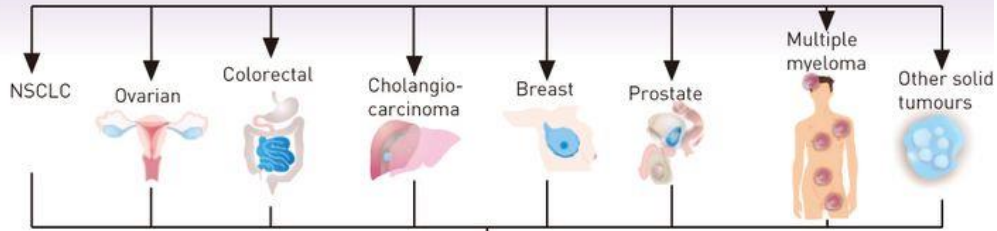
a)



b)

8 cohorts *BRAF*^{V600} positive cancers:
Metastatic solid tumors
Multiple myeloma

BRAF^{V600} testing
All *BRAF*^{V600} mutations
Tested by local routine methods
Retrospective optional evaluation with cobas 4800 *BRAF* mutation test



Vemurafenib
(960 mg orally twice daily)

Menis et al, Eur Respir Rev 2014

Regulatory Challenges

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New Medicines

- Innovative products and regulatory challenges (ITF trends)
- Biologicals and Biosimilars
- ATMPs (gene therapy, stem cell and tissue therapy)

Methodological Challenges

- Globalisation
- New marketing authorisation and monitoring procedures
- New ways to generate evidence (RWE)
- New evaluation methods (Medicines Adaptive Pathways to Patients, Prime, Joint HTA-SA)

Biologicals: rapid innovation + growth in many areas, e.g.

- **Monoclonal antibodies: realising their potential**
  - ***Antibody - Drug Conjugates:*** *Kadcyla (trastuzumab emtansine) - breast cancer {Ehrlich magic bullet}*
  - ***Bispecific antibodies****: Blincyto (blinatumomab) – B-cell ALL*
  - ***Programmed cell death 1 (PD1) inhibitors****: Keytruda (pembrolizumab), Opdivo (nivolumab) – metastatic melanoma*
- **Antimicrobial resistance / Health threats**
  - ***Bacteriophage therapy****: cocktail targeted to bacteria / resistance profile {EMA workshop, June 2015}*
  - ***Ebola*** *[e.g. Vesicular Stomatitis Virus vectored vaccines, mAbs (Zmapp)];* ***Zika*** *(viral safety in the supply chain of SoHO, e.g. plasma derived products)*
- **Improved manufacturing processes, diagnostics and analytical methods**
  - ***Modular, continuous manufacture, disposable technology****: flexible and reduced site footprint*
  - ***Companion diagnostics*** *used for personalised medicines, e.g. use mAbs or PCR for detection.*
  - ***Characterisation tools, in-vitro bioassays****: Quality foundation for biosimilars*

ATMP landscape in Europe (2009 - July 2017)

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~ 500 clinical trials using ATMPs in EU
(2009-2016)

~ 230 ATMP classifications
(2009-2016)

~ 215 scientific advice requests
(2009-2016)

16 MAAs reviewed or under review
(2009-2017)

10 positive opinions (9 products) (2009-2017)

market

3 withdrawn

6
licensed
ATMPs

Patients being treated?

Regulatory challenges
ATMPs (gene, cell and tissue engineered products)

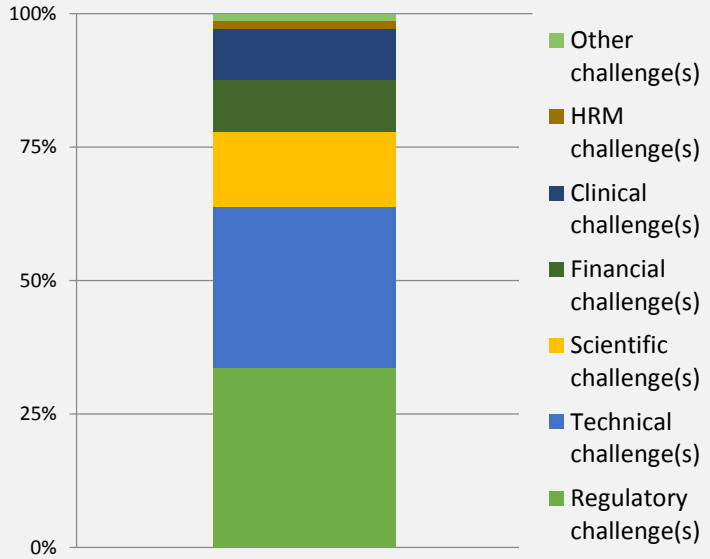
- **ATMP scientific field is moving rapidly**
  - Challenge to keep scientific guidelines up to date
  - Continous reflection if current regulatory framework needs to be adapted

    e.g. CAR-T cells*;* gene editing technologies (zinc finger nuclease, CRISPR technology): are they fitting in the definition of Gene therapy MP?

- **ATMPs are expensive products**
  - Small batches (e.g. autologous products: 1 batch = 1 patient) → High production and testing cost
  - Often orphan indication: *limited return on investment*
  - Early engagement with HTAs essential

Survey Results

Experienced Challenges – Grouped



Top 5 Experienced Challenges

1	16%	Meeting Country Specific Requirements
2	15%	Product Manufacturing
3	8%	Clinical Trial Design
4	6%	MAA Dossier Content Uncertainty
5	5%	Quality Standards

MAA = Market Authorisation Application

Utrecht University

EU regulation vs National Challenges

European Level

Orphan Designation →

Priority Medicine (PRIME) Scheme →

← Good Manufacturing Practice (GMP)

Scientific Advice → Marketing Authorisation Application

Committee for Advanced Therapies (CAT) →

SME office → ← Post Authorisation Commitment (PAC)

National Level

← ATMP Classification

← Clinical Trial Application (CTA)

← Genetically Modified Organisms (GMO) Legislation

← Hospital Exemption (HE)

Legend

→ Driver

← Barrier

Regulatory Challenges

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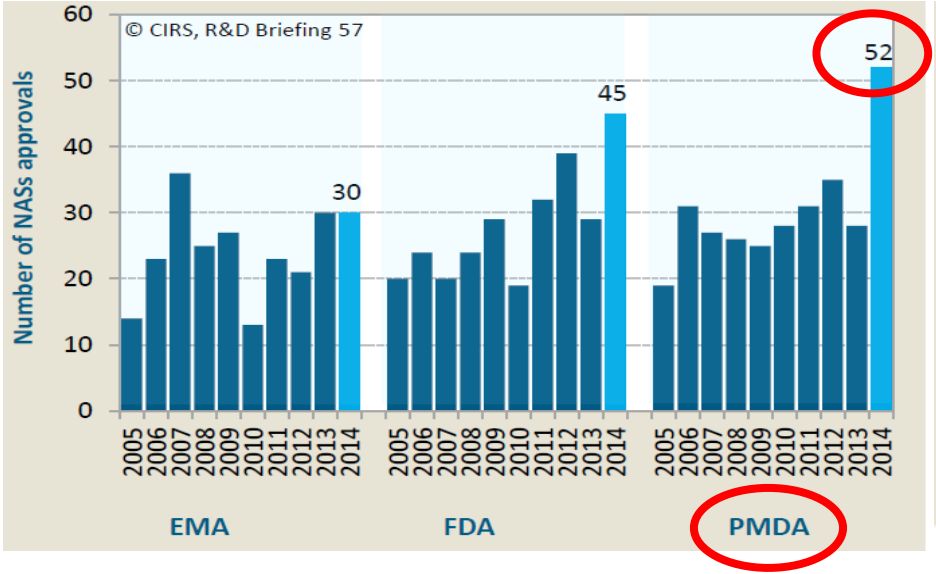
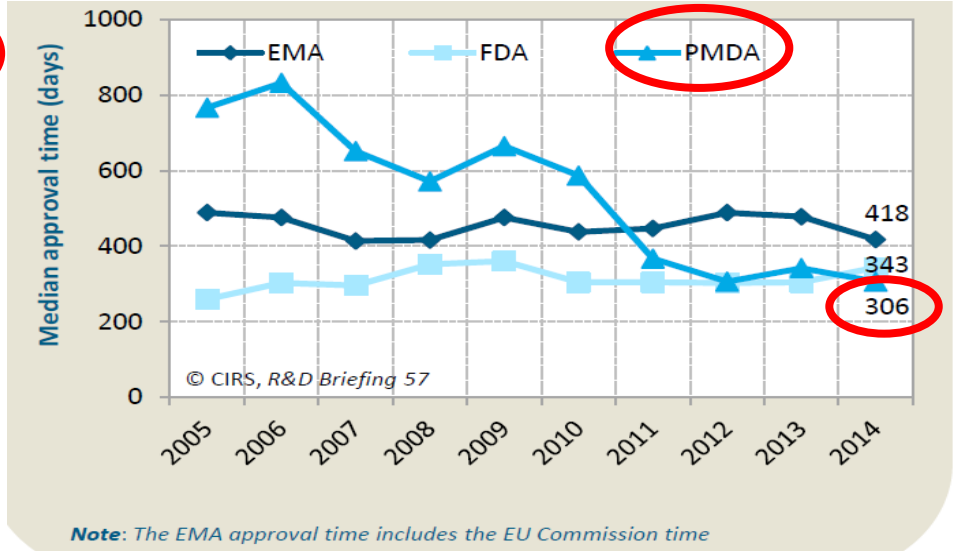
Number of NASs approved by ICH agencies by approval year



Median approval times for NASs approved by ICH agencies by approval year

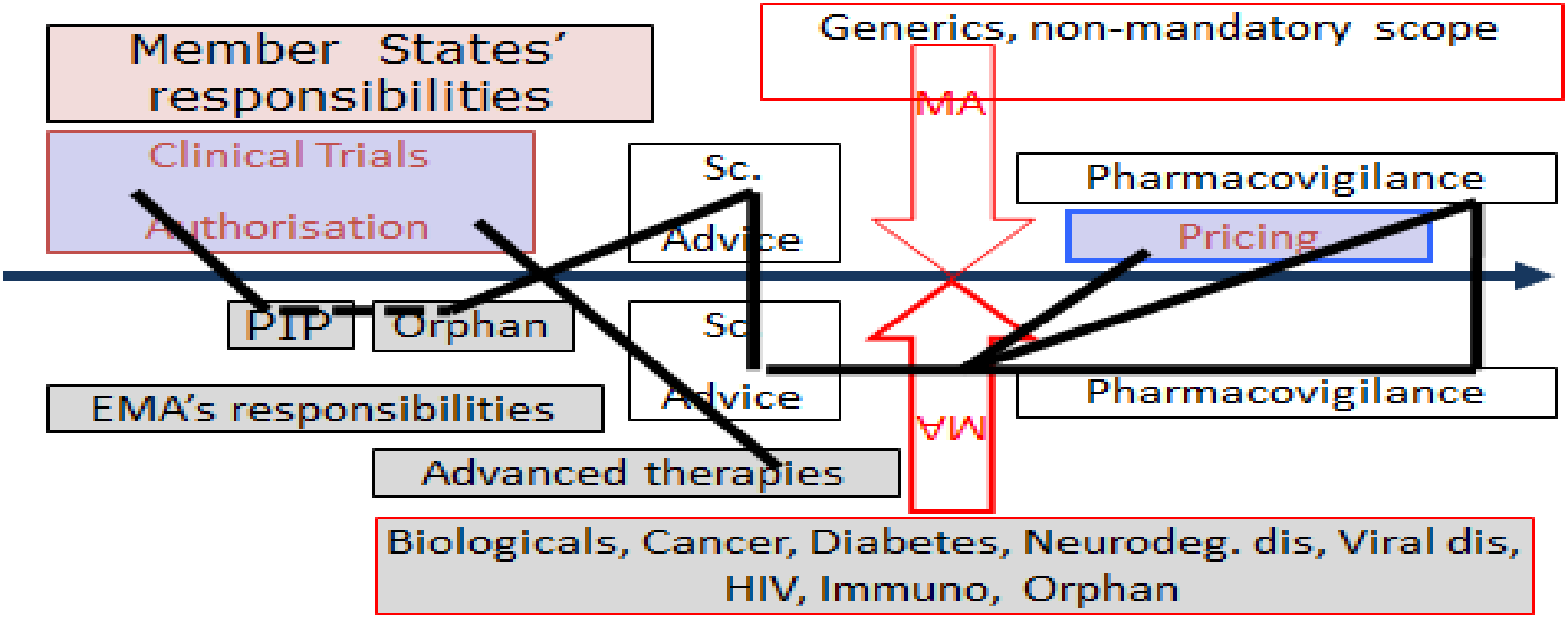


http://cirsci.org/sites/default/files/CIRS_R&D_57_ICH_%20approval_%20times_2005-2014_%2006072015.pdf

Going through the system is not always an easy walk…

Philippe Petit high-wire walk between the Twin Towers of the World Trade Center (7th of August of 1974)

Developing a medicine in EU does not follow a straight line



What we **do not** have

- A robust environment of venture capital
- A clear strategy to attract investments
- A single approach to access for patients
- A lean regulatory process

What we **do** have

- A strong and productive academic environment
- A sufficient number of start-ups and SME

and…

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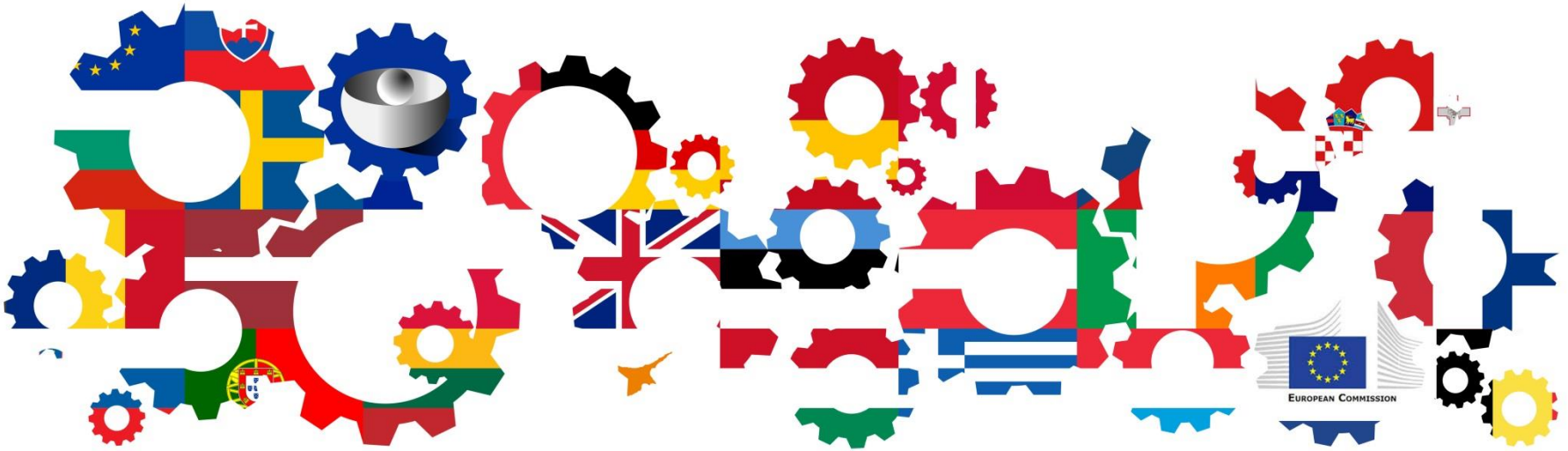
The European medicines regulatory network



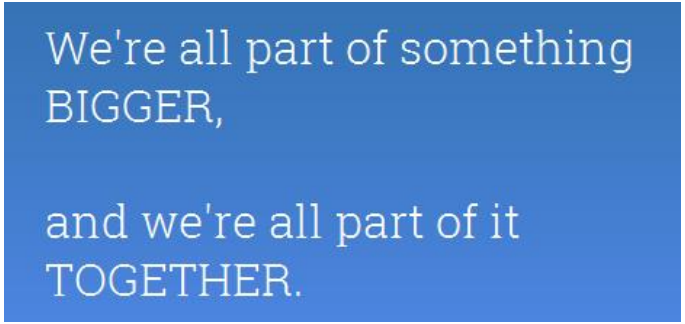
~ 50 national regulatory authorities

European Commission

European Medicines Agency

Part of a greater system
"Downstream" stakeholders include:

- **HTA bodies**
- Payers
- National/regional/local drug committees
- Prescribers
- **Patients**



Supportive legislation and developed regulatory services

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Legislative tools

- Conditional MA
- Exceptional circumstances
- Accelerated assessment
- Orphan, ATMP

Development support tools

- Scientific advice
- Parallel EMA/HTA advice
- Adaptive Pathways
- PRIME

EMA support

- Procedural and regulatory guidance
- SME office
- Innovation task force

National competent authorities support

- National innovation offices
- Clinical trials
- Compassionate use and early access schemes

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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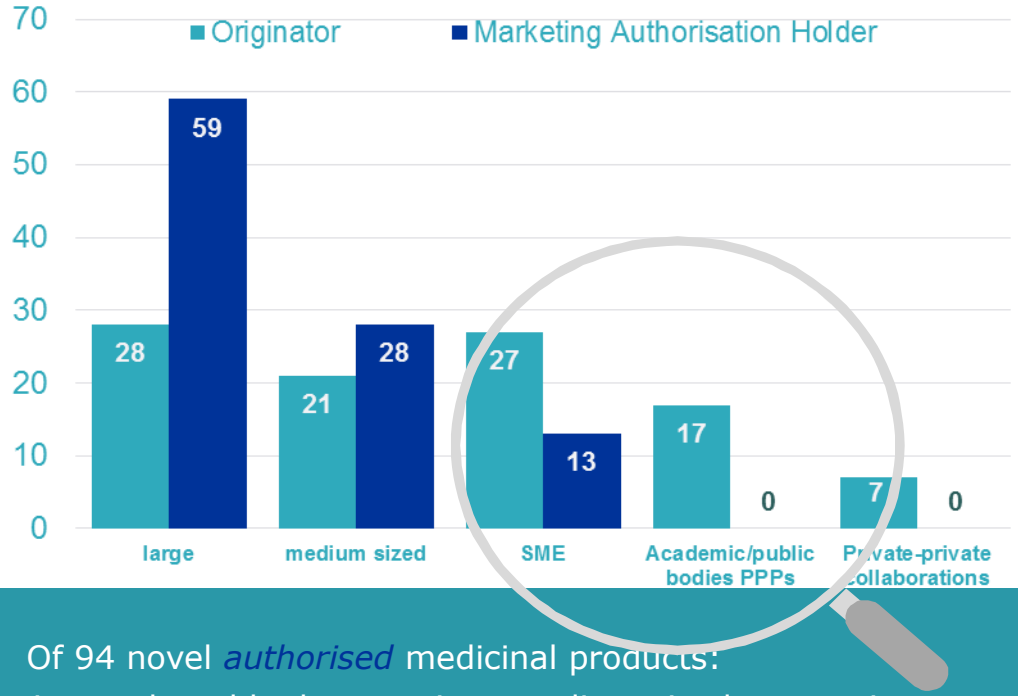
Origins of new medicines

*

*

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.

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%

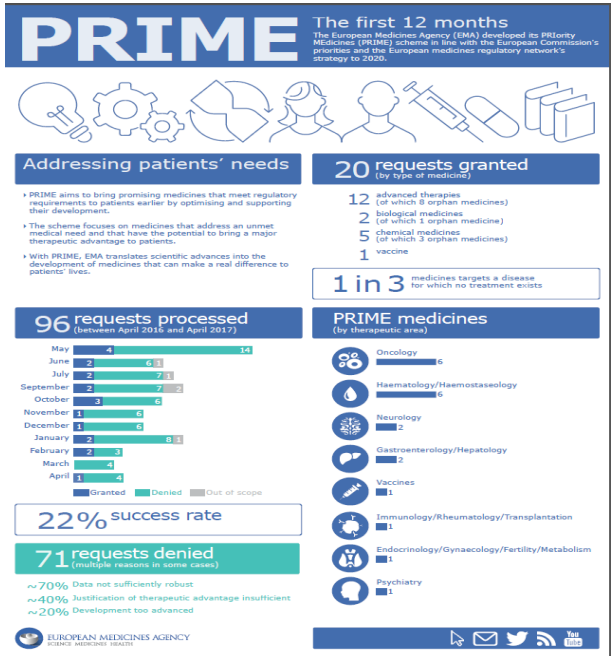
Regulatory provisions primarily targeting the time to access:

- Conditional MA,
- Accelerated Assessment,
- Compassionate Use …

Regulatory provisions primarily targeting the risk of development failure:

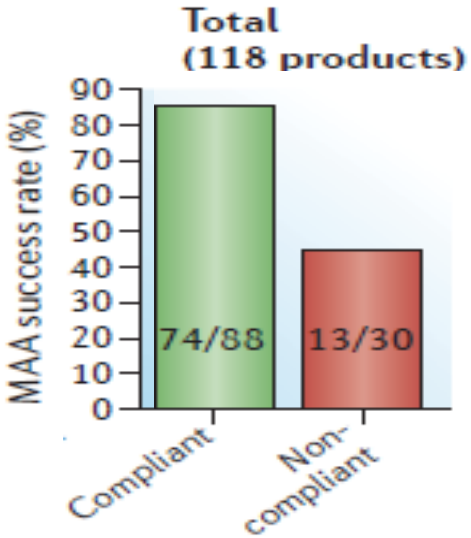
- Scientific advice
- Support to SMEs …

Supporting innovative medicines: PRIME Scheme



Positive impact of SA adherence on MAA outcome

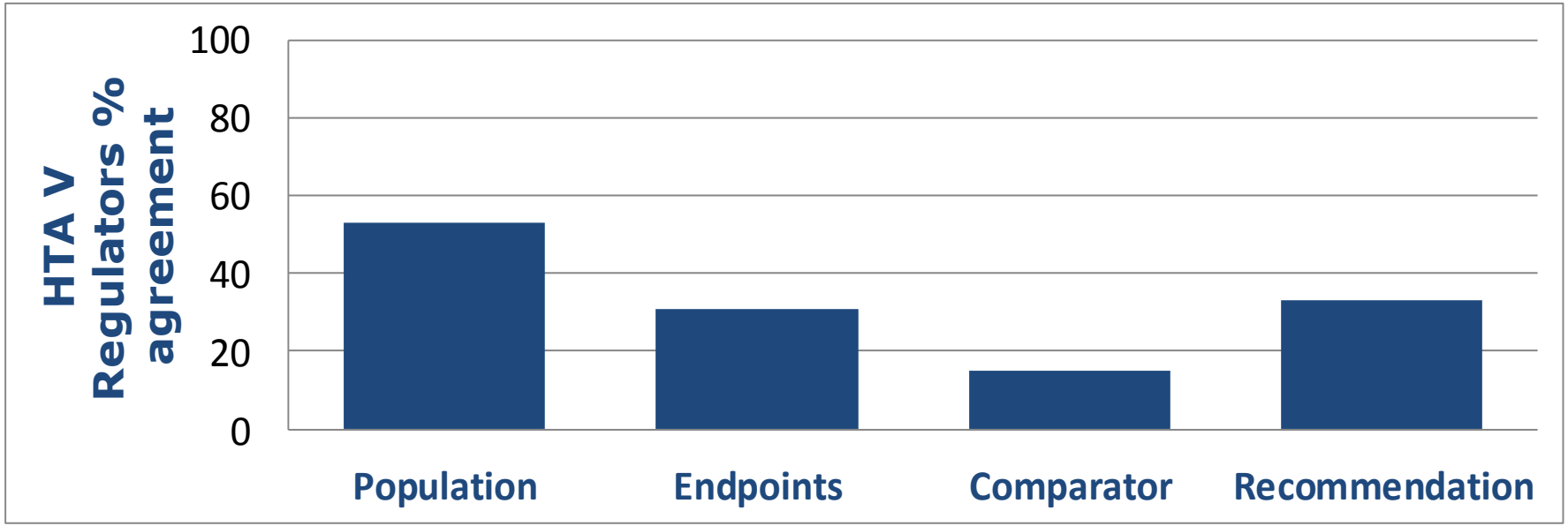
MAA success for MAAs with SA/PA submitted in 2008–2012



Hofer et al, Nat Rev Drug Discov. 2015

Making the case

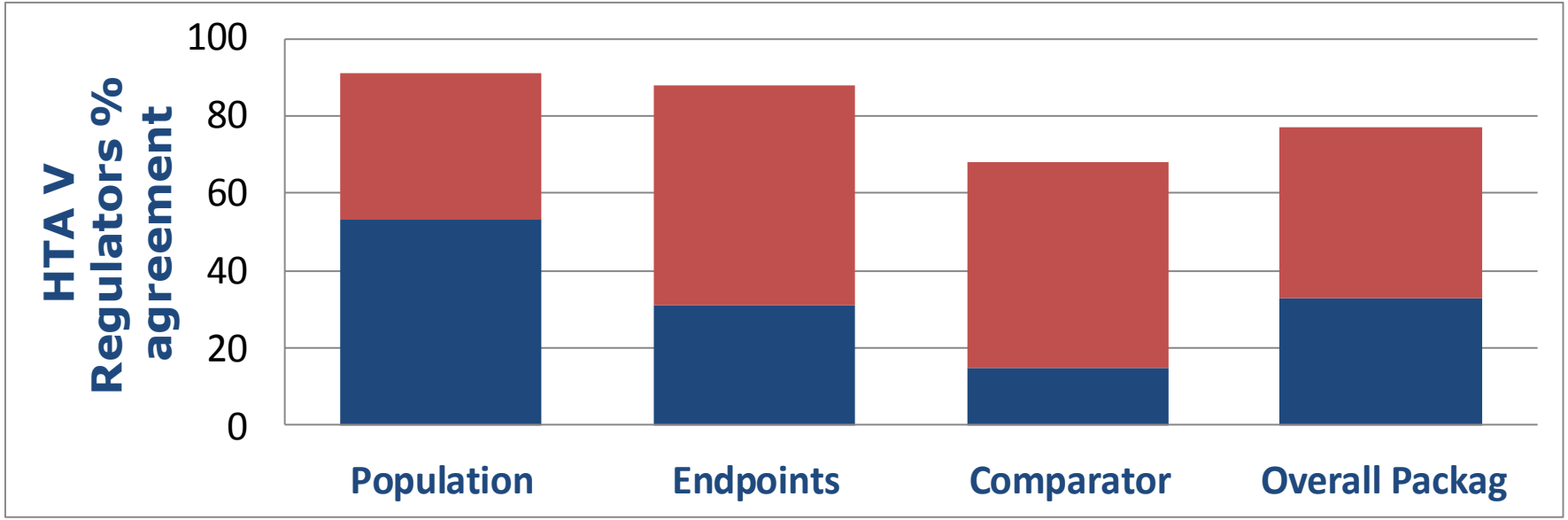
56 products



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

Can Parallel Advice Help?

Commonality?



The EU Orphan Drug Regulation continues to play, its one main role – i.e. **to attract investment in the development of therapies** for diseases which have today either no treatment at all or no satisfactory treatment.

Since 2000

1943 Orphan designations

156 Orphan designations included in authorised indication

143 Authorised OMPs

57 To be used in children

4 Removed from the market

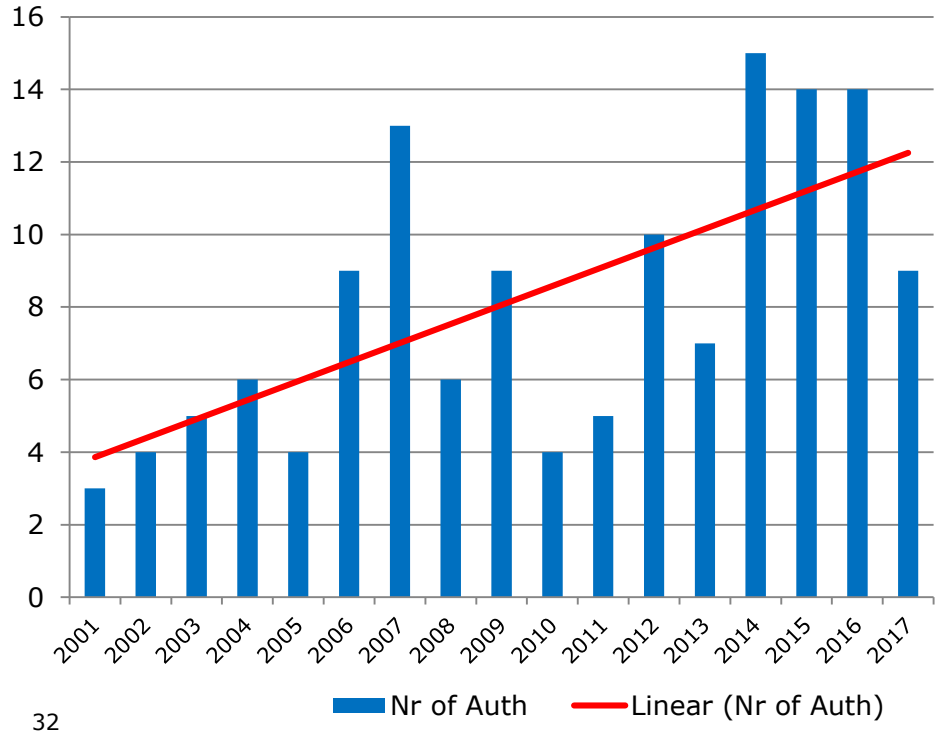
43 Marketed, but no longer "orphans"

To date

100

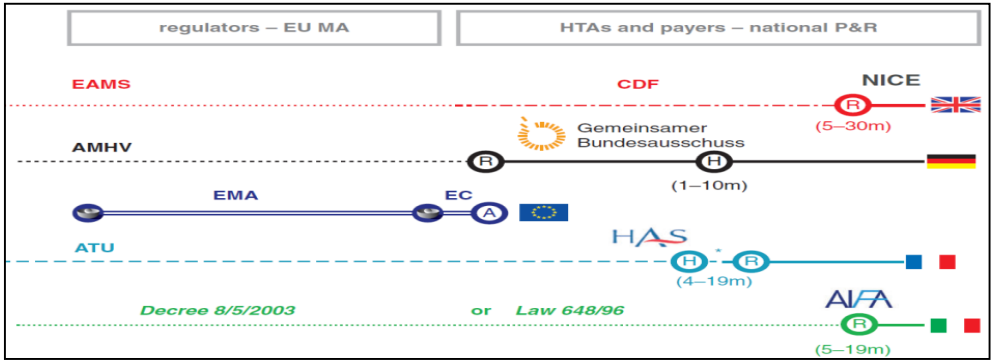
Products with a marketing authorisation and an orphan status in the European Union

Orphan environment after 17 years of EU legislation



- Success of EU orphan legislation !
- Cumulative rise in orphan MAAs 2000-2017
- ~ 70% require demonstration of SB
- Crowded areas, e.g. oncology, haematology, pulmonology
- Importance of adequate data to support SB

Reality check: from EU regulatory approval to national HTA/P&R decisions for orphan oncology products

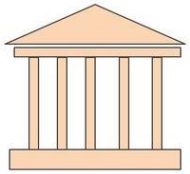


Orphan medicine	Indication	EU MA Approval	Time for HTA/P&R after MA (month)			
bosutinib (Bosulif)	chronic myeloid leukaemia	03/2013	7	7	11	18
cabozantinib (Cometriq)*	medullary thyroid cancer	03/2014	n/a	10	8	n/a

*first in class; MA = marketing authorisation; P&R = price and reimbursement cut-off: 15 September 2015

Martinalbo et al., Early access to cancer drugs in the EU. *Ann Oncol* 27: 96–105, 2016

Key pillars in the collaboration between regulators and HTA bodies to facilitate patient access



Advice on evidence generation plans to address different needs

Decision makers come together early during the development to discuss

- the study plans including populations / comparators / design of trial / endpoints
- the requirements for post-licensing evidence generation

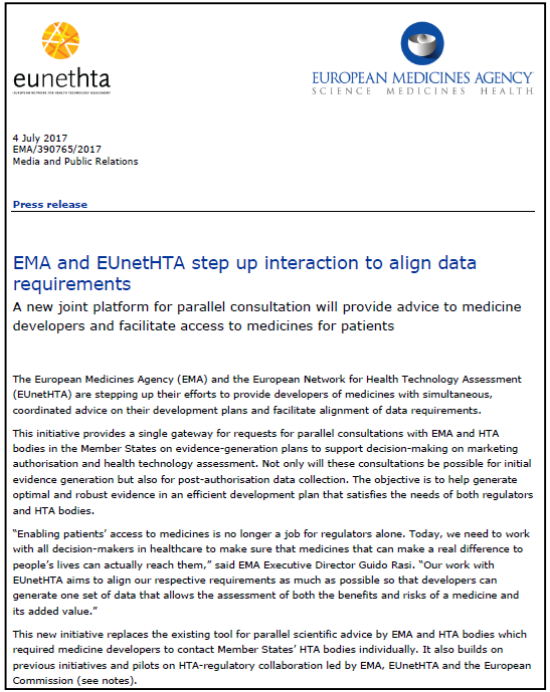
Bridge from regulatory opinion to relative effectiveness assessment

Decision makers come together at time of market entry to

- make available the final outcome of regulatory assessment for subsequent REA
- facilitate mutual understanding of the outcomes of the respective assessments

Synergy through alignment of evidence generation

- Experience shows that parallel scientific advice can **help to align regulatory and HTA views** on evidence needs
- There is close collaboration between EMA and EUnetHTA to **continuously optimise the processes** to facilitate such dialogue
- Whilst the focus so far has been on **evidence** needed **for market entry**, more engagement is needed on **post-licensing evidence generation**, which is particularly relevant for orphan medicines



eunethta

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SCIENCE · MEDICINES · HEALTH

4 July 2017
EMA/390765/2017
Media and Public Relations

Press release

EMA and EUnetHTA step up interaction to align data requirements

A new joint platform for parallel consultation will provide advice to medicine developers and facilitate access to medicines for patients

The European Medicines Agency (EMA) and the European Network for Health Technology Assessment (EUnetHTA) are stepping up their efforts to provide developers of medicines with simultaneous, coordinated advice on their development plans and facilitate alignment of data requirements.

This initiative provides a single gateway for requests for parallel consultations with EMA and HTA bodies in the Member States on evidence-generation plans to support decision-making on marketing authorisation and health technology assessment. Not only will these consultations be possible for initial evidence generation but also for post-authorisation data collection. The objective is to help generate optimal and robust evidence in an efficient development plan that satisfies the needs of both regulators and HTA bodies.

"Enabling patients' access to medicines is no longer a job for regulators alone. Today, we need to work with all decision-makers in healthcare to make sure that medicines that can make a real difference to people's lives can actually reach them," said EMA Executive Director Guido Rasi. "Our work with EUnetHTA aims to align our respective requirements as much as possible so that developers can generate one set of data that allows the assessment of both the benefits and risks of a medicine and its added value."

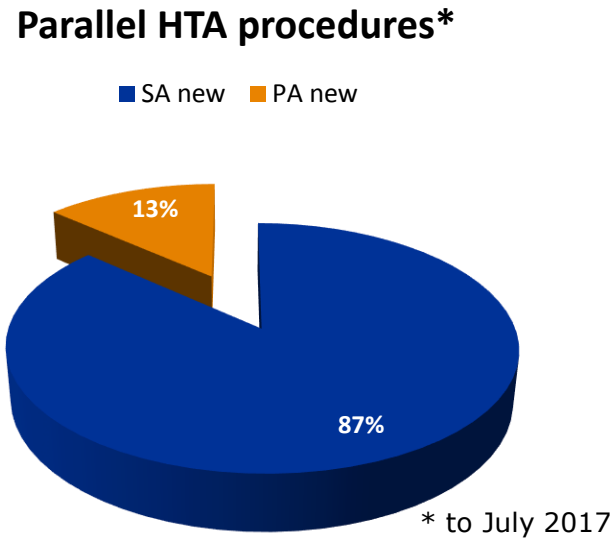
This new initiative replaces the existing tool for parallel scientific advice by EMA and HTA bodies which required medicine developers to contact Member States' HTA bodies individually. It also builds on previous initiatives and pilots on HTA-regulatory collaboration led by EMA, EUnetHTA and the European Commission (see notes).

Parallel regulatory/HTA advice for orphan medicines

Since the inception of parallel regulatory/HTA advice in 2010, there have been:

- 15 protocol assistance procedures on development of orphan medicines*
- 4 of these also covered questions related to the demonstration of significant benefit

* includes 2 follow-up requests



Opportunities to stimulate such discussions on development plan for orphan medicines.

Well-known ongoing EC activities and efforts:

- New **Notice** to facilitate designation of the best products;

- Revision of the concept of ”similarity”;

- Ongoing study on pharmaceutical incentives.

European Commission

Study on the incentives provided in the EU legislation on innovation, availability and accessibility of medicinal products – follow-up study

Health and Food Safety

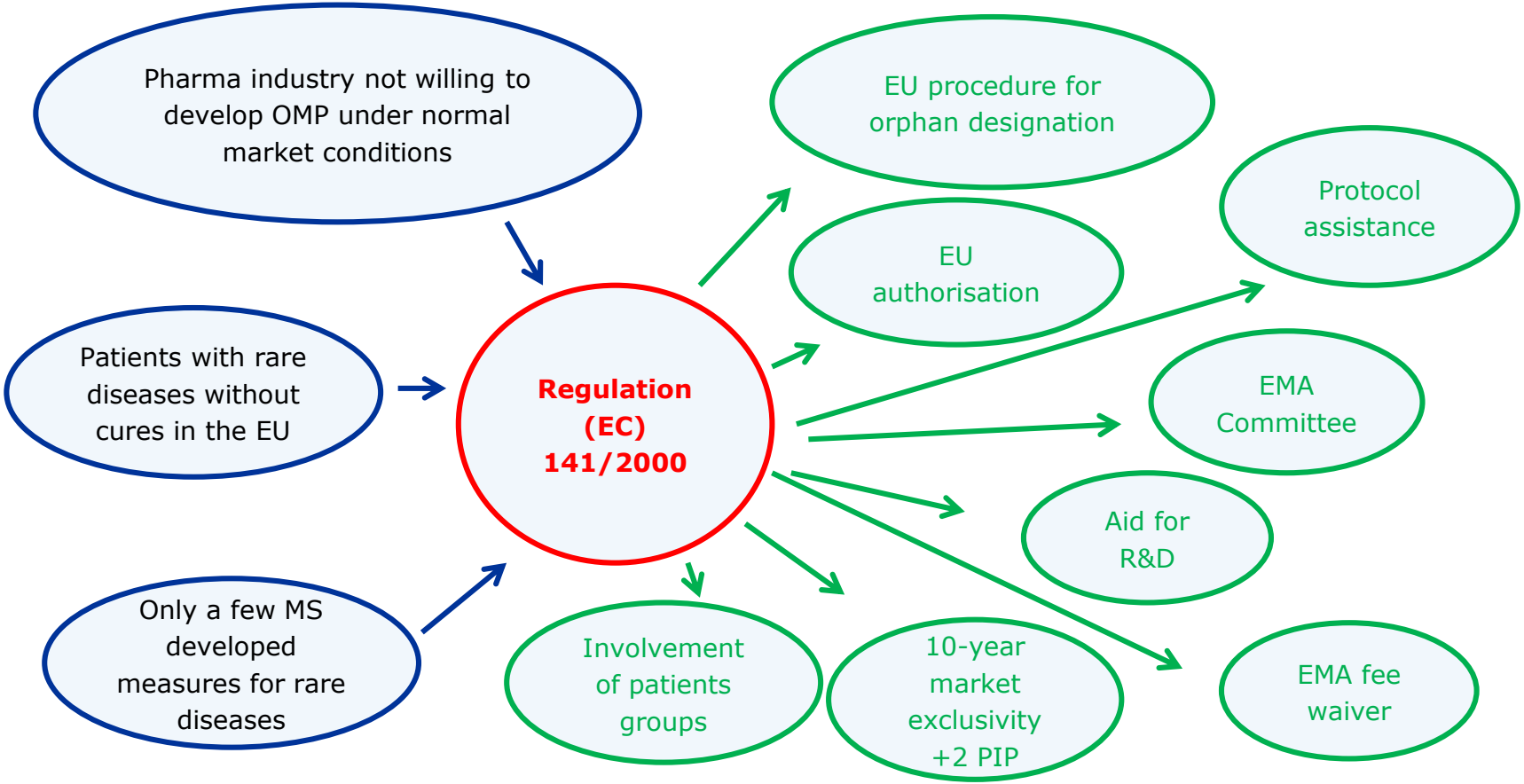
Challenges

Council Conclusions June 2016

"The incentives in orphan legislation need to be proportionate to the goal of encouraging innovation, improving patients' access to innovative medicines with therapeutic added value and budgetary impact, and it should be avoided that circumstances are created that might encourage inappropriate market behaviour of some manufacturers and/or hamper the emergence of new or generic medicinal products and in this way potentially limit patients' access to new medicines for unmet medical needs and that can affect the sustainability of health systems (…)"

Health and Food Safety

[adapted from Kaja Kantorska, 2017]


Pharma industry not willing to develop OMP under normal market conditions
Patients with rare diseases without cures in the EU
Only a few MS developed measures for rare diseases
Regulation (EC) 141/2000
EU procedure for orphan designation
EU authorisation
Protocol assistance
EMA Committee
Aid for R&D
EMA fee waiver
10-year market exclusivity +2 PIP
Involvement of patients groups

What is analysed?

- **Overview** of all incentives and **economic and statistical evidence** on how SPCs, data/market protection and market exclusivity are **used** in practice

- Analysis of the **overall effects of incentives and rewards** on innovation, availability and accessibility of medicinal products

  - Impact of **all** the incentives **jointly** and;

  - **Role of each** of the incentives **individually**.

  → *incentives used in combination? choices made? underlying reasons behind these choices?*

- Economic and econometric evidence on economic impact of SPC and pharmaceutical incentives for different medicines and effect of delayed generic and similar products and biosimilars' entry; pricing strategy; availability; accessibility; impact health budget.

Orphan legislation – state-of-play

- 2000-2015: 951 protocol assistance procedures completed (264 out of 951 involved SMEs)
- In 2016: €12 768 875 as fee reductions for designated OMP funded by the special contribution granted by the EU
- FP7: €620 million to over 120 research projects on rare diseases and OMP
- 10+2: 8 orphan products for paediatric use
- Most frequently authorised OMP are treatments for:
  - Pulmonary arterial hypertension
  - Acute myeloid leukaemia
  - Cystic fibrosis
  - Multiple myeloma
  - Acute or chronic lymphoblastic leukaemia

Challenges

High prices

Is Art. 8(2) implemented well?

Only 1% of rare diseases covered by OMP authorised in the EU

Almost no applications based on "insufficient return on investment"

?

Health and Food Safety

[adapted from Kaja Kantorska, 2017]

EUROPEAN
COMMISSION

Brussels, 26.10.2017
COM(2017) 626 final

REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL

State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation

Indiana Jones and the Raiders of the Lost Ark (1981)

Indiana Jones and the Raiders of the Lost Ark (1981)

Indiana Jones and the Raiders of the Lost Ark (1981)


LE FUTUR COMMENCE IMMÉDIATEMENT
APRÈS LA FIN DE CETTE PHRASE

Merci pour votre attention

Further information

Bruno Sepodes – bsepodes@ff.ulisboa.pt / bruno.sepodes@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000
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