The European pharmaceutical system: strengths and weaknesses

Specificities of rare diseases

XIII Foresight training course

Gianni Benzi Foundation - 23/10/2020

EURORDIS
23/10/2020

Progress in 2020

Two ways to look at the Orphan Drug Regulation

A great success

2219 designations, 188 authorised OMPs, 560 in R&D, 1,606 clinical trials…

Breakthrough innovations in some rare diseases

20 years ago, who would have imagine women with cystic fibrosis could give birth to a new-born?

A limited success

After 20 years, only 1%-2% of rare diseases have an OMP

Benefiting to 5 to 10% of rare disease patients

Benefit not always important

EC report on OMP regulation: *Of the 131 OMPs authorised since 2000, the Orphan Regulation is estimated to be responsible for at least 8-24 new ones*

Abuses / wrong perceptions

Thalidomide: from an EU production (4 producers) to an US MAH with price X4 to X7

Mexiletine price X50 with Orphan indication compared to hospital compounding

Imatinib cumulating orphan drug designations, then blockbuster

Same for lenalidomide (12 bio $)…

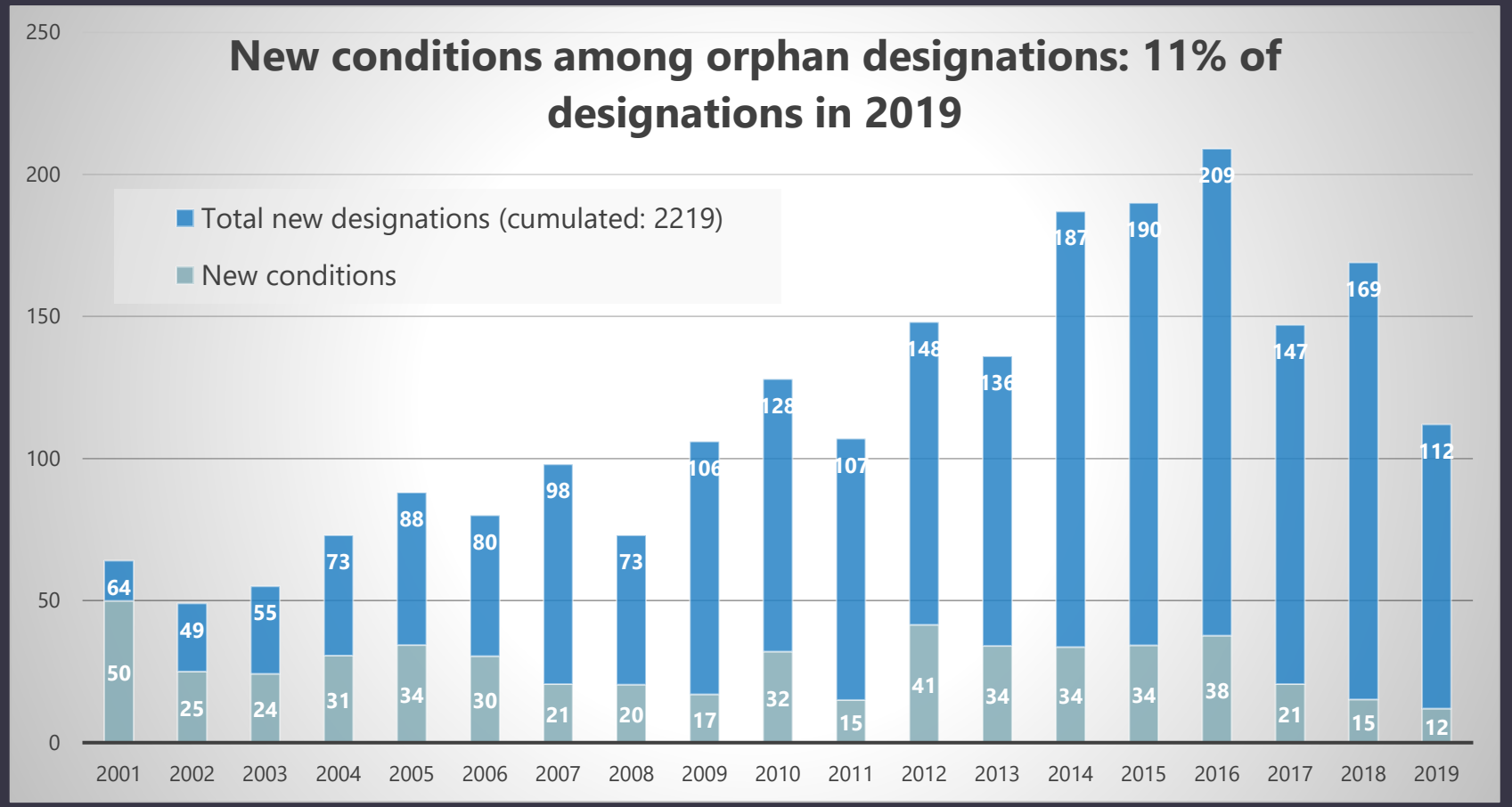
Etc.

Always the same indications?

Too few new conditions?

And only 8-10% make it to the market.

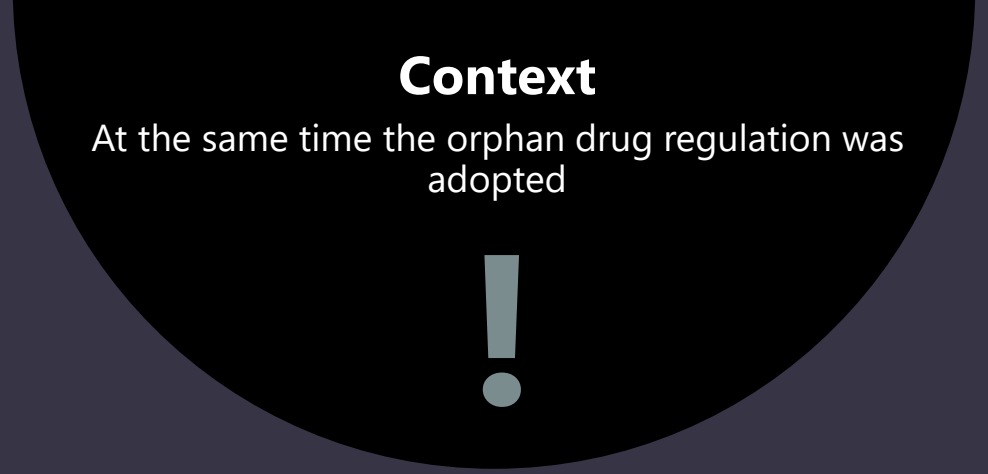
How can we change this?



Adapted from https://www.ema.europa.eu/en/documents/other/orphan-medicines-figures-2000-2019_en.pdf

Context

At the same time the orphan drug regulation was adopted



International patient movements acting against industry monopolies

- Advocated for WTO TRIPs agreements / Doha Declaration
- Considered 10-year market exclusivity as a gift to industry and an obstacle to access to care in many countries - OMP regulation as an abnormality
- Some initial “tolerance”, until payers started to complain
- Now their stock in trade as the orphan drug market is growing

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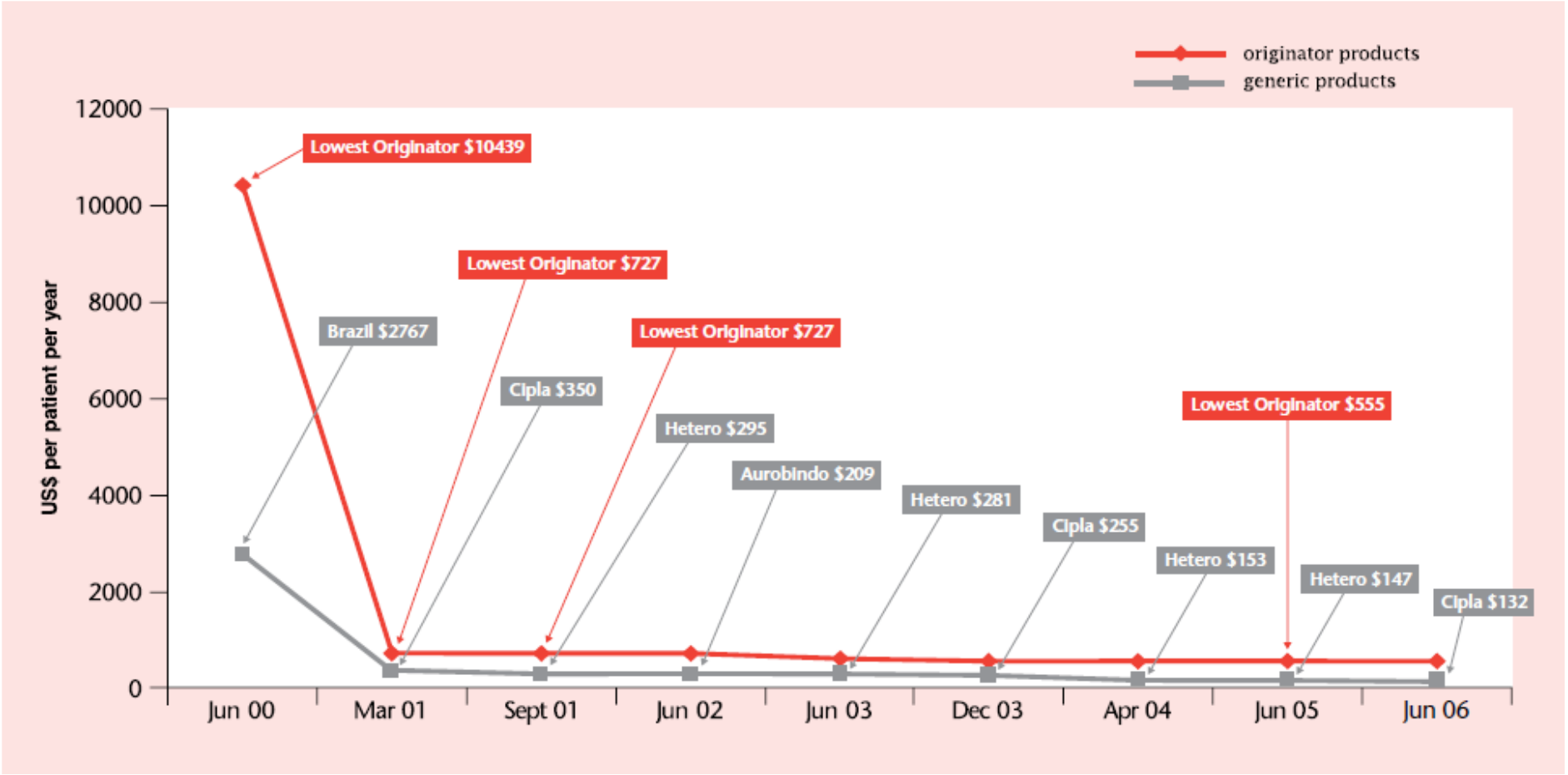
How to bring down prices?

GRAPH 3: GENERIC COMPETITION AS A CATALYST FOR PRICE REDUCTIONS.

The fall in the price of first-line combination of stavudine (d4T), lamivudine (3TC), and nevirapine (NVP), since 2000.



2019 Dolutegravir triple combination therapy at US 40$ / year

Generic competition and orphan drugs??

After 10-year market exclusivity (44 products)

Do we have generics for all them? *(preliminary results)*

Generic compensate low prices by large sales volumes. Relevant for RD?

57% *have at least 1 generic form authorised in member states (or active substance available different MAH but administratively not a generic)*

(25/44)

But not for *19*

- Price of generic can be 50% lower
- The 19: an estimated € 1,679 mio sales in EU
- ***Savings*** could be ***839 mio €***

Why not?

Expired recently	5	26%
Biologicals	9	47%
Risk management plan	1	5%
Unknown/other	4	21%
	19	

Do we need to amend the Orphan Drug Regulation?

Limit it to extremely rare diseases?
Shortening exclusivity period to 5 years?
Revising other incentives? National taxes…
OECD: to better target drugs whose development would not occur without such incentives: ok, but how? Which actionable elements?

Investments over 10-17 years: restricting incentives could have major drawbacks

— EU Pharma Strategy

Is OECD right?

Did all rare diseases benefit from the incentives? yes

Did incentives increase inequalities among RD? yes

Department of Economics, Uni. Verona
(Pertile et al .in press)

Inequality within rare diseases has increased:

The gap between the number of designations for a rare disease belonging to the highest and the lowest class of prevalence is much larger after 2008 than it was in 1983

This gap widened after 2000 (EU OMP Regulation).

The large weight of market exclusivity, when compared with the US legislation, combined with the large size of the EU market, may have contributed

Is OECD right?

Did all rare diseases benefit from the incentives?

Did incentives increase inequalities among RD?

Setti Raïs Ali & Sandy Tubeuf

UCL Louvain, Social Justice Research - May 2019

Distribution of R&D investments across RD measured by:

- number of research projects
- academic publications
- clinical trials
- orphan designations
- orphan authorisations

The most deprived category over all R&D investments is when average age at first symptoms is during infancy and childhood (75% of all RD)

Then uncertainty about the disease evolution (no natural history data)

The third is the group of diseases with an immediate danger of death

Changing incentives?

OECD: to better target drugs whose development would not occur without incentives

Innovation often by small biotech

Financial value of the product depends on potential revenues, potential revenues include revenues generated during 10-year market exclusivity

Maybe not to reduce incentives, rather to increase those stimulating research

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Incentives

10-year market exclusivity	7-year market exclusivity
Regulatory fee reduction	Regulatory fee reduction

Interesting for "marketers" more than for "developers"

Free protocol assistance	Free protocol assistance
> € 620 million FP7 research on RD/OMPs	Research grants earmarked for rare diseases
	50% tax credit for clinical trials

Encourage R&D even for lower prevalence diseases

MS: Limited tax credits for R&D only in Ger, Ire, Ita, Mlt, NLD, Slv, Spa

An EU fund

For clinical research and development

For purchasing EU supplies of critical medicines (health threats, orphan medicines)

DECISION No 1082/2013/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 22 October 2013

on serious cross-border threats to health and repealing Decision No 2119/98/EC

Attempt to use this Decision for an EU joint procurement of Sovaldi® in 2014
Italy started to negotiate on behalf of the EU
Two MS did so in parallel
EU negotiation stopped

Article 5

Joint procurement of medical countermeasures

1. The institutions of the Union and any Member States which so desire may engage in a joint procurement procedure conducted pursuant to the third subparagraph of Article 104(1) of Regulation (EU, Euratom) No 966/2012 of the European Parliament and of the Council of 25 October 2012 on the financial rules applicable to the general budget of the Union ([1]) and pursuant to Article 133 of Commission Delegated Regulation (EU) No 1268/2012 of 29 October 2012 on the rules of application of Regulation (EU, Euratom) No 966/2012 of the European Parliament and of the Council on the financial rules applicable to the general budget of the Union ([2]), with a view to the advance purchase of medical countermeasures for serious cross-border threats to health.

Shortages

Do we need to relocate production of medicines in the EU?

EURORDIS' analysis of 163 products

With past or current orphan designation

Focus on active substance

For a majority of OMPs, the active substance is **manufactured in the EU**

"Critical", "essential", or "major therapeutic interest" medicines: manufacturing in the EU means active substance and all raw materials

= the return of the chemical industry

Only if financial compensation for building sites, paying higher salaries, and respecting environmental standards

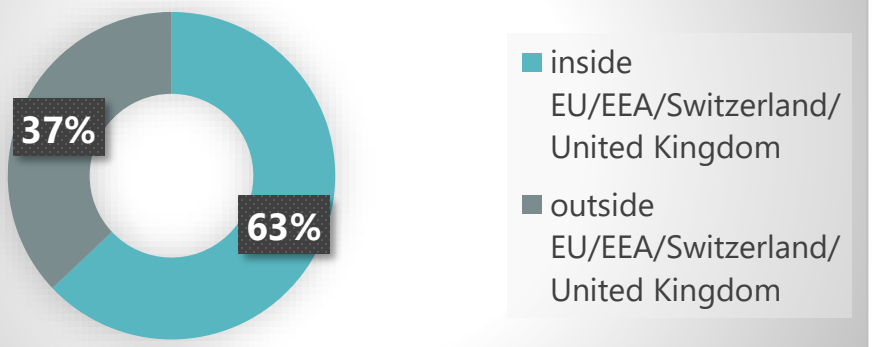
German study on cephalosporin

Hypothesis: manufacturing of 500t per year in Germany

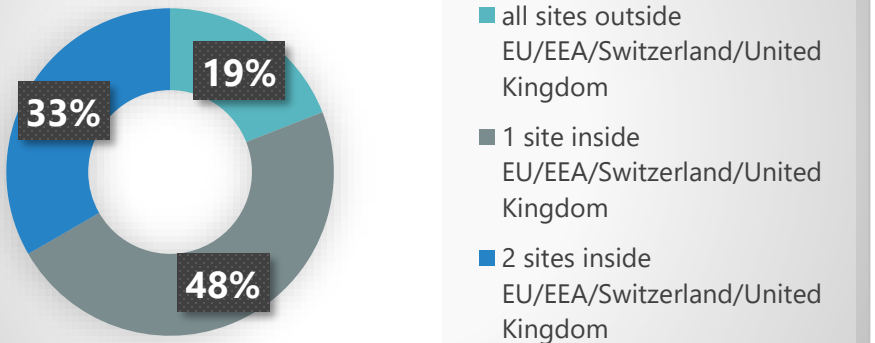
Additional cost of **€ 80 mio** for EU needs

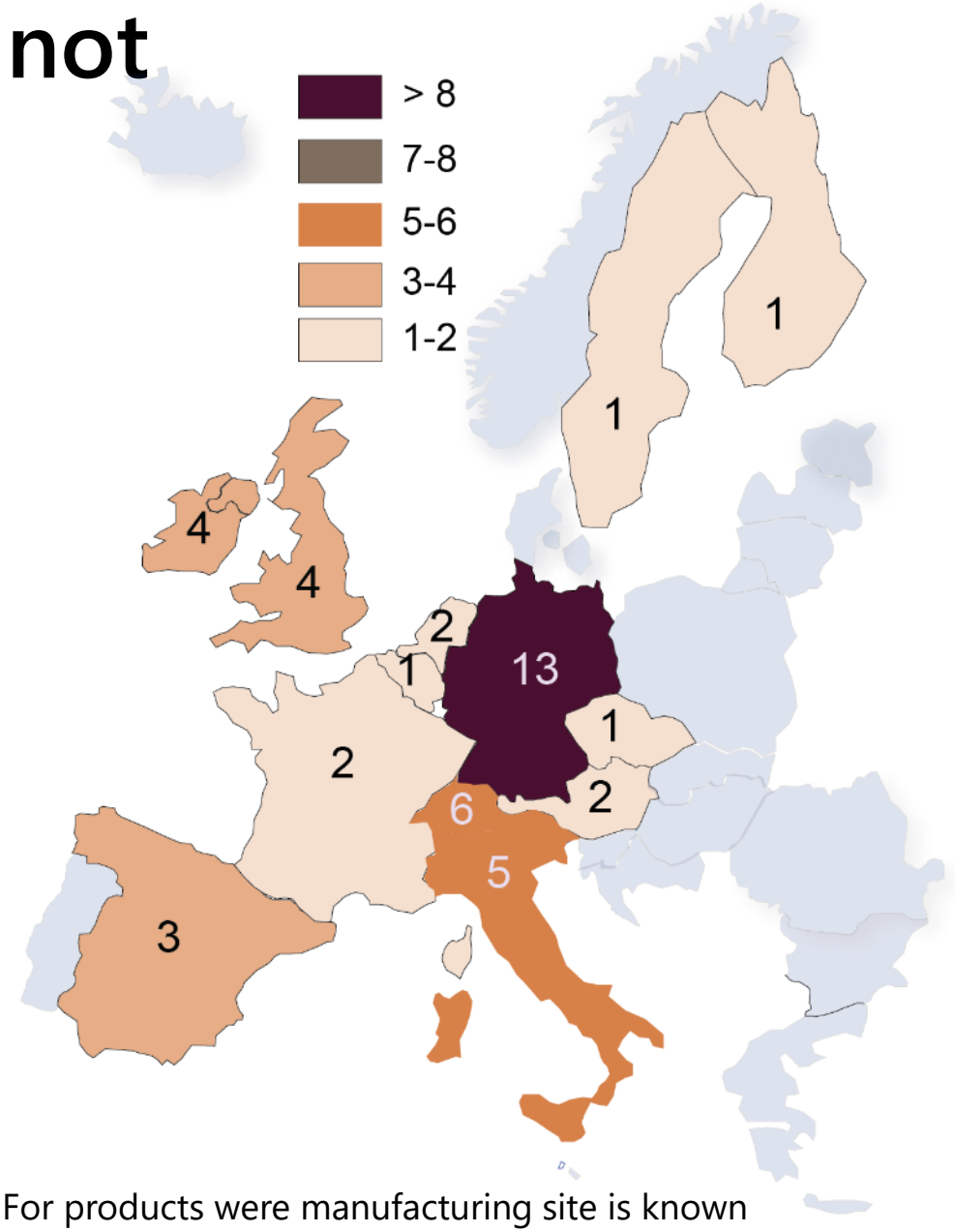
Products with site in the EU or not
(work in progress)

Single site: 81 products



Two sites: 22 products





For products were manufacturing site is known

Preliminary data - please do not disseminate

Shortages

Debated / voted at the EP

A new criteria for procurement?

The ability to secure supply of medicines should become a procurement / tendering criteria as important as the price

Non-profit as manufacturer/vendors?

Non-profit sector that could produce medicines when Marketing Authorisation holder no longer interested – too low price

Network of hospital pharmacies (Sweden, Netherlands)

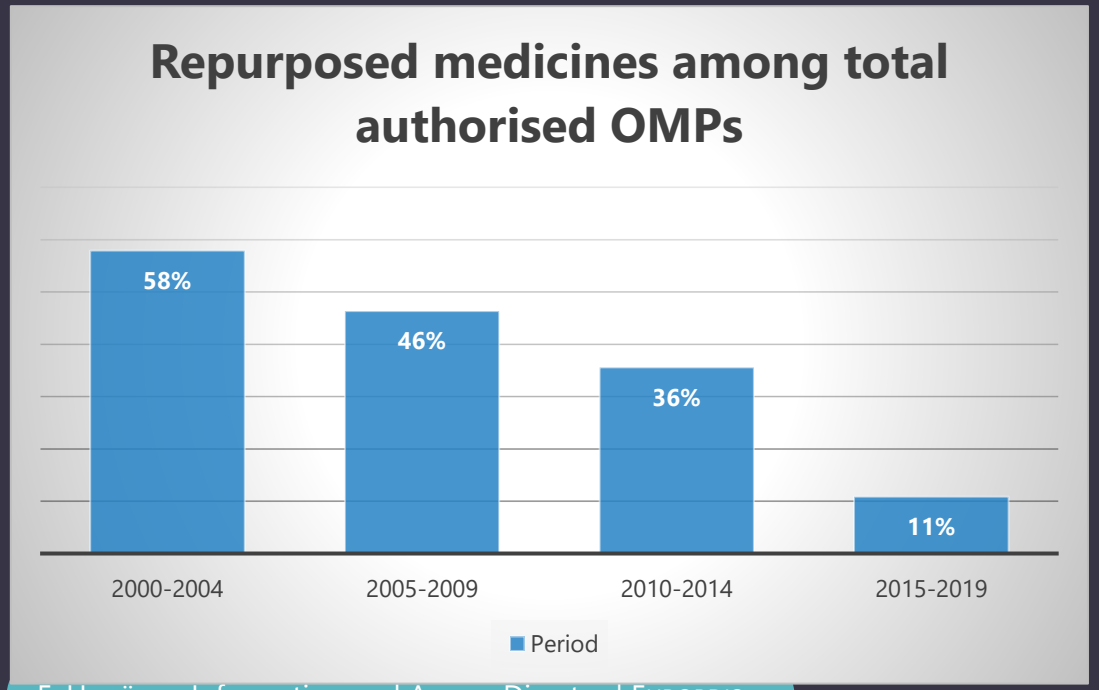
RescEU

EU management of shortages

EMA to be given the resources and power to regulate medicine supplies depending on the needs of each MS

Repurposing medicines

Treasures hidden with old drugs uncovered: mechanism needed for academic research to translate into proper R&D



More than creating incentives or adjusting patent rights: to create separate markets for separate indications of same drug

Separate markets:

- One for old uses, open to competition by all
- One for new use which, for a period, is exclusive to developer of that new use
- Requires transparency and linkage throughout the prescription / dispensation chain

Need for mandatory prescription by indication (as in Belgium for some, Denmark)

STAMP soon to announce initiative in favour of drug repurposing, with regulatory incentives (SA) but not financial ones

NEED TO HARMONISE COMPASSIONATE USE PROGRAMMES

NUMBER OF PROGRAMMES – ALL DISEASES

- 8 (AMHV here)

Germany 

- 3 (EAMS here)

United Kingdom 

- 5 (see here)

Netherlands 

- 27 (ATU here)

France 

LAST CHECK: 9 FEBRUARY 2020 (COHORT)

Obligation to market a medicine in all MS?

MAHs target their commercial territories. Other MS neglected. Single market for pharmaceuticals: does not exist

Objections

1/ Not possible for e.g. advanced therapies

2/ **Rather**, think in terms of "made available to centres belonging to an ERN" – and organise effective cross-border care

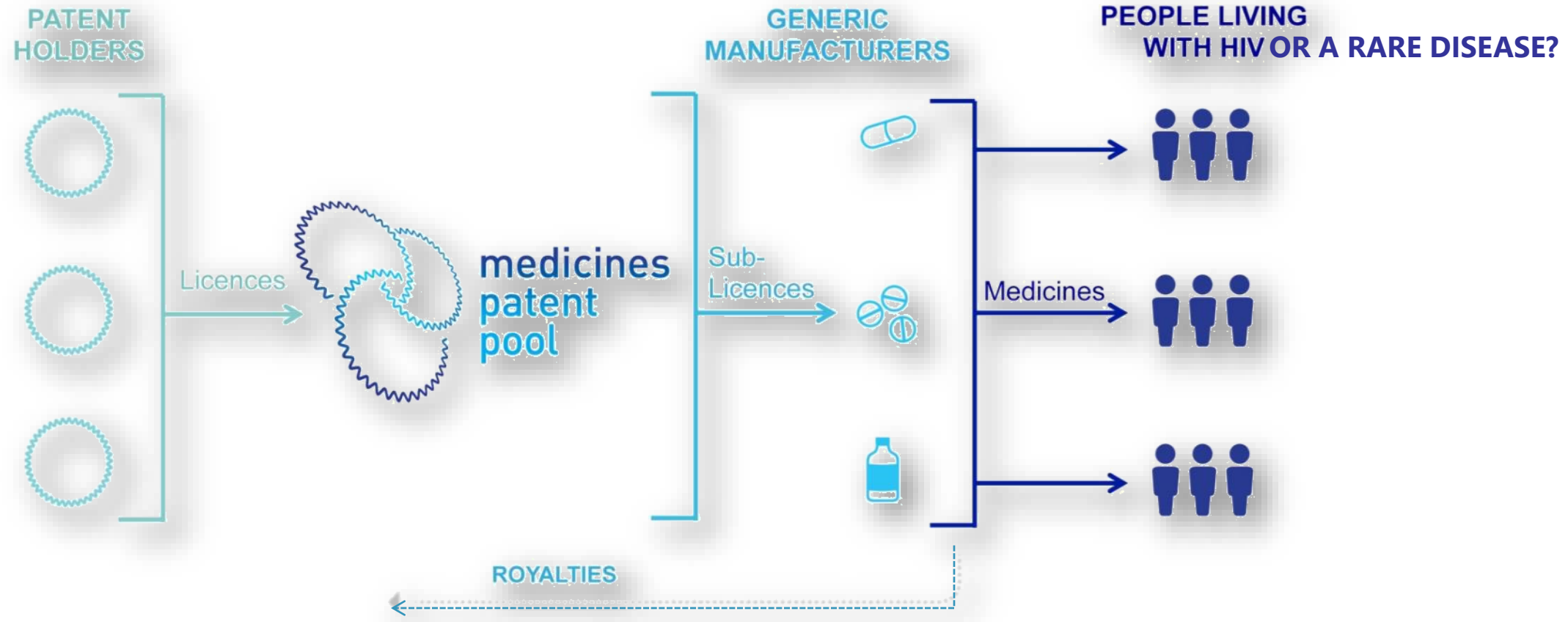
Recent case

- Patient in Sweden, request Strimvelis® (gene therapy – primary immune deficiency)
- Strimvelis® can only be prepared and administered in Italy
- Request rejected: cost of treatment paid to an Italian centre, not a to Swedish one
- Appeal – finally agreed

Medicine placed in several MS, not all.

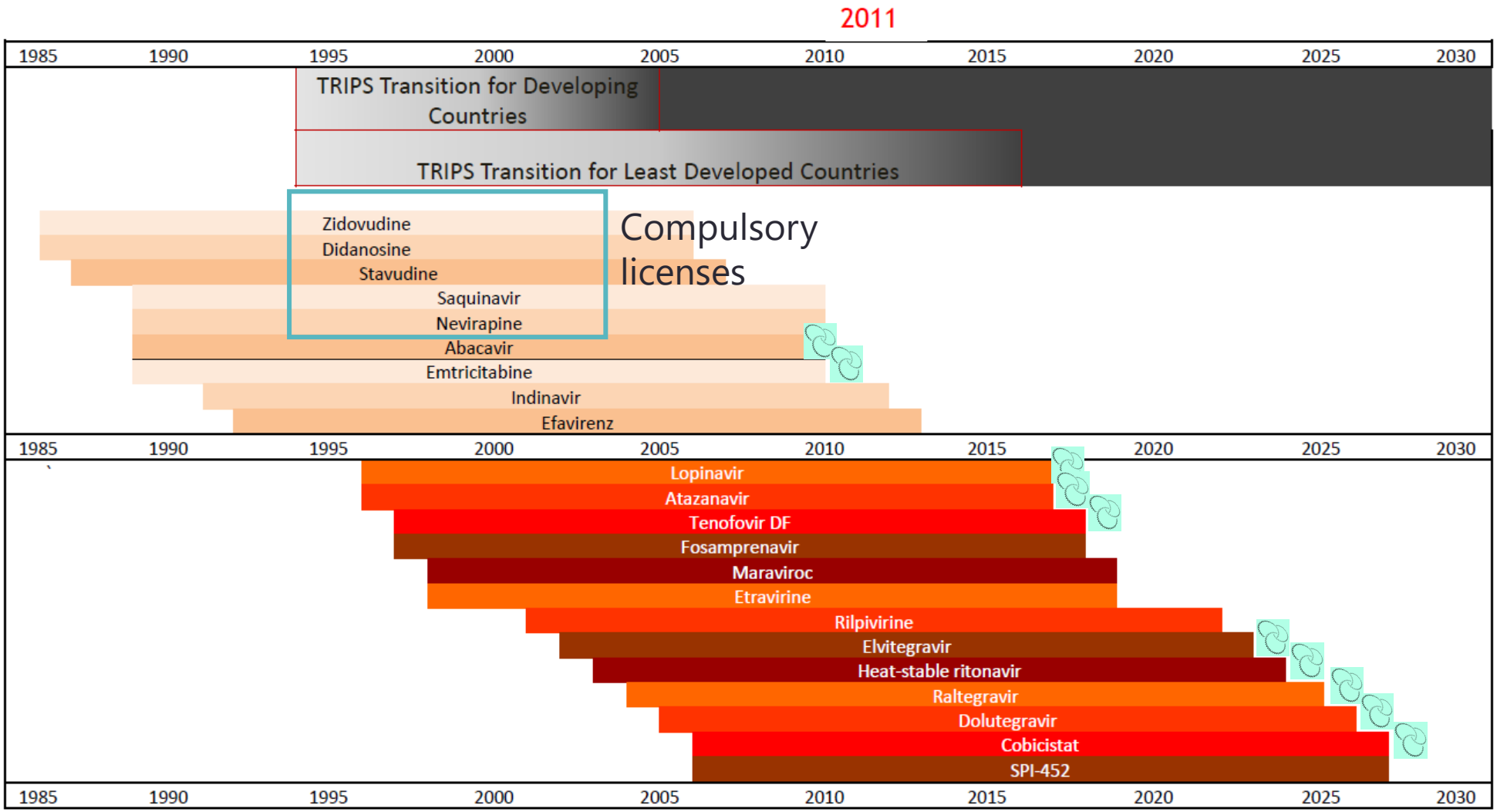
If patients' rights to cross-border care would exist, medicines could travel, like other goods (or the patient)

Patent pool / voluntary licensing



http://www.medicinespatentpool.org/about/

Changing ARV Patent Landscape



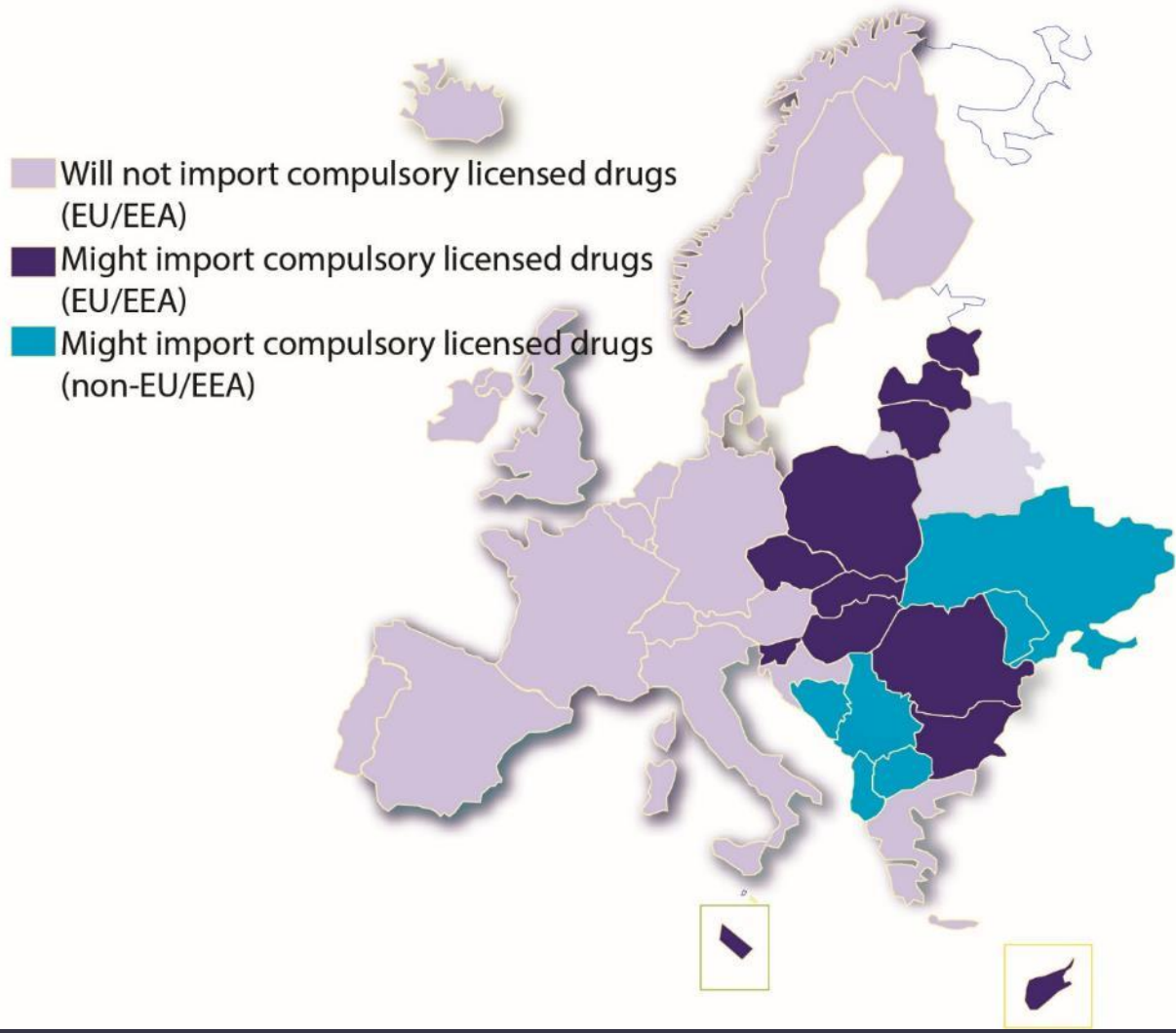
Voluntary license to Medicines Patent Pool

EU Regulation on Compulsory Licensing

Not all WTO Members will use the system as importing members

Commercial territories of originator companies preserved - no parallel trade for those products

REGULATION (EC) No 816/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 17 May 2006 on compulsory licensing of patents relating to the manufacture of pharmaceutical products for export to countries with public health problems



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Learning from COVID-19

Maybe the keyword is COOPERATION

Building on Ebola response 2013-2016

African CDC, Coalition for Epidemic Preparedness Innovations (CEPI), European Medical Corps (EMC), World Bank, Gates Foundation, Foundation Merieux, WHO…

invested a total of $2,5 billion – with industry R&D

As the classical R&D model was not fit

Classical model:

Competition first (to reach the market)
and **then Monopoly** (IP rights, regulatory protection)

Proposing a new one (for different health needs)

Cooperation first (e.g. to develop medicines for unmet needs / health threats)

And **Then competition** (call for tender to industry to produce high quality / reasonable price product)

(see Achal Prabhala - Advancing innovation and access to medicines)

Negotiating price considering:

1

The product added value (efficacy, safety, quality, relative efficacy, effect size)

Adopt the HTA Regulation proposal!

2

The revenues the MAH is expecting from the new product (the MAH economy lato sensu)

Reasonable pricing – DCF method – Nuijten 2018

3

The respective contribution of public and private investment in R&D

Not to pay twice

But how?

4

The healthcare system financial constrains (Budget Impact) and organisation (who pays, who gets the benefit)

Pay for performance, instalments…

5

The patent duration (timing of generic competition)

Issue of biosimilars, advanced therapies

AUSTRALIA'S "NETFLIX" MODEL HEPATITIS C

Also used in Denmark in 2018 between Amgros and Vertex for Orkambi® to treat cystic fibrosis

- 2014:
  - ~230,000 people with Hepatitis C
  - Hep C drugs: AU$ 71,400 ($54,000) per patient
  - Rationing to most severely ill
- 2015:
  - Lump-sum "prize" of ~AU$ 1 billion ($766m) over 5 years
  - Unlimited medicines supply → universal access offered
  - Initial government estimate: 61,500 patients
  - Effective per-patient price: AU$ 16,260 ($12,460)

- Our estimate 2016-21: 104,000 patients
  - 87% drop in per-patient price: AU$ 9600 ($ 7352)
- Savings: AU$ 6.4 billion or 93,000 patients
- Australia world leader in HCV treatment and control

Source: Moon S and Erickson E. (2019) Universal access through lump-sum remuneration – Australia's approach to Hepatitis C. N Engl J Med 2019; 380:607-610. DOI: 10.1056/NEJMp1813728

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GRADUATE INSTITUTE OF INTERNATIONAL AND DEVELOPMENT STUDIES

If you think the success of the OMP regulation is only relative

- Remember where we stood **20 years ago**
- Not asking for a special case for rare diseases, but in the **fight against inequity by disease**, to correct decades of not investing in rare diseases
- The **importance of sustaining investments** and research, not sending negative signals
- *The will **to persevere** is often the difference between failure and success* – David Sarnoff

Thank you for your attention.

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High Price Medicines and Health Budgets: The Role Patients' and Consumers' Organisations Can Play.
François Houÿez . European Journal of Health Law. 18 May 2020, Volume 27: Issue 3 309–323. DOI: https://doi.org/10.1163/15718093-BJA10008