ORPHAN MEDICINAL PRODUCTS AND HEALTH BUDGETS

The role advocates can play

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XII Foresight Training Course – Gianni Benzi foundation
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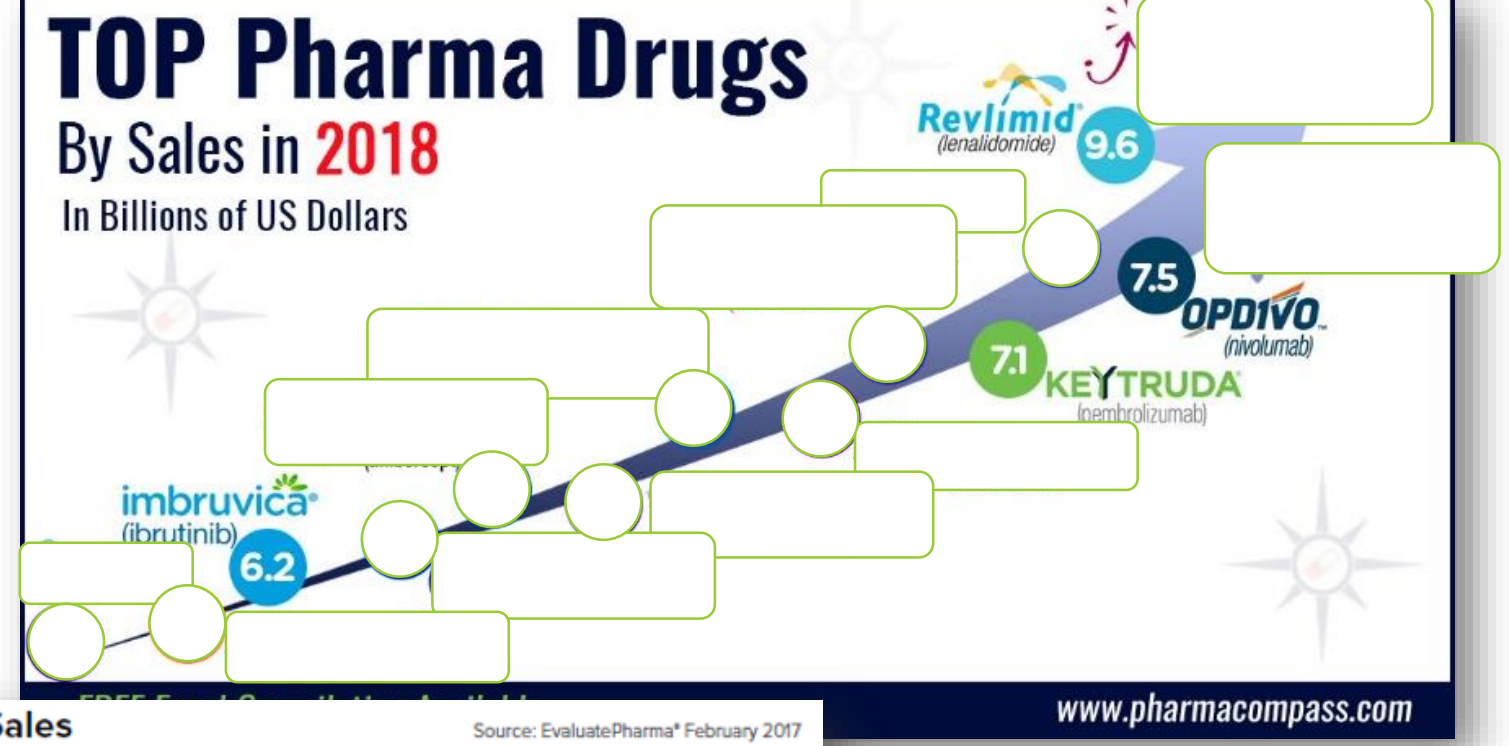
Wall Street, 24 March 1987. In 1989, 3rd action – Burroughs Wellcome decreased AZT price by 36% (orphan drug)

Too high prices?

Orphan Drug Regulation

Creating incentives for niche markets, or creating blockbusters?



4/15 are orphan / for rare diseases

- **Why these prices? How to attract investments in pharma research?**
  - *It takes a hundred EUROS of drug revenue 17 years from now to motivate someone to invest one EURO today*
  - *(composite factor, failure risks and duration)*

- —Eric Vallabh Minikel
- http://www.cureffi.org/2019/04/29/financial-modeling-in-rare-disease/

Gene therapy

- 300 children to be treated

Do the math

- **10 000 € / injection**? = 3 000 000 €
  - Can you recoup your R&D costs?
    - Phase 1 costs: 5 000 000 €
  - Regulatory costs EU: 5 000 000 €

- **100 000 € / injection**? = 30 000 000 €
  - Can you recoup your R&D costs? Organise pharmacovigilance across generations? Pay royalties? Invest in other treatments?

- **500 000 € / injection** = 150 000 000 €
  - Lentiglobin, B-thalassemia transfusion dependent:
    - N= 10 000 – Price: 900 000 €. 9 bn €?
  - onasemnogene abeparvovec, SMA type 1 <2 yo
    - N_{EU}= 5 000 – Price: 2 100 000 €. 3 bn €?

- **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

- **Or to suppress it?**

- — EC consulting on the matter – 17 June 2019

What else?

1. Use article 8.2 (“excess of profit”) or Art. 102 TFEU
2. Facilitate generic products or repurposed medicines
3. Estimate if price reasonable or not (DCF method)
4. If price abnormally high, consider compulsory licensing
5. Community Advisory Boards to decrease risks

Excess of profit?

Article 8.2 Orphan Drug Regulation

10-year period of market exclusivity

may be reduced to 6 years if, at the end of the 5th year, the designation criteria are no longer met

(evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity)

A definition and an expertise problem

- How to define “sufficiently profitable” (Alcimed report)
- MS asks COMP on whether or not the product is sufficiently profitable: competence?

And even if excessive profit demonstrated

- Will generics be introduced automatically?
- Will price decrease?

Generics?

After 10-year market exclusivity (44 products)

Do we have generics for all them?

57% *of products with expired period of protection have at least 1 generic form authorised in member states*

(25/44)

Preliminary results
Do not share

But not for ***19***

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

Why not?

Expired recently	5	26%
Manufacturing (biosimilars)	9	47%
Risk management plan	1	5%
Unknown/other	4	21%
	19	

Repurposing?

A new use for already authorised medicines

Example: Clarithromycin

- Authorised for bacterial infections
- On the market since the 90s
- At US$ 0.13 per 500mg tablet

Anticancer Fund

New use: in multiple myeloma

- Increases response rates to 1st-line treatments such as thalidomide and lenalidomide
- Can overcome resistance to lenalidomide and dexamethasone in MM patients

A STAMP initiative to facilitate the granting of an authorisation for new uses: launch in Nov. 2019

https://ec.europa.eu/health/documents/pharmaceutical-committee/stamp_en

Abuse of a dominant position?

Article 102 TFEU

public price increase	
Alkeran	1,540 %
Alkeran inj.	257 %
Leukeran	1,166 %
Purinethol	465 %
Tioguanina	306 %

Abuse of a dominant position within the internal market shall be prohibited in so far as it may affect trade between Member States. In particular:
(a) directly or indirectly imposing unfair purchase or selling prices or other unfair trading conditions
(b) limiting production, markets or technical development to the prejudice of consumers
…

2014: Altroconsumo (consumers' organisation, Italy) against Aspen

- Unilateral price increase for 5 cancer drugs (a) + products imported from high price countries if new price not accepted (b)
- Products became unavailable throughout Italy
- BEUC initiated an EC investigation in parallel

Italian National Competition Authority

- 2016: Aspen sentenced to pay a € 5 mio fine and to propose fair prices for the 5 drugs
- 2018 price reductions: 30% to 80%

Compulsory licensing: killing innovation?

Can governments reduce the price of a medicine using compulsory licensing? (WTO)

In the interest of public health

Only if

The products cannot be supplied in large enough quantities or good enough quality

Or at abnormally high prices

And

after seeking an agreement (royalties)

US Government in 2001

Anthrax attacks through the US Postal Service: the US Government threatened to issue a compulsory license for ciprofloxacin, if Bayer (EU) didn't lower the price

Bayer lowered the price

United Kingdom 2019

- Crown Use for Orkambi® (patent revocation)
- A newly-formed patient activist group called “Just Treatment” (https://justtreatment.org/about)
- The group and others such as #OrkambiNow have mobilised support via social media, including a message from Patients for Affordable Drugs, which is using the same lobbying tactics used by pharma to influence policy makers in Washington DC

Reichman, Jerome H (Summer 2009). "Compulsory licensing of patented pharmaceutical inventions: evaluating the options". Journal of Law and Medical Ethics. 37 (2): 247–263. doi:10.1111/j.1748-720X.2009.00369.x

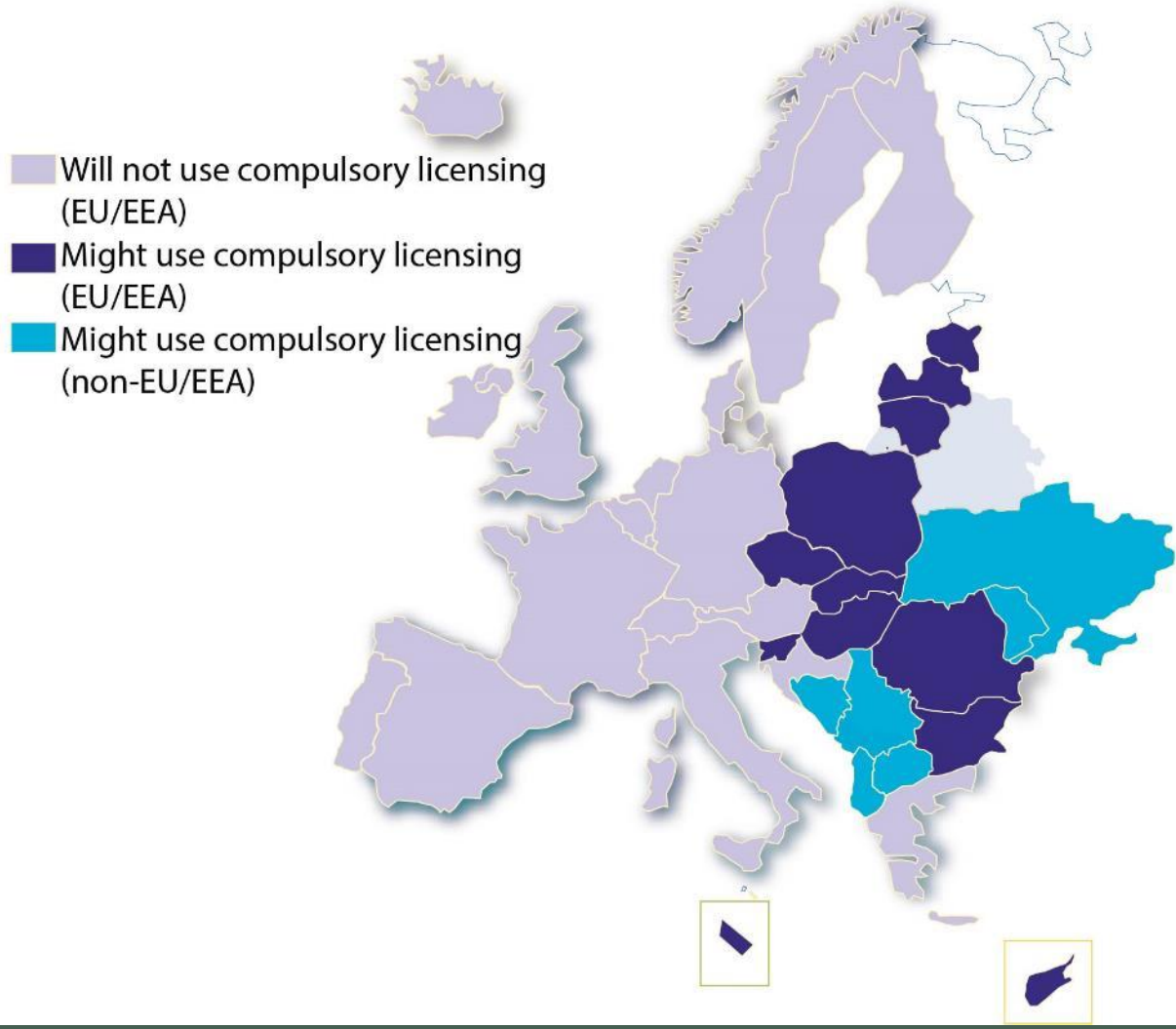
See also Reg. (EC) No 816/2006 on compulsory licensing of patents relating to the manufacture of pharmaceuticals for export to countries with public health problems

• EU Regulation on Compulsory Licensing

- Not all WTO Members will use the system as importing members

Commercial territories of originator companies preserved

- 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



Abnormally high price? Objective measurement?

Discounted Cash Flow method: from the investor's perspective

- For each product, can we calculate a price (called break-even price)
  - below which investors would loose money (no profits, no more investment)?
  - above which they would gain money (profits and further investments)?

Cystic Fibrosis

Mark Nuijten, PhD, MD, MBA
Nuijten et al. Int J Rare Dis Disord 2018, 1:005

Orkambi, Netherlands

- **Number of patients: 425**
- **Annual cost per patient: € 170,000**
- **OMP threshold in NLD: € 80,000 / QALY**
- **Cost-utility: € 360,000 / QALY**
- **= a 80% price reduction to reach the threshold (down to € 34,000/pat.)**
  - **You need a good reason to reduce your price by 80%**
  - **Is an invalid theory a good reason?***

*: presenter own comment

Beresniak et al. Validation of the underlying assumptions of the quality-adjusted life-years outcome: results from the ECHOUTCOME European project. Pharmacoeconomics. 2015 Jan;33(1):61-9. doi: 10.1007/s40273-014-0216-0

Break-even price based on the Discounted Cash Flow Model

Disease	Brand	Active substance	Proposed price (annual, per patient)	Break-even price	Difference
Cystic fibrosis	Orkambi®	Lumacaftor / ivacaftor	€ 169,386	€ 65,861	+157%
Spinal muscular atrophy	Spinraza®	nusinersen	€ 240,000	€ 95,860	+ 150%

Orkmabi®

Price = 2.5 higher than break-even price. Conclusion: € 170,000 not justified

Can be reduced by 40-50% (Vertex would still make profits)

Nuijten M, Fugel HJ, Vis J (2018) Evaluation and Valuation of the Price of Expensive Medicinal Products: Application of the Discounted Cash Flow to Orphan Drugs. Int J Rare Dis Disord 1:005
See also results for Soliris®, Elaprase®, Ocaliva®, Brineura®, Lamzede®, Myalepta®

Health budgets & patient advocacy

More transparency on the price structure: part of the R&D investments = public funding. Payers should not pay twice (3x real world data – registries and databases)

HTA is key to provide information to decision-makers.
EC proposal for a EU Cooperation on HTA: transparency, quality, efficiency

In the EU, healthcare expenditure represents 5 % (Romania) to 11.5% (France) of GDP. Average 9.9. *Who decides?*

No special case for rare diseases: but in the fight against inequity by disease, *to correct decades of not investing in rare diseases*

Thank you for your attention.

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