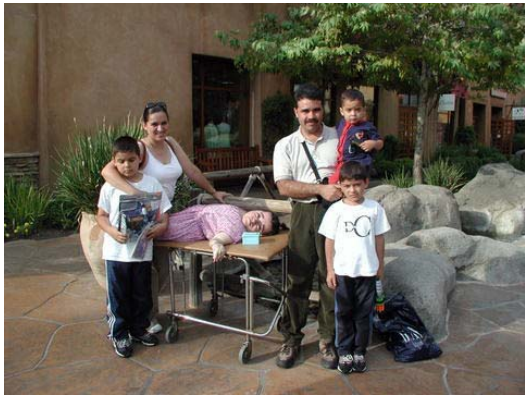
“Can we use this medicine to treat this other disease?”

- Other medical uses of well-established medicines

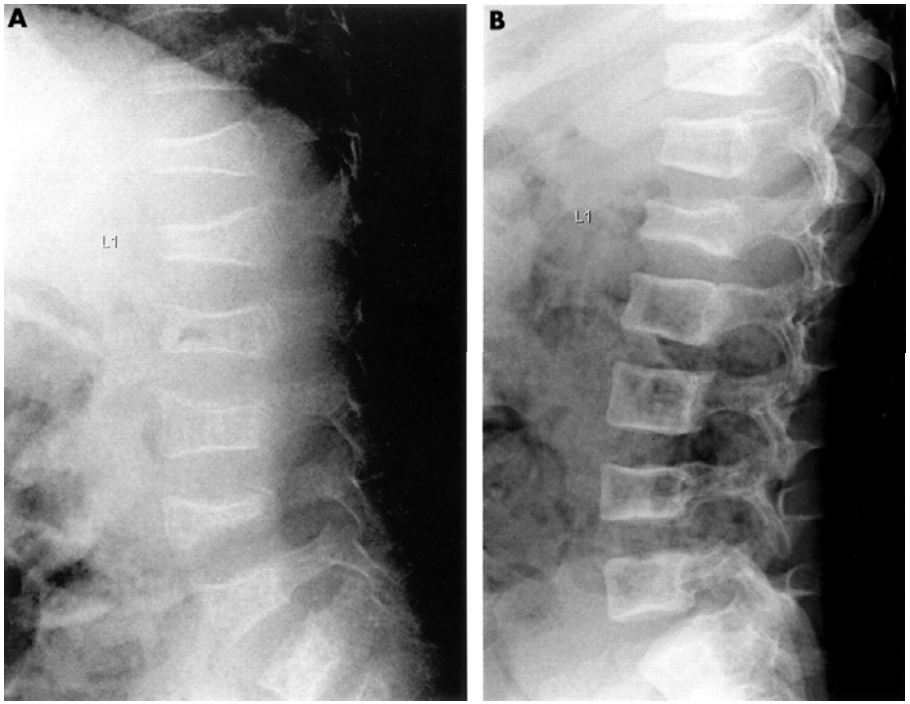
2005: Osteogenesis imperfecta – Brittle bone disease

- Biphosphonate (pamidronate) authorised for Paget disease, cancer (multiple myeloma, osteoporosis, and hypercalcemia
  - Proved to decrease fracture rates
  - Off-label use in OI
- Some evidence from clinical studies that it helps people with OI
- Romania
  - Pamidronate was delivered free in pharmacies
  - Was removed form the list of free drugs
  - For a child (5kg), treatment: 2 500 to 5 000 € (to be repeated)
  - Average salary: 200 €
- Objective: to obtain a marketing authorisation for OI so that pamidronate can be reimbursed (again)?



yesenia

An active treatment

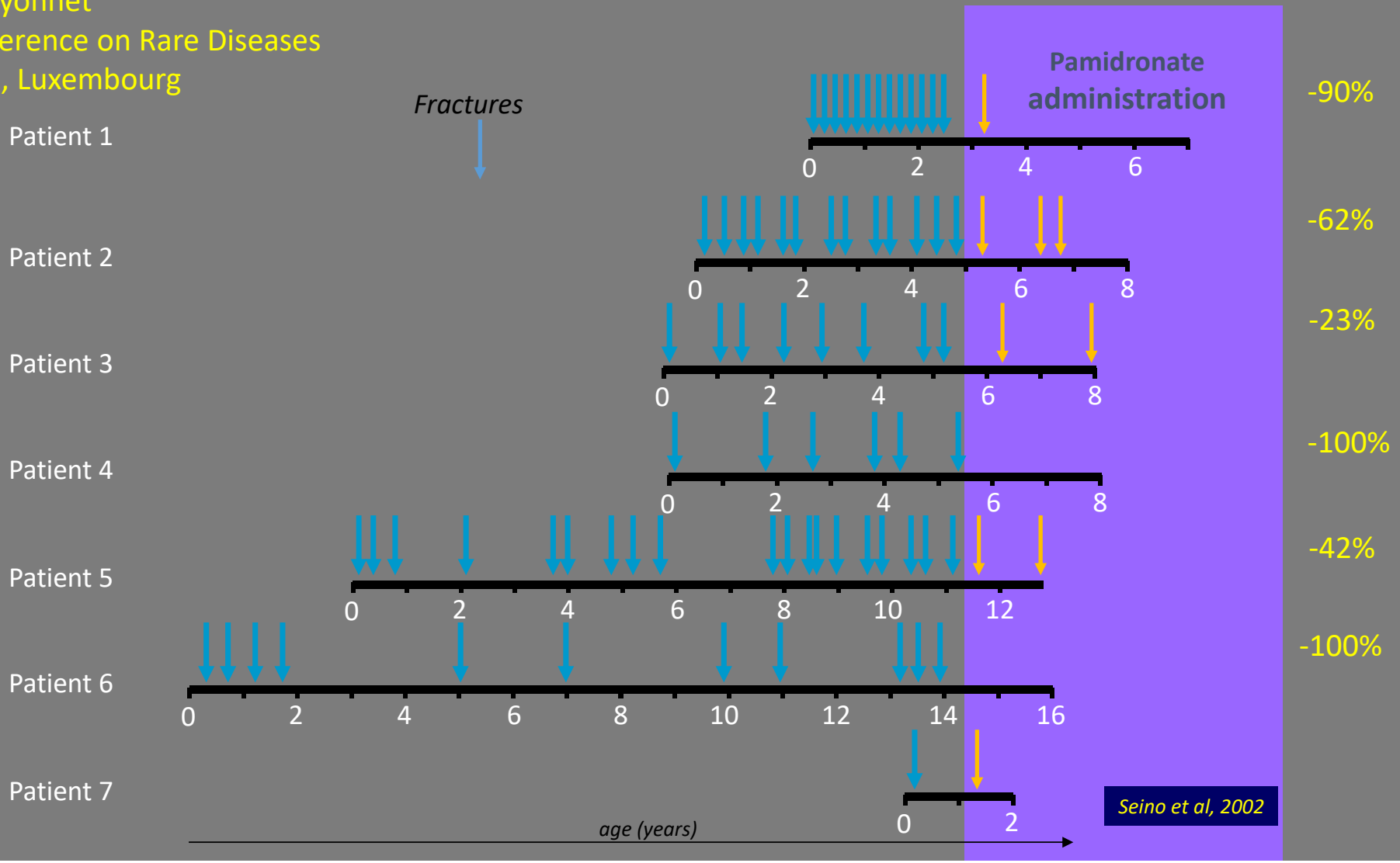


Radiographs (lateral view) of the lumbar spine of an 1.1 year old girl with osteogenesis imperfecta type IV. (A) Before start of treatment. (B) After two years treatment. A considerable increase of mineralisation and vertebral height can be seen, with almost complete regeneration of the vertebral height around L1

Astrom, E et al. Arch Dis Child 2002;86:356-364

Frequency of Bone Fractures in OI

Prof Stanislas Lyonnet
European Conference on Rare Diseases
June 21st 2005, Luxembourg



Questions

- A new use identified, with substantial evidence

- Marketing authorisation holder to ask for type II variation? (extension of marketing authorisation)

OI: maybe 25,000 patients in EU

Osteoporosis: 30% postmenopausal women

Why would MAH pay the development and regulatory work to obtain MA for OI?

- To continue off-label?

Off-label prescription not authorised everywhere

Above a certain budget: authorities will want some evidence to justify off-label reimbursement

2016, new risk identified with biphosphonates: osteonecrosis of the jaw

- To treat with a generic?

Less expensive, but again none of them specifically authorised to treat OI

So would be an off-label use of a generic product (can be reimbursed, national rules)

New uses in frequent diseases

Active substance	Initial indication	Second medical use
Daclizumab	Prevention of transplant rejection	Multiple sclerosis
Everolimus	Organ transplant rejection	Breast cancer
Finasteride	Prostate disorders	Androgenetic alopecia
Pregabalin	neuropathic pain, seizures	Generalised anxiety disorder

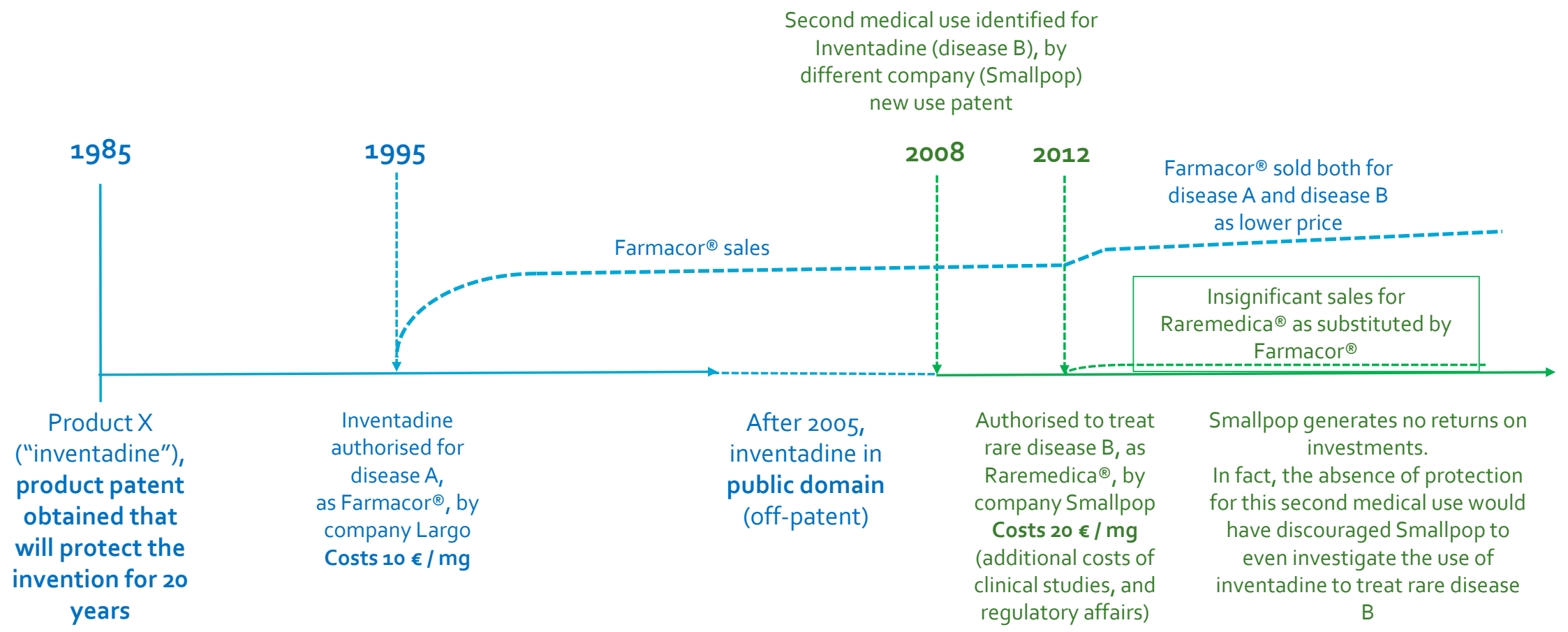
Large population → Another large population

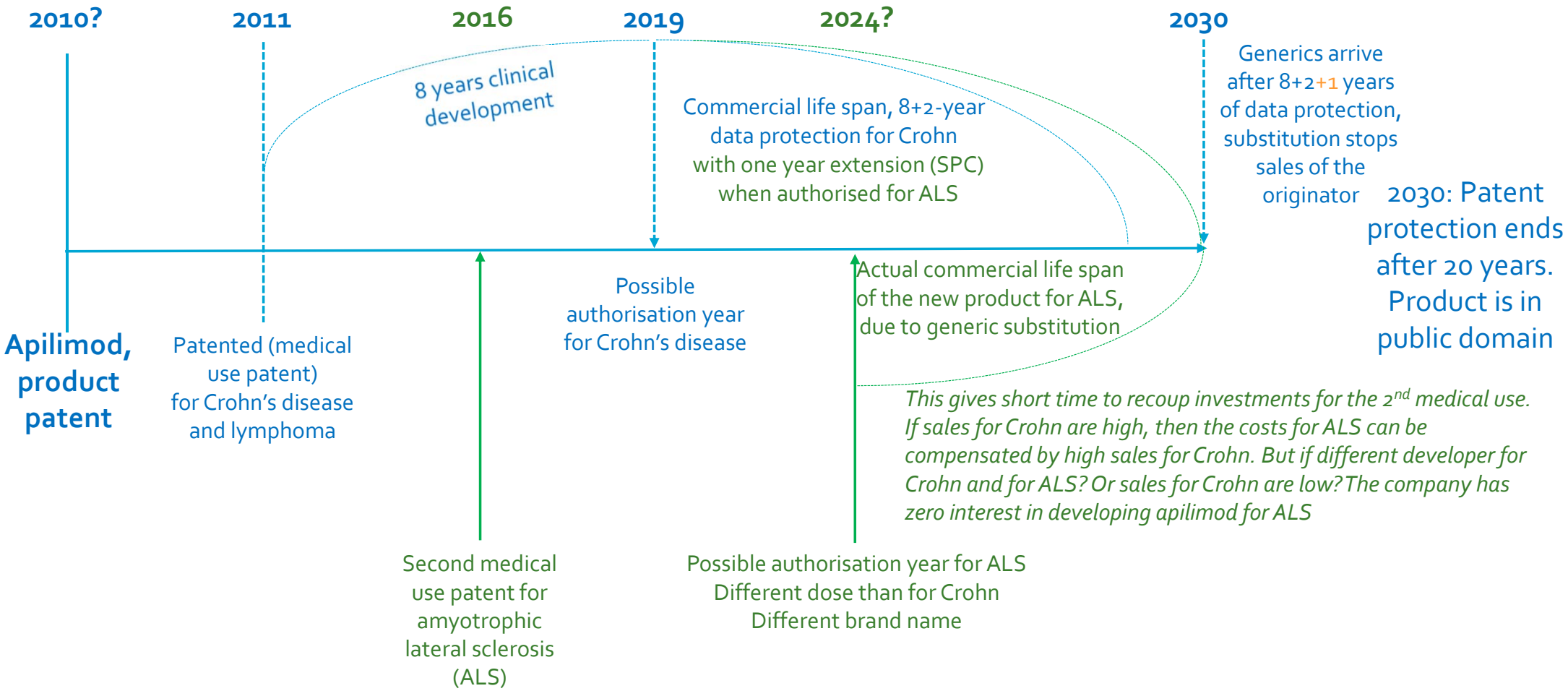
Other possible new uses in rare diseases

Active substance	Initial indication	Second medical use
Albendazole	Veterinary anthelmintic	Echinococcosis, neurocysticercosis
Ambisome	Broad spectrum antifungal	Visceral Leishmaniasis
Apilimod	Crohn's disease, cancer	Amyotrophic lateral sclerosis
Atovaquone	Pneumocystis (jirovecii) carinii	Malaria
Aztreonam	Antibiotic large spectrum	Pseudomonas aeruginosa in cystic fibrosis
Celecoxib	Rheumatoid arthritis	Familial adenomatous polyposis
Cycloserine	Urinary tract infections	Tuberculosis
Hydroxyurea	Myeloproliferative disorders	Sickle-cell disease
Ivermictin	Anti-parasitic, veterinary	Onchocerciasis
Metronidazole	Trichomonas vaginalis chronic	Amoebiasis
Quinidine	Anti-arrhythmic	Malaria
Sildenafil	Erectile dysfunction	Primary pulmonary hypertension
Thalidomide	Nausea in pregnancy	Leprosy, multiple myeloma
	Large population →	Small population

This is a problem of incentives, who gets the benefit of the new use | Intellectual Property Rights

We need to better understand patents


Second medical use identified for Inventadine (disease B), by different company (Smallpop) new use patent
1985
1995
2008
2012
Farmacor® sold both for disease A and disease B as lower price
Farmacor® sales
Insignificant sales for Raremedica® as substituted by Farmacor®
Product X ("inventadine"), **product patent obtained that will protect the invention for 20 years**
Inventadine authorised for disease A, as Farmacor®, by company Largo **Costs 10 € / mg**
After 2005, inventadine in **public domain** (off-patent)
Authorised to treat rare disease B, as Raremedica®, by company Smallpop **Costs 20 € / mg** (additional costs of clinical studies, and regulatory affairs)
Smallpop generates no returns on investments. In fact, the absence of protection for this second medical use would have discouraged Smallpop to even investigate the use of inventadine to treat rare disease B


2010?
2011
2016
2019
2024?
2030
8 years clinical development
Commercial life span, 8+2-year data protection for Crohn with one year extension (SPC) when authorised for ALS
Generics arrive after 8+2+1 years of data protection, substitution stops sales of the originator
2030: Patent protection ends after 20 years. Product is in public domain
Apilimod, product patent
Patented (medical use patent) for Crohn's disease and lymphoma
Possible authorisation year for Crohn's disease
Actual commercial life span of the new product for ALS, due to generic substitution
This gives short time to recoup investments for the 2nd medical use. If sales for Crohn are high, then the costs for ALS can be compensated by high sales for Crohn. But if different developer for Crohn and for ALS? Or sales for Crohn are low? The company has zero interest in developing apilimod for ALS
Second medical use patent for amyotrophic lateral sclerosis (ALS)
Possible authorisation year for ALS
Different dose than for Crohn
Different brand name

At what price? Price comparison of selected medicines for common and rare indications in Belgium in 2011 (Source: Prof Marc Dooms)

Active substance name	Brand name common disease	First indication	Marketing date	Brand name rare disease	Second medical use	Marketing date	Price difference per mg
aztreonam	Azactam	Antibiotic large spectrum	1984	Cayston	Pseudomonas aeruginosa in cystic fibrosis	2004	x 40
Celecoxib	Celebrex	Rheumatoid arthritis	2000	Onsenal	Familial Adenomatous Polyposis	2001	x 1.05
Cladribine	Leustatin	Hairy cell leukaemia IV	1991	Litak	Hairy cell leukaemia SC	2001	x 4.5
Dexrazoxane	Cardioxane	Cardio protective agent	2000	Savene	extravasation after IV anthracycline chemotherapy	2001	x 35
Everolimus	Certican	Organ transplant rejection	2006	Afinitor	Advanced breast cancer	2007	x 2.5
Histamine	Histamine	Inflammatory response	1970	Ceplene	Acute Myeloid Leukaemia	2005	x 200
Sildenafil	Viagra	Erectile dysfunction	2002	Revatio	Primary Pulmonary Hypertension	2003	x 1.3
Tadalafil	Cialis	Erectile dysfunction	2004	Adcirca	Primary Pulmonary Hypertension	2008	x 0.6
Tobramycin	Obracin	Various types of bacterial infections	1996	Tobi Podhaler	Cystic fibrosis infections	2003	x 2.8

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Issues at stake

- 85% of other uses discovered in the 18 months after approval, however 85% of these uses are labelled only when generics come in
- Inherent limitations to the patent system make non-patent incentives essential (the least innovative drugs can be protected to have longer post authorisation patent life than innovative drugs)
- Costs
  - 200 million $, 3.5 years for phase 3 second use trial (median)
  - 25-33% of the cost of development for a first use
- Commercial life of an innovative product: 12 years. For a SMU: 6.
- Benefits: same return on investments than with an innovative product
- Industry invests much more in innovative products, as there is no market for second medical use (even if these products cost much less and should attract payers)
- Lost opportunities for treatment options to the detriment of patients and public health

Nota: credits to be completed when report available

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Proposals / possible solutions

- Data Protection of the patent of second medical use: can only work if the indication appears on the prescription to prevent substitution (as in Netherlands, Belgium)
  - With this, substitution will be ok for no longer patented indications, and substitution will not take place if the indication is still patented
  - Prescribing by indication: MAH to communicate the expiry dates of patents to EMA for each indication? As in Belgium, France
- Data exclusivity voucher (200 to 350 Mio $)? Priority Review voucher (200 to 350 Mio $)?
- Cash reward for SMU: but which level? Who would pay?
- Generic manufacturer to pay royalties? But putting them at financial risk
- Incentives borrowed from OMP incentives?
- Shortened regulatory process for drugs about which much is known already? But what will HTA say?

⇒ To change the narrative: to move away from the status quo in a context where policy makers are 100% convinced the incentives have created too much monopolies already

Nota: credits to be completed when report available

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

- 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
- Obstacles:
  - Press and the general public express outrage when an existing medicine is sold at a higher price for a new indication
  - A lot of education and communication needed – a campaign – and an Elon Musk

Nota: credits to be completed when report available

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Thank you for your attention.

François Houÿez

Treatment Information and Access Director

francois.houyez@eurordis.org

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Some examples

- Priority review vouchers
  - Can be sold to a different company (up to $350Mio)
  - *If you develop a new drug fro malaria, your profitable lipid lowering drug could go on the market one year earlier* Bill Gates Davos 2008
  - Stretch FDA resources
  - Only 12 issues so far
  - Only for blockbusters

Nota: credits to be completed when report available

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About EURORDIS's position

- Views expressed in this presentation are the views of the presenter together with members of EURORDIS task force on Drug, Information, Transparency and Access (volunteers)
- It does not yet represent the position of EURORDIS – to be adopted
- Discussions notably with
  - EURORDIS Therapeutic Action Group – Virginie Hivert
  - Amitava Banerjee, University College London, Farr Institute of Health Informatics
  - Brian Cordery, Bristows LLP
  - Prof Mondher Toumi, University of Marseille
  - Daniel O'Connor, MHRA UK and COMP / EURORDIS Symposium on Incentives 21 February 2018
  - Jürgen Dressel, Novartis Pharma IP
  - Conference on *Fair and Effective Incentives for New Uses of Established Drugs* *8-9/02/2018, Washington DC*
    - Prof. Sir Robin Jacob, President of the Intellectual Property Judges' Association, UCL
    - Judge Rian Kalden, Senior Judge, Court of Appeal, The Hague

What is the ideal system for the patients?

1. The New Medical Entity drug is approved **as soon as possible** after its discovery
2. At approval, clinical data provides the **clearest possible picture of safety**
3. Clinical data clearly defines patients **who can benefit from the medicine**
4. The drug is **initially approved for as many indications as possible**
5. Further approved uses come **as quickly as possible** after initial approval
6. The drug is **accessible, affordable** to patients who can benefit from it
7. Generic drug entry is assured after an **appropriate period** of IP protection
8. For generic drugs, the drug's cost is just above its **manufacturing costs**
9. Even after generic drug entry, **mechanisms remain** for developing new uses
10. The post generic new use mechanism includes **mandatory prescription by indication**

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•Proposal

Commission Expert Group on Safe and Timely Access to Medicines for Patients | STAMP

A pilot

What EFPIA / Medicines for Europe are proposing

- For multi-sources products (same active substance – many manufacturers MAH)
- When the label can be changed and only the label (same dose, same name, same package, same administration mode, price unchanged)
- Idea for new use proposed by champions*
- Not just the idea, but also the data that support the new indication
- based on which regulators can give a scientific advice on what needs to be generated to get the new indication authorised
- And then all MAHs will change the label

*Champion can be a person/academia/research fund/company with a particular interest in repurposing a product for a new indication

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Definitions and remarks

- Repurposing is defined as the process of facilitating the justification of a new therapeutic use for an existing medicine outside the scope of the original indication(s), with the purpose of seeking a marketing authorisation.
- Repurposing may occur in situations where the medicine is still protected by basic patent/supplementary protection certificates (SPC) / data and market exclusivity, as well as where the medicinal product is outside of these intellectual property (IP) / regulatory protections.
- The elements discussed below cover only one possible scenario of repurposing of medicinal products, namely the one where medicines are already out of basic IP/regulatory protection.
- Mandate: no changes in the Regulatory environment / Framework

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Scope

1. The proposed new indication should be in a condition distinct to the currently authorised indication(s) listed in section 4.1 of the relevant summary of product characteristics (SmPC) of a Member State (MS) or the European Union (EU)

2. There should be a valid marketing authorisation for the medicinal product containing the same active substance in the same formulation / dosage form, granted in a Member State or in the European Union

3. Repurposing should be encouraged in an area where significant public health benefits / Union interests are likely to be achieved

4. All authorised medicinal products containing the active substance should be out of basic patent/ SPC protection, and data & market exclusivity periods

5. The repurposing project is not conducted by a business organisation

6. There should be supporting evidence e.g. proof of concept from clinical data. It could include documentation from off label use, registry data, clinical trials or reported case studies

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Champion

- Champion has been identified who is willing and able to take forward the roles and responsibilities required of the framework. A champion can be a person/academic unit/learned society/research fund or payer with a particular interest in repurposing a compound/product for a new indication and who has data evidence/scientific rationale to do so. Criteria to qualify as a champion include:

a. Is not a pharmaceutical company / business organisation

b. Is able to coordinate and or foster the development programme up until the point of full industry engagement

c. Is initially responsible for liaising and leading the interactions with regulatory authorities and industry / other stakeholders such as patient groups

d. Is transparent regarding interactions with relevant pharmaceutical company(s)

e. Files the request for regulatory advice on the basis of the available data

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Limiting steps

- Terms of regulatory routes and requirements
- What additional data need to be generated
- How to find non-published clinical and non-clinical data
- How to find a manufacturer of the finished product to collaborate with etc.
- The administrative steps of filing a marketing authorisation application (MMA) submission and validation is also a high threshold for Champions. Champions are normally not equipped or have the resources to legally take the role as MAH when seeking approval or fulfilling post-marketing responsibilities but are understood to have conducted the data gathering

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Scientific advice

- Scientific Advice (SA) is the main regulatory tool that is considered important to support repurposing projects.
- Guidance can be provided to the Champion on the regulatory and scientific aspects of the project, e.g. data generation and the data package required to support the suggested indication.
- The outcomes of the SA could potentially be made more widely available in the context of encouraging engagement with MAH(s), but this will remain at the discretion of the Champion.

Incentives

- Both legal and non-legal incentives may be important to different stake-holders.
- There are some incentives within the regulatory framework and other types of incentives may exist in different MS.
- For Champions it may be to fulfil medical needs to patients, scientific, economic (grants/funds) and reputational issues.
- For industry the nature of the business case will be important as well as minimising the perceived barriers.

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Opinion on EFPIA / Medicines for Europe proposal

- Only part of the problem, and maybe a tiny part
- Been there, done that. OrphanXchange difficulties:
  - Disputes over IP rights
  - R&D and evaluation costs, how to cover them ? Return on investment
  - No reward for the person/institution that proposed the new use
- Needs discipline by all industrial actors: can only work if all manufacturers/MAH change the label
  - If not: some might escape PASS and their costs will rely only on those who changed the label
    - Who in return might increase the price to compensate the cost of pharmacovigilance activities
    - And then substitution with a lower price product will prevail
- Recognition of champion: how?
- Incentives for the champion to generate the supportive data? None. Going round in circles
- Generic manufacturers don't seem to understand they're in the same basket as originator companies

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Thank you for your attention.

Name

Job title

Tel: Phone number

Email address

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