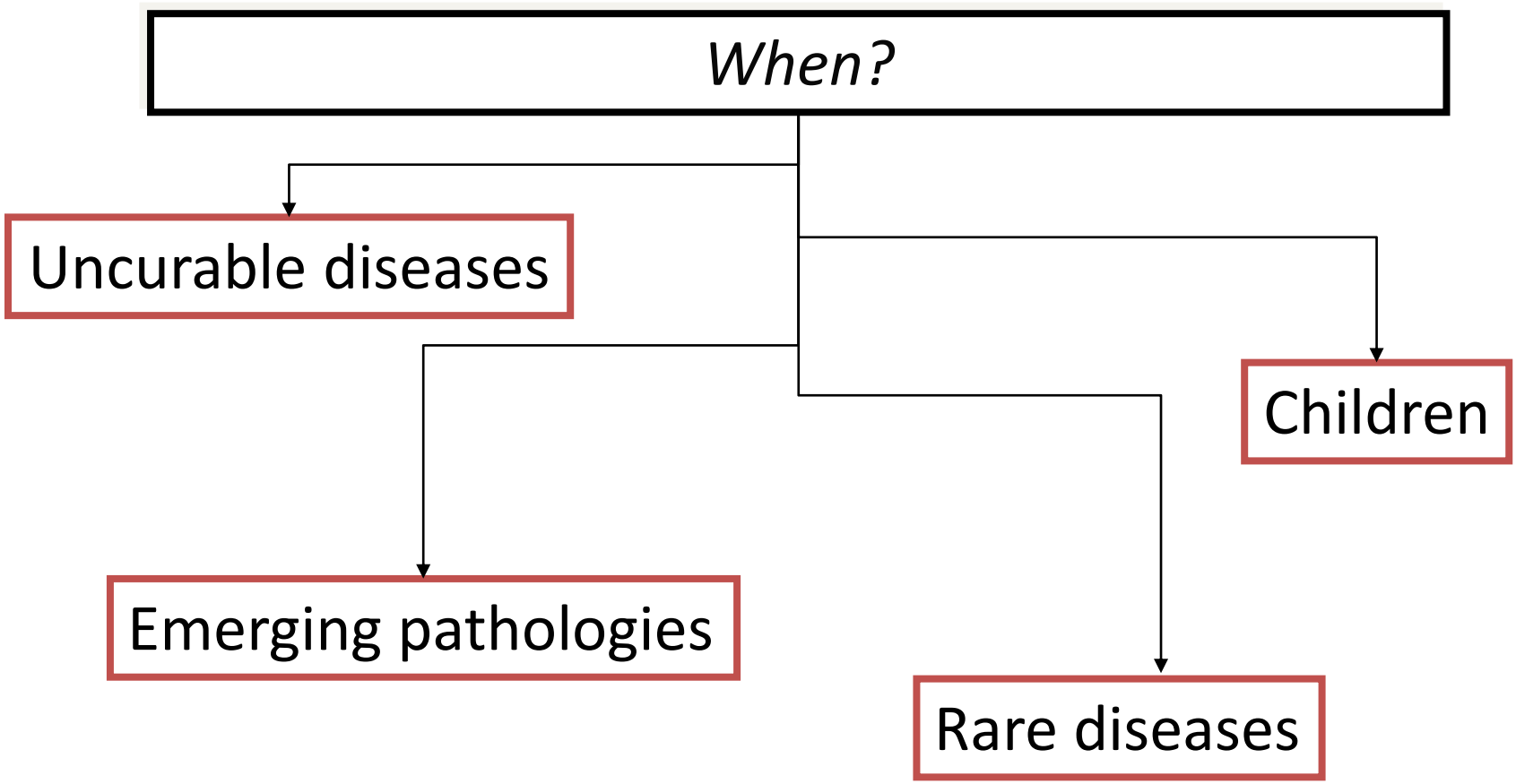
UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI
SCIENZE FARMACEUTICHE

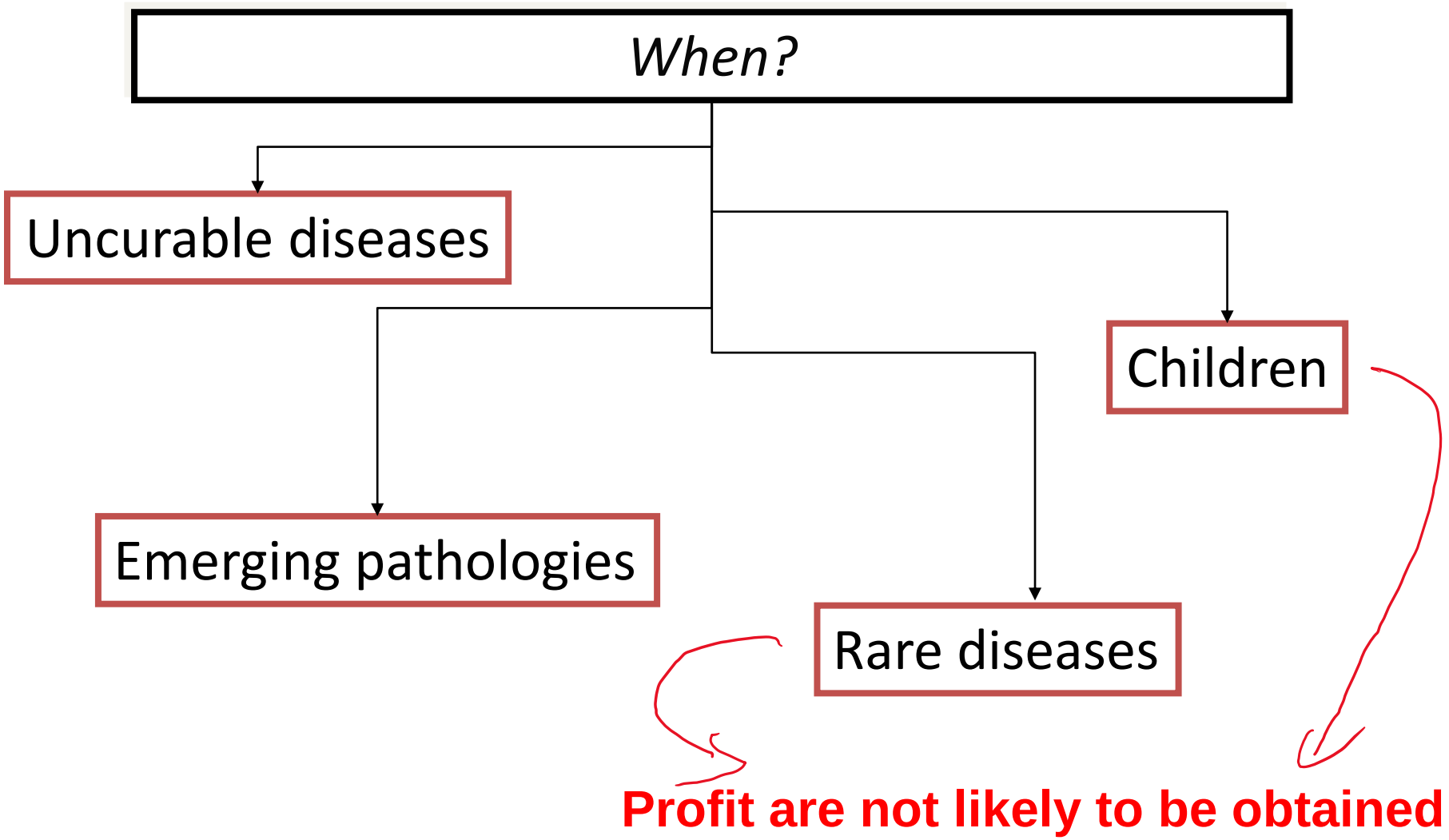
Drug repositioning: is it always worth?

Prof. Paola Minghetti

Unmet medical need

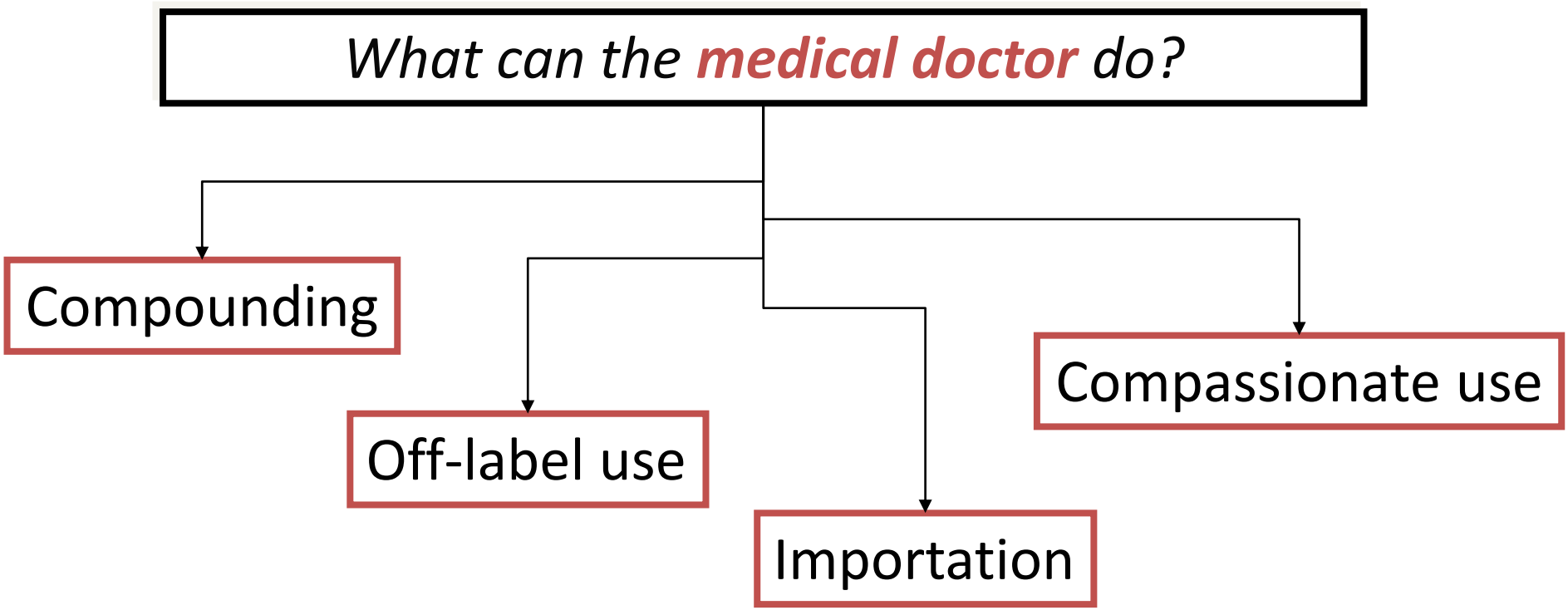


Unmet medical need



What happens when an industrial medicinal product is not available for a specific disease/patient?

Unmet medical need



If none of these alternatives are available → **Clinical trial**

In all these situations the public administration rules sets to guarantee

Quality

Safety

Efficacy

and…

Economic sustainability

are not fully respected

Industrial medicinal products

Quality, **safety** and **efficacy** are guaranteed through:

- Manufacturing Authorization (**quality**)

  National medicine agency

Identical for all kinds of medicinal products

- Marketing Authorization (**quality**, **safety** and **efficacy**)

  National medicine agency or EMA

Different for different types of products

Research & development

*In which can **Pharmaceutical industries** invest?*

Developing first-in-humans medicines

- High innovation (technological, clinical)
- High therapeutic value
- High development costs and risks

Improving existing medicinal products

- Medium/high innovation (technological)
- Improvement of therapeutic value
- Medium development costs and low risks

Developing copies

- Low innovation
- No improvement of therapeutic value
- Improve economic competitiveness
- Low development costs and risks

Unmet medical need

*What can **Pharmaceutical industries** do?*

New MA for first-in-humans drugs

New MA for new medicinal product containing old API

New indication for medicinal product already authorized

New MA/therapeutic indication for an old drug

Drug repurposing

Find new therapeutic indications for existing active ingredients. The process required investments in R&D to develop a new drug products and sustainment of the drug and in supporting MA application for the new indication.

(Sleigh SH, Barton CL, Repurposing Strategies for Therapeutics. Pharm Med. 2010;24(3):151-159)

Data protection

Intellectual protection for the novel therapeutic indication

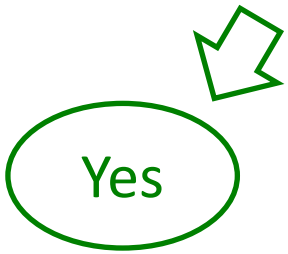
Article 54(5) of the European Patent Convention does not exclude the patentability of any substance or composition for any specific use in a method referred to in Article 53(c) [i.e., methods for treatment of the human or animal body by surgery or therapy and diagnostic methods], provided that such use is not comprised in the state of the art.

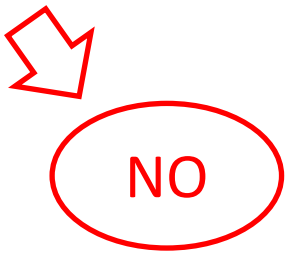
In other words, an already known substance/composition may be patented for a second therapeutic indication, if it is new and innovative.

(European Patent Office - Pharmaceutical Directives. www.epo.org/law-practice/legal-texts/html/guidelines/e/g_vi_7_1.htm)

Drug repurposing: how is the old API identified?

Are there some hypotheses a priori?





- Off-label use
- Literature evidence on new mechanism of action
- Data from magistral formula

- text mining (IA)
- in silico screening
- in vitro/ex vivo screening
- study in animal disease models
- observational studies from human trials.

Oprea TI, Overington JP. Assay Drug Dev Technol. 2015;13(6):299-306.

Repurposing vs off-label use vs new entities

	Main characteristics and implications											
	Safety	**Efficacy**	**Availability of information**	**Required investment**	**Clinical Development**	**Risk of investment**	**Development times**	**Time to market**	**Patent protection**	**Legally liable party**	**Attitudes of payers**	**Attitudes of health policy systems**
Off-label use	Limited evidence	Limited evidence 73% used have little or no evidence	Limited availability	Low	Absence of formal development phases. Some evidence of safety and efficacy	Not measurable	Short	Immediate	No patent protection	Physicians under clinical freedom to prescribe	Variable arrangements for reimbursement	Some incentives due to economic reasons
Repurposed drug	Robust evidence required	GPC trial evidence required	All medical information needs are fulfilled	Medium	All regulatory requirements must be met for the new indication	25% success from Phase II to launch	Medium Typically 3-8 years	Short-medium	Second medical use patent	Manufacturer, Physician	Product value usually not well recognized	Product value usually not well recognized
New drug	Robust evidence required	GPC trial evidence required	All medical information needs are fulfilled	High	All regulatory requirements must be met.	10% success from Phase II to launch 5% overall	Long Typically 10-17 years	Long	Patent protection in place	Manufacturer, Physician	Variable	Variable

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From off-label to repurposed drug in non-oncological rare diseases: definition and state of the art in selected EU countries

Paola Minghetti[1], Elena P. Lanati[2], Josie Godfrey[3], Oriol Solà-Morales[4], Olivier Wong[5], Sonia Selletti[6]

Repurposing vs off-label use vs new entities

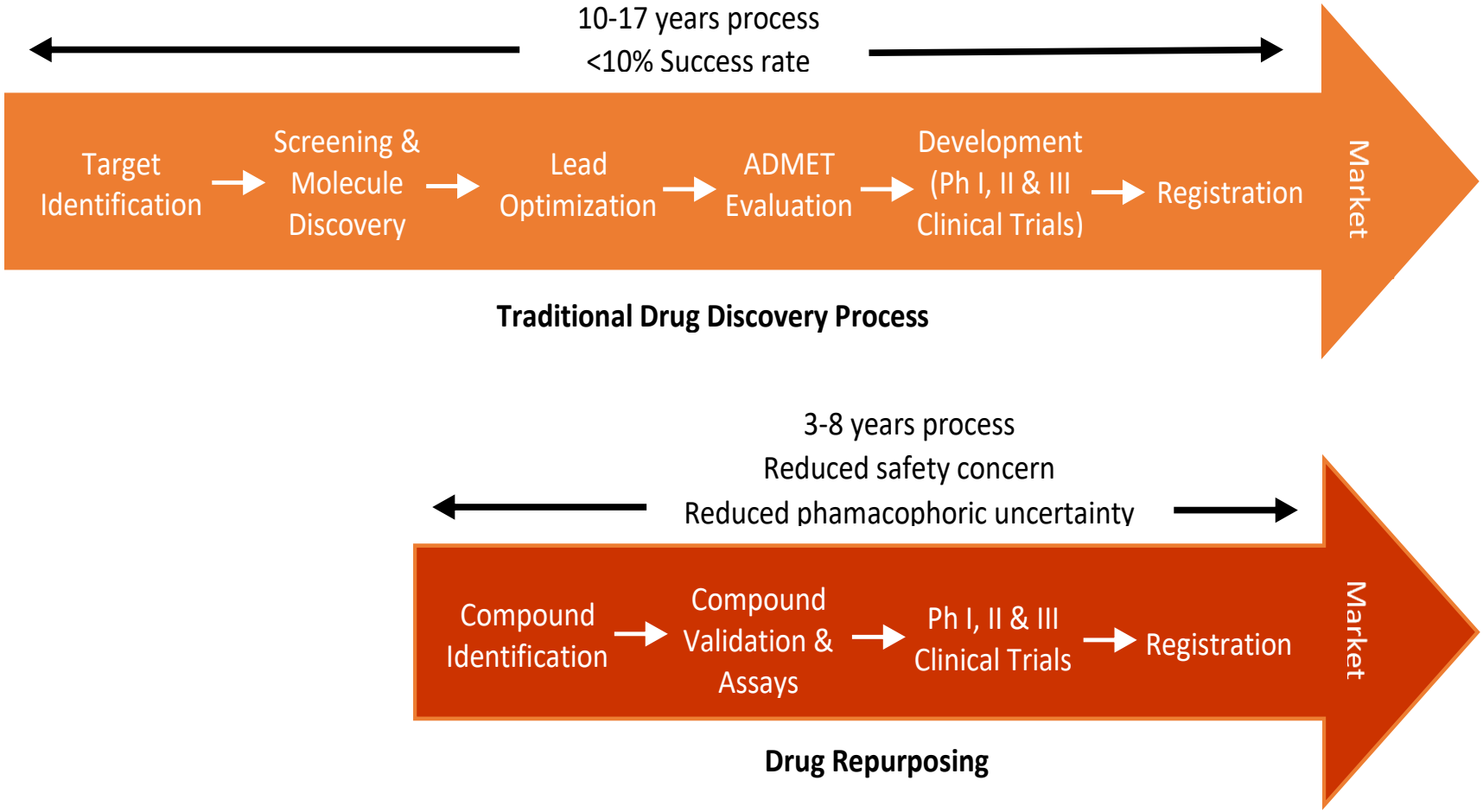
Developing repurposed medicines may be worth since:

- Availability of solid and public medical evidence on product efficacy and safety (derived from off-label use, use of magistral formula or post-marketing clinical trials);
- Investment in economic terms and time in R&D is moderate;
- No need for phase I studies that represent the greatest obstacle in the success of a new molecule (45% of new active substances fail phase I studies) (**hybrid CTD**)
- The new therapeutic indication may get a patent protection

Naylor S, Kauppi DM, Schonfeld JM. Therapeutic drug repurposing, repositioning and rescue part II: business review. Drug Discovery World. 2015;16(2):57-72.

Repurposing vs new entities

R&D timing



Repurposing vs off-label use vs new entities

Repurposed drug approval times

Product NAME	Original indication	Current indication	Date of EMA market authorisation	Days to P&R Decision			Average (days)
				Italy	France	Spain	
TECFIDERA	Psoriasis	Relapsing-remitting multiple sclerosis (MS)	30/01/2014	359	511	29	**299,7**
ORFADIN	Weed killer	Hereditary tyrosinemia type 1 (HT 1)	21/02/2005	2674	NA	3779	**3226,5**
REVATIO	Angina pectoris	Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	28/10/2005	763	110	48	**307,0**
ORPHACOL	Gallstones	Inborn errors in primary bile acid synthesis due to 3β-hydroxy-Δ5-C27-steroid oxidoreductase deficiency or Δ4-3-oxosteroid-5β-reductase deficiency	12/09/2013	1247	383	490	**706,7**
KETOCONAZOLE HRA	Prostate carcinoma, antimycotic	Cushing's syndrome	19/11/2014	499	469	Not commercialized	**484,0**
THALIDOMIDE	Anti-Nausea	Multiple Myeloma	16/04/2008	322	91	NA	**206,5**
Average				**977,3**	**312,8**	**1086,5**	

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Repurposing: attempt rate e success rate (FDA)

TABLE 1

Repurposing rates ('attempts') and corresponding commercial launch rates ('success') in the same and different therapeutic area as the first attempted clinical development path for two subgroups: first attempted clinical development path yielding a market launch ('first success'); and first attempted clinical development path terminated ('first failure')

Repurposing	Same therapeutic area	Different therapeutic area
First success, $N = 167$	Attempts: (52/167) = 31% Successes: (35/52) = 67%	Attempts: (30/167) = 18% Successes: (10/30) = 33%
First failure, $N = 667$	Attempts: (104/667) = 16% Successes: (9/104) = 9%	Attempts: (65/667) = 10% Successes: (6/65) = 9%

Neuberger A, Oraiopoulos N, Drakeman DL. Renovation as innovation: is repurposing the future of drug discovery research? Drug Discov Today. 2019 Jan;24(1):1-3.

Repurposing vs off-label use vs new entities

Developing repurposed medicines may not be worth but:

- Some countries promote off-label use of drugs/compounded preparation rather than repurposing medicines.
- It can be difficult to establish the right price, considering the recognition of the R&D costs and added value;
-

In the Netherland, chenodeoxycholic acid capsules mainly **compounded** (**€ 20,000/patient/year**) for treating patient affected by Cerebrotendinous Xanthomatosis due to the too high cost of the **authorized** medicinal product (**€ 170,000/patient/year**).

Naylor S, Kauppi DM, Schonfeld JM. Drug Discovery World. 2015;16(2):57-72.
Sheldon T. BMJ 2018;361:k2103

Repurposing vs off-label use vs new entities

Prices of repurposed drugs

Product NAME	Pharmaceutical form	Pack size	Price % (to average)				
			Average	Italy	France	UK	Spain
TECFIDERA	Oral capsules	120mg (14 capsules)	251,04 €	57%	107%	161%	75%
ORFADIN	Capsules	2mg (60 capsules)	816,41 €	109%	NA	82%	110%
REVATIO	Tablets	20mg (90 tablets)	527,37 €	108%	85%	100%	107%
ORPHACOL	Capsules	50mg (30 capsules)	2.469,22 €	109%	95%	89%	107%
KETOCONAZOLE HRA	Tablets	200mg (60 tablets)	548,80 €	98%	98%	103%	NA
THALOMID	Capsules	50mg (28 capsules)	356,34 €	108%	94%	99%	NA
Mean				**98%**	**96%**	**106%**	**100%**

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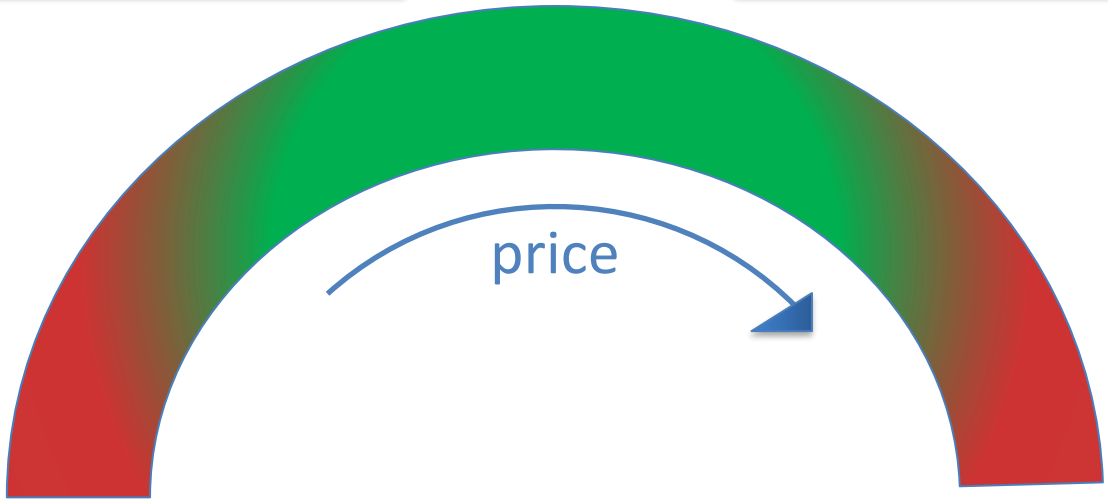
Criticisms



Lower price medicinal product

Higher price medicinal product

Product withdrawn for commercial reasons.

Product withdrawn for commercial reasons

Shortages

Example: Nadolol

Example: Chondrocelect

Thank you for your kind attention!