Drug rediscovery:

Regulatory considerations and challenges

Joris Langedijk/Hubert Leufkens
Medicines Evaluation Board/Utrecht University

Medication Repurposing in Pediatric Patients: Teaching Old Drugs New Tricks

Martha M. Rumore, PharmD, JD, MS, LLM

Department of Social, Behavioral and Adminis
Counsel, Sorell, Lenna, & Schmidt, LLP, Haup

OBJECTIVES: Gaps in pediatric therape
existing medications, termed "drug repu
Resource Center of a large metropolitan p

Therapeutic Discovery

Molecular Cancer Therapeutics

New Use for an Old Drug: Inhibiting ABCG2 with Sorafenib

Yinxiang Wei[1,3], Yuanfang Ma[3], Qing Zhao[1,4], Zhiguang Ren[1,3], Yan Li[1], Tingjun Hou[2], and Hui Peng[1]

-binding cassette transporter superfamily, represents a promising
otherapy. Although lots of ABCG2 inhibitors were identified, none of
ecause of several problems such as toxicity or safety and pharma-
novel chemical structures. One efficient solution is to rediscover new
macokinetics and safety profiles. Here, we found the new use for
y inducing ABCG2 degradation in lysosome in addition to inhibiting

Drug repositioning and repurposing: terminology and definitions in literature

Joris Langedijk[1,2], Aukje K. Mantel-Teeuwisse[1], Diederick S. Slijkerman[2] and Marie-Hélène D.B. Schutjens[1,3]

[1] Department of Pharmacoepidemiology & Clinical Pharmacology, Utr
The Netherlands
[2] Medicines Evaluation Board, Utrecht, The Netherlands
[3] Schutjens de Bruin, Tilburg, The Netherlands

Drug repositioning and similar terms have be
development strategies. We analysed in a qua
used and defined in the literature. In total, 2
repurposing', 'drug reprofiling', 'drug redirec

PLOS ONE

Drug rediscovery/repositioning is booming

RESEARCH ARTICLE

Drug Repositioning for Cancer Therapy Based on Large-Scale Drug-Induced Transcriptional Signatures

Haeseung Lee, Seungmin Kang, Wankyu Kim*

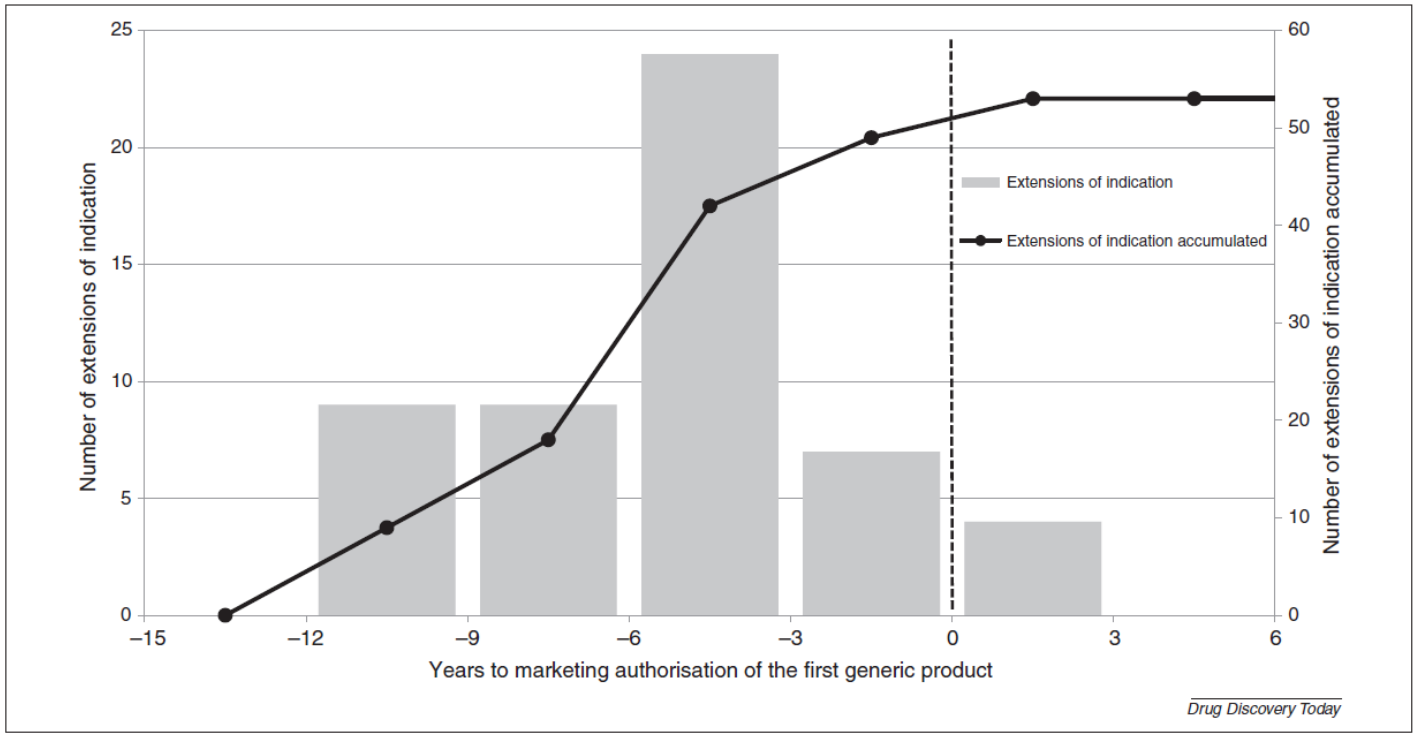
Ewha Research Center for Systems Biology, Division of Molecular & Life Sciences, Ewha Womans University, Seoul, Korea

* wkim@ewha.ac.kr

Main drivers of drug rediscovery/repositioning

- Alternative, more efficient, way of drug research, therapeutic innovativeness.
- Better science on molecular pathways, enabling cross-cutting, common language between 'drug targets and diseases'.
- Societal need for regulation of pharmacy compounding and off-label use.

Post-generic innovation remains hard work



Langedijk J et al. Extensions of indication throughout the drug product lifecycle: a quantitative analysis. Drug Discov Today. 2016; 21: 348-55.

Innovation scenarios in drug rediscovery

		Value creation, viable business case	
		Not likely	Yes
Regulatory constraints	Yes		
	Limited		

Regulators can make a difference

Conditional marketing authorisation Thiosix (tioguanine)

News item | 02-04-2015 | 16:39

The Medicines Evaluation Board (MEB) has decided this afternoon to award a conditional marketing authorisation for the medicinal product Thiosix (tioguanine). This medicinal product can be used in the treatment of Crohn's disease and ulcerative colitis in adults.

The medicinal product can be used by patients who do not respond adequately to the standard medication for inflammation of the bowel (Crohn's disease and ulcerative colitis).

Tioguanine has been used for decades as the active ingredient in a medicinal product used to treat leukaemia. It is no longer used often for this application. A number of years ago it was found that this active ingredient was also suitable for the treatment of certain groups of patients with bowel diseases.

Bert Leufkens, MEB chairman: "The MEB has provided an impulse for drug re-discovery with the authorisation of this new indication. It is always interesting when we are able to authorise an existing product for a different indication. I am pleased that the MEB can now authorise this medicinal product for the treatment of a group of bowel patients who do not benefit adequately from the existing medicinal products. With this judgement, we can continue to monitor the quality, efficacy and risks of this medicinal product."

Year of approval Legal basis	All drugs (n=121)		Old drugs + new use (n=16)	
8.3 – Full dossier	97	80,2%	9	56%
10a – Well-established use	3	2,5%	2	13%
10b – Fixed dose combination	12	9,9%	2	13%
10.3 – Hybrid	9	7,4%	3	19%
Scientific advice				
Yes	93	76,9%	7	44%
No	28	23,1%	9	56%
Company size				
Small	18	14,9%	8	50%
Medium	40	33,1%	7	44%
Large	63	52,1%	1	6%

EMA approvals 2014-2015

Langedijk J, 2016 (submitted)

Drug rediscovery through the EMA, sample 2014 …..

Drug	Old use	New use (innovation)
Hemangiol (propranolol)	e.g. cardiovascular diseases	Infantile haemangioma
Ketoconazole	Fungal infections	Cushing's syndrome
Tecfidera (dimethyl fumarate)	Psoriasis	Multiple sclerosis
Mirvaso (brimonidine)	Open-angle glaucoma or ocular hypertension	Facial erythema of rosacea
Granupas (para-aminosalicylic acid)	Tuberculosis	Improved safety profile, new dosage form
Simbrinza (brinzolamide/ brimonidine)	Open-angle glaucoma or ocular hypertension	Introduction of a fixed dose combination

R&L DR projects, results so far ..... (1)

- Off-label use of existing products for clinically/widely accepted indication or large scale compounding of not-licensed product; doctors say that it works; virtually no recorded data on effectiveness or safety.
- MAH wants to suspend products due to lack of commercial interest; product is of clinical importance; quality of dossier often not up-to-date; transfer of license to other MAH is a challenge from a quality perspective.
- Not granting a license often means maintaining an off-label scenario, large scale compounding, etc.

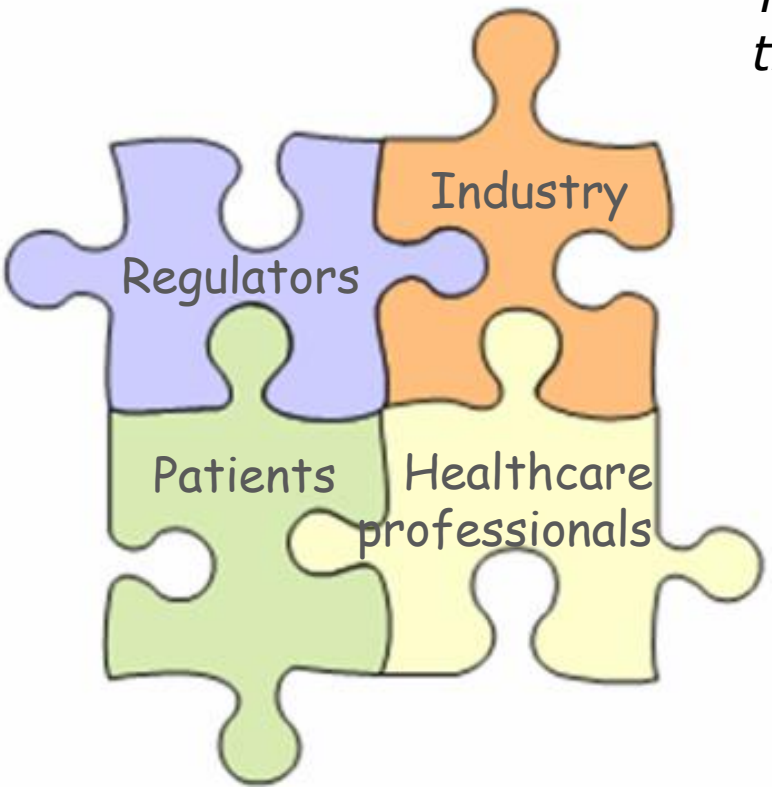
R&L DR projects, results so far ..... (2)

- The assessment and requirements of DR cases are in principle identical to any other assessment.
- Lack of data as such is not always the issue; justification by the applicant why this does not hamper B/R, is critical.
- Expertise (mainly regulatory) of applicants is often poor; prevalence of repeating players in DR is low.
- A less robust positive B/R may result in a last resort therapeutic indication.
- Registry proposed to fill the uncertainty gap; there is hardly any incentive for registry building.

R&L DR projects, results so far ..... (3)

- Regulators try to find informed balance between stimulating DR and being consistent with other regulatory procedures.
- DR is not a solely national activity; parallel trade or other EU lincences are driving national DR; National authorities may be 'overruled' by Europe.
- HTA and payers are sometimes reluctant to approach positively of what they coin as 'unproven' B/R; risk aversion highly prevalent.

How to continue?



'Every new drug is a potential old drug. Together we should aim to use drugs to their full potential'

Look for a new drug development paradigm with incentives and an satisfactory business case for drug repositioning in which quality, efficacy and safety are supported by adequate and robust data and/or justification.