SN5:
How therapeutic equivalence can influence the cost of drugs

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Barcelona, March 2014

1

Conflict of interest:
nothing to disclose

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Learning objectives:

To estimate the impact of strategies developed by the pharmaceutical industry to prolong the life of their successful products

To be sensitized to the importance of considering a societal perspective when economic choices have to be done

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Patented Drug Extension Strategies on Healthcare Spending: A Cost-Evaluation Analysis

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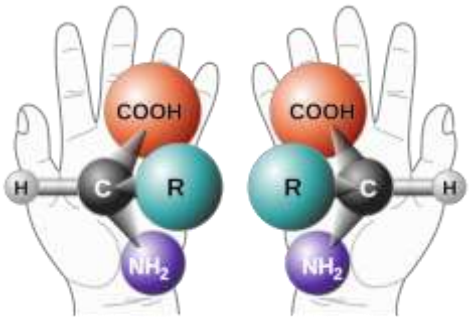
Chiral drugs



Same chemical structure

Different 3dimentonal arrangements

The Nobel Prize in Chemistry 2001

William S. Knowles,
Ryoji Noyori,
K. Barry Sharpless

Somogyi A. BF, Foster D (2004) Inside the isomers: the tale of chiral switches. Australian Prescriber 27: 47-49

Agranat I, Caner H, Caldwell J (2002) Putting chirality to work: the strategy of chiral switches. Nat Rev Drug Discov 1: 753-768

Potential Health benefits

Different pharmacodynamic and pharmacokinetic properties

- Improved safety margin through increased receptor selectivity?
- Reduce side effets? => more appropriate dosing frequency?
- a longer or shorter duration of action?
- decreased inter-individual variability?
- decreased potential for drug-drug interactions?

Somogyi A. BF, Foster D (2004) Inside the isomers: the tale of chiral switches. Australian Prescriber 27: 47-49

Clinical Evidence

Rare clinicial study facing "head to Head" or
40mg esomeprazole compared to 20 mg d'omeprazole
Lind, T., et al. Aliment Pharmacol Ther, 2000. 14(7): p. 861-7.

Somogyi A, BF, Foster D (2004) Inside the isomers: the tale of chiral switches. Australian Prescriber 27: 47-49
"Need to be provided … that chiral switches have advantages for the prescriber and the consumer"

Hughes DA, Ferner RE New drugs for old: disinvestment and NICE. Bmj 340: c572
"any resulting improvement in health outcome, is often lacking"

Svensson S, Mansfield PR (2004) Escitalopram: superior to citalopram or a chiral chimera? Psychother Psychosom 73: 10-16.
"Methodological flaws in the trials… superiority for escitalopram over citalopram are unwarranted"

Agranat I, Caner H, Caldwell J (2002) Putting chirality to work: the strategy of chiral switches. Nat Rev Drug Discov 1: 753-768
" The chiral switch is a usufull option for the owners of existing racemate to achieve line extensions, especially if the switch can be marketed immediately before expiry of patent on the racemate"

Evergreening strategies

3 categories of drugs marketed

at the same time
at different prices
by the same pharmaceutical company (1 & 2)

1) the initially patented drug

2) the **follow-on** drug: **slightly modified drugs of already approved drugs**

3) the generic version of the brand drug

Evergreening strategies

Combination formulations

alendronic acid combined **with** colecalciferol - alendronic acid alone
simvastatin combined **with** ezetimibe - simvastatin alone

Structural analogues

pregabalin for gabapentin

Active metabolic

desloratadine for loratadine

Slow-release forms

zolpidem **extended release**

Single enantiomer

omeprazole – **eso**meprazole; citalopram – **es**citalopram
cetirizine – **levo**cetirizine

Patents: eligibility criteria

"non obvious"

- Base compound or active ingredient
- Related chemical structure and compositions or formulations
  - prodrug
  - polymorph
- Manufacturing methods and processes
- Method of treatment
  - New use
  - Other deseases

A. T, Kesselheim et al.Health Aff (Millwood)

EAHP, Barcelona March 2014

Patents: eligibility criteria

Ritonavir et lopinavir/ritonavir

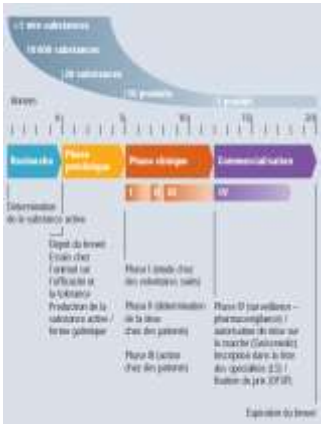
- 108 additional patents -> 2028

Patent categories	Ritonavir	Lopinavir	Lopinavir/ritonavir	Ritonavir and/or lopinavir with other compounds	Total
Total	—[a]	—[a]	—[a]	—[a]	210
Base compound or active ingredient	1	1	0	0	2
RELATED CHEMICAL STRUCTURES AND COMPOSITIONS OR FORMULATIONS (82)					
Composition and formulation[b]	18	9	15	7	49
Intermediate compounds	13	9	0	0	22
Polymorphs	2	2	0	0	4
Prodrugs	2	2	1	1	6
MANUFACTURING METHODS AND PROCESSES (68)					
Processes[c]	36	27	5	0	68
METHODS OF TREATMENT OF HIV INFECTION AND OTHER DISEASES (31)					
First method of treatment or administration for HIV	4	4	5	5	18
New uses for HIV or other diseases	6	1	1	5	13
GENERAL PATENTS (28)					
General formulations	—[d]	—[d]	—[d]	—[d]	5
Processes and methods for preparing general formulations	—[d]	—[d]	—[d]	—[d]	11
Other technologies or test systems	—[d]	—[d]	—[d]	—[d]	12

SOURCE Authors' analysis. **NOTE** Intermediate compounds, polymorphs, and prodrugs are defined in the text. [a]Not applicable. Because the categories are not mutually exclusive, patents with claims in more than one category are listed more than once. [b]Includes combinations with other HIV-treating compounds, salt forms, ester derivatives, and dosage forms. [c]Processes for making analogs, intermediates, formulations or compositions, and polymorphs. [d]General patents that could be applied to ritonavir, lopinavir, or both.

A. T Kesselheim et al. Health Aff 2013

Price of innovation



Interpharma, *Le marché du médicament en Suisse.* 2008

Estimated drug cost:

- $802 million in 2000 par molécule
- $1,318 million in 2005 biologiques

Patent last 20 years

DiMasi, J. A., Hansen, R. W. & Grabowski, H. G. The price of innovation: new estimates of drug development costs. *J. Health Econ.* ***22, 151–185*** (2003).

DiMasi, J. A., Grabowski, H. G. The cost of biopharmaceutical R&D. *Manage. Decis. Econ.* ***28,*** 469–479 (2007).

EAHP, Barcelona March 2014

Life cycle management

Grandfils, N., V. Paris, and C. Sermet, *Les laboratoires pharmaceutiques face à l'arrivée des génériques: quelles stratégies pour quels effets?*, in *Institut de recherche et documentation rn économie de santé*. 2004, 84.

Objectives:

1) Drug company invent a new drug
   a patent (20 years)
   monopoly
   make profit

2) After 20 years
   generic companies
   prices competition

3) Patent and market slightly modified drugs

hypothesis: maximise their profit

Squeezing the balloon

Pressure applied in one area pushes the air into another area of less resistance

Financial reduction expected from the generics would not be as effective in reality

Setting & methods

- The database of Swiss pharmacist's organisation OFAC

  Administrative intermediary for 92% of affiliated pharmacies
  Couvers 80% of the insureds population

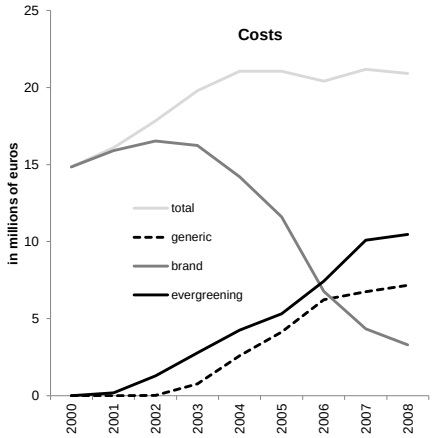
- Study period: 2000 to 2008

- Simulation techniques

Costs: 3 categories of drugs

	Euro (millions) (95% CI)
total	173.208 (173.171 - 173.246)
Brand	103.744 (103.713 - 103.775)
Follow-on	41.835 (41.817 - 41.854)
Generic	27.629 (27.619 - 27.640)

omeprazole - esomeprazole
citalopram - escitalopram
simvastatin - simvastatin and ezetimibe
alendronic acid - alendronic and colecalciferol
zolpidem - zolpidem CR
loratidine - desloratidine
gabapentin - pregabalin
cetirizine - levocetirizine



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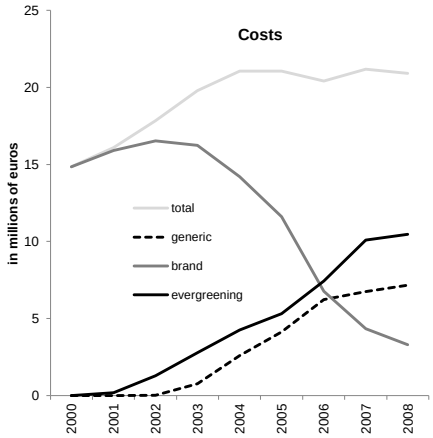
Swiss regulations

2001: Pharmacists -> generic substitution

2006: a 20% patient co-payment



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Extra Costs

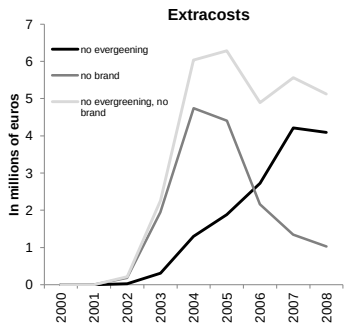
3 scenarios

Assume the replacement with the corresponding generic equivalent when available for prescriptions of

- Scenario 1: All follow-on drugs (no evergreening strategies)
- Scenario 2: All brand drugs (no brands drugs)
- Scenario 3: All brand & follow-on drugs

Extra Costs

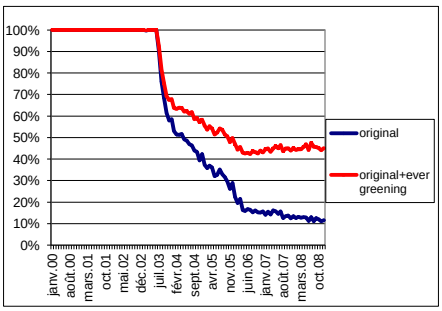
	Euro (millions) [CI95%]
No evergreening	**14 546** [14 495;14 597]
No brand	**15 816** [15 765;15 867]
No evergreening, no brand	**30 362** [30 313;30 411]

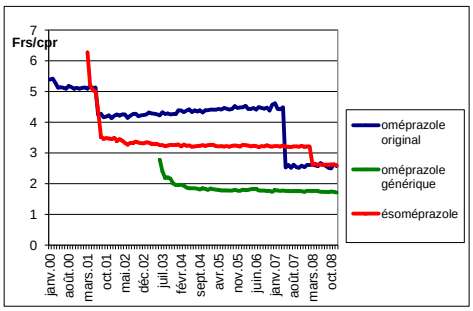


Extra Costs

	Scenario 1 (no evergreening)			Scenario 2 (no original)			Scenario 3 (no evergreening, no original)		
	Euro (millions)	[CI95%]	% of total	Euro (millions)	[CI95%]	% of total	Euro (millions)	[CI95%]	% of total
omeprazole - esomeprazole	5·262	[5·225;5·299]	36·2%	7294	[7·259;7·329]	46·1%	12·556	[12·521;12·591]	41·4%
citalopram - escitalopram	4·873	[4·851;4·895]	33·5%	4795	[4·773;4·817]	30·3%	9·668	[9·548;9·688]	31·8%
simvastatin - simvastatin and ezetimibe	2·636	[2·620;2·652]	18·1%	2697	[2·679;2·715]	17·1%	5333	[5·317;5·349]	17·6%
alendronic acid - alendronic and colecalciferol	203	[189;217]	1·4%	199	[185;213]	1·3%	402	[388;416]	1·3%
zolpidem - zolpidem CR	64	[58;70]	0·4%	418	[412;424]	2·6%	482	[476;488]	1·6%
loratidine - desloratidine	371	[367;375]	2·6%	43	[37;49]	0·3%	414	[410;418]	1·4%
gabapentin - pregabalin	630	[612;648]	4·3%	132	[114;150]	0·8%	762	[744;780]	2·5%
cetirizine - levocetirizine	507	[501;513]	3·5%	238	[232;244]	1·5%	745	[739;751]	2·5%
Total	14·546	[14·495;14·597]		15·816	[15·765;15·867]		30·362	[30·313;30·411]	

Esomeprazole - omeprazole





Spillover effect

Action taken in one environment impacts another environment

Tribune de Genève, 4 mars 2011

Spillover effect

PacifiCare®

omeprazole-lansoprazole
↓
Rabeprazole-pantoprazole

~~PacifiCare®~~

↗ Rabeprazole
↗ pantoprazole

Wang, Y.R. and M.V. Pauly, *Spillover effects of restrictive drug formularies: a case study of PacifiCare in California.* Am J Manag Care, 2005. **11**(1): p. 24-6.

Restrictive drug formularies

Hospitals:
- to minimise acquisition costs
- to limit the number of medications available
- to teach

Pharmaceutical companies:
- to buy and use their drug
- spillover effect

Hypothesis

Hospital prescription patterns may influence prescription patterns in the community

Settings & Methods

(1) inpatient setting (during hospitalisation)

2000 beds

(1) hospital spillover setting: *medications prescribed by HUG physicians but dispensed by community pharmacies*

(1) community setting

464'000 inhabitants

- The hospital registry & OFAC database
- Study period: 2000 to 2008
- Simuation techniques & Time Series analysis

Different rules

community setting | the inpatient setting

$ hospital spillover setting (mg)

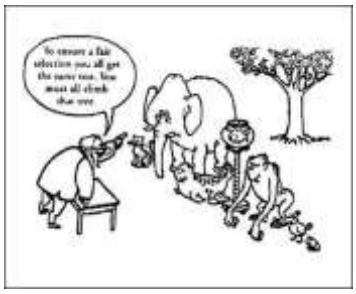
Prices **fixed**	≠	Drug prices **negotiated**
Prescriptions **unrestricted**		Prescriptions **restricted**

Prescribing market share

$$\frac{\text{\% follow-on (DDD)}}{\text{brand+generic+follow-on (DDD)}}$$

Same scale 3 settings

Drug class



Muijrers PE et al (2005) Fam Pract 22: 624-630

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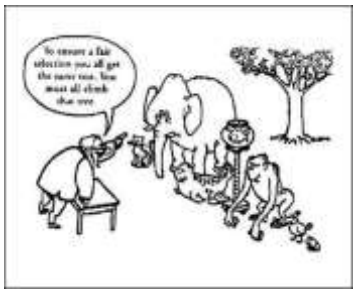
Prescribing market share

$$\frac{\%\ \text{ESO (DDD)}}{\text{brand OME +generic OME +ESO (DDD)}}$$

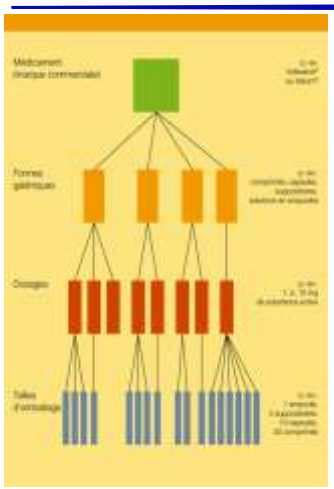
Same scale
3 settings

Drug class



Muijrers PE et al (2005) Fam Pract 22: 624-630

Defined Daily Dose

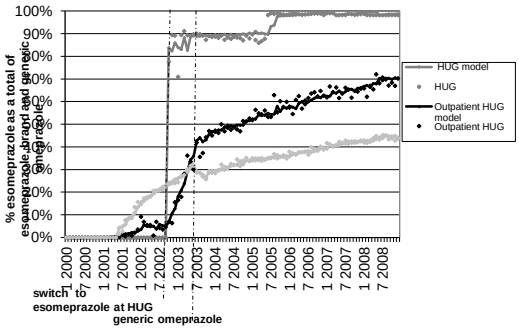


Interpharma, *Le marché du médicament en Suisse*. 2008

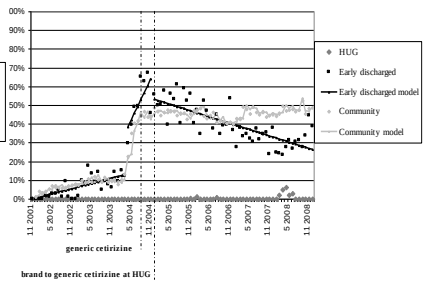
Ex: Co-Amoxiclav
80 references

http://www.whocc.no/atc_ddd_index/

Spillover effect

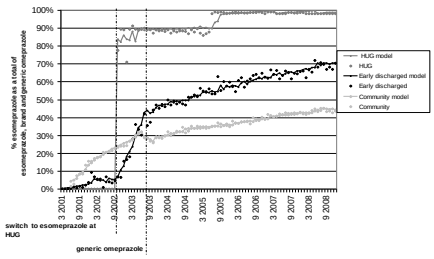


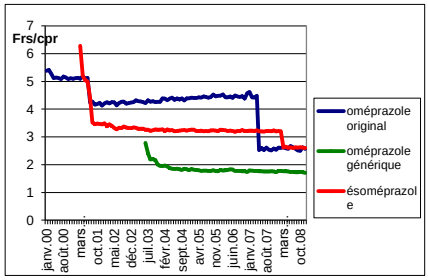
100% evergreening
All PPI prescriptions are switched to esomeprazole at admission from October 2002



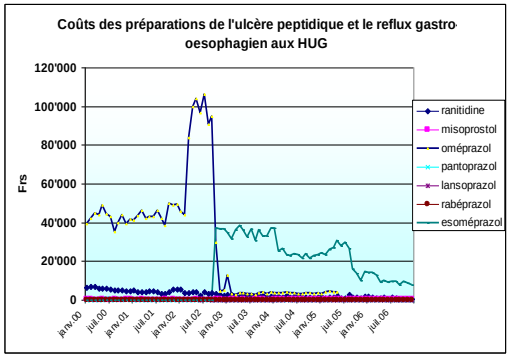
0% evergreening
levocetirizine or brand cetirizine prescriptions are switched at admission from septembre 2004

Spillover extra costs





« Hospital RDF »



	Decision for the RDF	2001	2002	2003	2004	2005	2006	2007	2008	2000 - 2008
omeprazole - esomeprazole	**In October 2002 the RDF switched from omeprazole to esomeprazole. All the PPI prescriptions are switched to esomeprazole at admission.**	**13·0 [8·4;17·5]**	**53·0 [48·5;57·5]**	**-0·9 [-5·3;3·5]**	**30·3 [26·1;34·4]**	**27·4 [23·3;31·6]**	**71·4 [67·4;75·4]**	**81·1 [77·1;85·1]**	**54·5 [50·9;58·0]**	**329·7 [317·2;342·3]**
citalopram - escitalopram	RDF switched to the generic citalopram in December 2003. Escitalopram is unrestricted.	0 [-2·3;2·3]	1·2 [-1·0;3·4]	6·0 [3·5;8·4]	24·8 [22·3;27·3]	36·3 [33·9;38·7]	52·5 [50·2;54·8]	42·9 [40·8;45·1]	29·8 [27·9;31·6]	193·5 [186·6;200·4]
gabapentin - pregabalin	RDF switched to the generic gabapentin in February 2008. Pregabalin is unrestricted.	0 [-1·8;1·8]	0 [-1·9;1·9]	0 [-2·2;2·2]	0 [-2·5;2·5]	1·2 [-1·4;3·9]	4·0 [1·3;6·6]	3·0 [0·3;5·7]	0·7 [-2·1;3·6]	**9·0 [1·9;16·0]**
zolpidem - zolpidem CR	RDF switched brand zolpidem to generic in June 2006. Modified release zolpidem is restricted.	0 [-0·5;0·5]	0 [-0·6;0·60]	0 [-0·6;0·6]	0 [-0·6;0·6]	0·8 [0·2;1·5]	1·4 [0·9;2·0]	1·1 [0·6;1·6]	1·0 [0·5;1·5]	**4·3 [2·7;6·0]**
loratidine - desloratidine	RDF switched brand to generic loratidine and desloratidine to generic cetirizine in February 2006 at admission.	0 [-0·3;0·3]	0 [-0·4;0·4]	0 [-0·4;0·4]	0 [-0·5;0·4]	0 [-0·5;0·4]	0·3 [-0·1;0·7]	0·6 [0·2;0·9]	0·3 [-0;0·7]	**1·1 [0·0;2·2]**
alendronic acid - alendronic and colecalciferol	Neither alendronic acid nor its combination is included in the RDF. Those prescriptions are unrestricted.	0 [-0·8;0·8]	0 [-1·0;1·0]	0 [-1·1;1·1]	0 [-1·1;1·1]	0 [-1·2;1·2]	0 [-1·2;1·2]	-1·5 [-2·6;-0·5]	0 [-0·8;0·8]	**-1·5 [-4·6;1·5]**
cetirizine - levocetirizine	**RDF switched brand cetirizine and levocetirizine to generic in December 2004 at admission.**	**0 [-0·4;0·4]**	**0 [-0·1;0·8]**	**0 [-0·5;0·5]**	**0 [-0·5;0·6]**	**-0·2 [-0·7;0·3]**	**-0·7 [-1·2;-0·2]**	**-2·1 [-2·60;-1·6]**	**-2·7 [-3·2;-2·3]**	**-5·3 [-6·7;-3·9]**
simvastatin - simvastatin and ezetimibe	RDF switched brand simvastatin to generic in August 2004. Combined simvastatin and ezetimibe are unrestricted.	0 [-1·4;1·4]	0 [-1·3;1·3]	0 [-1·2;1·2]	9·5 [8·3;10·7]	21·8 [20·8;22·8]	-11·3 [-12·1;-10·5]	-21·3 [-22·2;-20·3]	-18·0 [-19·1;-16·8]	**-19·1 [-22·8;-15·5]**
Total		**13·0 [7·3;18·7]**	**54·7 [49·0;60·3]**	**5·0 [-0·8;10·9]**	**64·6 [58·8;70·4]**	**88·3 [82·5;94·1]**	**118·9 [113·3;124·6]**	**105·0 [99·4;11·0]**	**66·5 [61·4;71·7]**	**516·0 [499·1;532·9]**

EAHP, Barcelona March 2014

Strenghs & limitations

Strenghs

- robust data
  73% of the total of insured patients
- robust methodology

Limitations

-some patients may benefit
-substitution
-promotional activities

Conclusions

Spillover effect

Financial impact of listing drugs in hospital restrictive drug formularies on the healthcare system as a whole

Evergreening strategies

Financial impact of the evergreening strategies on overall healthcare costs

Σ ε ® C][