



Génériques et fausse innovation exemples de l'evergreening et du spillover

**COLLOQUE DE PHARMACOLOGIE
CLINIQUE GENEVE – VAUD
Nyon, jeudi 5 décembre 2013**

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Pharmacienne adjointe,
Responsable secteur Achat/Distribution**





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

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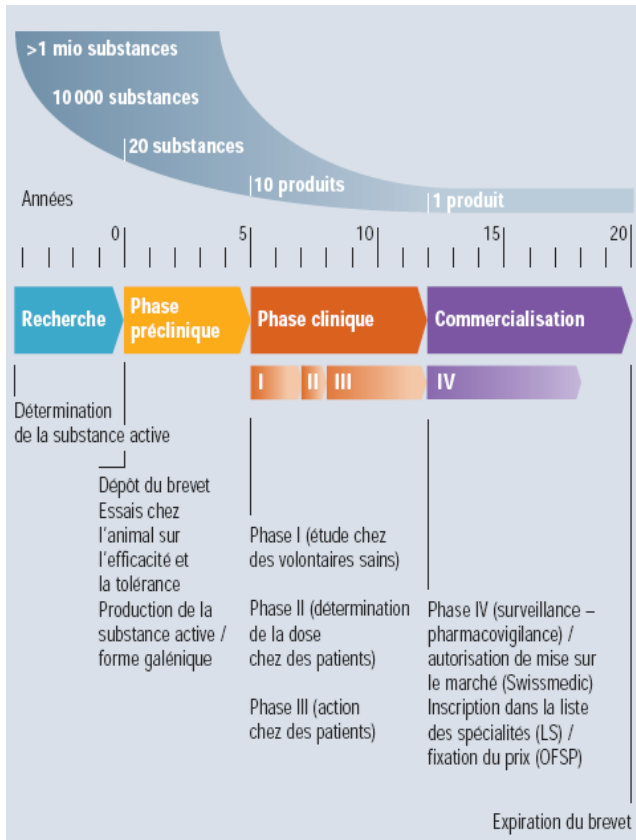


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ZAPIRO



Génèse du médicament



DiMasi estime le coût de la recherche à
- \$802 million in 2000 par molécule, and
- \$1,318 million in 2005 biologiques

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).

Pour encourager l'innovation et comme tous les autres produits, les médicaments sont protégés par des brevets dont la durée a été harmonisée à **20 ans**.

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



Brevets: critères d'éligibilité

- “non obvious”
 - brevet sur la molécule et ses différentes structures chimiques, ses métabolites actifs
 - le mode de synthèse,
 - la forme galénique (ex: retard),
 - les méthodes de traitement,
 - les indications,
 - le procédé de fabrication,
 - association de composés, etc.

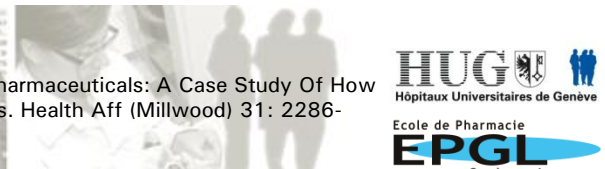


Ritonavir et lopinavir/ritonavir

- 108 brevets additionnels -> 2028

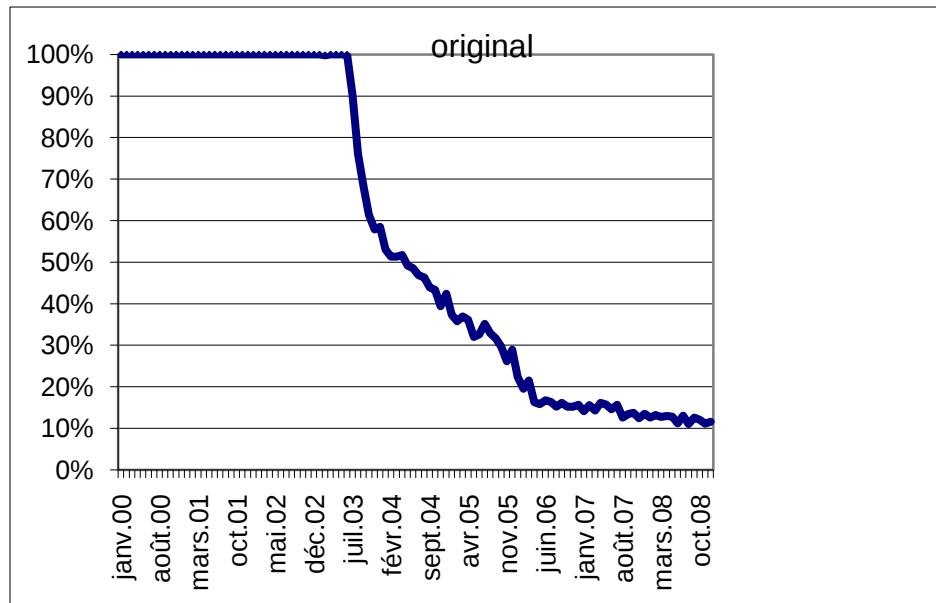
Patent categories	Ritonavir	Lopinavir	Lopinavir/ritonavir	Ritonavir and/or lopinavir with other compounds	Total
Total	— ^a	— ^a	— ^a	— ^a	210
Base compound or active ingredient	1	1	0	0	2
RELATED CHEMICAL STRUCTURES AND COMPOSITIONS OR FORMULATIONS (81)					
Composition and formulation ^b	18	9	15	7	49
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. ^aNot applicable. Because the categories are not mutually exclusive, patents with claims in more than one category are listed more than once. ^bIncludes combinations with other HIV-treating compounds, salt forms, ester derivatives, and dosage forms. ^cProcesses for making analogs, intermediates, formulations or compositions, and polymorphs. ^dGeneral patents that could be applied to ritonavir, lopinavir, or both.



Amin T, Kesselheim AS Secondary Patenting Of Branded Pharmaceuticals: A Case Study Of How Patents On Two HIV Drugs Could Be Extended For Decades. Health Aff (Millwood) 31: 2286-2294

Vraie vie: eso-omeprazole



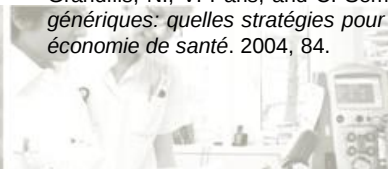
Evergreening

Stratégies des laboratoires pour freiner le développement des génériques pour les dix molécules étudiées

DCI	Nom de la spécialité en France	Nom de la spécialité à l'étranger	Classe thérapeutique	Nom du laboratoire	Stratégies observées				
					Dépôt incremental de brevets	Recours en justice contre génériques	Nouvelles formulations, extensions d'indications	Molécule dérivée	Passage en automatisation
Amoxicilline-acide clavulanique	Augmentin®	Augmentin® (RU, USA) Augmentan (A)	Antibiotique	Glaxo Smith-Kline	x	x	x		
Buspirone	Buspar®	Bespar® (A) Buspar® (RU, USA)	Anxiolytique	Bristol Myers Squibb	x	x			
Cétirizine	Zyrtec® Virlix®	Zyrtec® (A, USA) Reactine® (A) Zirtec® (RU)	Anti-histaminique	UCB Pharma Sanofi Synthelabo			x	x	
Citalopram	Seropram®	Cipramil® (A, RU) Celexa® (USA)	Antidépresseur serotoninergique	Lundbeck			x	x	
Fluoxétine	Prozac®	Prozac®	Antidépresseur serotoninergique	Eli Lilly		x	x		
Gabapentine	Neurontin®	Neurotin® (A, RU)	Anticonvulsivant	Pfizer	x	x	x	x	
Loratadine	Clarityne®	Claritin® (US) Clarityn® (RU) Lisino® (A)	Anti-histaminique	Schering-Plough		x	x	x	x
Omeprazole	Mopral® Zoltum®	Antra® (A) Losec® (RU) Prilosec® (USA)	Inhibiteur pompe à protons	Astra Zeneca Aventis		x	x	x	x
Paroxétine	Deroxat®	Paxil® (USA) Seroxat® (A, RU)	Antidépresseur serotoninergique	Glaxo Smith-Kline		x	x		
Zolpidem	Stilnox®	Stilnoct® (RU) Ambien® (USA)	Hypnotique	Sanofi-Synthelabo			x		

- Arsenal de stratégies =
- 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 en économie de santé*. 2004, 84.



Chiralité: un peu d'histoire



Study of Praying Hands
Albrecht Dürer (1508)

Prix Nobel de chimie en 2001

« Travaux sur les réactions d'hydrogénation catalysées par chiralité »

- **William S. Knowles** Saint-Louis, Missouri, USA
- **Ryoji Noyori** Nagoya University, Chikusa, Nagoya, Japon,

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



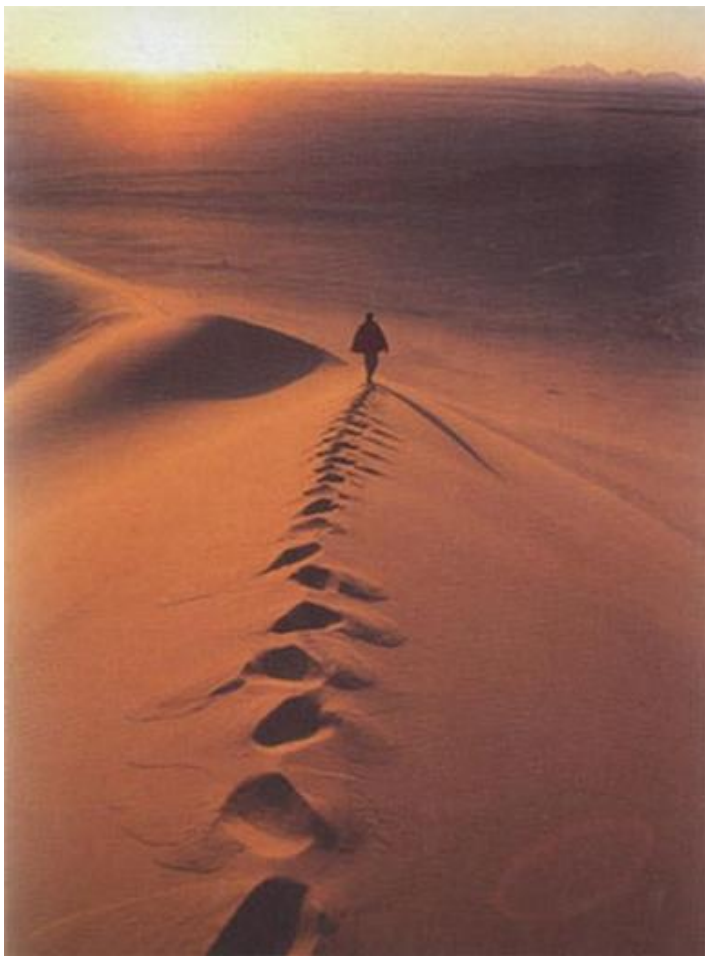
Bénéfices cliniques attendus

- Amélioration de la sécurité
 - > Augmentation de l'affinité aux récepteurs
 - > Diminution des effets secondaires
- Modification de la demi-vie
 - > dosage plus approprié
- Diminution de la variabilité interindividuelle
- Diminution de l'interaction entre médicaments

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



Bénéfices cliniques démontrés



Pas d'étude clinique "head to Head" ou alors

compare 40mg esomeprazole à 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 usefull 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

- **Breveter et mettre sur le marché des molécules légèrement modifiées de médicaments déjà enregistrés -> à l'arrivée des génériques**
- **Associations de médicaments**
Acide alendronique combiné au colecalciferol et alendronic acid, simvastatin combinée à ezetimibe et simvastatin
- **Analogues structurels**
pregabalin et gabapentin
- **Métabolites actifs**
desloratadine et loratadine
- **Formes retards**
zolpidem retard et zolpidem
- **Single enantiomer**
omeprazole et esomeprazole
citalopram et escitalopram
cetirizine et levocetirizine

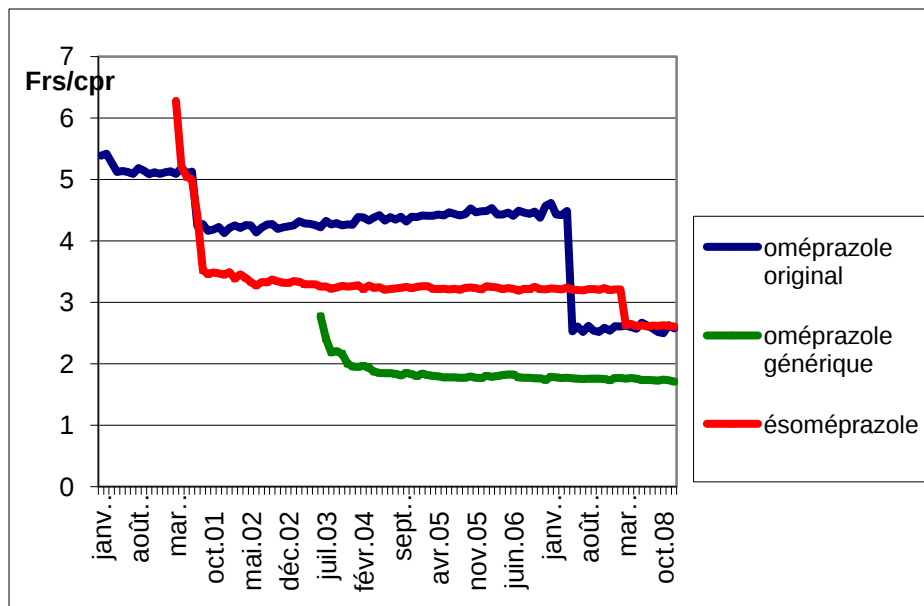


3 catégories de médicaments

- Original
 - Son générique
 - Son evergreening: médicament “original” sur lequel une stratégie d’evergreening est appliquée
-
- Médicaments commercialisés en même temps
 - Pas au même prix



Vraie vie: eso-omeprazole



Etude: les données

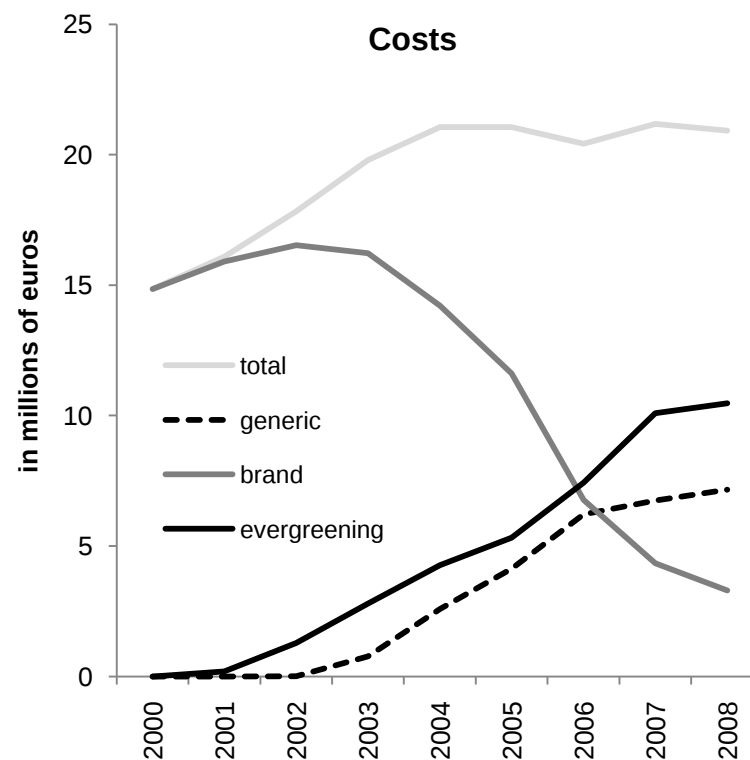
- OFAC: intermédiaire entre les pharmacies de ville et les assurances
 - Ordonnances GE (ville + HUG)
 - Couvre 92% des officines
 - 80% des assurés (pas Assura)
- HUG
- Janvier 2000 à décembre 2008



3 catégories

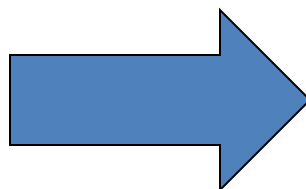
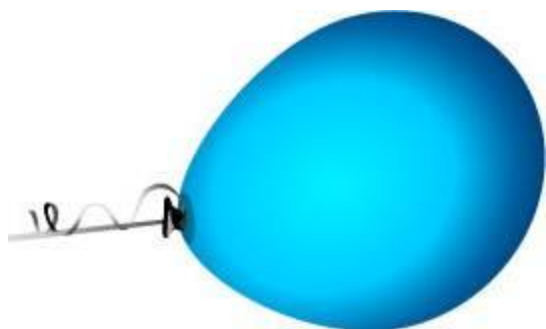
	Coûts en millions euros (95% IC)
total	173.208 (173.171 - 173.246)
originaux	103.744 (103.713 - 103.775)
evergreening	41.835 (41.817 - 41.854)
génériques	27.629 (27.619 - 27.640)

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



Hypothèse: « Squeezing the balloon » »

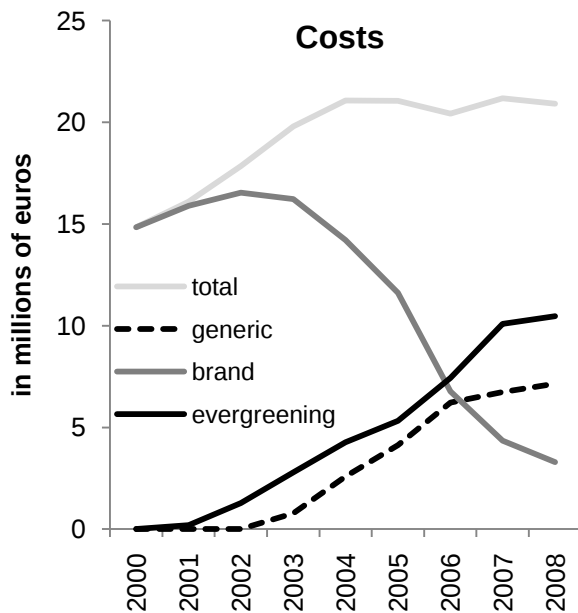
le volume dans lequel les molécules de l'air libres de se déplacer est réduit, elles mettent une grande énergie à traverser les frontières



la réduction financière attendue lors de l'arrivée des génériques ne serait pas aussi effective en réalité



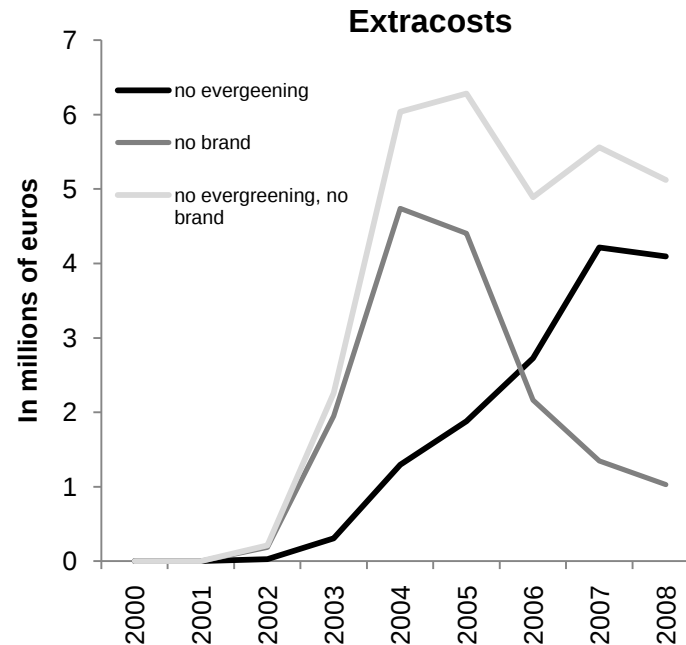
3 stratégies



- 1) Si tous les originaux étaient au prix des génériques
- 2) Si tous les evergreening étaient au prix des génériques
- 3) Si tous les originaux et les evergreening étaient au prix des génériques



Surcoût calculé



	Scenario 1 (no evergreening)			Scenario 2 (no original)			Scenario 3 (no evergreening, no original)		
	Euro (millions)	[CI95%]		Euro (millions)	[CI95%]	% of total	Euro (millions)	[CI95%]	% of total
<i>Total</i>	14·546	[14·495;14·597]		15·816	[15·765;15·867]		30·362	[30·313;30·411]	

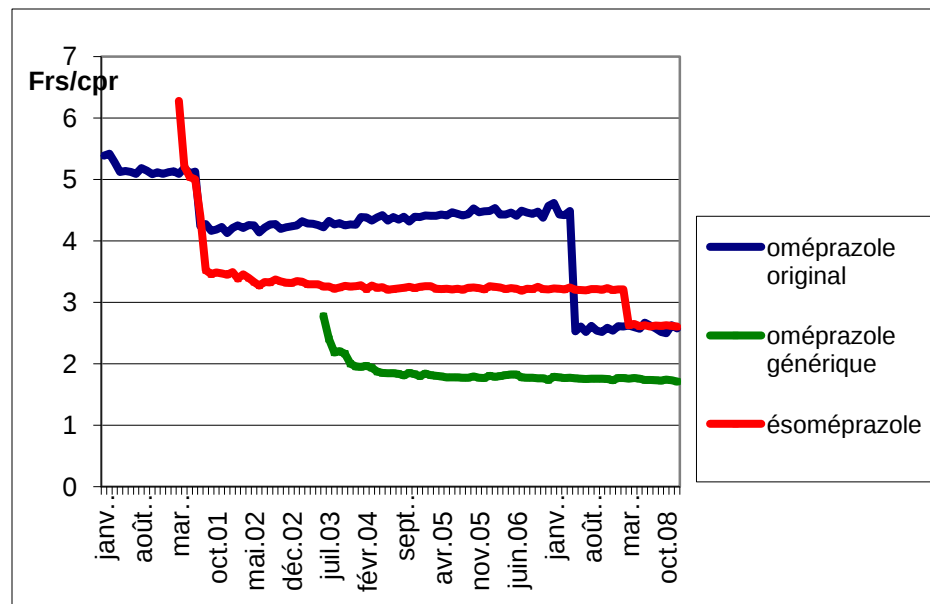
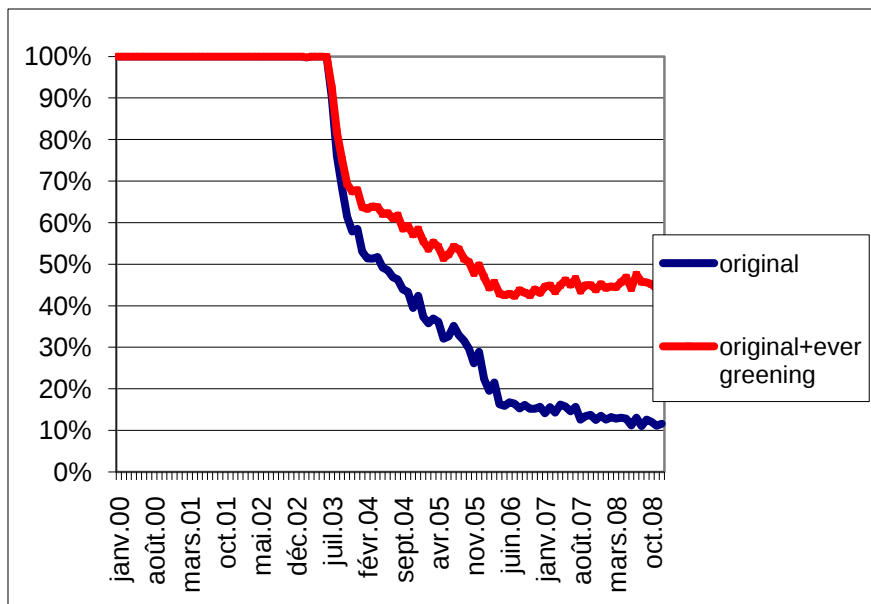


Surcoût calculé

	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
<i>omeprazole - esomeprazole</i>	5.262	[5.225;5.299]	36.2%	7294	[7.259;7.329]	46.1%	12.556	[12.521;12.591]	41.4%
<i>citalopram - escitalopram</i>	4.873	[4.851;4.895]	33.5%	4795	[4.773;4.817]	30.3%	9.668	[9.548;9.688]	31.8%
<i>simvastatin - simvastatin and ezetimibe</i>	2.636	[2.620;2.652]	18.1%	2697	[2.679;2.715]	17.1%	5333	[5.317;5.349]	17.6%
<i>alendronic acid - alendronic and colecalciferol</i>	203	[189;217]	1.4%	199	[185;213]	1.3%	402	[388;416]	1.3%
<i>zolpidem - zolpidem CR</i>	64	[58;70]	0.4%	418	[412;424]	2.6%	482	[476;488]	1.6%
<i>loratidine - desloratidine</i>	371	[367;375]	2.6%	43	[37;49]	0.3%	414	[410;418]	1.4%
<i>gabapentin - pregabalin</i>	630	[612;648]	4.3%	132	[114;150]	0.8%	762	[744;780]	2.5%
<i>cetirizine - levocetirizine</i>	507	[501;513]	3.5%	238	[232;244]	1.5%	745	[739;751]	2.5%
<i>Total</i>	14.546	[14.495;14.597]		15.816	[15.765;15.867]		30.362	[30.313;30.411]	



Vraie vie: eso-omeprazole



Spillover effect

Spill: renverser
over: dessus

Répercussion d'une décision-action prise dans un environnement sur un autre environnement



Tribune de Genève, 4 mars 2011

21



Liste des médicaments

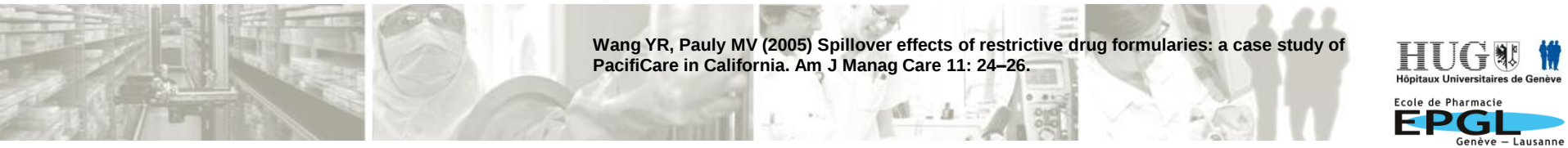
Objectif

- Hôpitaux
 - minimiser coûts d'acquisition -> négociation
 - limiter le nombre de médicaments
 - enseignement
- Maisons pharmaceutiques:
 - prescription et administration des médicaments
 - Spillover effect



Hypothèse

Impact de la liste de médicaments sur les coûts en ville



Wang YR, Pauly MV (2005) Spillover effects of restrictive drug formularies: a case study of PacificCare in California. Am J Manag Care 11: 24–26.

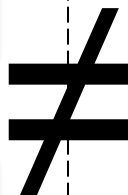
3 Environnements



464'000
habitants

Prix des
médicaments
fixe

Liberté de
prescription



Prix des
médicaments
négociés

Liste des
médicaments
restrictives

2'000 lits



ville

Ordonnances
de sortie HUG

HUG



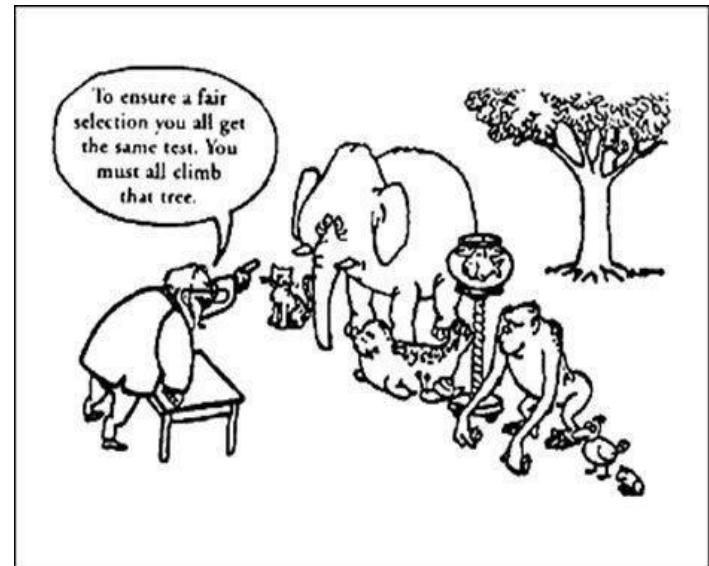
Indicateur de la prescription

% evergreening (DDD)

original + générique + evergreening
(DDD)

Même
échelle

Classe de
médicaments

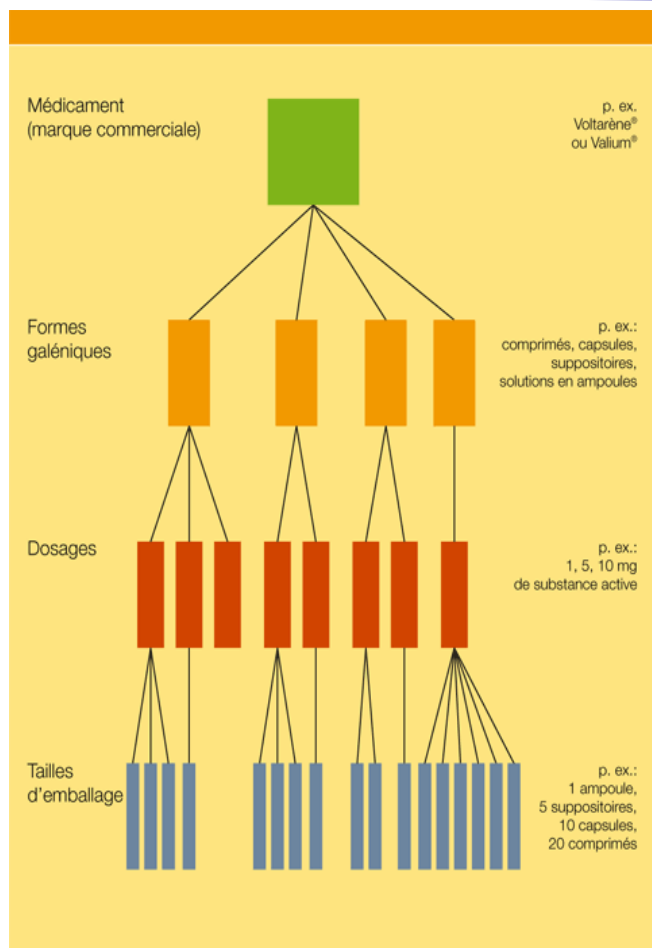


Muijters PE et al (2005) Fam Pract 22: 624-630

24



Defined Daily Dose





WHO Collaborating Centre for
Drug Statistics Methodology



Norwegian Institute of Public Health

News

ATC/DDD Index

Updates included in the ATC/DDD Index

ATC/DDD methodology

ATC

DDD

ATC/DDD alterations, cumulative lists

ATC/DDD publications

Use of ATC/DDD

Courses

Meetings/open session

Deadlines

Links

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J ANTIINFECTIVES FOR SYSTEMIC USE

J01 ANTIBACTERIALS FOR SYSTEMIC USE

J01C BETA-LACTAM ANTIBACTERIALS, PENICILLINS

J01CR Combinations of penicillins, incl. beta-lactamase inhibitors

ATC code	Name	DDD	U	Adm.R	Note
J01CR02	amoxicillin and enzyme inhibitor	1 g		O	Refers to amoxicillin
		3 g		P	Refers to amoxicillin

[List of abbreviations](#)

Last updated: 2010-12-21

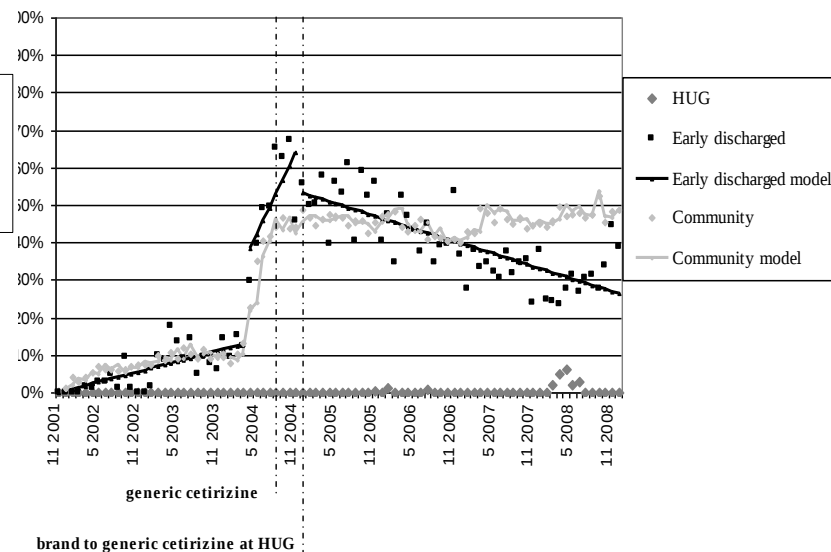
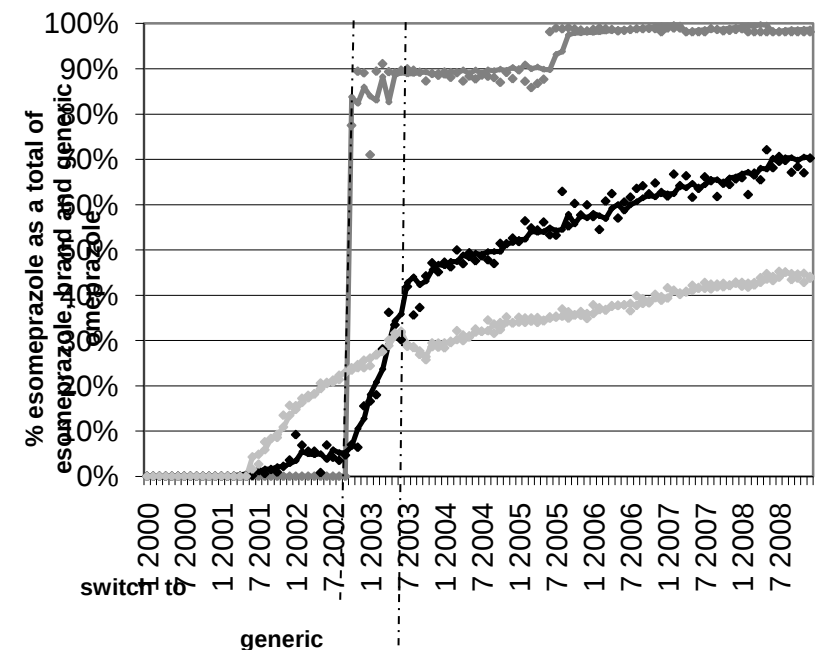
Ex: Co-Amoxiclav
agrégation 80 références en une seule

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

Interpharma, Le marché du médicament en Suisse. 2008



Mesure du spillover effect



Spillover effect

Changement dans le formulaire des patients affiliés au réseau PacifiCare:

Inclusion du rabéprazole et du pantoprazole et retrait de l'oméprazole et du lansoprazole

Patients non-PacifiCare :

10% increase in PacifiCare share of practice led to a 3.3% share increase for rabeprazole and a 1.6% share increase for pantoprazole, respectively (both $P < .001$).

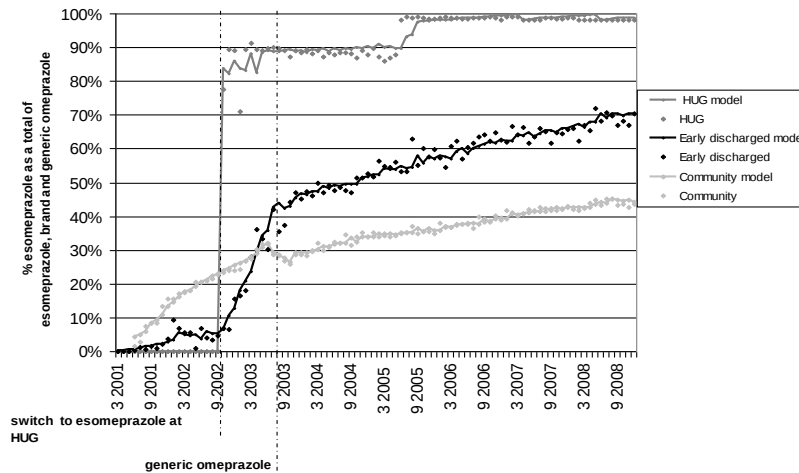
Wang, Y.R. and M.V. Pauly, *Spillover effects of restrictive drug formularies: a case study of PacifiCare in California*. Am J Manag Care, 2005. **11**(1): p. 24-6.

Virabhak, S. and J.A. Shinogle, *Physicians' prescribing responses to a restricted formulary: the impact of Medicaid preferred drug lists in Illinois and Louisiana*. Am J Manag Care, 2005. **11 Spec No**: p. SP14-20.

Feely, J., et al., *The influence of hospital-based prescribers on prescribing in general practice*. Pharmacoeconomics, 1999. **16**(2): p. 175-81.



Calcul des coûts



- Différence de proportion de prescription des catégories de médicaments

**ordonnance de sortie HUG
ville**



Effet indésirable de la liste restrictive des médicaments

	Decision for the RDF	2000 - 2008
omeprazole - esomeprazole	All the PPI prescriptions are switched to esomeprazole at admission from October 2002	330.3 [276.1;383.8]
citalopram - escitalopram	RDF switched to generic citalopram in December 2003. Escitalopram is unrestricted.	192.3 [168.5;215.9]
gabapentin - pregabalin	RDF switched to generic gabapentin in February 2008. Pregabalin is unrestricted.	5.0 [1.3;8.8]
zolpidem - zolpidem CR	RDF switched brand zolpidem to generic in June 2006. Modified release zolpidem is restricted.	4.3 [3.0;5.6]
loratidine - desloratidine	RDF switched brand to generic loratidine and desloratidine to generic cetirizine in February 2006 at admission.	2.4 [0.7;4.5]
alendronic acid - alendronic acid and colecalciferol	Neither alendronic acid nor its combination is included in the RDF. Those prescriptions are unrestricted.	-0.7 [-2.4;1.0]
cetirizine - levocetirizine	RDF switched brand cetirizine and levocetirizine to generic in December 2004 at admission.	-7.7 [-11.1;-4.1]
simvastatin - simvastatin and ezetimibe	RDF switched brand simvastatin to generic in August 2004. Combined simvastatin and ezetimibe are unrestricted.	-22.3 [-36.7;-8.2]
Total		503.6 [444.5;563.1]

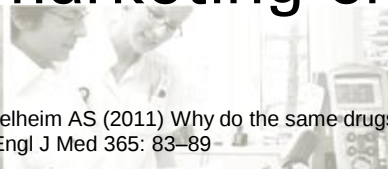
Forces et limites

Forces

- Source de l'information unique
- Longue période 9 ans
- 73% patients assurés
- Situation particulière du canton de Genève avec un seul hôpital universitaire

Limites

- pas de différence clinique entre les 3 catégories de médicaments: même outcome
- adhérence des patients
- pas de mesure du marketing en ville



Greene JA, Kesselheim AS (2011) Why do the same drugs look different? Pills, trade dress, and public health. N Engl J Med 365: 83–89

Take home message: Be aware of evergreening



Hallmarks of evergreening—when to be suspicious of a new medicine

- It is described as an isomer/enantiomer (its name may be prefixed lev-, dex-, or es-), active metabolite, or analogue
- It is a modified release or fixed dose combination product
- It is promoted over the drug it supersedes on the basis of theoretical advantages, perhaps with some non-clinical data, but not substantiated by robust clinical evidence
- It is promoted as being less expensive than the drug it supersedes, but the price comparison fails to take account of their different patent expiry dates



$\Sigma \varepsilon \textcircled{R} C] [$

