



World Health
Organization

New medicines at any cost?

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Declaration of interests

- I work for WHO; the opinions in this presentation are mine as an individual and do not represent those of WHO.
- I have no financial ties to any commercial entity.

Where we started from

Period	Number of NCEs	Innovation index	NCEs listed in WHO EDL	NCEs listed in WHO EDL indicated for a neglected disease
1975-79	248	0-339	2*	0
1980-84	256	0-308	18†	6
1985-89	277	0-278	8‡	4
1990-94	280	0-314	4§	1
1995-99	332	0-324	7¶	5
Total	1393	..	37	16
5-year average	279	0-313	7	3

NCEs=new chemical entities. *Cisplatin, levotyrosine. †Actosol, benzotiazol, captopril, cimetidine, ceftriaxone, clavulanic acid, factor VIII concentrate, factor IX complex, lomefloxacin, nifedipine, nitroglycerin, osimertinib, perindopril, praziquantel, pyrazinamide, testosterone enanthate, ‡Arbuzolone, ceftriaxone, ciprofloxacin, fluconazole, levamisole, halobutolone, metoprolol, zidovudine. §Atraxone, ciclosporin, atorvastatin, imipenem-cilastatin. ¶Lacosamide, amphotericin B, artemether, atovaquone, etoposide, nevirapine, rifabutin, rifampicin. Italics indicate approval for a neglected-disease indication. Sources: EMEA and FDA data; IMS statistics; WHO essential drug list (EDL, available at www.who.int/medicines/en/edl-alpha.html); reference 5.

Trouiller et al, Lancet 2002;359:2188-2194 .



Forbes Pharma & Healthcare

The Little Black Book

APRIL 11, 2017 @ 11:39 AM 185,122 VIEWS

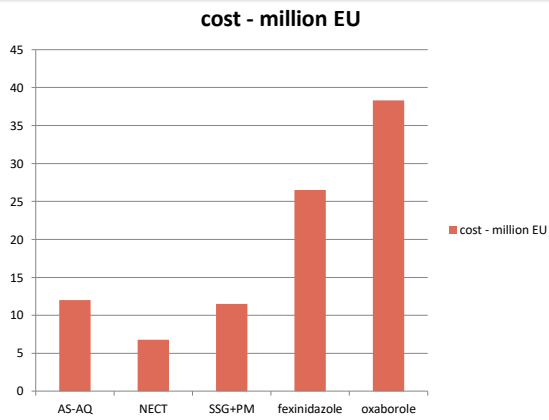
The Cost Of Creating A New Drug Now \$5 Billion, Pushing Big Pharma To Change

The \$2.6 Billion Pill — Methodologic and Policy Considerations

Jerry Avorn, M.D.



DNDi product development costs



http://www.dndi.org/images/stories/pdf_aboutDNDi/DNDiModel/DNDi_CostOfDev_FactsFigures



A changing industry

Table 1
Recent history of large pharmaceutical mergers (revisions are noted by 2010 worldwide sales)

1.	Pfizer 2008: Acquired Wyeth (which resulted from 1994 merger of American Cyanamid and American Home Products) 2009: Acquired Pharmacia (which acquired Upjohn in 1995) 2009: Acquired Warner-Lambert.	3.	Sandoz-Abbott 2011: Acquired Genzyme 1998: Name changed after merger of Rhône-Poulenc and Hoechst 1995: Hoechst acquired Marion Merrell Dow 1992: Rhône-Poulenc acquired Stearns 1988: Rhône-Poulenc acquired ICI.
2.	Johnson & Johnson (no major mergers)	4.	Glaxo-SmithKline 2008: SmithKline Beecham merged with Glaxo 1995: Wellcome merged with Glaxo 1989: Beecham merged with Searle/Kline.
3.	Novartis 2011: Acquired Alcon 1996: Resulted from merger of Ciba Geigy and Sandoz	5.	Abbott (no major mergers)
4.	Roche 2008: Consolidated 1999 acquisition of Genentech 1995: Acquired Sandoz	10.	Astra-Zeneca 1999: Zeneca Group merged with Astra AB
5.	Rayn (no major mergers)	11.	EE Lilly (no major mergers)
6.	Merck 2008: Acquired Schering-Plough	12.	Bristol-Myers Squibb 2001: Acquired Hoffman Pharmaceuticals 1988: Bristol-Myers and Squibb merged; name change

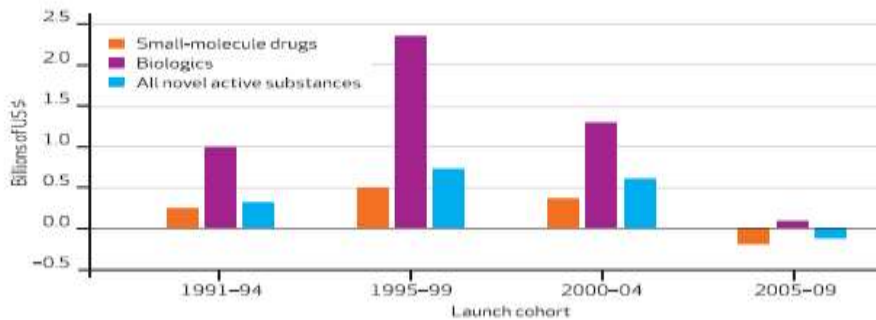
Comanor & Schering *J Health Econ* 2013;32:106-113.

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EXHIBIT 4

Average Lifetime After-Tax Net Returns Of Novel Active Substances, By Launch Cohort, 1991–2009



SOURCE Authors' analysis of 1991–2012 data from IMS Health Inc.'s MIDAS database.

Berndt et al, *Health Affairs* 2015;34:245-252.

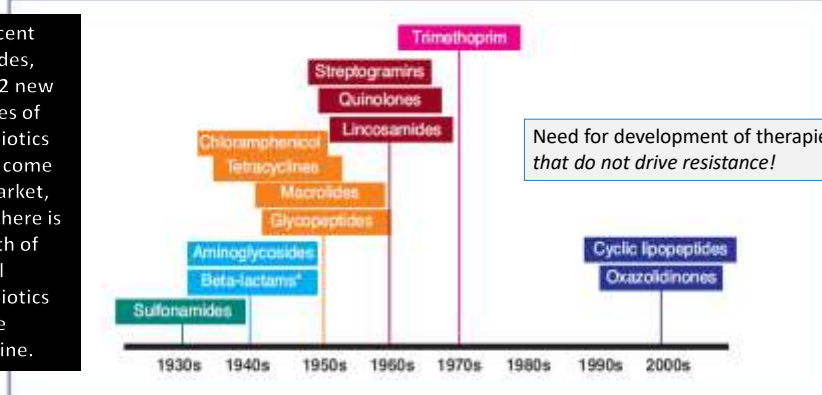
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And what are we missing?

Discovery of new classes of antibacterial drugs (1930s to 2000s)

In recent decades, only 2 new classes of antibiotics have come to market, and there is dearth of novel antibiotics in the pipeline.



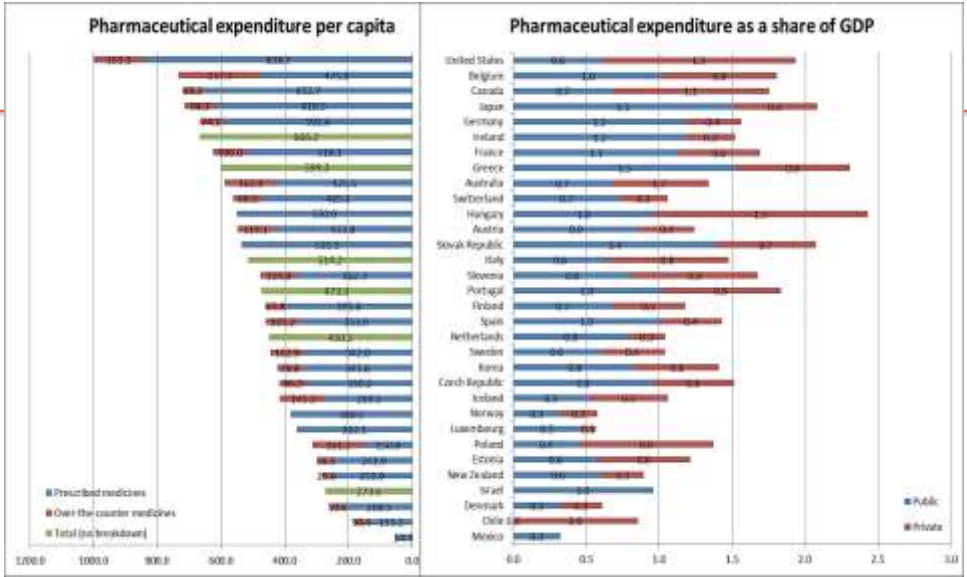
Need for development of therapies that do not drive resistance!

* Penicillins were the first beta-lactams. This class includes cephalosporins and carbapenems, developed in the 1960s and 1980s, respectively.

Source: Reproduced with data from ¹⁰. Modified with permission from Thomson Reuters (Professionals) Ltd

WHO, 2012. The evolving threat of antimicrobial resistance. Options for action.

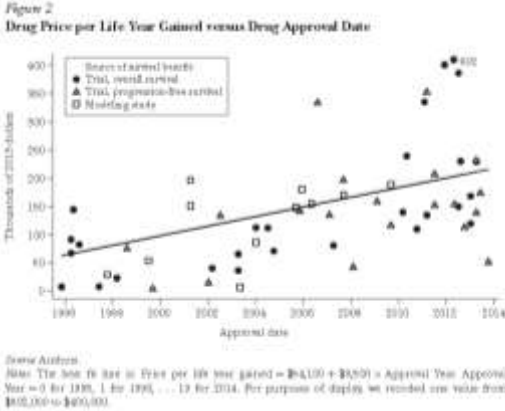
What are we spending?



OECD, 2014

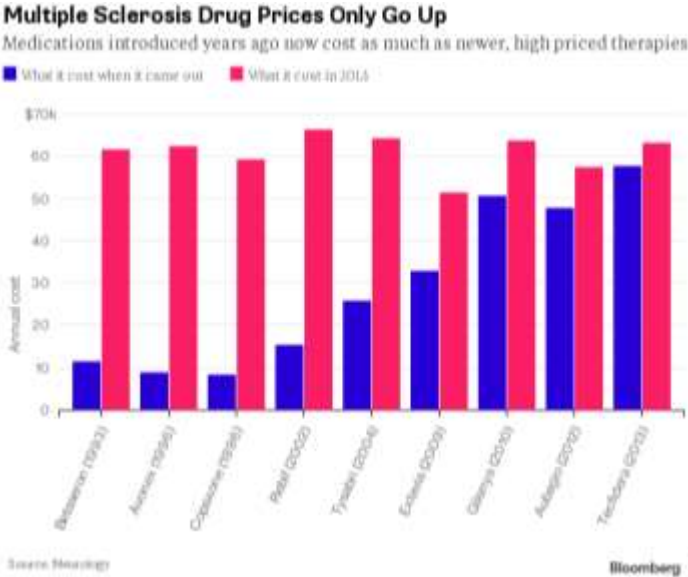


What is happening with market entry prices?



Howard DH, Bach PB, Berndt ER, Conti RM. Pricing in the market for anticancer drugs. *J Econ Persp* 2015;29: 139–162.

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From the payers perspective



Luo, Avorn & Kesselheim. JAMA Intern Med 2015;175:1681-1686.

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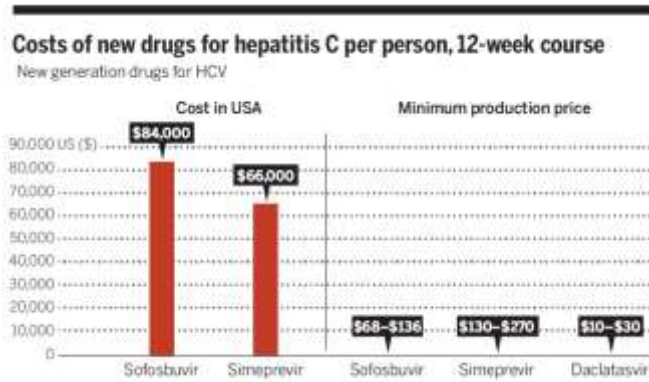
Estimated price for sofosbuvir



Iyengar S, Tay-Teo K, Vogler S, Beyer P, Wiktor S, et al. (2016) Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. PLOS Medicine 13(5): e1002032. doi: 10.1371/journal.pmed.1002032

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Cost of hepatitis C treatments?

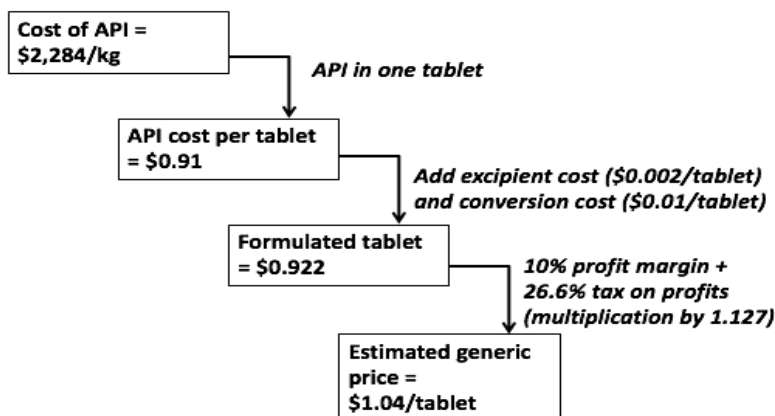


Hill A, Cooke G. *Science* 2014; 345(6193):141-142

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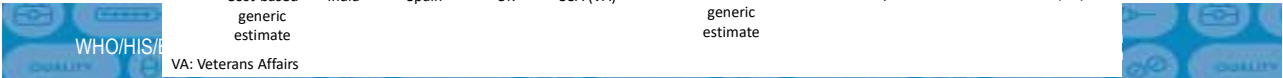
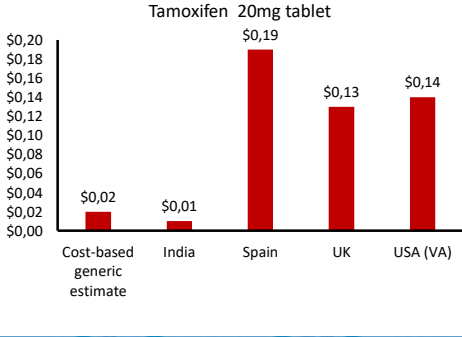
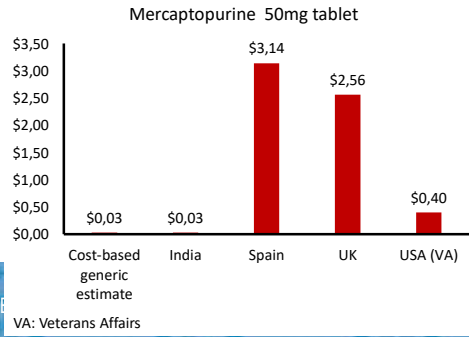
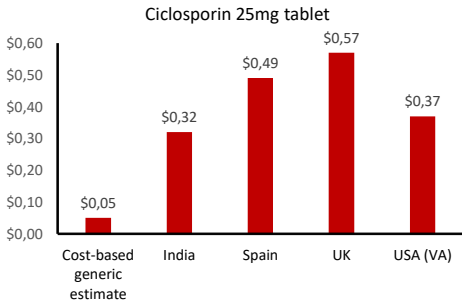
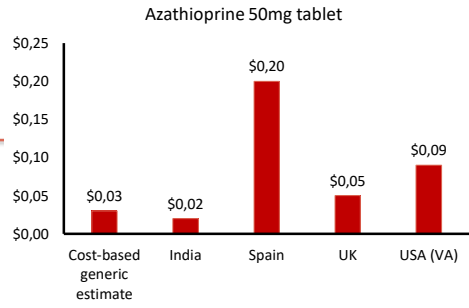
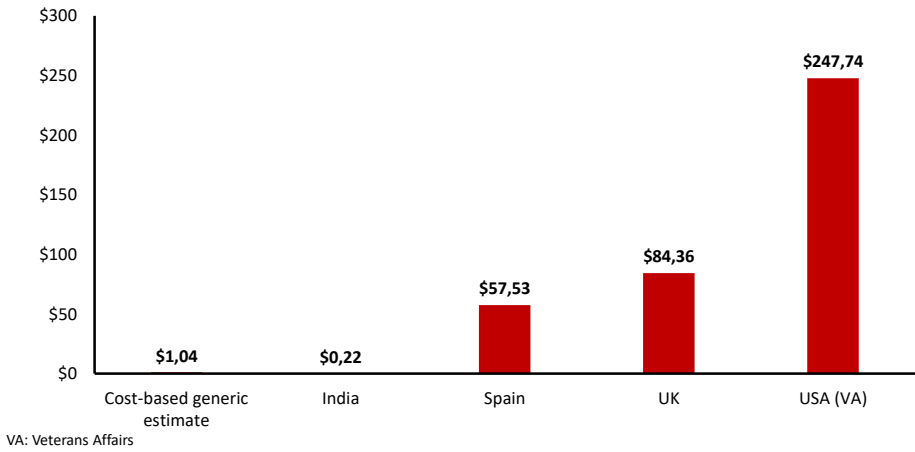
Calculating the Cost-based generic price of Imatinib



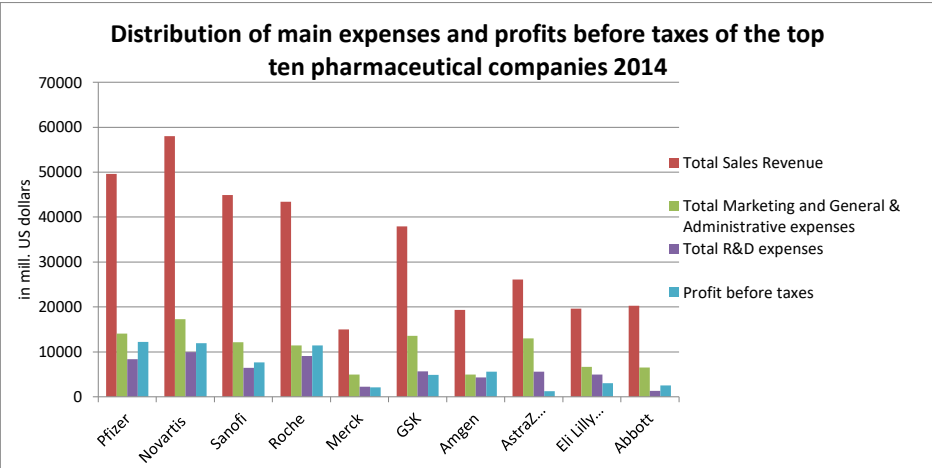
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Imatinib 400 mg tablet



Is R&D the main cost driver?

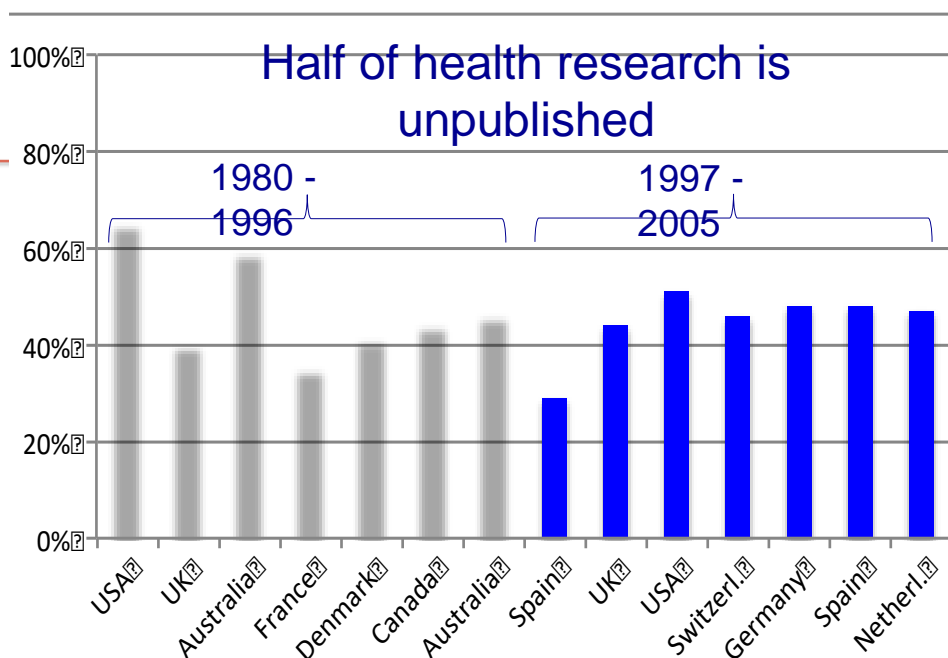
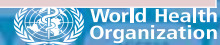


What do we know about clinical trials?

Clinical trial registration/results policies: some highlights

1986	First call for international registry (Simes R J Clin Oncol 1986)
2000	ClinicalTrials. Gov launched
2004	ICMJE policy announced, to start in 2005
2005	WHA resolution on universal registration; Chinese trial registry launched
2005	WHO ICTRP launched; WHO minimum registration dataset agreed
2007	U.S. FDA Amendments Act; Indian registry launched
2008	Updated Declaration of Helsinki mandated trial registration
2009	Registration mandatory for all clinical trials in India
2010	EU Clinical trials register launched
2012	Registration mandatory for phase I-IV trials in Brazil
2015	WHO launches position calling for public disclosure of results from all clinical trials – norm of 12 months from study completion date

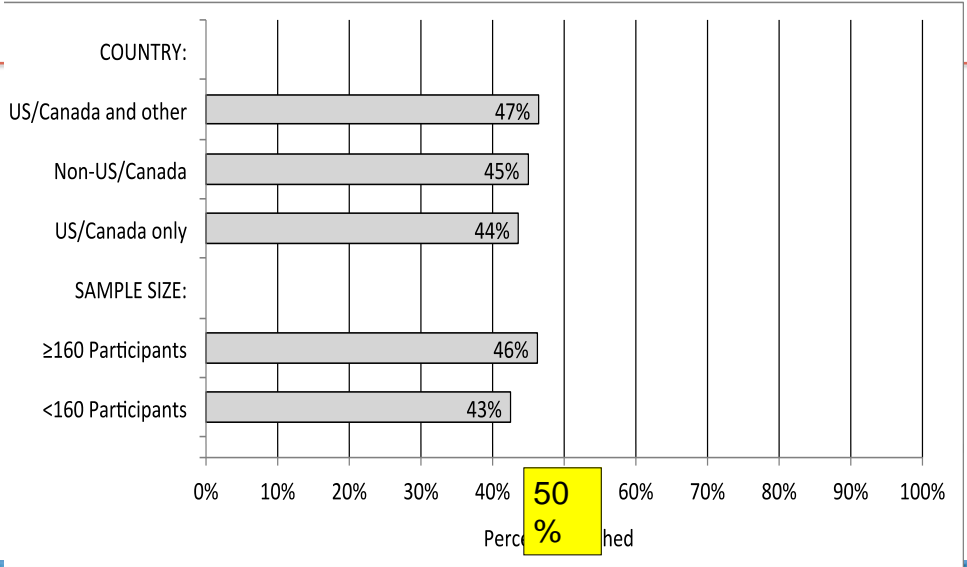
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Song F et al, *PLoS ONE* 2010

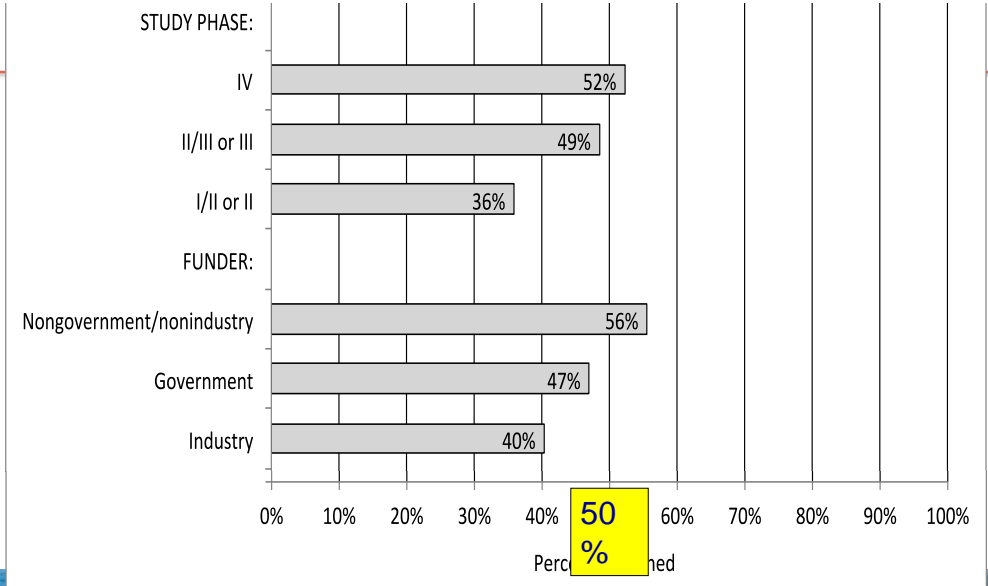
Non-publication affects all types of trials



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Ross J et al, PLoS Med 2009 World Health Organization

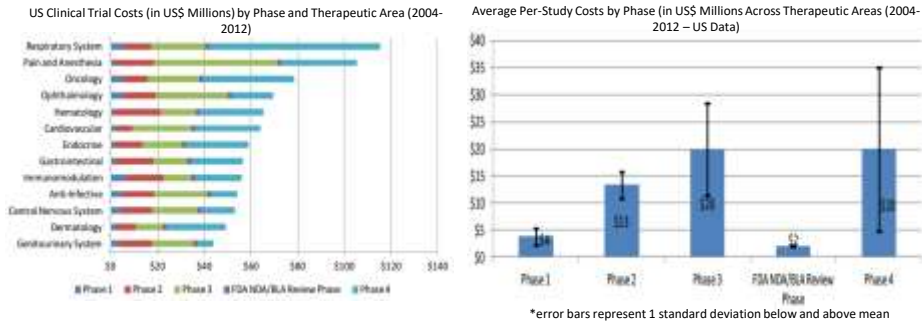
Non-publication affects all types of trials



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Ross J et al, PLoS Med 2009 World Health Organization

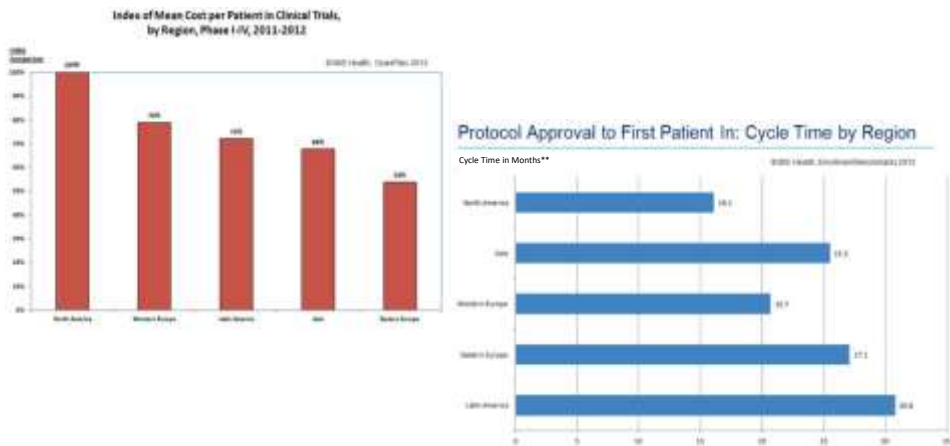
Costs of clinical trials?



Source: Sertkaya A, Birkenbach A, Berlind B, Eyraud J. 2014. Examination of Clinical Trial Costs and Barriers for Drug Development. Available: <https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development>



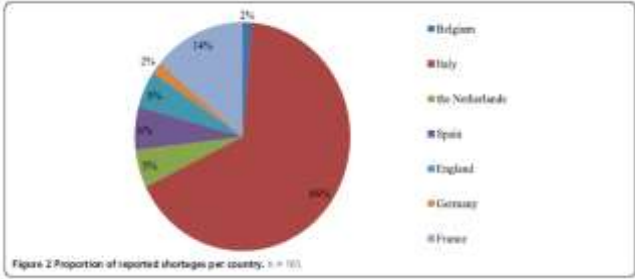
International cost of clinical trials vs. Time to first patient



THE OTHER SIDE OF THE PROBLEM

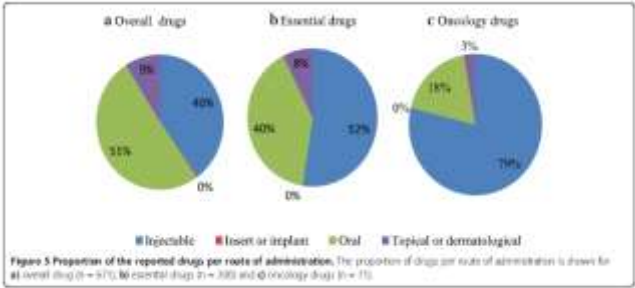


Shortages



Pauwels et al. BMC Health Services Research 2014;14:438.





Price to buyer and supplier?

Methotrexate



Vincristine 1mg



Table 2. Oncologists' Experiences With Shortages of Specific Drugs

Drug	Any Experience With Shortage				Needed to Use Equally Effective Alternative				Needed to Use Less Effective Alternative				Not Affected by Shortage	
	No.	%	Mean No. of Patients Affected [†]	SD	No.	%	Mean No. of Patients Affected [†]	SD	No.	%	Mean No. of Patients Affected [†]	SD	No.	%
Any drug	246	74	15.6	28.1	201	61	14.9	29.7	92	28	8.8	10.6	95	28
Lactoside	218	66	13.1	14.9	167	51	13.2	12.5	49	15	11.8	17.8	101	31
Fluorouracil	68	21	9.2	12.6	67	17	8.1	9.1	11	3	13.0	14.7	252	76
Dexamethasone [‡]	61	16	25.6	46.5	35	11	20.8	62.4	16	5	11.9	10.2	272	82
Cyclophosphamide	42	13	7.0	12.1	30	8	8.1	12.9	22	7	5.8	12.9	377	84
Podofilox	36	11	5.0	3.7	26	8	5.2	3.6	9	3	4.7	4.2	286	86
Capecitabine	27	8	4.8	5.5	19	4	3.9	2.0	14	4	5.6	7.6	393	89
Etoposide	27	8	3.6	2.7	12	4	2.3	0.8	15	5	4.5	3.2	396	89

Abbreviation: SD, standard deviation.

[†] Among patients of the physician reporting any experience with the shortage or needing to use an alternative.[‡] Supportive medication.Kehl et al. *J Onc Practice* 2014;11:e154-e162

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WHAT TO DO?

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The policy menu



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FROM: Policy Options for pharmaceutical pricing and purchasing: issues for low and middle income countries.
Nguyen et al Health Policy and Planning 2015.

Policy group	Strategy
Pricing techniques	<ul style="list-style-type: none"> • External reference pricing • Internal reference pricing • Pharmacoeconomic evaluation for value based pricing (HTA) • Cost plus pricing • Profit ceilings
Implementing pricing policies	<ul style="list-style-type: none"> • Fixing prices at retail/pharmacy level, Maximum Retail Prices • Fixing prices at wholesale level – maximum whole sale price • Fixing price at ex-manufacturer and importer level • Limiting price increases, price freezes • Price cuts • Margin cuts • Fixed mark-ups • Capped mark-ups • Regressive mark-ups • Fixed dispensing fees • Prohibiting discounts
Purchasing policies	<ul style="list-style-type: none"> • Positive list • Negative list • Price volume agreement • Health outcome agreement • Tender • Pooled procurement
Others	<ul style="list-style-type: none"> • Co-payments • Brand premiums • Safety nets • Generic substitution

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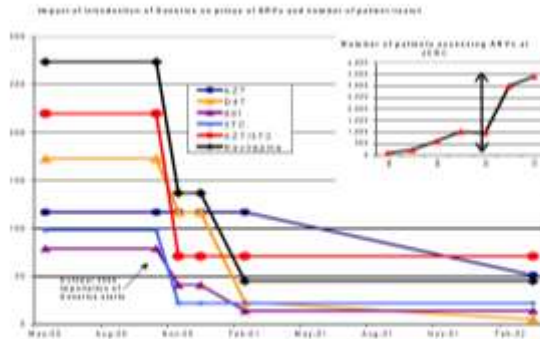


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What has worked?



Generic competition



OXFAM Briefing Paper 26 2002.



Reference pricing

Implications for US Prescription Drug Spending

■ Table 3. Impact of Reference Pricing on Expenditures and Resource Consumption

Policy	Author (Year)	Drugs Class	Time Frame ^a	Percent Change	Absolute Change
Monthly Patient Expenditure					
Canada 1997	Schneeweis (2000)	Calcium channel blockers		-12%	-\$6
Canada 2003	Mitasa (2006)	Proton pump inhibitors		-12%	-\$8
Germany 2005	Stargardt (2005)	Statins		-16%	-\$49
US 2005	Johnson (2005)	Proton pump inhibitors		-7%	-\$7
Changes in Annual Payer Expenditure					
Canada 1995	Grotenhuis (2002)	Statins		-52%	-\$2.8 million ^b
Canada 1997	Gronmeyer (2002)	ACE inhibitors			-\$84,000
		Calcium channel blockers			-\$1.09 million ^b
	Gronmeyer (2006)	NSAIDs		-44%	-\$4 million ^b
Norway 2002	Breke (2007)	Multiple classes ^c		-14%	-\$76 million NOK
Germany 2005	Margardt (2005)	Statins			-\$94.4 / \$98.7 million
US 2005	Johnson (2005)	Proton pump inhibitors	at 1 year		-\$2.5 million
			at 2 years		-\$2 million
			at 3 years		-\$1.6 million

Lee et al. *Am J Managed Care* 2012;18(11):e429-e437

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Current approaches

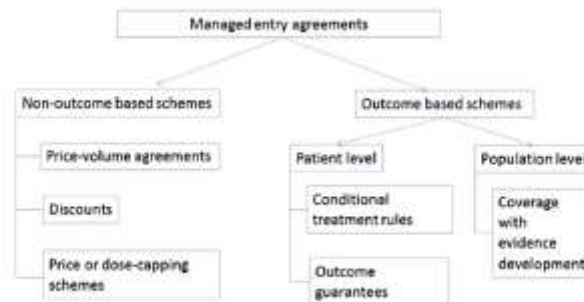


Fig. 1. Taxonomy of managed entry agreements.

Vitry & Rougehead *Health Policy* 2014;117:345-352.

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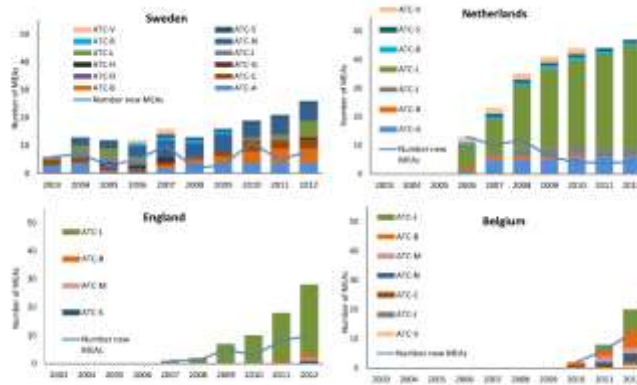


Fig. 3. Trends in MA implementation since the introduction of the first MA in the four study countries. Notes: ATC classification: A, Anesthetics and sedatives; B, Blood and blood-forming agents; C, Cardiovascular system; D, Dermatologicals; E, Gastrointestinal system and sex hormones; F, Genitourinary preparations, excl. sex hormones and insulin; G, Anti-infectives for systemic use; H, Antineoplastic and immunomodulating agents; K, Musculo-skeletal system; M, Nervous system; N, Respiratory system; S, Sensory organs; V, Various. Source: MYRCC, ATC index 2013.

Ferrario & Kanavos. Soc Sci Med 2015; 124:39-47.

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Product development - updated

	NCE (n=336)	Other new product (n=420)*	Vaccine or biological (n=94)†	Total (n=850)
Neglected diseases				
Malaria	3 (1%)	9 (2%)	0	12 (1%)
Tuberculosis	0	7 (2%)	0	7 (1%)
Diarrhoeal diseases	1 (<0.5%)	3 (1%)	3 (3%)	7 (1%)‡
Neglected tropical diseases	0	5 (1%)	0	5 (1%)§
Other	0	1 (<0.5%)	5 (5%)	6 (1%)¶
Subtotal	4 (1%)	25 (6%)	8 (9%)	37 (4%)
Other infectious diseases	35 (10%)	48 (11%)	66 (70%)	149 (18%)
All other diseases	297 (88%)	347 (83%)	20 (21%)	664 (78%)

Data are n (%). NCE=new chemical entity. *New indication, new formulation, or fixed dose combination. †Includes immunoglobulins and other biological products. ‡For diarrhoea, cholera, cryptosporidiosis, and giardiasis. §For human African trypanosomiasis, Chagas disease, and leishmaniasis. ¶For Japanese encephalitis, haemorrhagic fevers, and snakebite.

Table 1: New therapeutic products approved or recommended, by disease category (2000-11)

Pedrique et al. Lancet Global Health 2013

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What alternatives are there?

The screenshot shows the WHO website page for 'Medicine Pricing and Financing'. At the top, it features the WHO logo and navigation tabs for 'Home', 'Publications', 'Countries', 'Programs', 'Communities', and 'About WHO'. Below the navigation is the heading 'Essential medicines and health products' and a sub-heading 'Medicine Pricing and Financing'. The main content area contains a word cloud with terms like 'PRICES', 'ACCESS', 'HEALTHY', 'MEDICINES', 'EFFECTIVE', 'FINANCING', 'AFFORDABLE', 'QUALITY', 'EVIDENCE', 'INNOVATION', 'RESEARCH', 'DEVELOPMENT', 'PRODUCTION', and 'DISTRIBUTION'. Below the word cloud is a section titled 'Promoting affordable and fair pricing and effective financing' with a short paragraph of text.

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Is it time for a change?



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Home

- Objectives of the Fair Pricing Forum
- Invitation & Registration
- Preliminary Programme
- Venue & Practical Information
- Registration & Contact
- Media Links

Welcome to the
Fair Pricing Forum 2017 website

Access to medicines is a major challenge for all, including for patients, governments and industry. Both quality health and innovation are at stake when access is not guaranteed. Fair pricing of essential medicines could mitigate these challenges while at the same time providing space for innovation for health technologies to address existing unmet needs.

To discuss the challenge and the way ahead, a Fair Pricing Forum will be held on **Thursday 11 May 2017** in Amsterdam, The Netherlands.

The main objective of this forum is to discuss options for a fair pricing system, that is sustainable for both health systems and innovation.

The Forum is an initiative of the **World Health Organization** and is organized in collaboration with the **Dutch Ministry of Health**.

The Forum is for invitation only.
Registration is open from 27 March 2017.
Due to organisational reasons, we would like to welcome a maximum of two persons per Government and one per organisation.

www.fairpricing.nl

Amsterdam, 11 May
Fair Pricing

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Key messages

- We need transparency about costs versus prices
- Expanding new models of R&D, such as public private partnerships, should be explored
- Market models for neglected areas will not work for innovation.