UNIVERSITY OF LIVERPOOL

Generics

Saye Khoo

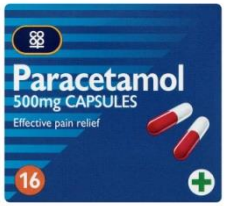
HIV Pharmacology Group

Declaration of Thanks

- Andrew Hill
- Marta Boffito
- David Back
- Andrew Owen
- Marco Siccardi

Which is better ?

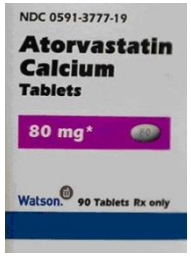
£1.65 (16 tablets)



£0.15 (16 tablets) average

£1.90 (16 tablets)

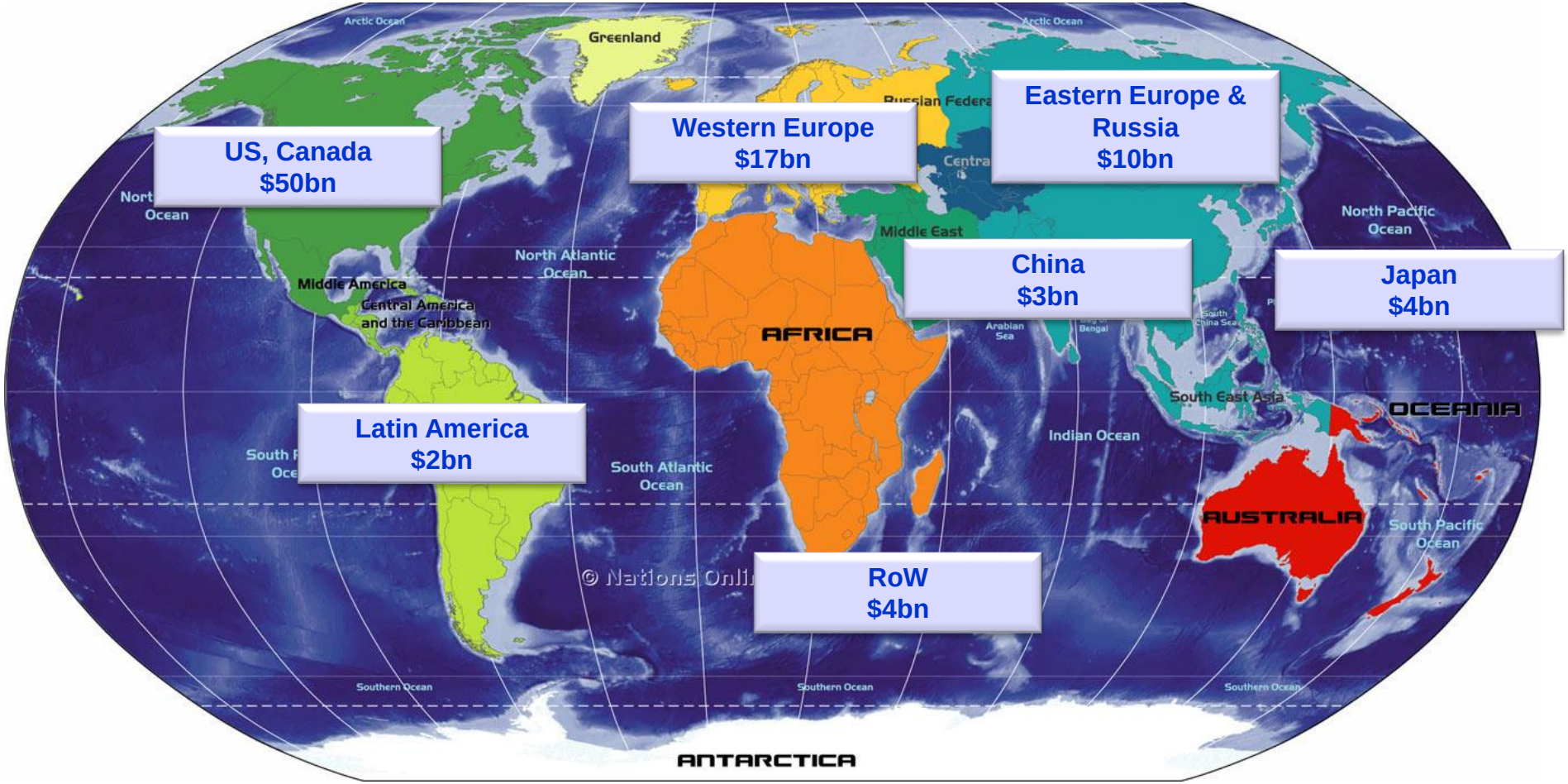
£0.28 (16 tablets) average



NHS Saving in first year (2013) of generics - £1m a day

Generics: A $90 Billion Opportunity

Total world pharmaceutical sales – $600 bn

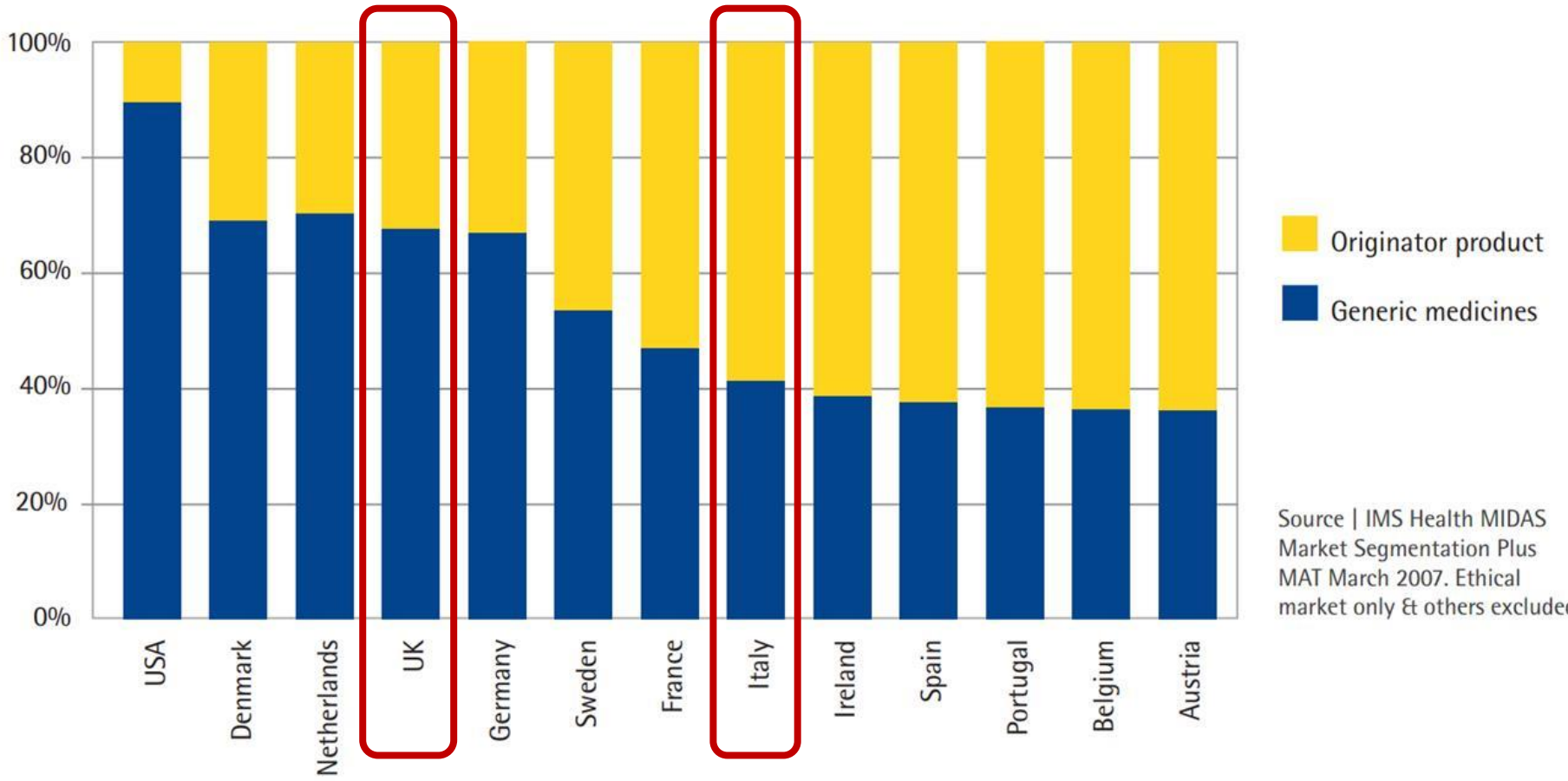


Source: IMS Health, VOI Pharma Handbook

EUROPEAN GENERIC MEDICINES ASSOCIATION

Making Medicines Affordable

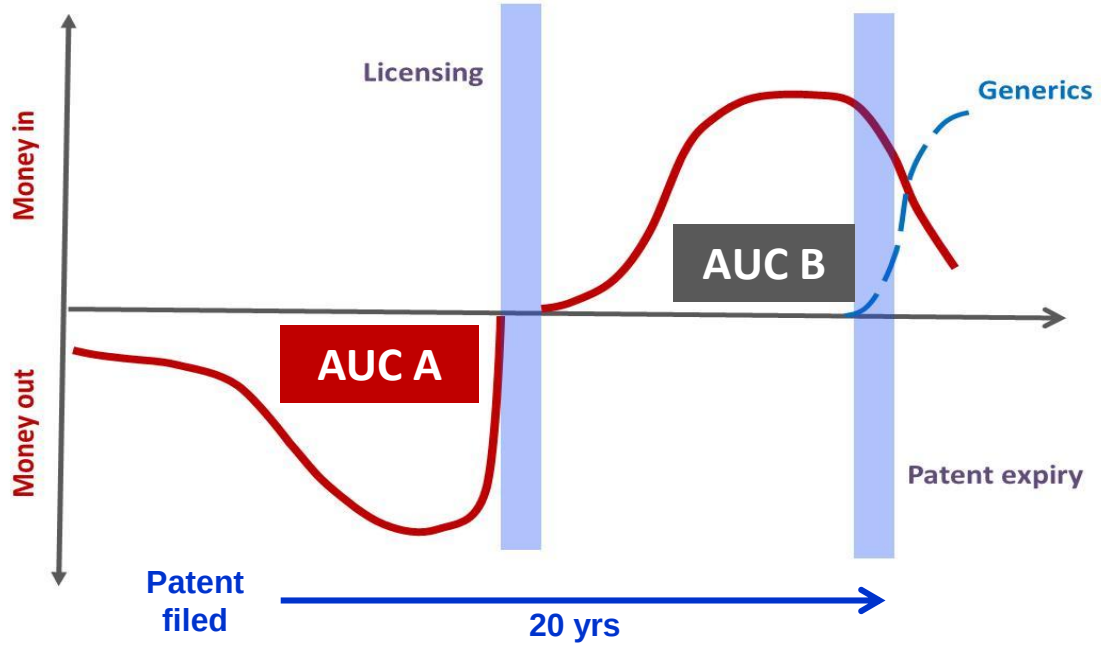
Figure 5 | Generic medicines market share volume 2007 (unprotected market)



Source | IMS Health MIDAS Market Segmentation Plus MAT March 2007. Ethical market only & others excluded.

Generics

– a natural part of the life cycle of any drug



Patent validity

- Depends on territory (US 20 years)
- Can have extensions eg changes to indications, formulations, dose
- 'Evergreening' strategies – chemical modifications, metabolites
- Differs from 'exclusivity', which may be granted beyond patent

“Evergreen patenting”

Additional patents which can protect manufacturing techniques, co-formulations or special properties. Examples:

Drug	Additional patent	Extension to patent life:
ritonavir	soft-gel formulation	2013 to 2020 (7 years)
abacavir	hemi-sulphate salt	2010 to 2019 (9 years)
tenofovir	Co-formulation TDF/FTC	2017 to 2024 (7 years)
3TC	Co-formulation ZDV/3TC	2010 to 2017 (7 years)

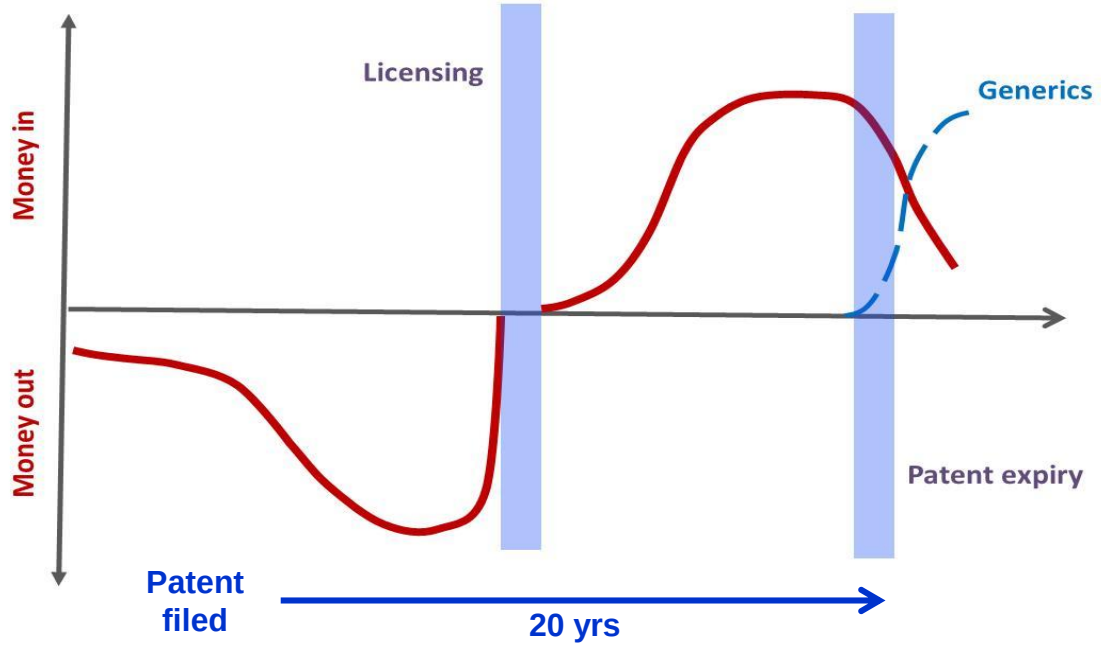
These “evergreen patents” could be overruled in some countries (e.g. India), but may exclude generics for longer times.

Slide courtesy of A Hill

MSF: Untangling the web of Antiretroviral Price Reductions, 2011

Generics

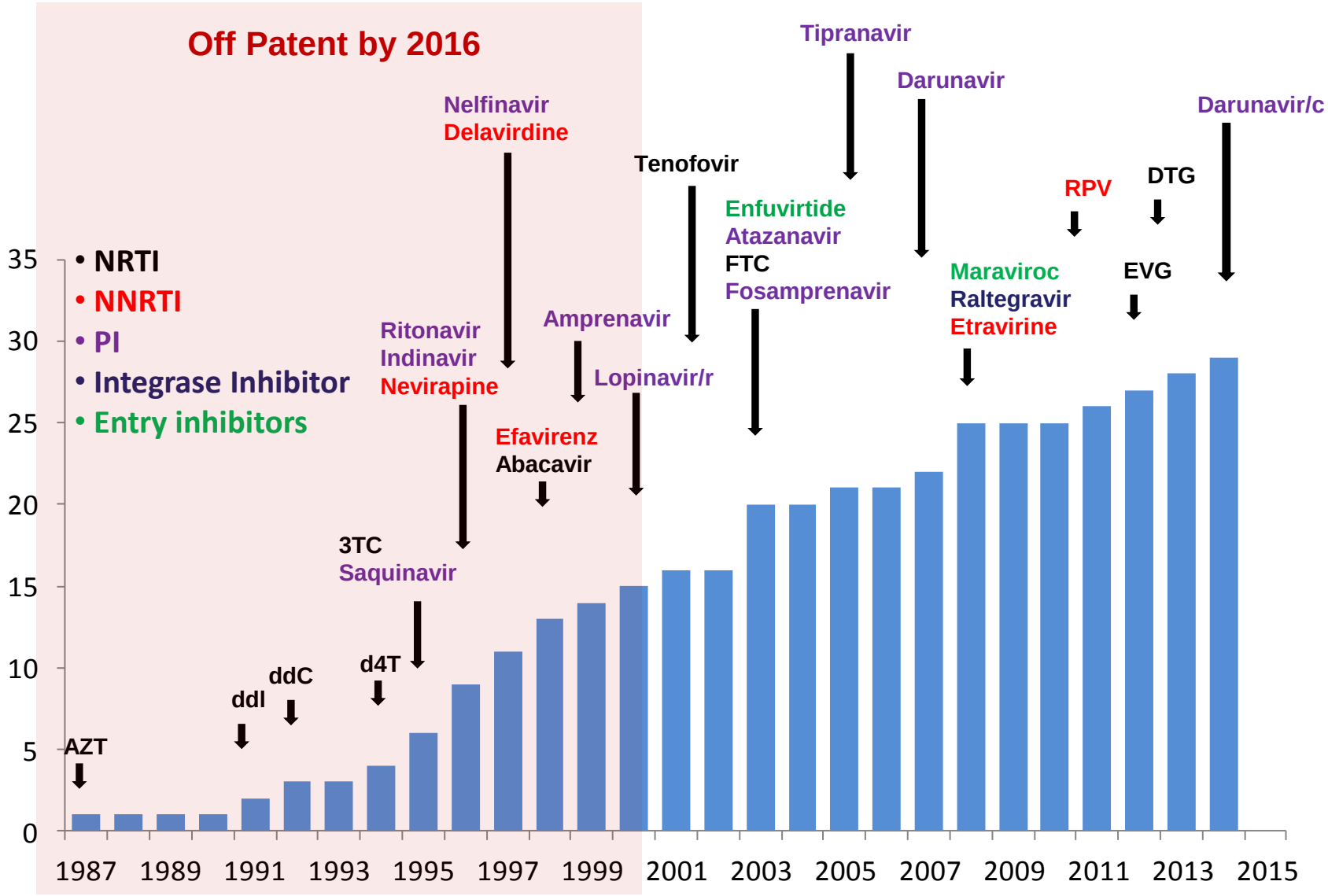
– a natural part of the life cycle of any drug



Generic Manufacture

- Patent expiry
- Under license, +/- royalties
- Under sub-license, via the Medicines Patent Pool
- Under Compulsory license

HIV drug development (1987-2015)



ORIGINAL RESEARCH | Annals of Internal Medicine

Economic Savings Versus Health Losses: The Cost-Effectiveness of Generic Antiretroviral Therapy in the United States

Rochelle P. Walensky, MD, MPH; Paul E. Sax, MD; Yoriko M. Nakamura, BA; Milton C. Weinstein, PhD; Pamela P. Pei, PhD; Kenneth A. Freedberg, MD, MSc; A. David Paltiel, PhD; and Bruce R. Schackman, PhD

Background: U.S. HIV treatment guidelines recommend branded once-daily, 1-pill efavirenz–emtricitabine–tenofovir as first-line antiretroviral therapy (ART). With the anticipated approval of generic efavirenz in the United States, a once-daily, 3-pill alternative (generic efavirenz, generic lamivudine, and tenofovir) will decrease cost but may reduce adherence and virologic suppression.

Objective: To assess the clinical effect, costs, and cost-effectiveness of a 3-pill, generic-based regimen compared with a branded, coformulated regimen and to project the potential national savings in the first year of a switch to generic-based ART.

Design: Mathematical simulation of HIV disease.

Setting: United States.

Patients: HIV-infected persons.

Intervention: No ART (for comparison); 3-pill, generic-based ART; and branded ART.

Measurements: Quality-adjusted life expectancy, costs, and incremental cost-effectiveness ratios (ICERs) in dollars per quality-adjusted life-year (QALY).

Results: Compared with no ART, generic-based ART has an ICER of $21 100/QALY. Compared with generic-based ART, branded ART increases lifetime costs by $42 500 and per-person survival gains by 0.37 QALYs for an ICER of $114 800/QALY. Estimated first-year savings, if all eligible U.S. patients start or switch to generic-based ART, are $920 million. Most plausible assumptions about generic-based ART efficacy and costs lead to branded ART ICERs greater than $100 000/QALY.

Limitation: The efficacy and price reduction associated with generic drugs are unknown, and estimates are intended to be conservative.

Conclusion: Compared with a slightly less effective generic-based regimen, the cost-effectiveness of first-line branded ART exceeds $100 000/QALY. Generic-based ART in the United States could yield substantial budgetary savings to HIV programs.

Primary Funding Source: National Institute of Allergy and Infectious Diseases.

Ann Intern Med. 2013;158:84-92. www.annals.org

For author affiliations, see end of text.

The choice for UK NHS in 2014-5 – pill counts versus price?

Single pill
£5000 - £7500

TDF/FTC/EFV
TDF/FTC/RPV
TDF/FTC/ETG/c
ABC/3TC/DTG
TDF/FTC/DRV/c

Three pills once daily
£1018

Generic ABC (£378)

Generic 3TC (£285)

Generic EFV (£355)

The generic version may be better tolerated, if the EFV dose is lower

Slide courtesy of A Hill

Sources: BNF 2013, generic company prices

Potential HIV drug prices: 2014-8

Minimum = cost price (African access programmes)
NHS prices 30% lower than list price
Generic prices 80% lower than NHS price

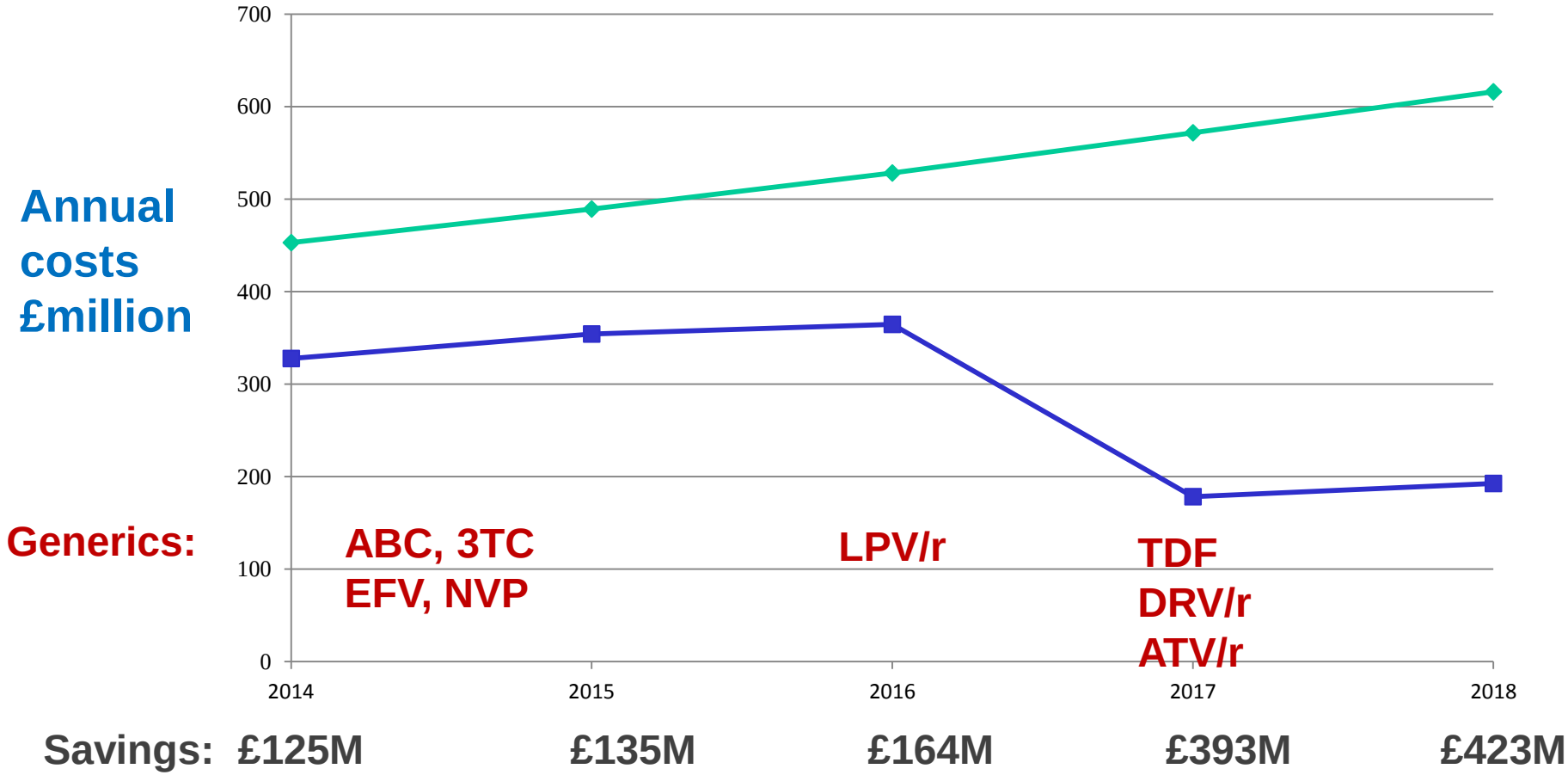
Drug	Minimum	UK NHS	UK Generic (80% reduction)
3TC	24	1424	284 (now)
Zidovudine	60	1418	709 (now)
Tenofovir	55	2172	434 (2017)
Nevirapine	24	973	389 (now)
Efavirenz	40	1774	355 (now)
Abacavir	140	1889	378 (2014)
Etravirine	600	2724	2723
Lopinavir/r	268	2618	523 (2016)
Atazanavir/r	204	2975	595 (2017)
Darunavir/r	500	2823	565 (2017)
Raltegravir	450	3973	3938

Slide courtesy of A Hill

Sources: CHAI 2011, MSF 2011, BNF 2011

UK ARV treatment costs, 2014-2018:

Total saving = £1.24 billion over 5 years



Slide courtesy of A Hill

Additional Advantages of Generics

- **fewer barriers to co-formulation**
  - **eg bPIs**

- **more or better pediatric formulations**
  - **pediatric FDCs**
  - **innovative scored tablet for EFV**

Innovator FDCs

2 drugs

ABC + 3TC 

TDF + FTC 

ZDV + 3TC 

LPV + RTV 

DRV + cobi 

Single Tablet Regimen

ZDV + 3TC + ABC 

TDF + FTC + EFV 

TDF + FTC + RPV 

TDF + FTC + EVG + Cobi 

ABC + 3TC + DTG 

Generic FDCs

2 drugs

ABC + 3TC
TDF + FTC
ZDV + 3TC
d4T + 3TC
LPV + RTV**
ATV + RTV
TDF + 3TC

Single tablet Regimen

ZDV + 3TC + EFV
TDF + FTC + EFV
TDF + 3TC + EFV
d4T + 3TC + EFV
ddI + 3TC + EFV
ZDV + 3TC + NVP
d4T + 3TC + NVP**

** specific pediatric FDCs

Lowering the cost of generics

Branded

% of the cost of pill

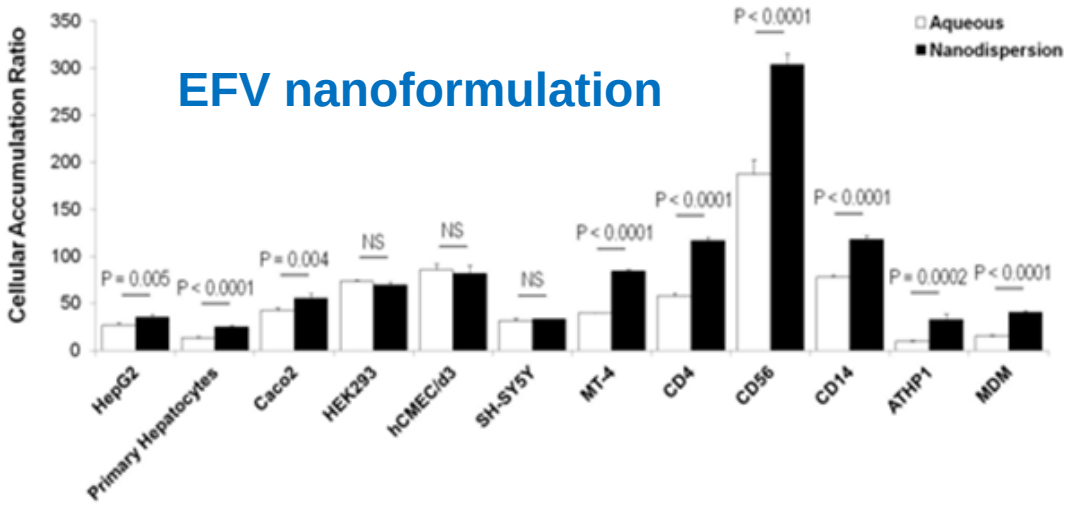
Generic

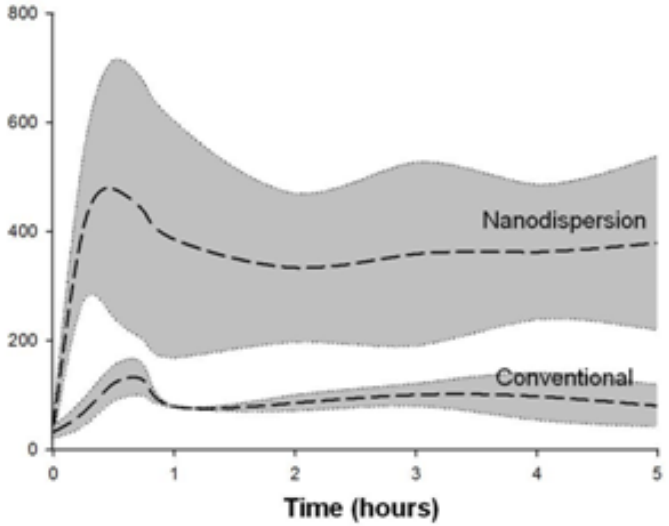
Profit

R & D

API

EFV nanoformulation





Generics - Key Drivers of Uptake 1

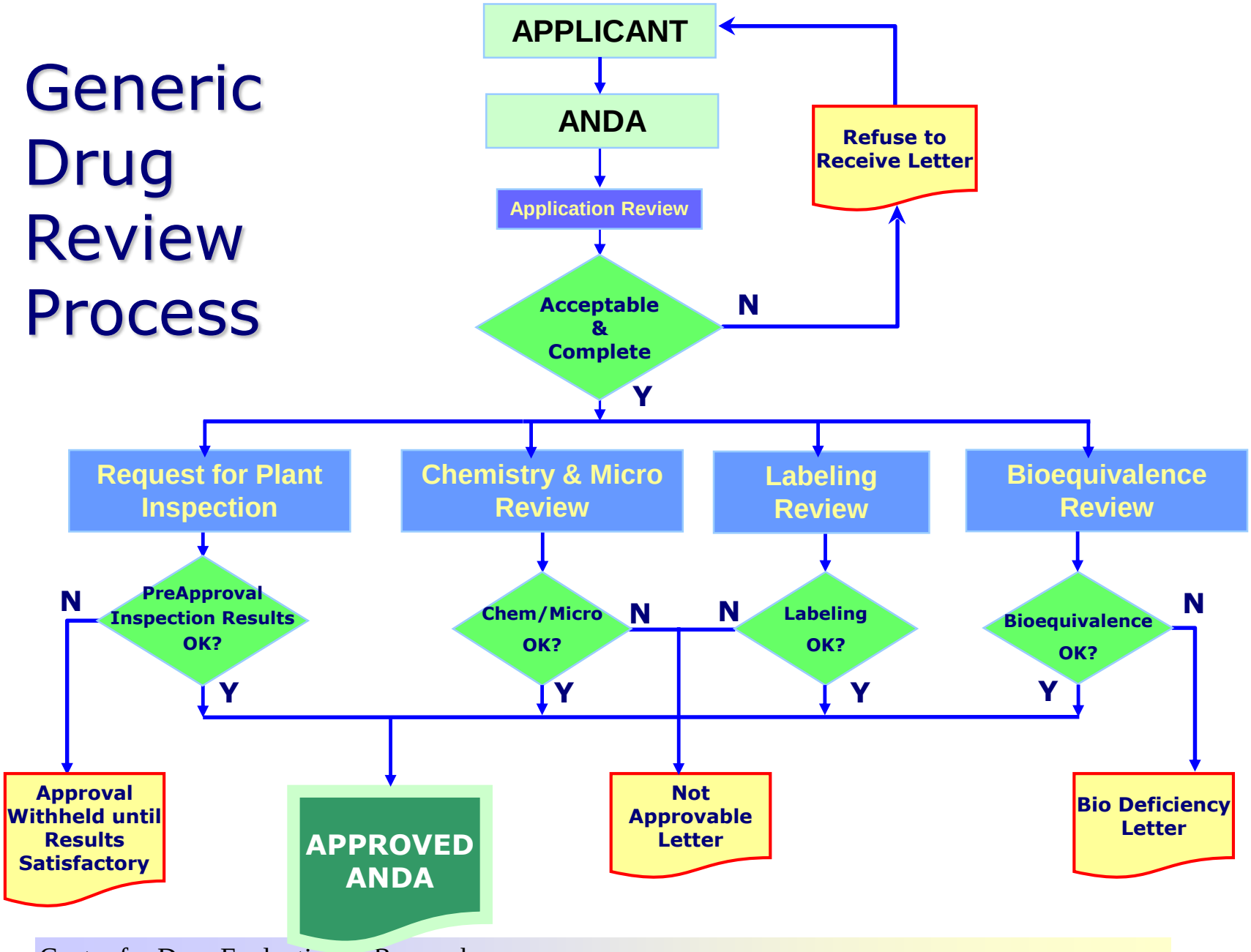
Hatch-Waxman Act (1984)

- compromise interests of Innovators vs Generics
- allowed use of prior safety/efficacy data from innovator
- FDA approval through proof of bioequivalence
- Abbreviated New Drug Application (ANDA) process
- increased generics in US from 12% (1984) to 44% (2000)
- Regarded as one of the most effective examples of US legislation

NDA vs. ANDA Review Process

Brand Name Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies	
7. Clinical Studies	6. Bioequivalence
8. Bioavailability	

Generic Drug Review Process



Generics - Key Drivers of Uptake 2

Rising drug costs in developed and developing countries

Humanitarian imperative to expand global access

Expedited Generic Drug Review

WHO Prequalification of Medicines Programme

(can take as little as 3 months)

316 medicines for priority diseases by 2012

US FDA and other Regulators

theguardian | TheObserver

News | Sport | Comment | Culture | Business | Money | Life & style

How drug giants let millions die of Aids

Revealed: Ed Vulliamy reports from Washington on how the pursuit of profit by Western companies - and their political allies - stalled South Africa's fight against HIV, and sees the tragic cost in the townships

The Observer, Sunday 19 December 1999

1997 **South Africa passes Medicines and Related Substances Control Amendment Act**

Clause 15c allowed compulsory licensing and parallel importing

1998 **Pharmaceutical company lawsuit (49 applicants)**

2001 **Legal action dropped**

Why the fuss ?

Perception that generics are inferior:

- Made in sub-standard facilities
- Low or variable quality
- Stability issues
- Not as safe
- Not as efficacious
- Contain less drug
- Take longer to act in the body

Branded vs 'Approved' Generics - Similarities

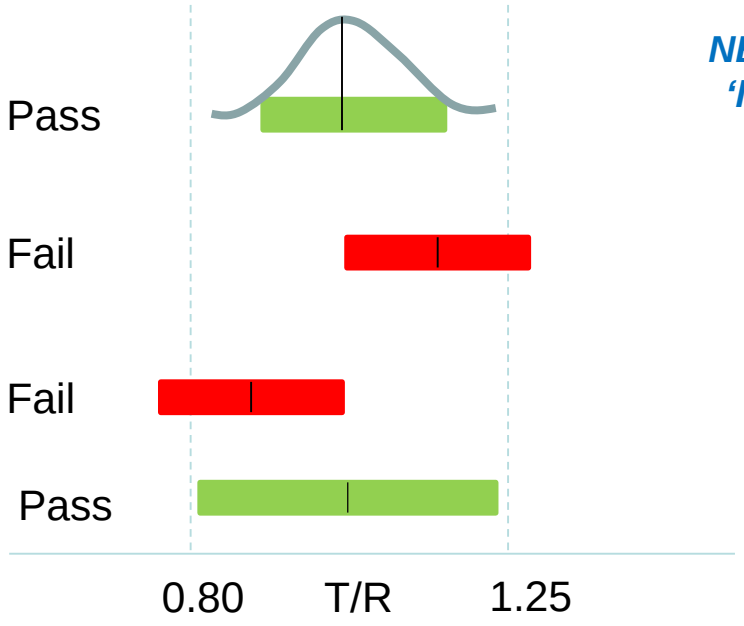
- Same amount of active compound
- Same dose
- Same 'strength'
- Same route of administration
- Same Indications
- Bioequivalence - same absorption (rate and extent) into the bloodstream AND same plasma concentrations over time = same safety and efficacy
- Similar packaging insert/ product information

Bioequivalence

- **Ratios, not absolute values**
- **Metrics : Cmax, Tmax, AUC**
- **Statistical measures: GMR, log-transformed AUC & Cmax, 90% CI**
- **Comprises two one-sided tests (Schuirmann) at 5% level of confidence:**
  - **H_1 Test is not less than Reference by >20% (80/100=80%)**
  - **H_2 Reference is not less than Test by >20% (100/80=125%)**
- **The 90% confidence interval (90%CI) of the *geometric mean ratio* must be within the acceptance interval of [0.80–1.25] (or [0.90–1.11] for drugs with narrow therapeutic index).**

Schematic diagram illustrating possible bioequivalence study outcomes

T/R = test/reference



NB tests are for 'Not Different' rather than 'The Same'

AUC, Cmax Food effect

Davit et al 2009

Branded vs 'Approved' Generics – not necessarily the same

- Price
- Pill appearance, size, shape, colour or taste
- excipients
- Reliability of supply chain
- (checks over time to monitor 'drift' in quality of some providers)

Is Bioequivalence = Therapeutic Equivalence ?

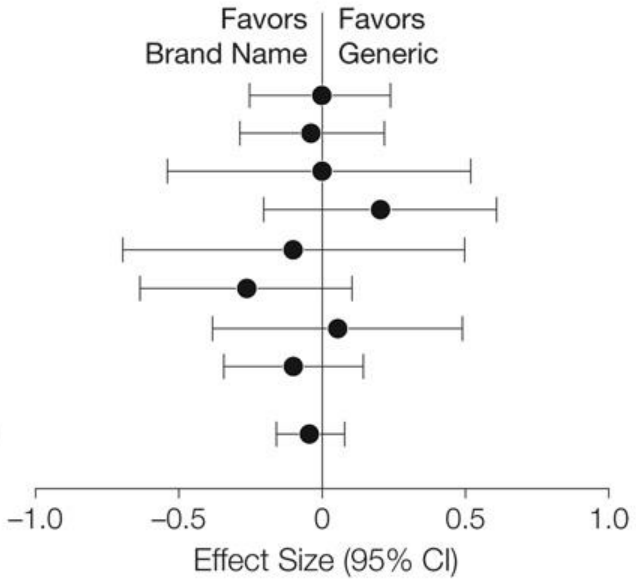
- **Risk of medication error during changeover**
  double-dose, or under-dose
- **Difference in adherence to brand vs generic ?**

- **Difference in population variance (esp at C_{min})**
  unsubstantiated
- **Difference from improved branded formulations**
  e.g. NVP XR, Aluvia, ritonavir, raltegravir
- **Differences in coformulations**
  e.g. Atripla vs separates
- **Generic STRs**

Are Generics *less* Effective ?

- **Systematic Review of cardiovascular drugs**
- **Clinical efficacy and safety endpoints**
- **47 publications covering 9 drug subclasses (81% RCTs)**

Drug Class	No. Studies	No. Subjects	Effect Size (95% CI)
β-Blockers	6	135	0.00 (–0.24 to 0.25)
Diuretics	10	135	–0.03 (–0.28 to 0.22)
Calcium channel blockers	4	242	0.00 (–0.53 to 0.53)
Antiplatelet agents	2	50	0.21 (–0.19 to 0.61)
ACE inhibitors	1	23	–0.09 (–0.68 to 0.50)
Statins	2	71	–0.25 (–0.62 to 0.12)
α-Blockers	1	43	0.06 (–0.37 to 0.50)
Warfarin	4	138	–0.09 (–0.33 to 0.15)
Overall	30	837	–0.03 (–0.15 to 0.08)

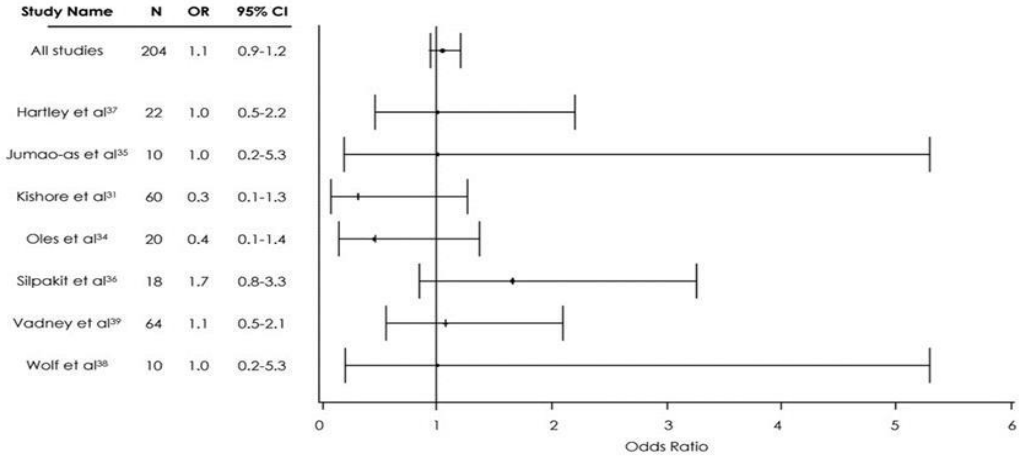


- **No evidence that brand-name drugs are superior**

Kesselheim et al. JAMA. Dec 3, 2008; 300(21): 2514–2526

Are Generics *less* Effective ?

- **Systematic Review of Antiepileptic Drugs, comparing branded versus generic formulations**
- **16 studies: RCT (9), prospective (1), observational (6)**
- **Endpoint – seizure control**

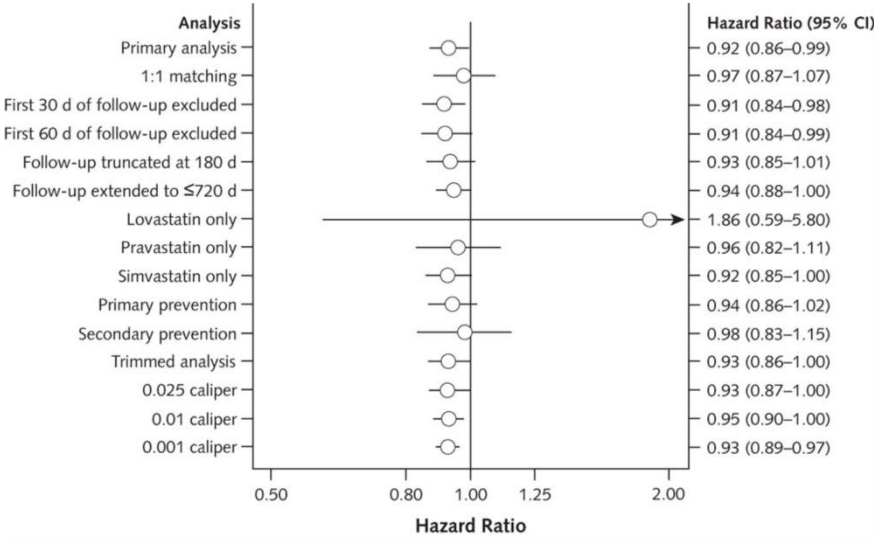


- **RCT (phenytoin, carbamazepine, valproate) - No evidence of change in seizure control**
- **Observational – trend for increased 'switchback' and rate of healthcare utilisation – many confounders**

Kesselheim et al. Drugs 2010:70: 605

Are Generics *more* Effective ?

- US Medical and pharmacy claims for statin use (N=90,111)
- Insurance programmes require co-payments (mean $10 vs $48 for generics vs branded)



- Adherence (proportion of days covered) – 77% (generics) vs 71% (branded); P < 0.001
- Composite Outcomes (ACS/stroke/all-cause mortality) in favour of generics (HR, 0.92 [95% CI, 0.86 to 0.99])
- (study funded by Teva)

Gagne, et al. Ann Intern Med. 2014;161(6):400-407

Does Appearance of the Pill Matter ?

- ‘trade dress’ – size, shape, colour, texture, aroma, flavour considered IP under trademark law (Greene 2011, Engleberg 2011)
- Challenged by US Supreme Court (1995) on the basis that product appearance cannot be protected to identify product, only source of the product
- Subsequent legal hearings supported this decision on the basis appearance also helps to improve adherence

Kesselheim et al. Ann Intern Med. 2014;161(11):840
Greene et al NEJM 2011;365:83
Engleberg et al. J Manag Care Pharm 2011;17:321

Change in Pill Appearance leads to Treatment Discontinuation

- Cohort & nested case–control study of MI survivors (2006-2011) initiating a generic β-blocker, ACE inhibitor, A2RA or statin.
- 3,286/11,513 (29%) patients had changes in pill colour/shape
- Persistence measured by refills

Table 3. Association Between Nonpersistence and Color/Shape Discordance in Medications After MI

Change	Discordance Among Case Group (n = 4573), n (%)	Discordance Among Control Group (n = 19 881), n (%)	OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR for Pharmacy Change (95% CI)†	Adjusted OR for Use of a Mail-Order Pharmacy (95% CI)‡
Color	177 (3.9)	587 (3.0)	1.34 (1.13–1.59)	1.34 (1.12–1.59)	1.10 (0.91–1.32)	1.16 (0.97–1.39)
Shape	242 (5.3)	644 (3.2)	1.67 (1.43–1.95)	1.66 (1.43–1.94)	1.41 (1.19–1.66)	1.38 (1.18–1.62)
Color or shape	309 (6.8)	922 (4.6)	1.50 (1.31–1.71)	1.49 (1.30–1.71)	1.25 (1.08–1.45)	1.25 (1.09–1.44)
Color and shape	110 (2.4)	309 (1.6)	1.58 (1.27–1.98)	1.58 (1.27–1.98)	1.32 (1.05–1.66)	1.37 (1.09–1.72)

MI = myocardial infarction; OR = odds ratio.
* Adjusted for age, year, combined comorbidity score, revascularization procedure during the index hospitalization for MI, prior use of nonindex study drugs, and number of distinct drugs used during baseline (all drug use was assessed during the 6 mo preceding the index hospitalization for MI).
† Adjusted for all covariates in the primary adjusted OR model and an additional covariate for change in pharmacy defined by evaluating the 2 refills before the outcome date (the same refills used to assess pill appearance) to determine whether these refills were linked to the same (concordant) or a different (discordant) pharmacy identification number.
‡ Adjusted for all covariates in the primary adjusted OR model and an additional covariate defined by having the last prescription before an outcome date filled through a mail-order pharmacy.

Kesselheim, et al Ann Intern Med. 2014;161(2):96-103

Health and Commerce

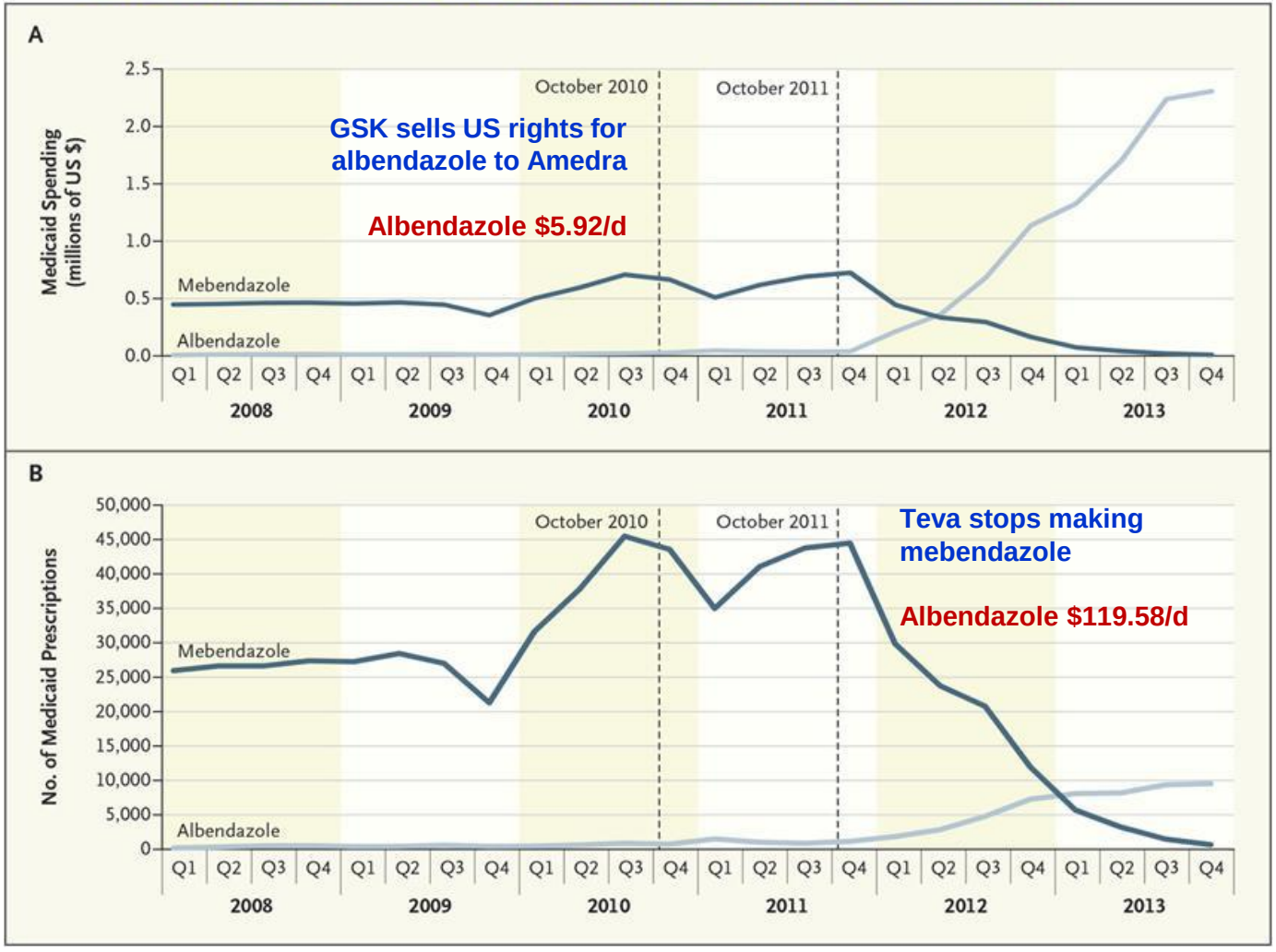
- **Campaign against generics by some brand-name manufacturers**
- **'Pay for Delay' settlements**
  - process initiated by challenges to invalidate patents
  - settlements which leave patent intact
  - some successful challenges using anti-trust legislation
  - 'headline' cases – eg clopidrogel (BMS & Apotex)

But …

- **Tendency to over-simplify issues**
  - demonising brand manufacturers
  - Generic manufacturers as 'champions' of access to medicines

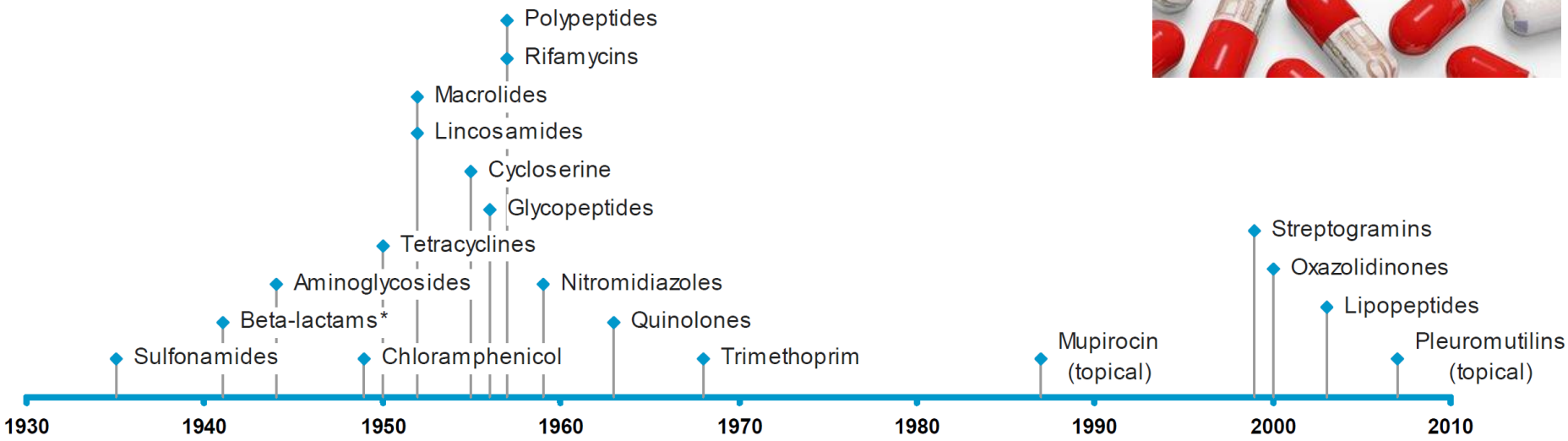
Generic Manufacturers and monopoly

Medicaid Spending and Prescriptions for Albendazole and Mebendazole, 2008–2013.



Alpern JD et al. N Engl J Med 2014;371:1859-1862.

The Antibiotic Pipeline

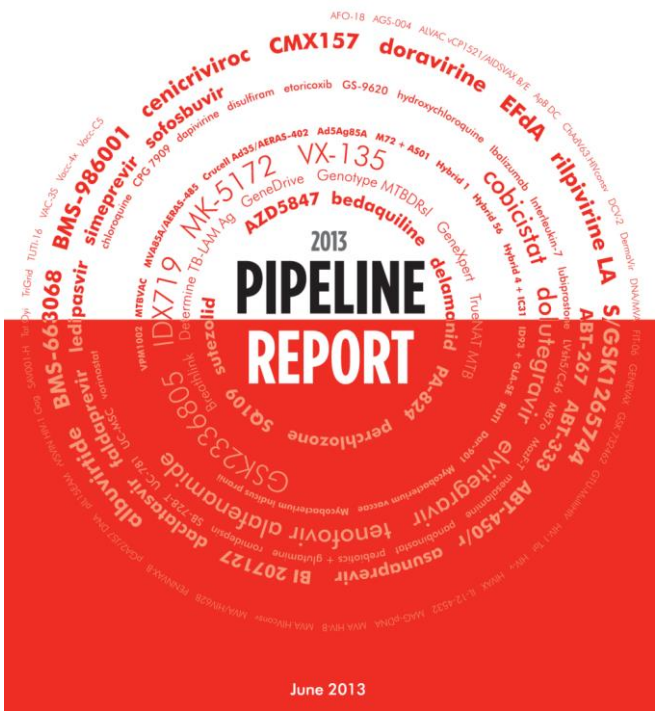


* Beta-lactams include three groups sometimes identified as separate classes: penicillins, cephalosporins, and carbapenems.

- **14 new classes of antibiotics were introduced between 1935 – 1968**
- **Since then, only 5 have been introduced**
- **Since 1980, 75% new drugs in 2 classes- quinolones & ß lactams**

Could this happen with HIV pipeline ?

- **no new PI for past 6 years**
- **better compounds within class**
- **what new targets are being pursued ?**



	INSTIs	NRTIs	PIs	NNRTIs	Other
Approved	Dolutegravir		DRVc		
Phase 3		TAF		Doravirine (MK1349) RPV-LA	TAF/FTC/EVGc Cenicriviroc BMS663068
Phase 2	GSK126744	Racivir Amodoxovir Elvucitabine			ABC/3TC/DTG TAF/FTC/DRVc

Summary 1

- Generics are a natural part of the life cycle of a drug
- 'Pharmacologically equivalent' (bioequivalent)
- In general, 'Therapeutically equivalent'
- Caveats are risk of medication error, adherence
- Any process of transition must be carefully managed

- In the absence of approval for EFV 400mg dose, would it be possible for generic manufacturers to sell a single 400mg strength EFV pill ?

Summary 2

- **Concerns over Quality**
  - Quality assurance assessment
    - packaging, labelling and information leaflets
    - manufacturing
- **Concerns over Safety**
  - Procurement - robust, reliable supply chain
- **Reducing Error**
  - Managed process for switching formulation
  - Patient engagement, information, support
  - Patient information leaflets
  - explain differences (appearance, tablet strength)
  - Stocking options – automatic substitution
  - Retaining ‘patient choice’ may introduce potential for error

Summary 3

Role of Clinicians and Academics

- **Treatment advocacy**
  - explain the importance of generics to patients
  - recognise contribution of Pharma
  - Global access

- **Drug Development**
  - current capitalist model has limitations
    eg creates adverse or perverse incentives
  - public-private partnerships (TB alliance, MMV)
  - identification of new targets

- **Resource Utilisation**