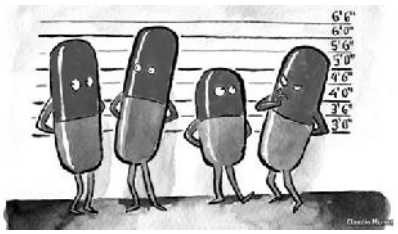
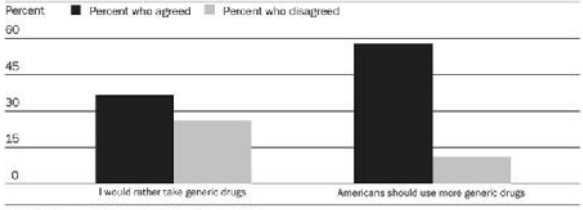


Generic Drugs: What's in a (Brand) Name

Dan Hartung, PharmD, MPH
Assistant Professor Oregon State University College of Pharmacy

EXHIBIT 3
Differences In Individual Preferences For Generic Medications And Perceptions About Generics For Society, 2007



SOURCE: Survey about Prescription Drug Choices, 2007.
NOTES: "Percent who agreed" is the sum of respondents who somewhat or strongly agreed with each statement. "Percent who disagreed" is the sum of respondents who somewhat or strongly disagreed with each statement.

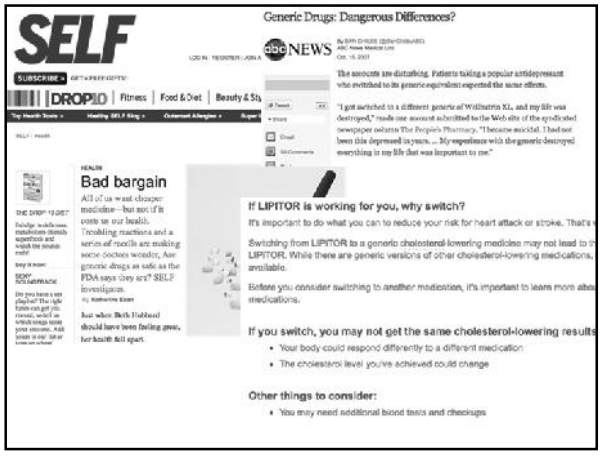
Shrank W. *Health Affairs*, 28, no.2 (2009):546-556

Disclosures

- Career Development Award – Comparative Effectiveness Research
  - K12HS019456-01
- Sedative Hypnotic use by the mentally ill: a Medicaid prescription policy study
  - Co-I: R01MH086310-03
- Consulting: Alkermes Inc.

Objectives

1. Be aware of common misconceptions about generic and brand drug equivalence
2. Summarize FDA bioequivalence standards for generic drugs to patients and other providers
3. Describe advantages of prescribing generic drugs when available
4. Be aware of strategies used to deter generic drug use


SELF

Generic Drugs: Dangerous Differences?

abcNEWS

Bad bargain

If LIPITOR is working for you, why switch?

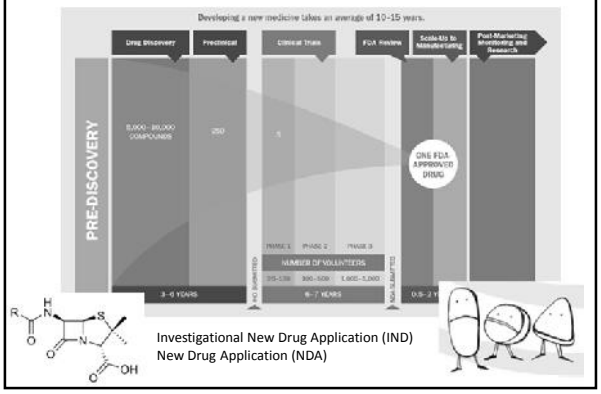
If you switch, you may not get the same cholesterol-lowering results

- Your body could respond differently to a different medication
- The cholesterol level you've achieved could change

Other things to consider:

- You may need additional blood tests and checkups

How a molecule becomes a prescription drug



Investigational New Drug Application (IND)
New Drug Application (NDA)

Innovator Drug Patent Life

- Once new molecular entity (NME) is discovered, it is typically patented.
  - 20 year patent life
  - A new drug will only have 5-10 years of exclusivity once approved for marketing
- Prior to 1984 generic drugs were required to complete identical preclinical and clinical tests as innovator branded drugs

Intended and Unintended Consequences of Hatch-Waxman

- Generic use has soared:
  - 1000 new generics approved within 1st 2 years
  - 1984 – 18.6% of US prescriptions were generic drugs
  - 2012 - >80% of US prescriptions are dispensed as generics
- Brand drug firms game patent/legal system
  - "Ever greening" multitude of trivial patents (color, taste) – 10 per drug
  - Brand firm infringement claim triggers automatic delay of generic release for up to 30 months

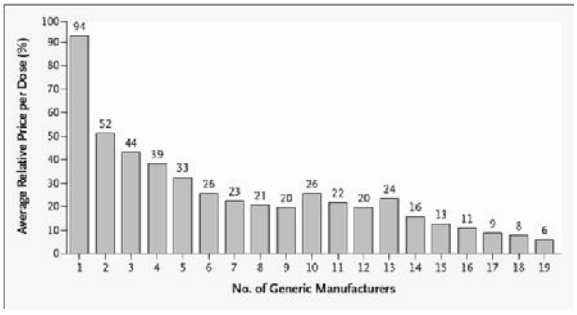
Drug Price Competition and Patent Term Restoration Act (1984) – Hatch-Waxman Act

- Allow up to 5 extra years of patent life to innovator drugs that experience delays in FDA approval process
- Allows generic firms to file Abbreviated New Drug Applications (ANDA)
  - Must demonstrate bioequivalence to originator
  - Clinical trials of efficacy and safety NOT required
- Allows generic firms to apply for FDA approval and conduct tests of bioequivalence before the relevant patents expire
- Clarifies process for patent disputes between firms
  - 1st firm to that successfully challenges a patent granted 180 day marketing exclusivity

NDA vs ANDA Review Process

Brand Name Drugs	**Generic Drugs**
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	

As number of generic products increases price is reduced



Frank RG. NEJM. 2007;357:1993-96

Requirements for Generic Drug Approval

1. Meet same batch requirements for identity, strength, purity, and quality
2. Be manufactured under the same strict standards of FDA good manufacturing practice regulations as for innovator product
3. Contain same active ingredient(s), same dosage, and route
4. Be therapeutically equivalent → bioequivalent

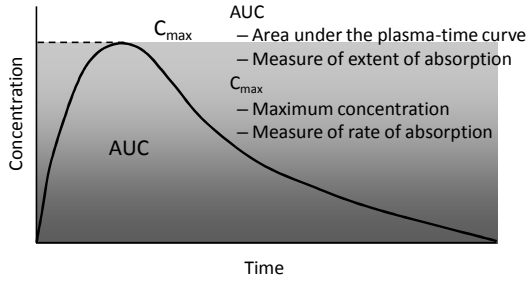
Bioequivalence (BE)

The absence of a significant difference in the ***rate and extent*** to which the active ingredient becomes available at the site of drug action when two drugs are administered at the same dose, under similar conditions, in an appropriately designed study

Meredith P. Clin Ther 2003;25:2875-90

Bioavailability (BA)

The measure of the rate and extent of a drug's absorption

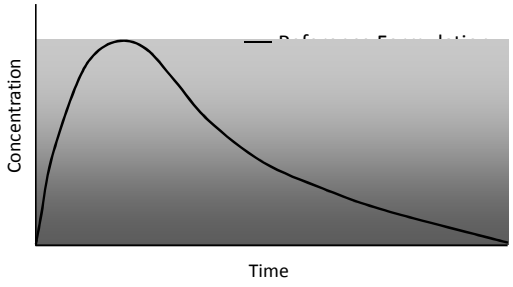


Food and Drug Administration Web site. Approved Drug Products with Therapeutic Equivalence Evaluations. Available at: http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Statistical%20Criteria%20for%20Bioequivalence. Accessed February 16, 2006.

"I've heard that generic drugs can contain 20% less active drug than branded drugs"

NOT TRUE

Pharmacokinetic Profile of a Reference Drug

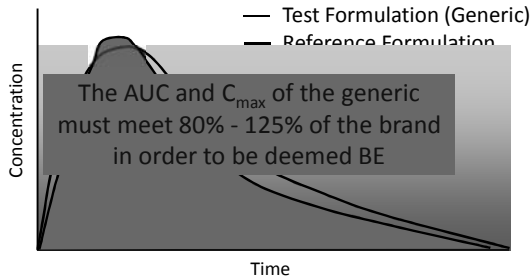


Food and Drug Administration Web site. Approved Drug Products with Therapeutic Equivalence Evaluations. Available at:

Bioequivalence Testing (BE)

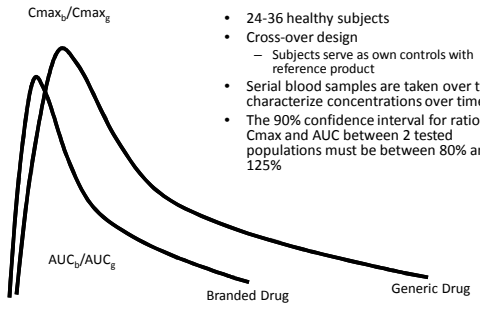
- Prove therapeutic equivalence
- BE products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring
- BE is commonly assured through two pharmacokinetic parameters
  - Cmax
  - AUC

Comparison of PK Profiles to Determine Bioequivalence



Food and Drug Administration Web site. Approved Drug Products with Therapeutic Equivalence Evaluations. Available at: http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Statistical%20Criteria%20for%20Bioequivalence. Accessed February 16, 2006.

Typical BE Study



- 24-36 healthy subjects
- Cross-over design
  - Subjects serve as own controls with reference product
- Serial blood samples are taken over time to characterize concentrations over time
- The 90% confidence interval for ratio of Cmax and AUC between 2 tested populations must be between 80% and 125%

Implications

- Average difference in AUC and Cmax between branded and generic drugs (n=2070)
  - AUC: 3%
  - Cmax: 4%
  - 98% of studies - differences <10%
- This is similar to batch to batch variability of same branded drug

Davit BM. Ann Pharmacother 2009;43:1583-97

Application of Confidence Interval Criteria (80-125% or 0.80 -1.25)

	Example 1	Example 2
Brand/Generic – AUC		
Subject 1	1.10	1.10
Subject 2	1.20	1.70
Subject 3	1.10	0.50
Subject 4	1.10	1.30
Subject 5	0.90	0.90
Subject 6	1.10	1.10
Mean	1.10	1.10
Confidence Interval	0.99-1.15	0.75 – 1.40
Bioequivalent	**Yes**	**No**

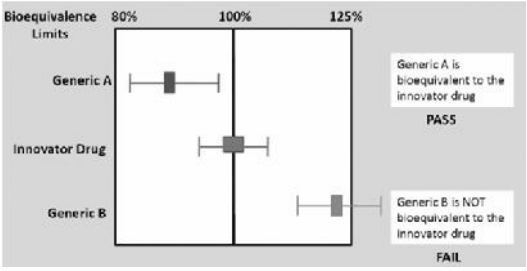
APPROVED DRUG PRODUCTS – WITH THERAPEUTIC EQUIVALENCE EVALUATIONS "Orange Book"

- All FDA approved drug products listed (NDA's, OTC's & ANDA's)
  - Therapeutic equivalence codes
    - ➔ "A" = Substitutable (AB –demonstrated by BE studies)
    - ➔ "B" = Inequivalent, NOT Substitutable
  - Expiration dates: patent and exclusivity
  - Reference Listed Drugs/brand drugs identified by FDA for generic companies to compare with their proposed products

Center for Drug Evaluation & Research
U.S. Food & Drug Administration

http://www.fda.gov/cder/ob

FDA Requirement for Bioequivalence



Bioequivalence for Atypical Delivery Systems

- Controlled release formulations
  - Additional multiple dose trials
  - Food effects
- Locally acting drugs
  - Creams/ointments: specific to products (e.g. skin blanching for topical steroids)
  - FEV1 changes for equivalent bronchodilators

Narrow Therapeutic Index Drugs

- NTI - The range between therapeutic and toxic doses is small
- Examples: Levothyroxine, anti-epileptic drugs (phenytoin, carbamazepine, lamotrigine), warfarin, transplant drugs, lithium
- FDA bioequivalence determinations apply equally to NTI and non-NTI drugs
- Some states recognize NTI drugs as a separate category and restrict substitution

Special Article

AMERICAN ACADEMY OF NEUROLOGY

Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy

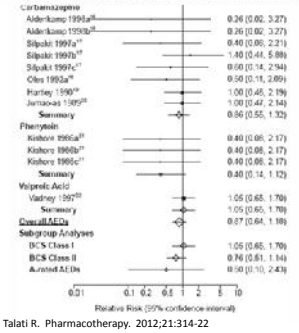
K. Liow, MD; G.L. Barkley, MD; J.R. Pollard, MD; C.L. Harden, MD; and C.W. Bazil, MD, PhD

The AAN opposes generic substitution of anti-convulsant drugs for the treatment of epilepsy without the attending physician's approv-al. The Food and Drug Administration has allowed

A SELECTIVE OVERVIEW OF CLINICAL EVIDENCE

Efficacy and Safety of Innovator versus Generic Drugs in Patients with Epilepsy: A Systematic Review

Ripple Talati, Pharm.D., Jennifer M. Schollie, Pharm.D., Olivia P. Phung, Pharm.D., Erika L. Baker, Pharm.D., William L. Baker, Pharm.D., Ajibade Ashaye, M.B.B.S., M.P.H., Jeffrey Kluger, M.D., Craig I. Coleman, Pharm.D., and C. Michael White, Pharm.D., FCP, FCCP



Initiation of branded versus generic AED in **randomized clinical trials**

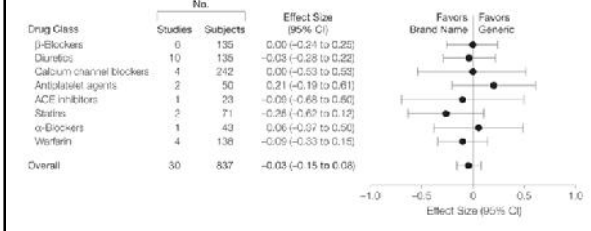
Talati R. Pharmacotherapy. 2012;21:314-22

JAMA

"Evidence does not support the notion that brand-name drugs used in cardiovascular disease are superior to generic drugs"

Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease

A Systematic Review and Meta-analysis



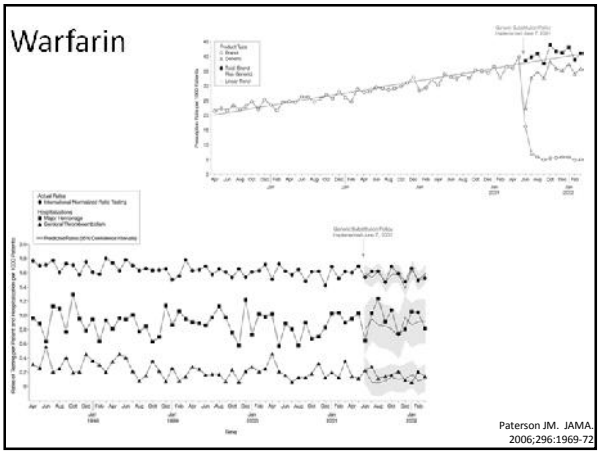
Kesselheim AS. JAMA 2008;300:2514-26

Observational Studies AED substitution

Author	Methodology	Drug(s)	Association / Outcome
Zachry	Case-control	Zonisamide (42%) Gabapentin(15%) Phenytoin (14%) Clonazepam (18%) others	**1.81 (95% CI 1.25 – 2.63)** -ED, hospital, ambulance for epilepsy
LeLorier	Retrospective cohort design	Lamotrigine	**1.13 (95% CI 1.09 – 1.18)** -all outpatient visits
Rascati	Case-control	Not reported (AED)	**1.84 (95% CI 1.44 – 2.36)** -ED, hospital, ambulance for epilepsy
Duh	Retrospective cohort design	Topiramate	**1.65 (95% CI 1.28 – 2.13)** -all hospitalizations following multiple generic drug use
Andermann	Retrospective cohort design	Lamotrigine Clobazam Depakene	Healthcare utilization not assessed
Hansen	Case-control	Zonisamide (27%) Phenytoin (26%) Clonazepam (16%) CBZ (10%)	**1.57 (95% CI 1.17-2.10)** -ambulance, ED, inpatient for epilepsy
Devine	Case-control		**1.08 (95% CI 0.91 – 1.29)** -ED, hospital for epilepsy
Gagne	Case-crossover	Carbamazepine Phenytoin VPA	**1.19 (95% 0.35-3.99)**

Kesselheim AS, et al. *Drugs* 2010:70:605-21

Warfarin



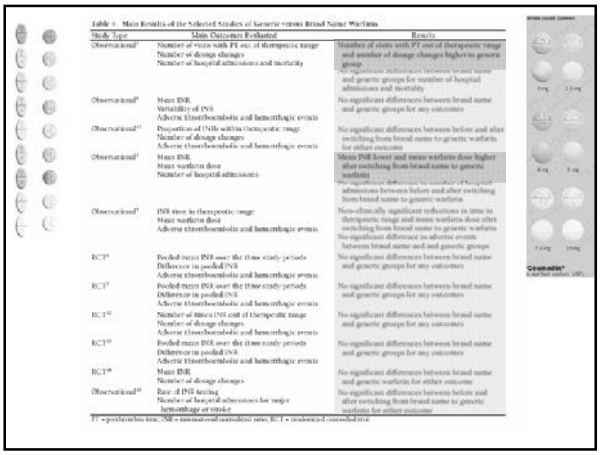
Paterson JM. JAMA. 2006;296:1969-72

Thyroid Hormone Replacement

Brand Name	Manufacturer	AB rating			
Synthroid	Abbott	AB1	AB2		
Levoxyl	King	AB1		AB3	
Unithroid	Jerome Stevens	AB1	AB2	AB3	
Levo-T	Alara	AB1	AB2	AB3	
Levothyroxine (T4)	Merck		AB2	AB3	
Levothroid	Lloyd				AB4
Levothyroxine (T4)	Mylan	AB1	AB2	AB3	AB4
Tirosint	Akrimax				

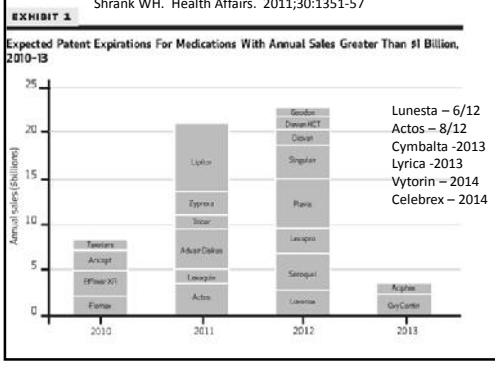
T4 is sensitive to degradation – batch to batch variability

It is prudent to keep patients on same T4 product



We Have Entered the Golden Age of Generic Drugs

Shrank WH. Health Affairs. 2011;30:1351-57



Thyroid Hormone Replacement

- Turbulent history
  - BE study suppression (synthroid/levoxyl)
  - Past stability issues
- Synthetic levothyroxine (T4) became commercially available in the 50s
  - Kefauver-Harris amendment to FDCA requiring evidence of efficacy (1962)
- 1997 FDA required all T4 to receive a new NDA (2000)
- FDA has approved several AB rated generic T4 products and reformulated brands

Evidence that Generic Drug Use Should Encouraged

- Generic drugs improve adherence
- Generic drugs save money for patients and other payers
- Generic drugs are typically around longer and have better safety record
  - Most new warnings occur within first 2 years of drug approval

Shrank WH. Arch Intern Med 2006;166:332-37
Shrank WH. Health Affairs 2011;30:135157
Shrank WH. Health Affairs 2010;29:1383-90

Strategies Used To Mitigate Patent Loss

With the *Lipitor For You* program You Get the #1 Prescribed Cholesterol lowering Medicine in the World* For as Low as a $4 Co-pay per Month

You can get LIPITOR for less than the average cost of a generic statin.† Eligible patients can get the #1 prescribed branded cholesterol-lowering medicine in the world* for as low as a $4 co-pay per month with the LIPITOR $4 Co-Pay Card. Terms and conditions apply.

- Evergreening
  - Filing patients of questionable validity that can be legally challenged and invoke additional 30 month monopology
- Pay for delay
  - Financial arrangements to delay generic drug entry
- Develop "new" molecule that has a trivial variation on original (e.g. nexium, clarinex, many XL products)

"No expensive brand name, if you please. Just give me a few milligrams of phenylpropanolamine hydrochloride, with a touch of chlorpheniramine maleate added."

Sue, Reformulate, Repeat…

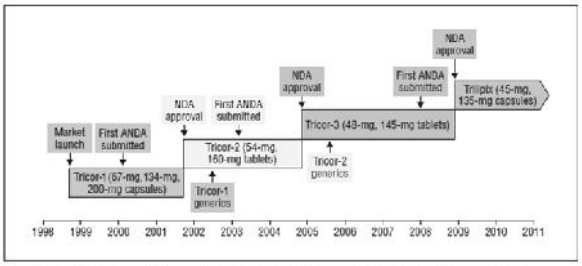
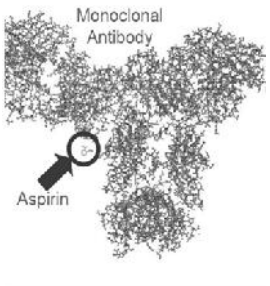


Figure 2. Evolution of Abbott Laboratories' fenofibrate franchise relative to generic competition. ANDA indicates abbreviated NDA; NDA, new drug application.

Downing NS. Arch Intern Med 2012;Online April 9/12

Generics, Bioequivalence, and **Biosimilars**….**oh my**



- Biosimilars = a biologic product that is highly similar to a previously approved biologic
  - Structural
  - Biologic functioning
- Biologics Price Competition and Innovation Act (PPACA)
  - Biologic analogue of ANDA
  - 12 patent exclusivity