



Generic Drugs: What You Need to Know

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Disclosures

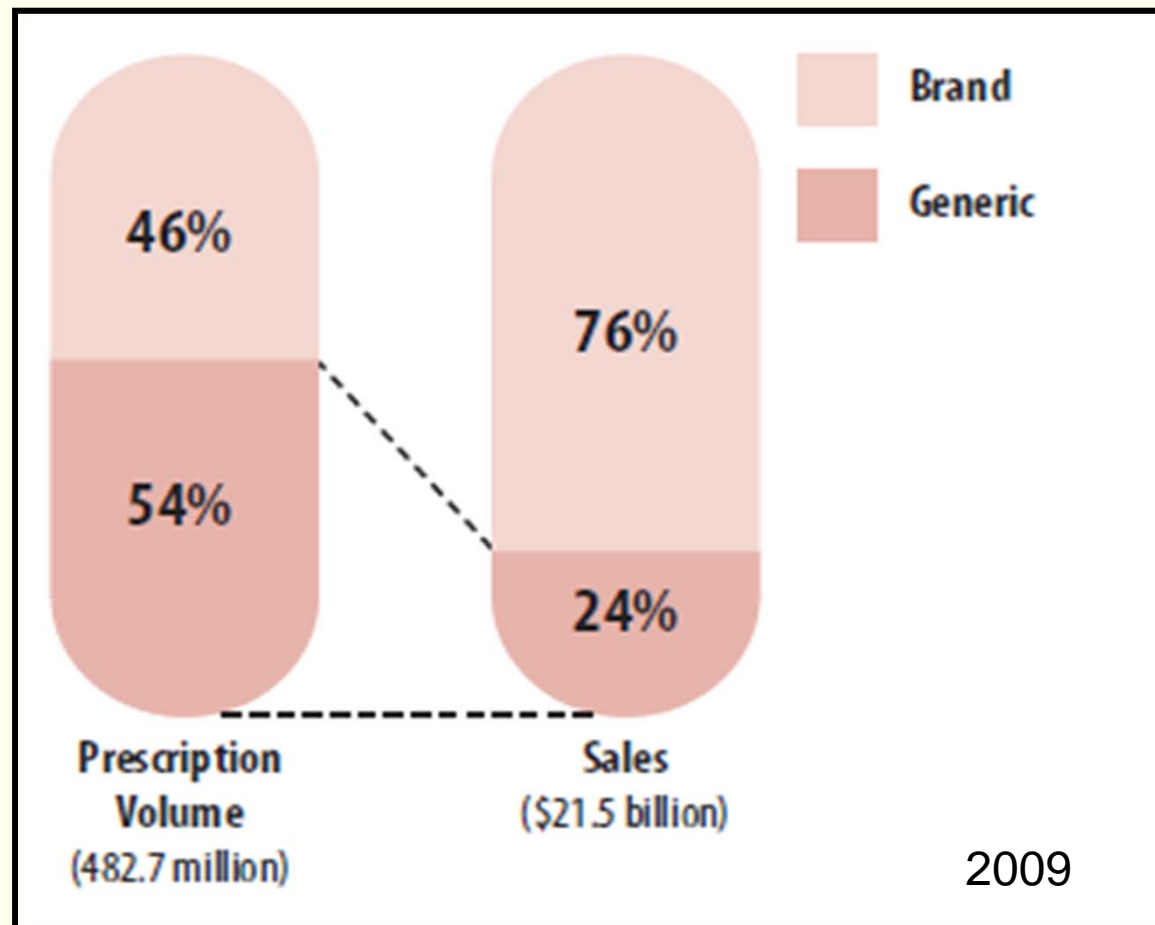
- In the last 12 months I have been the recipient of speaker honoraria and have participated in Advisory Boards for Roche Canada and Astellas



Learning Objectives

1. To describe current regulatory criteria for approval of generic medications in Canada and concerns regarding their application to certain drugs
2. To highlight the central controversies regarding the use of generic and 'biosimilar' drug products
3. To review key challenges of integrating generic drugs into clinical practice

Generic vs. Brand: Rx Volume and Sales in Canada



Generic Drug Pricing and Access in Canada: What are the Implications?
Available at <http://healthcouncilcanada.ca/en/index.php>



Are these drugs good copies?

Terminology

■ Pharmaceutical equivalence

- Drugs that contain the same active ingredient in the same strength and dosage form and are intended for the same route of administration

■ Bioequivalence (BE)

- Absence of a significant difference in rate and extent to which active ingredients become available at the site of drug action in the body under similar conditions

■ Therapeutic equivalence

- Same efficacy and toxicity assumed on the basis of BE
- NOT defined by a measured clinical effect

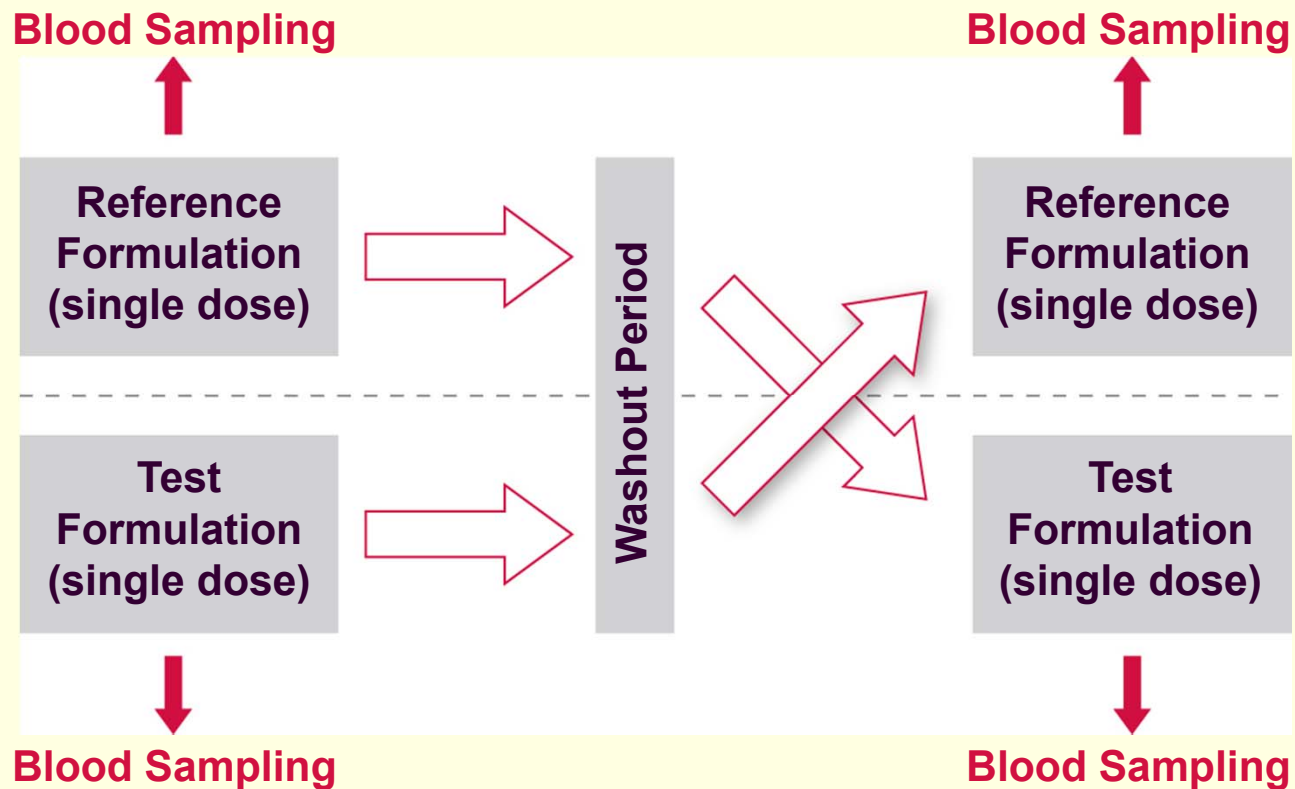
Requirements for Generic Medications

- Must have pharmaceutical equivalence
 - identical amount(s) of active ingredient(s), strength, dosage form, route of administration
 - same therapeutic indication
- May differ in:
 - inactive ingredients (excipients)
 - shape, colour, scoring, release mechanism
 - packaging, labeling, expiration time
- Must demonstrate **bioequivalence**

Standard Design of Bioequivalence (BE) Studies

- 12 – 36 healthy adults, ages 18 to 55
- 2-way cross-over
- Single oral doses of both products
- Usually performed using the highest strength of a drug's product line
- Determination of plasma concentration vs. time curves with calculation of mean PK parameters
 - C_{max} – reflects rate of absorption
 - AUC – reflects extent of absorption

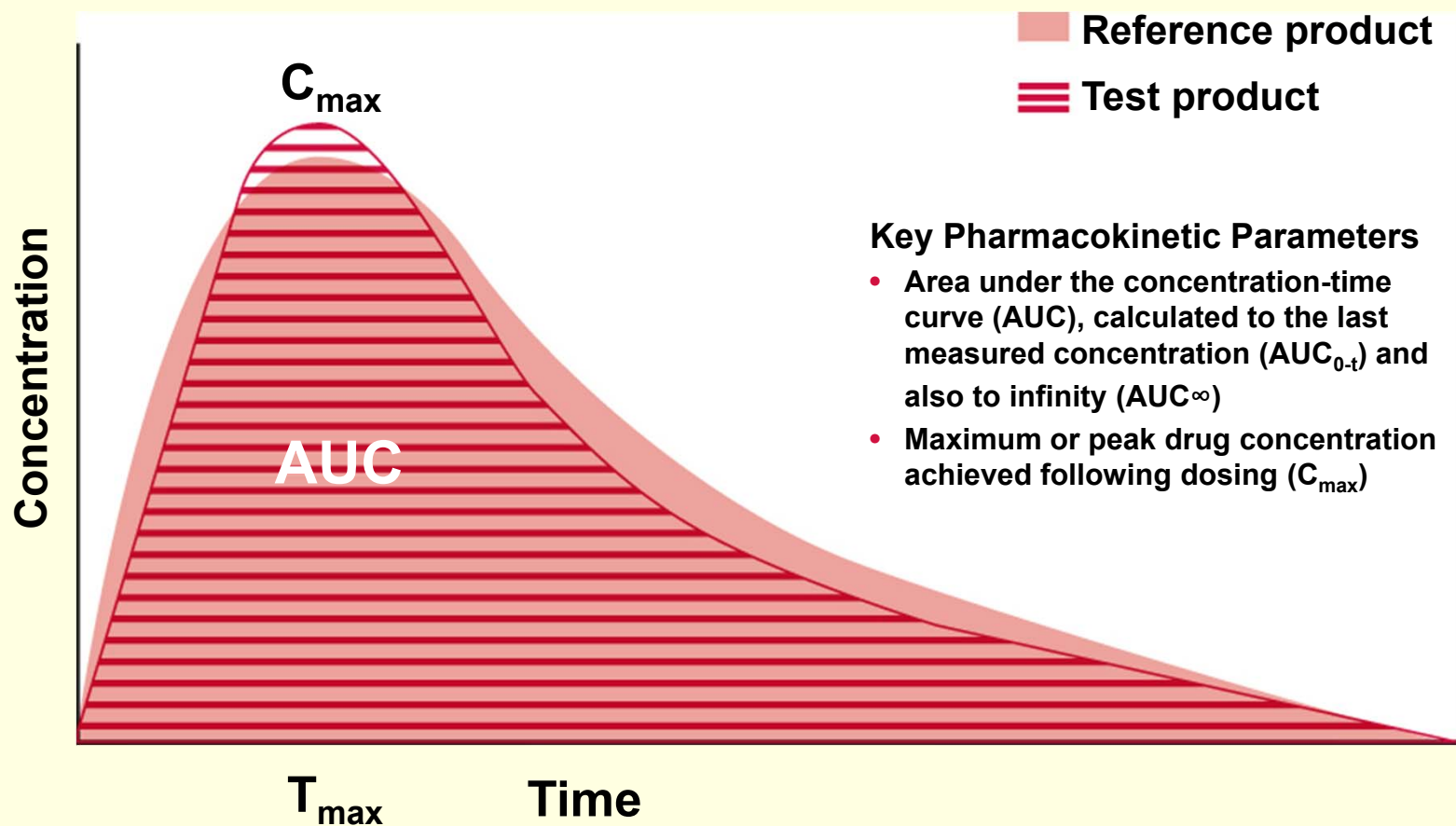
Typical Design of a Bioequivalence Study



EMA (CHMP) Guideline on the Investigation of Bioequivalence. Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

Bioequivalence Assessment

Comparison of the key pharmacokinetic parameters, AUC and C_{\max}

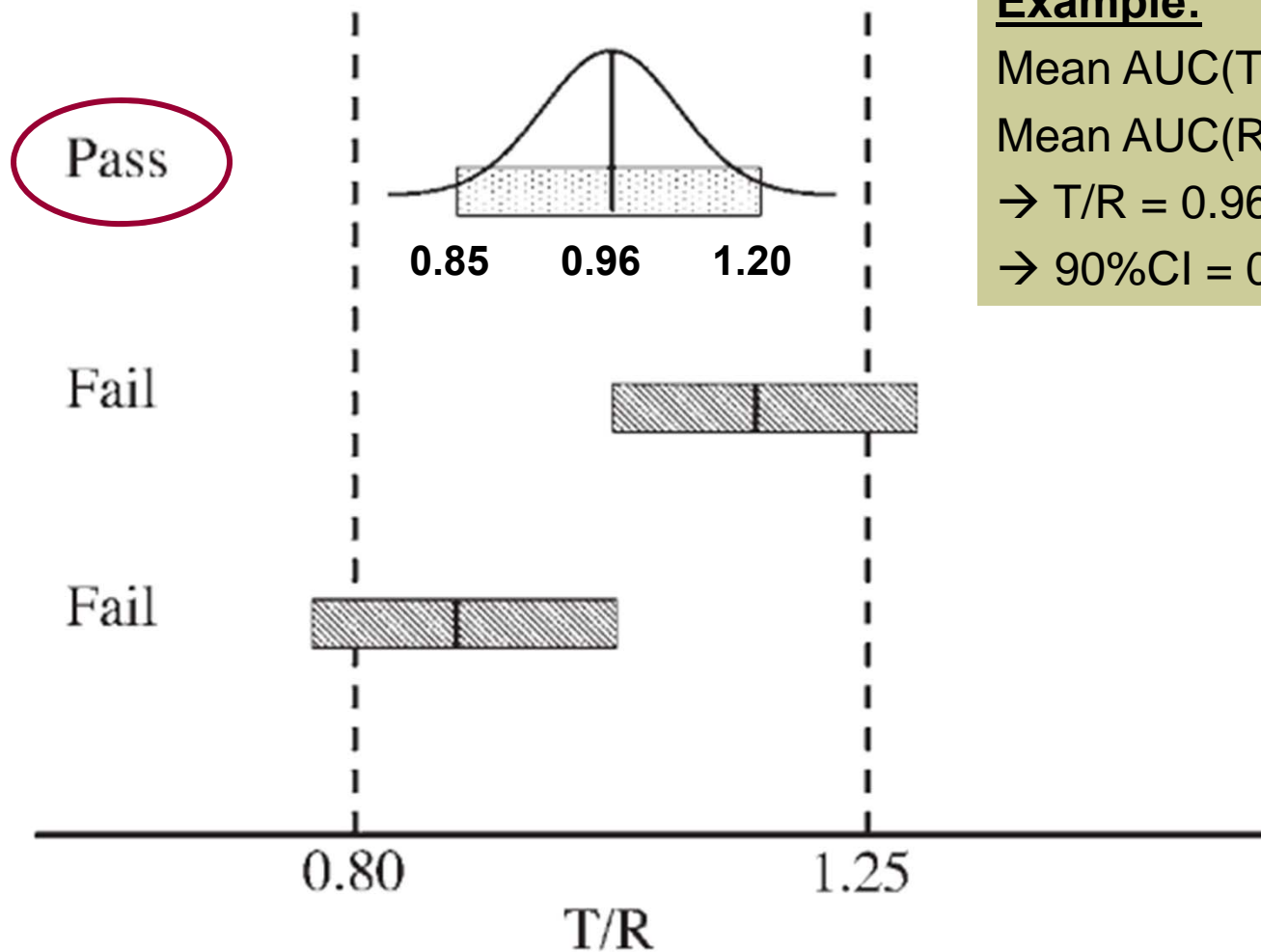


Bioequivalence Test Standards

- Mean AUC and Cmax for the generic and brand products are determined from the BE study population
- Ratio of means for test/reference products for both AUC and Cmax are calculated
- Data is log-transformed and two one-sided ANOVA tests are used to determine 90% CI

Products are considered bioequivalent if 90% CIs for AUC and Cmax mean ratios fall entirely within the acceptance limits of 0.8 to 1.25

Possible BE Study Outcomes



Example:

Mean AUC(T) = 48

Mean AUC(R) = 50

→ T/R = 0.96

→ 90%CI = 0.85, 1.20

Health Canada: Critical Dose Drugs

- *“Drugs where comparatively small differences in dose or concentration may lead to dose and concentration-dependent serious therapeutic failures and/or serious adverse drug reactions”*
- Typically require individual dose titration / TDM
- Tighter acceptance range for AUC → ↑ assurance of similarity of reference and generic products
- Includes cyclosporine, tacrolimus, sirolimus, digoxin, phenytoin, flecainide, theophylline, warfarin, lithium

Bioequivalence Acceptance Limits

| | Canada ¹ | US ² | Europe ³ |
|-----------------------------------|--|---|---|
| Standard limits of 90% CI* | 80-125% for AUC and Cmax <i>Both fed and fasted states required for modified-release products</i> | 80-125% for AUC and Cmax <i>Must test in fed state if on innovator label</i> | 80-125% for AUC and Cmax <i>Must test in fed state if on innovator label</i> |
| Critical Dose Drugs | 90-112% for AUC 80-125% for Cmax <i>Both fed and fasted states required</i> | As above | 90-111% for AUC and Cmax <i>Must test in fed state if on innovator label</i> |

*90% confidence interval for mean AUC and Cmax ratios of test/reference products

¹<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/bio-a-eng.php>

²<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=320>

³http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

What is NOT Required for Bioequivalency

- Individual bioequivalence and subject-by-formulation interaction
- Testing at steady state/ multiple dose studies
- Testing of different dose levels (usually)
- Validation of therapeutic drug monitoring strategies
- Studies with commonly co-administered medications
- Testing in target population(s)
- Clinical efficacy and safety studies

Central Controversy #1



Does bioequivalence in
healthy subjects
guarantee
bioequivalence
AND
clinical equivalence
in an individual
of the specific
target population?

Controversial Generic Drugs

- Anti-epileptic drugs
- Immunosuppressants
- Thyroid hormone
- Oral contraceptives
- Psychiatric agents
- **Warfarin**
- **Clopidogrel**
- **LMWHs**



What is the evidence?



PHARMACOTHERAPY

Brand Name vs. Generic Warfarin: A Systematic Review of the Literature



- 6 RCTs → INRs, TTR and # dose changes similar
- 5 observational pre/post studies → differences in INR, warfarin sensitivity and/or # dose changes in 3
- Clinical outcomes and adverse effects similar in all 11
- Author conclusions:
 - generic warfarin probably as safe and effective as brand
 - close monitoring is reasonable when switching as variation in individual response may be seen
 - recommend to minimize changes between products (note: 4 generics currently available on Canadian market)

Clopidogrel



- Patent expires in Aug 2012 (Canada)
- Not considered a critical dose drug
- BE testing on parent drug vs. active metabolite?
- Few studies, inconsistent results:
 - generic is BE to brand^{1,2}; generic not BE for parent compound³
 - no difference in platelet function measures^{1,4,5}
 - poor inter-therapy agreement in platelet reactivity measure
 - switching may ↑ risk of ischemic events in some patients and caution is advised⁶

¹Rao et al. Curr Ther Res Clin Exp 2003;64(9):685-696

²Di Girolamo et al. Clin Ther 2010;32(1):161-70

³Pawlowska et al. Arzneimittelforschung 2009;59(6):289-96

⁴Shim CY et al. Clin Ther 2010;32(9):1664-73

⁵Ashraf et al. J Pak Med Assoc 2005;55(1):443-8

⁶Jeong et al. Korean J Int Med 2010;25:154-61

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

A Systematic Review and Meta-analysis

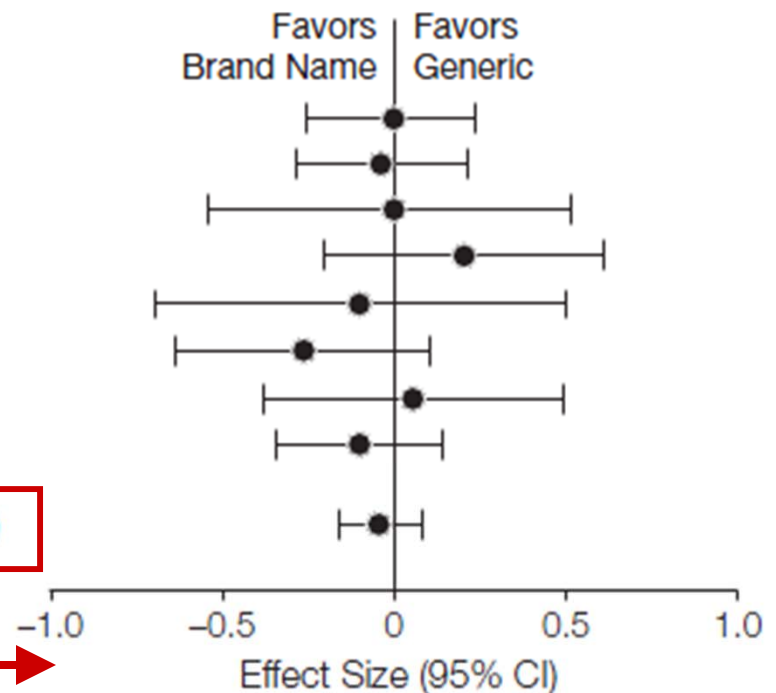
- Inclusion criteria for meta-analysis
 - published in English between 1984 – 2008
 - RCT or observational study design
 - brand name drug is FDA-approved
 - compare generic vs. brand for efficacy and/or safety endpoints and mean \pm SD reported

- Aggregated different endpoints across studies to determine effect sizes
 - for each CV drug class
 - for all studies included (overall aggregate effect size)

Meta-Analysis Results

Figure 2. Drug Class and Aggregate Meta-analyses of Trials Comparing Generic and Brand-Name Drugs Used in Cardiovascular Disease

| Drug Class | No. | | Effect Size (95% CI) |
|--------------------------|-----------|------------|------------------------------|
| | Studies | Subjects | |
| 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) |



**Cohen D effect size:
< 0.5 considered 'small'**



ACE indicates angiotensin-converting enzyme; CI, confidence interval.

Meta-Analysis – Conclusions

- Generic and branded formulations appear similar in clinical outcomes
 - best quality evidence from RCTs in patients with CV disease on BBs, CCBs and statins
- Limitations of literature – small numbers, not powered to detect differences in clinical outcomes, use of superiority hypotheses (vs. non-inferiority)
- Reasonable for clinician to rely on FDA BE rating as a proxy for clinical equivalence

Do we really need stricter requirements for generics?

- Manufacturing standards, BE test requirements, and regulatory oversight are rigorous and same as for innovator products
- Changes in PK due to disease, drug interactions, diet, renal or hepatic function, etc. may pose as much of a risk as a switch to a generic formulation
- TDM, dosing adjustments and/or clinical titration may compensate for potential changes in bioavailability
- Small differences in PK do not necessarily translate into differences in clinical endpoints

FDA Review of Generic and Innovator Drugs

- Retrospective analysis of 2070 single-dose BE studies of PO generics approved by FDA between 1996 – 2007
- Mean difference in C_{max} and AUC between generic and innovator products was 4.35% and 3.56% respectively
- In > 90% of the BE studies, C_{max} and AUC for generic differed from innovator by less than 10%
- Author conclusion: FDA criteria for BE support the objective of approving generic formulations that are therapeutically equivalent to the innovator product.

FDA Approves First Generic Blood Thinner July 23, 2010

- Generic enoxaparin (Sandoz & Momenta) approved by FDA in July 2010
- Approved under usual ANDA process
- Interchangeable with Lovenox[®] for all approved indications



Should it have been treated differently?

Biologic Drugs and Subsequent Entry Biologics (SEBs)

- **Biologic drugs:** derived through metabolic activity of living organisms; more variable and structurally complex than chemically synthesized drugs
- **Subsequent Entry Biologic (SEB):** a biologic drug that enters the market subsequent to a previously authorized version
 - Aka 'biosimilars', 'follow-on biologics'

Central Controversy #2

Should existing regulatory guidelines for generics be applied to biosimilars?



How are Biosimilars Different?

- High molecular complexity → sensitive to differences in manufacturing process
- May be heterogeneous compound mixtures
- Differences in impurities and/or breakdown products can have serious health implications
- May not always know what active ingredient(s) are
- Immunogenicity concerns
- *“SEBs are not ‘generic biologics’ and many characteristics associated with the authorization process and marketed use for generic pharmaceutical drugs do not apply” – Health Canada*

Current Requirements for Approval of an SEB in Canada

- Manufacturing process considerations
- Quality attributes
 - includes physicochemical properties, biologic activity, immunochemical properties, purity, etc.
- Determination of similarity based on the above
- Non-clinical data (*in vitro* and animal studies)
- Clinical data (PK, PD, efficacy and safety trials)
- Risk Management Plan
- Post-marketing requirements

Should SEBs be Interchangeable?

- *“Authorization of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug” – Health Canada*
- Health Canada approval for generics or SEBs does not imply interchangeability
 - Substitution determined provincially (Committee to Evaluate Drugs (CED) in ON)
- In Canada we have one approved SEB (Omnitrope[®]) – not interchangeable with brand



***Can generic drugs be safely
integrated into clinical practice?***

Potential Concerns with Generics in Practice

1. Prescribability vs. switchability
2. Managing switches
3. Drug interchangeability and notification of generic substitution
4. Medication adherence and patient confusion

1. Prescribability vs. Switchability

Prescribability

“The willingness to prescribe a drug to a patient for the first time because confidence in the drug’s efficacy and safety has been assured by population bioequivalence”

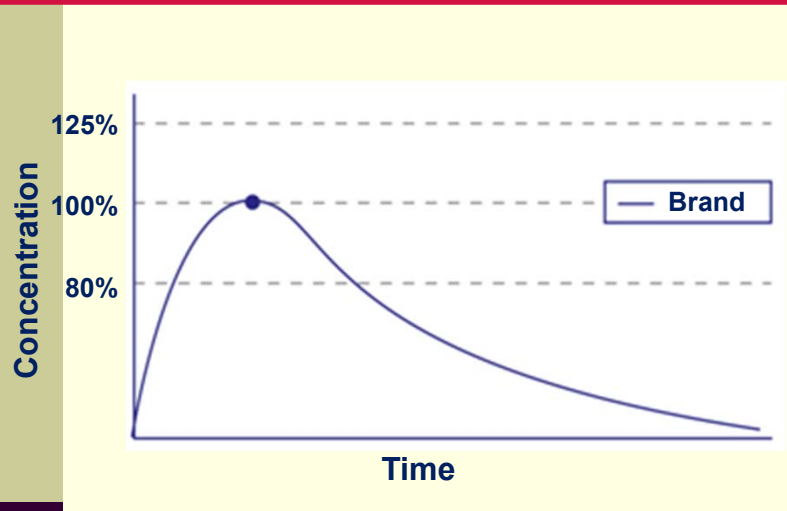
Switchability

“The ability to appropriately transfer a patient from one formulation of the drug to another... high confidence in switchability is assured by individual bioequivalence”

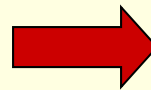
Current BE regulatory criteria focus only on prescribability

In the setting of multiple generics...

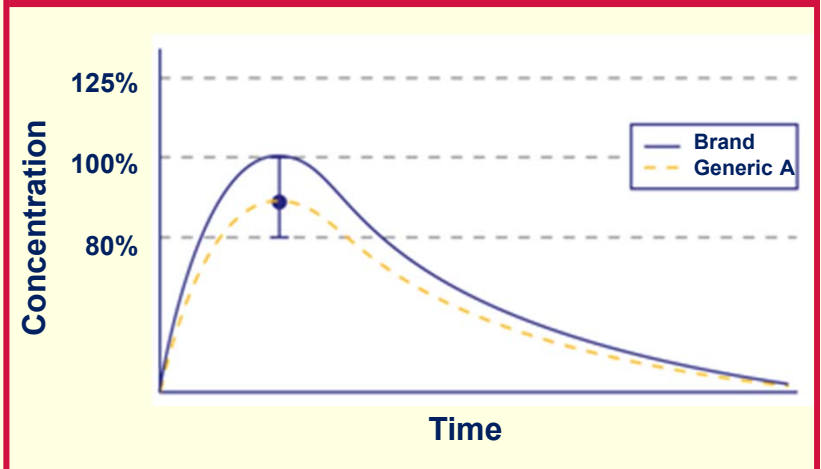
On leaving hospital, patient receives a 2-month supply of branded medication



Pharmacokinetic profile of patient's branded medication



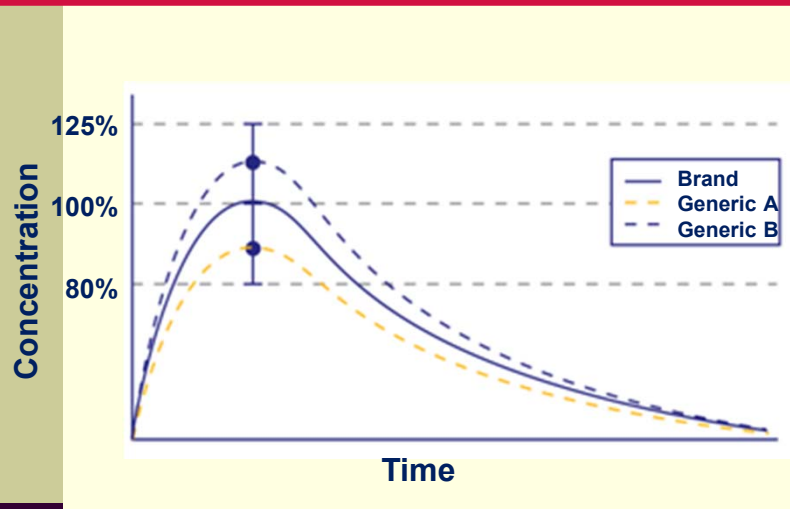
After 2 months, patient's pharmacist dispenses Generic A in place of his branded medication



Generic A is bioequivalent to patient's branded medication

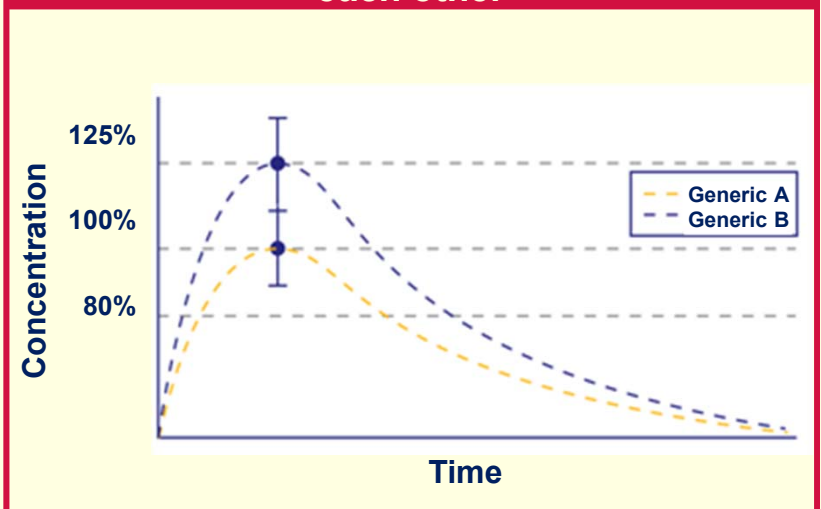
...generics may not be bioequivalent with each other

After 6 months, patient's pharmacist dispenses Generic B in place of Generic A



Generics A and B are both bioequivalent to patient's branded medication

Patient may be switching between therapies that are not bioequivalent with each other



Generic B may not necessarily be bioequivalent to Generic A

Potential for ↑ intra-subject variability with multiple generics

2. Managing Switches

- May need heightened surveillance strategy if switching between brand and generic(s), esp. with critical dose drugs^{1,2}
- TDM of product in question and other critical dose drugs in the regimen, until new steady state is established... but beware...
 - PK and TDM approaches are formulation-sensitive and relationship may be different for generics^{1,3-5}
- Increased clinical monitoring¹⁻⁵

¹Uber et al. J Heart Lung Transplant 2009;28:655-660

²Kesselheim et al. JAMA 2008; 300(21):2514-2526

³Durlik et al. Transplant Proc 2003; 35: 1304-1307

⁴Pollard et al. Clin Ther 2003;25(6):1654-1669

⁵Hibberd et al. Transplantation 2006;81(5):711-717

3. Drug Interchangeability and Notification

- Pharmacies may commonly change supplier based on price and availability
- Under the *Drug Interchangeability and Dispensing Fee Act* (DIDFA):
 - Pharmacist may substitute a generic product if designated as 'interchangeable'
 - Not obligatory to inform patient or prescriber
- Even if notified, prescriber may not know when patient started taking new formulation
- Changes may occur at interfaces of care (e.g. patient admitted to hospital)

4. Will generics improve medication adherence?

YES

- where Rx cost is a factor for patient

NO

- confusion
 - > 1 bottle → may mix Rxs together or duplicate therapy
 - generic appearance
 - generic name
- beliefs about generics

Confusion between generic and trade names is the most common medication-related risk factor associated with poor health outcomes¹

¹Sorensen et al. Age and Ageing 2005;34:626-632

So what does it all mean?

- Humans are complex and variable biologic systems, and population BE does not guarantee individual BE
- BE margins are arbitrary and may not reflect the level at which a difference in clinical effect would be observed in an individual patient
- Bottom line:
 - generic substitution for most drugs not likely an issue, but ↑ vigilance in some scenarios may be advised
 - no way to definitively identify who may do poorly on one product vs. another
 - need to evaluate risk, *i.e.* how critical is it that the generic offers equivalent clinical performance in my patient?

Evaluating the Risk

1. What are the potential consequences of clinical destabilization?

- *i.e.* can patient recover back to baseline?

AND

2. Is there a clinical endpoint that is relevant and practical to measure?

- BP, lipid panel, INR, blood glucose vs.
- degree of immunosuppression, seizure threshold
→ we can do TDM but is this enough?

AND

3. Will we know when we need to get a measurement?

Practice Recommendations

1. Identify high risk scenarios in your practice
2. Where possible, prescriber and patient should be involved in any decision to switch formulation
3. Where possible, specify intended formulation
4. Exercise caution by increasing clinical monitoring and frequency of TDM where appropriate
5. Avoid frequent switches and mixing of formulations
6. Perform medication reconciliation and document drug product in medication history
7. Educate clinicians and patients (drug names, pictures)
8. Collect data and report issues with generics

Questions?

