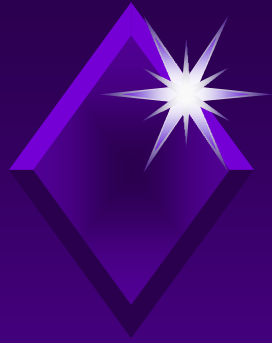


*Generic AEDs:  
Is There a Problem? Can we Separate  
the Science from the Politics?*



**Prof. Meir Bialer  
Hebrew University  
Jerusalem, Israel**

**European Chapter Convention (20.09.2008)**



# *New Drug - NDA*

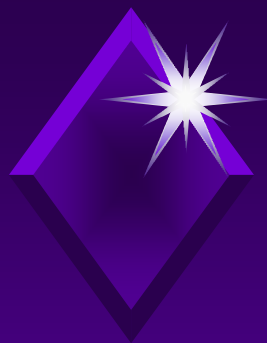
## *Generic Product - ANDA*

- u A new drug has to prove **efficacy & safety (NDA)**
- u A generic product of an existing drug has to be bioequivalent to the brand (reference) product by demonstrating the same *in vivo* **(absorption) performance (ANDA)**



# *Bioequivalence*

- ⌋ Bioequivalence studies are designed to assess the relative bioavailability of a drug from test (generic) and reference (brand) formulations
- ⌋ Ideally, the test and reference formulations should give essentially superimposable plasma concentration versus time profiles, but practically it is impossible
- ⌋ Bioequivalent generics are regarded as **essentially similar** to the brand product



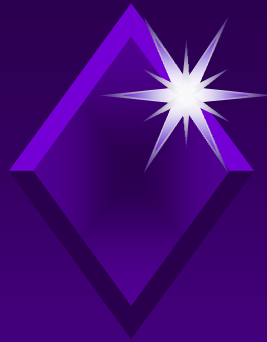
## *Generic Products - ANDA*

A generic product has to be bioequivalent to the brand (reference) product by demonstrating the same *in vivo* (absorption) performance



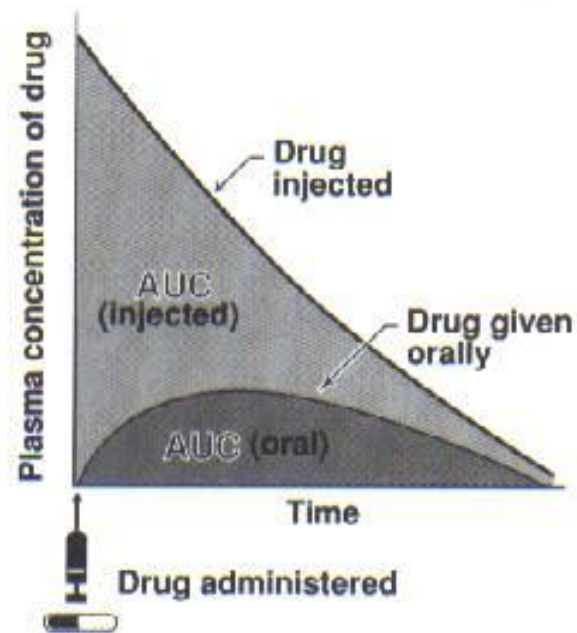
## *The Three Major PK Parameters to Assess Bioequivalence are:*

- 1) **AUC** - extent of absorption
- 2) **C<sub>max</sub>** - rate (but also extent) of absorption
- 3) **t<sub>max</sub>** - rate of absorption

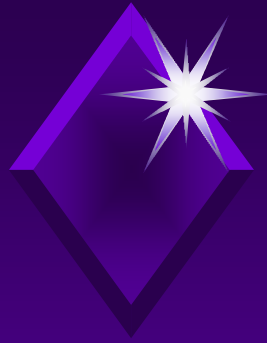


# *AUC & Bioavailability*

$$\text{Bioavailability} = \frac{\text{AUC oral}}{\text{AUC Injected}} \times 100$$

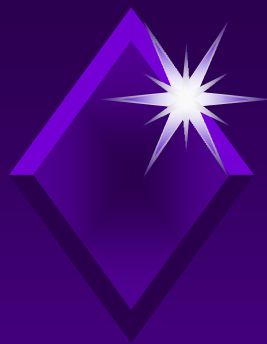


**Figure 1.7**  
Determination of the bioavailability  
of a drug. (AUC = area under curve.)



# *Area Under the Curve (AUC)*

- u **AUC is a robust parameter which takes into consideration all the experimental points collected in each phase of a bioequivalence study**
- u **AUC is the principal criterion to characterize the extent of absorption and to assess bioequivalence**
- u **This applies to single and to multiple dose studies of immediate and CR formulations**



# *Bioavailability & Bioequivalence*

**Absolute bioavailability**

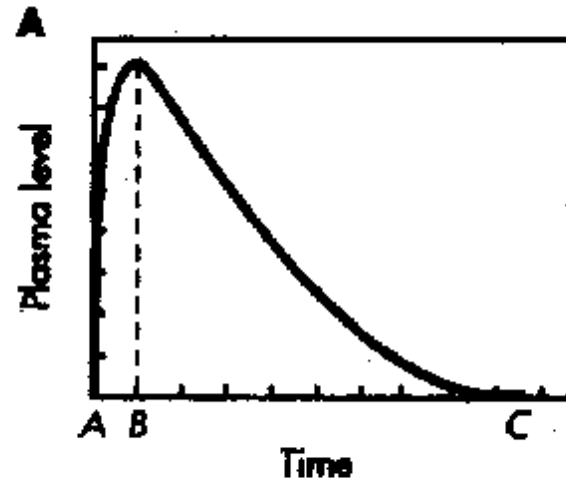
$$F = \frac{\text{AUC}_{\text{po}} / D_{\text{po}}}{\text{AUC}_{\text{iv}} / D_{\text{iv}}}$$

**Relative bioavailability  
(Bioequivalence)**

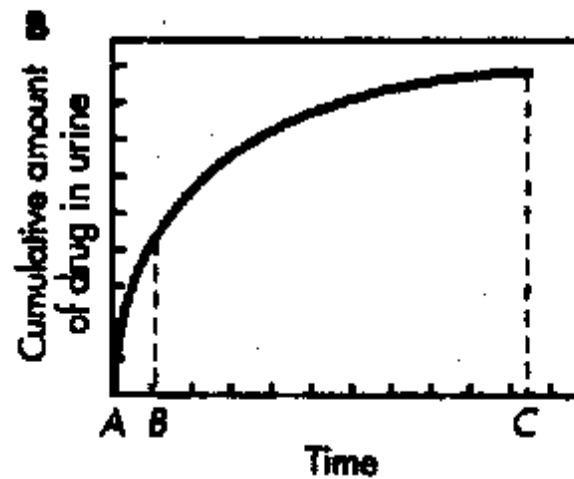
$$F' = \frac{\text{AUC}_{\text{test}} / D_{\text{test}}}{\text{AUC}_{\text{ref}} / D_{\text{ref}}}$$

**AUC** is calculated by **numeric** (non-compartmental) method  
**Absorption rate** : **C<sub>max</sub>** and **t<sub>max</sub>** are determined by visual inspection of the experimental **plasma** data

# Bioequivalence – Extent of Absorption

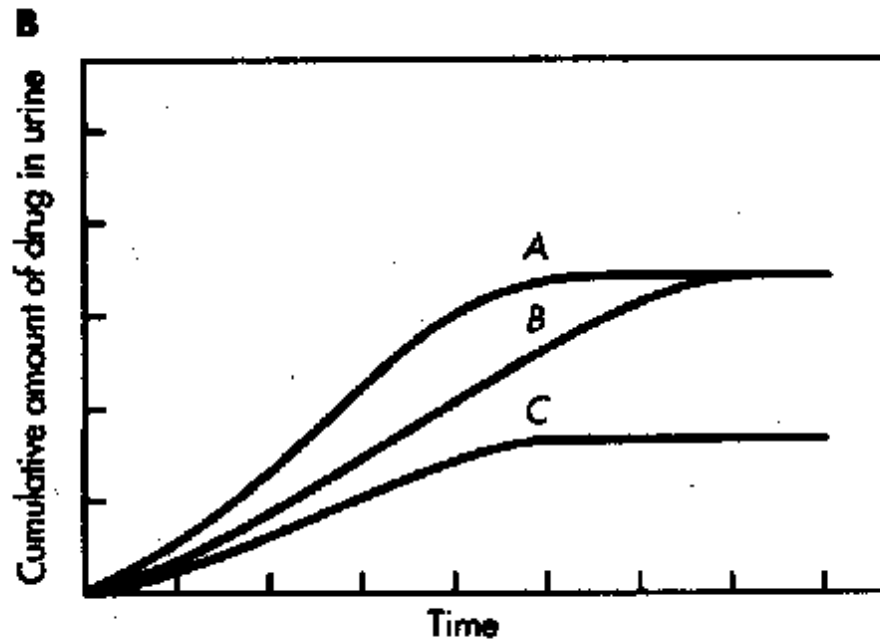
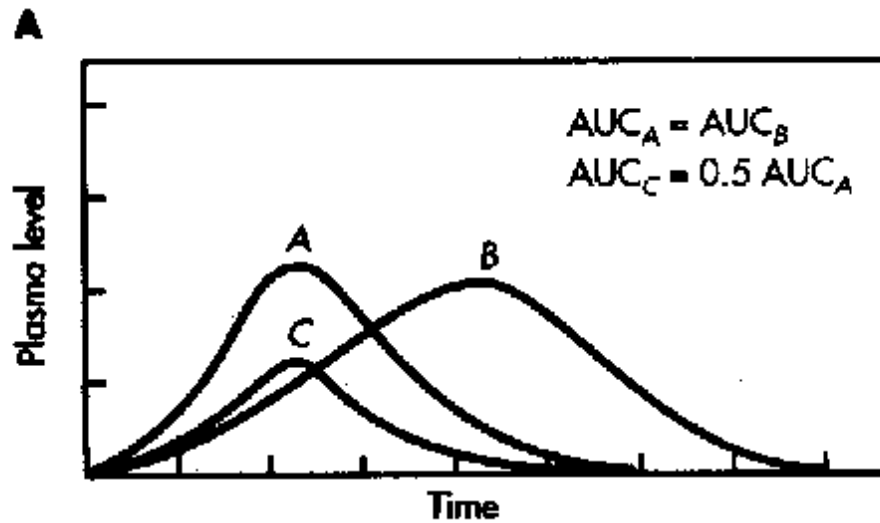


**Plasma data-AUC**



**Urine data-**  
Cumulative amount  
excreted unchanged  
in urine (**Ae**)

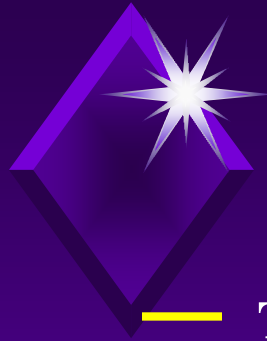
# Bioequivalence – Extent of Absorption



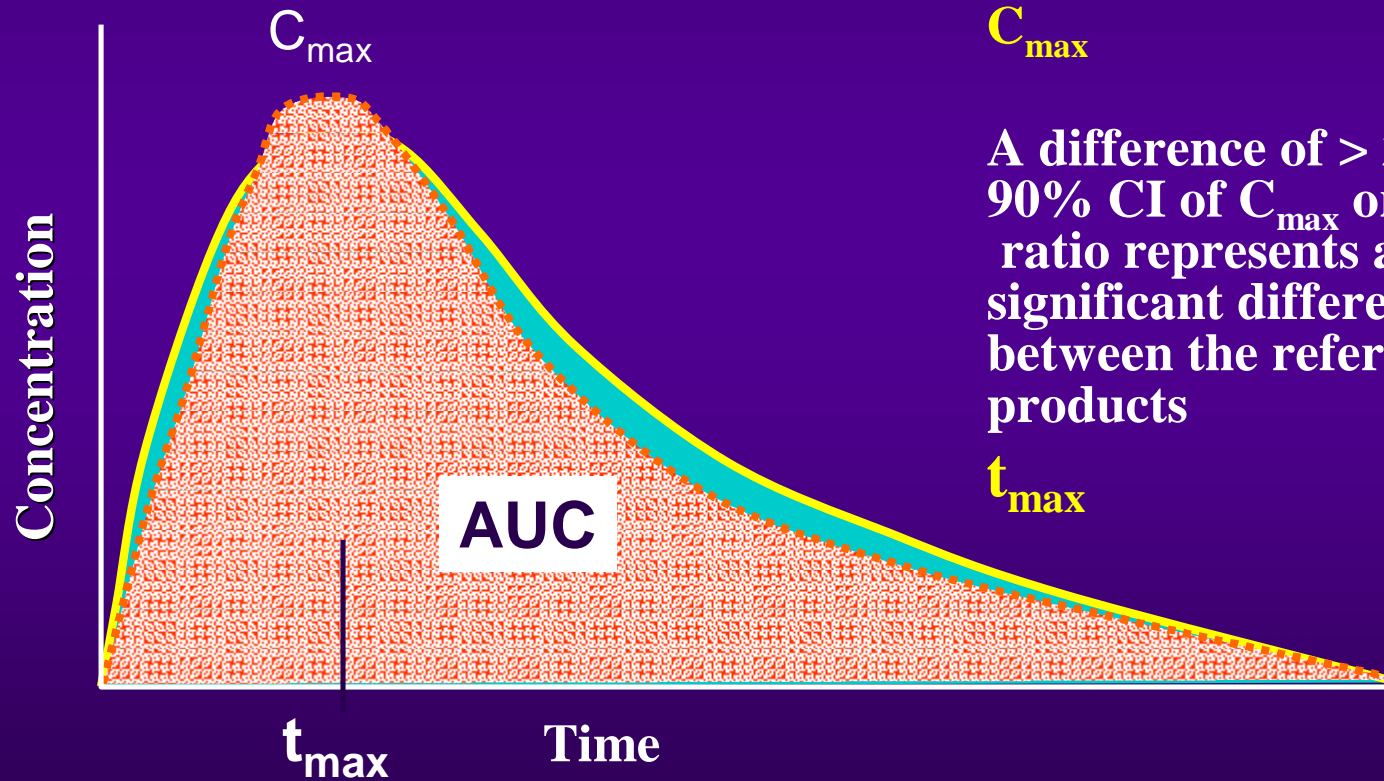
**Plasma data**

**Urine data**

# Bioequivalence Criteria



— Test (generic)  
- - - Reference

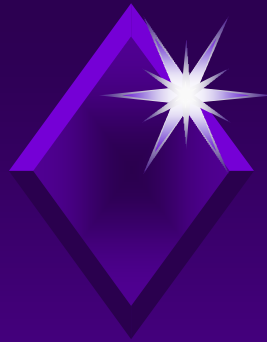


AUC

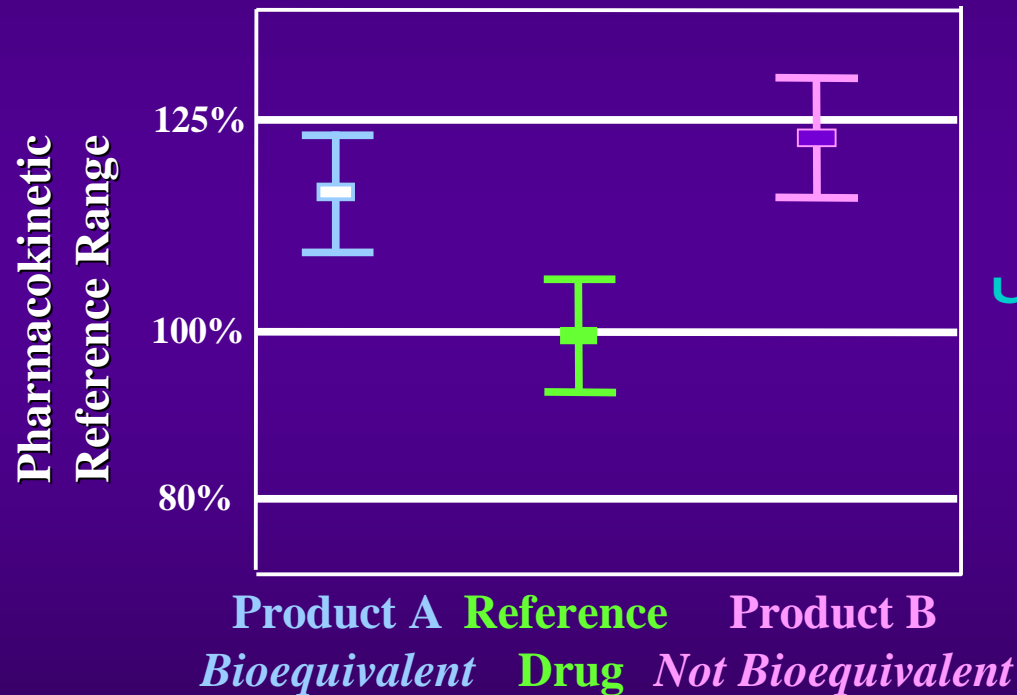
$C_{max}$

A difference of  $> 20\%$  in the 90% CI of  $C_{max}$  or the AUC ratio represents a significant difference between the reference & test products

$t_{max}$



# FDA Requirements for Bioequivalence



- Product A is **bioequivalent** if the 90% CI of its AUC ratio ( $AUC_{test}/AUC_{ref}$ ) and  $C_{max}$  ratio falls within 80-125%
- Product B is **not bioequivalent** if the 90% CI of its AUC ratio ( $AUC_{test}/AUC_{ref}$ ) and  $C_{max}$  ratio falls outside 80-125%



# *Bioavailability (BA) & Bioequivalence (BE)*

⌋ **Bioavailability (BA)** is measured by assessing the rate and extent to which an active drug or active drug moiety is absorbed from the drug product and becomes available at the site of action

⌋ **Bioequivalence (BE)** is the science of **comparing** the bioavailability of a drug from two different formulations of that drug

⌋ **Within-subject variability (WSV)** is more important in BE than in BA



## *Within-Subject Variability (WSV)*

- ▣ **WSV** or intrasubject variability is a measure of variability in response within the same subject, when the subject is administered two doses of a solution (preferably) on two different occasions
- ▣ **WSV** may be intrinsic to the drug substance and/or formulation
- ▣ **WSV** is more important in BE than in BA, since BE is concerned with **interchangeability within a subject**



# *Within-(WSV) vs Between-Subject Variability (BSV)*

**WSV** is estimated from ANOVA

The fixed effects in the ANOVA model are typically:

Formulation

Period

Sequence

Subject (Sequence)

} These account for all the **BSV**

Residual Variance (MSE) } **WSV**

Many drugs have a large **BSV**, but **BE** is concerned with **interchangeability**. Therefore, **WSV** and not **BSV** is a **critical determinant** for **BE**

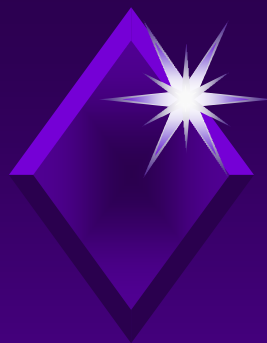


## *PK Parameters to Assess Bioequivalence: Systemic Exposure Concept*

- ⌋ **AUC** - A measure of total **exposure**, assesses extent of absorption
- ⌋ **C<sub>max</sub>** - A measure of **peak exposure**, assesses rate (but also extent) of absorption
- ⌋ **t<sub>max</sub>**- assesses rate of absorption
- ⌋ **AUC<sub>E</sub>**- Partial AUC truncated at t<sub>max</sub>, a measure of **early exposure** (MR, rapid onset)

Meeting the acceptable **90% CI** of **80-125%**, implies that plasma levels (**AUC**) of a **bioequivalent generic** with **linear PK** will not differ by **>5-7%** from those observed with the brand product

Perucca et al, *Epilepsia*, 2006; Bialer, *Epilepsia*, 2007; Midha & McKay, *BA & BE Conference*, Athens, October 1-2, 2007



## *Residual (WSV) Variance*

- u The residual variance has **four components:**
- u True PK WSV plus a component of analytical variability
- u Within formulation (tablet to tablet) variability
- u Subject by formulation interaction
- u Unexplained random variation

These variance components cannot be separated in a standard two-period design



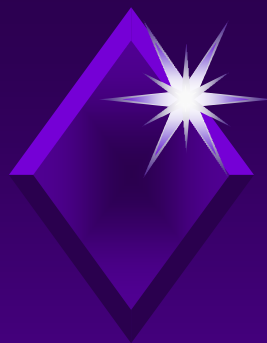
# *Standard vs Replicate Designs*

## **Standard 2-period Design**

- u 2-formulations, 2-period, 2-sequence crossover design
- u The two sequences are: **TR & RT**

## **Replicate Design**

- u The test & reference formulations are given twice
- u A 4-period replicate design with two sequences is: **TRTR & RTRT**



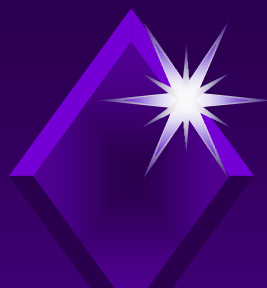
## *Physicians' Concern*

**Concern persists that the criteria used to establish bioequivalence of generic drug products may not adequately guarantee the interchangeability of drugs, particularly CR formulations**



# *Bioequivalence is a More Demanding Criterion than Therapeutic Equivalence*

“The **present requirements** to prove bioequivalence, at least in the US and Canada, are already so **rigorous** and constrained that there is very little possibility, even for NTI drugs, that dosage forms meeting regulatory criteria could lead to therapeutic problems”



*Epilepsia*, 48(10):1825–1832, 2007  
Blackwell Publishing, Inc.  
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## Generic Products of Antiepileptic Drugs (AEDs): Is It an Issue?

Meir Bialer

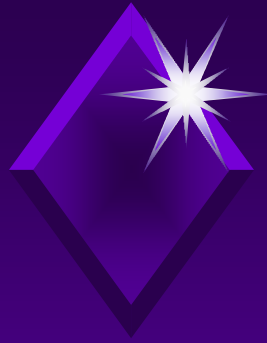
*Department of Pharmaceutics, School of Pharmacy and David R. Bloom Center for Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel*

Do **bioequivalent** generic AEDs work as well as brand AEDs?  
Can **generic** AEDs be used as **substitutions** for **brand** AEDs?  
Can **generic** AEDs be used **interchangeably**?



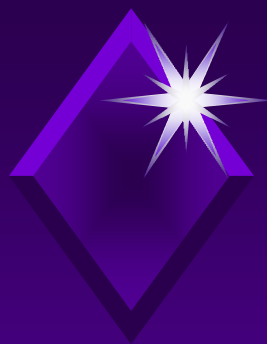
## *Issues Specific to Epilepsy & Generic Products of AEDs*

- ⌋ Epileptic patients require **consistency** in their AED treatment
- ⌋ This is particularly true for **seizure-free patients**
- ⌋ The **generic switch** itself may cause breakthrough seizures as patients are averse to changes
- ⌋ Patients prescribed with generics may face **switches** from one **generic product to another**
- ⌋ In an unpredictable subset of epileptic patients **generics** may have a **higher intrasubject variability (WSV)** than the brand AEDs



# *Average vs Individual Bioequivalence (BE)*

- ⌋ **Average BE**- Compares **population** means between the test (generic) and reference (brand) products
- ⌋ **Individual BE**- Can evaluate **switchability**
- ⌋ **Individual BE Concept**: Each patient has an individual therapeutic window & intrasubject variability (WSV)
- ⌋ **Individual BE models** are more complicated



# *Individual Bioequivalence (BE)*

Individual Difference Ratio

$$\text{IDR} = \frac{T - R}{R - R}$$

Difference in bioequivalence metric  
(AUC, Cmax) between test & reference

Difference between reference &  
reference

## **Replicate Design**

For individual BE analysis the generic and brand products must be administered twice to the same group of subjects

**Chen & Lesko, *Clin Pharmacokinet*, 2001; Bialer, *Epilepsia*, 2007**



# *Individual & Average Bioequivalence (BE)*

## Individual BE

$(\text{Difference of means})^2 + \text{Interaction} + \text{Difference of variances} \leq (\text{Preset limit})^2$

## Average BE

Lower preset limit (80%)  $\leq$  Difference of means  $\leq$  Upper preset limit (125%)

When the within subject variances of the generic & brand products are the same and there is no interaction: **Individual BE = Average BE**

# Individual Bioequivalence - Has its Time Come?



*Pharmaceutical Research*, Vol. 15, No. 9, 1998

*Commentary*

## Individual Bioequivalence: Attractive in Principle, Difficult in Practice

Laszlo Endrenyi,<sup>1,5</sup> Gordon L. Amidon,<sup>2</sup> Kamal K. Midha,<sup>3</sup> and Jerome P. Skelly<sup>4</sup>



ELSEVIER

*European Journal of Pharmaceutical Sciences*, 6 (1998) 271-277

## Individual bioequivalence—has its time come?

Laszlo Endrenyi<sup>1,\*</sup>, Kamal K. Midha<sup>1</sup>

<sup>\*</sup>University of Toronto, Department of Pharmacology, and Department of Preventive Medicine and Biostatistics Toronto Ont. M5S 1A8, Canada  
<sup>1</sup>University of Saskatchewan College of Pharmacy and Nutrition 110 Science Place Saskatoon Sask. S7N 5C9, Canada



## LEADING ARTICLE

*Clin Pharmacokinet* 2001; 45 (10): 701-706  
0312-5965/01/0010-0701/\$22.00/0

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## Individual Bioequivalence Revisited

Mei-Ling Chen<sup>1</sup> and Lawrence J. Lesko<sup>2</sup>

- 1 Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland, USA
- 2 Office of Clinical Pharmacology and Biopharmaceutics, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland, USA

# *FDA Current Thinking on BE of Highly Variable Drugs (HVD)*

- ▣ An FDA survey: 20% of the acceptable bioequivalent generics between 2003-2005 were HVD
- ▣ **What % were generic AEDs?**
- ▣ Are AEDs except phenytoin HVD?
- ▣ BE studies of HVD enrolled 50% more subjects
- ▣ HVD – WSV (root mean square error-MSE) or %CV>30%



**B. M. Davit, OGD, CEDAR, FDA**

# *FDA Current Thinking on Bioequivalence (BE) of Highly Variable Drugs (HVD)*

It is possible to reduce number of study subjects when the 90% CI are adjusted to the within-subject variability (**WSV**) of the reference product

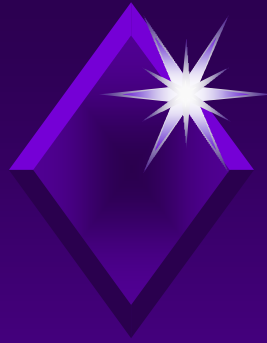
The **WSV** is determined in a partially replicate crossover study (**generic** product administered **once**, **reference** administered **twice**)

The FDA would also impose a point estimate constraint on the generic/reference mean ratio to eliminate the potential for approving a generic product with a large T-R difference



# *Average vs Individual Bioequivalence (BE) - Conclusions*

- ▣ **Approved generic AEDs** with documented average BE data are **prescribable** & represent a valuable choice for drug “naïve” patients
- ▣ The **switch** to generic is **well tolerated** by many patients and is cost-effective but is less likely to be published than case reports with **bad news**
- ▣ Until we have individual BE data or the tool to *apriori* identify susceptible patients, seizure-free patients should not be switched



# *Average vs Individual Bioequivalence (BE): Questions*

- ☐ Did **average BE fail** to assess BE of generic AEDs, aside from anecdotal reports?
- ☐ Is subject-by-formulation **interaction important** in BE analysis?
- ☐ What is the right population for individual BE, healthy **subjects or patients**?
- ☐ Is the within subject variability of patients to a **switch** from a **brand** to **generic** greater than from one **batch** to another?



# *Generic AEDs: We Must Separate the Politics from the Science*

## **Politics**

- ⌋ A pressure against generic AEDs by physicians & patients associations
- ⌋ Only “bad news” get published. A soft substitution from brand to generic does not merit publication
- ⌋ Many Pharmas produce a “manufacturer's own” generic identical to the brand. Is it a problem?
- ⌋ AEDs global sales rose from \$4.4 billion in 2000 to \$10.7 billion in 2005
- ⌋ Pharmas want to keep up this trend. Governments and HMOs do not!

**Kramer et al, *Epilepsy Behav*, 2007; Bialer, *Epilepsia*, 2007**

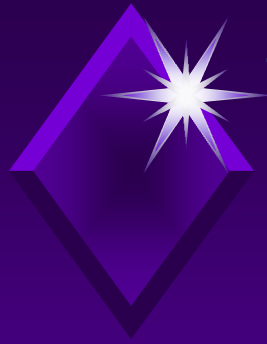


## *Industry Fights Switch To Generics for Epilepsy Big Drug Makers Help Patient Groups Lobby; More Attention to States*

In state legislatures across the country, the **Epilepsy Foundation (EF)** has been campaigning for bills that would make it harder for pharmacists to switch patients to inexpensive generic epilepsy pills. The effort is getting behind-the-scenes support from drug companies - a sign of how the industry, long & potent lobbying force in Washington, is increasingly looking to states to achieve its goals.

**EF**, a nonprofit group supported by the drug industry, says **switching to generics could cause dangerous seizures**. The **FDA** says it hasn't seen persuasive evidence for that, and it believes each **generic is equivalent to the brand-name drug it copies**.

*Sarah Rubenstein, The Wall Street Journal, July 13, 2007*





# *National Guidelines for Generic Prescription of AEDs*

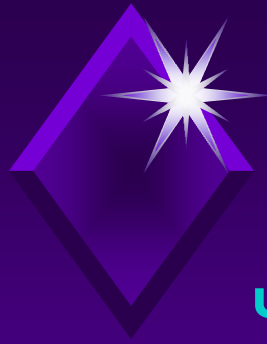
<b>Country</b>	<b>Principal recommendations</b>
<b>England</b>	<b>Small differences in absorption can result in large differences in therapeutic effect</b>
<b>Germany</b>	<b>Never switch patients who are well controlled</b>
<b>Italy</b>	<b>In seizure free patients switching is not recommended</b>
<b>Sweden</b>	<b>A switch between formulations is considered to carry a risk of unstable seizure control</b>
<b>The Netherlands</b>	<b>Generic substitution of AEDs is risky. SR formulations should not be substituted</b>

# *Generic Products of AEDs: What is so Specific?*

The patients, the disease pattern, the AEDs?

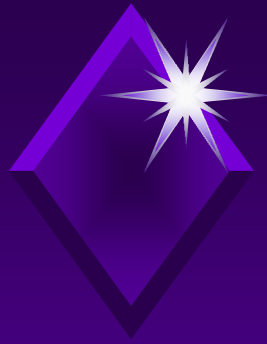


 <p>AMERICAN ACADEMY OF NEUROLOGY</p> <p>Special Article</p> <p><b>Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy</b></p> <p>K. Liow, MD; G.L. Barkley, MD; J.R. Pollard, MD; C.L. Harden, MD; and C.W. Bazil, MD, PhD</p>
<p>NEUROLOGY 2007;69:1245-1246</p> <p>Editorial</p> <p><b>What's the problem with generic antiepileptic drugs?</b></p> <p><b>A call to action</b></p> <p>Michel J. Berg, MD</p>



## *AAN Position Statement on Generic AEDs*

- ▣ AAN believes that formulary policies should support complete **physician autonomy** in prescribing & epileptic patients in accessing the full range of AEDs
- ▣ AAN **opposes** policies that would result in **arbitrary switching** among AEDs
- ▣ AAN supports legislation that would require **informed consent** of **physicians** and **patients** before **generic substitutions** of AEDs are made at the point of sale



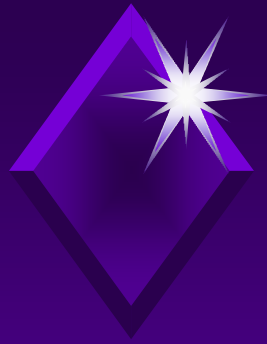
## *AAN Position Statement on Generic AEDs*

- ⌋ AAN believes that the use of **AEDs in epilepsy** should be **distinguished** from their use in **other** disorders
- ⌋ Unlike other diseases, a **single breakthrough** seizure due to change in delivered medication dose (formulation) can have **devastating consequences** including loss of driver's license, injury, and even death



## *French League's (LFCE) Considerations on Generic AEDs*

- ⌋ Epilepsy differs from chronic diseases. A single seizure may have serious and even irreversible consequences
- ⌋ AEDs are a particular class whose substitution in epilepsy is problematic (**all AEDs?**)
- ⌋ FDA acceptable range for bioequivalence is too large for epileptic patients and thus does not guarantee therapeutic equivalence (**disagree**)
- ⌋ Seizure recurrence after substitution of a brand by a generic AED (**no prospective studies**)
- ⌋ Ambiguity in terms of legal responsibility in case of an accident



## *LFCE Recommendations on Generic AEDs*

- u AEDs are a particular class whose substitution in epilepsy is problematic**
- u No substitutions of AEDs without the agreement of the physician and the patient especially in seizure-free patients**
- u Opposed to the practice that allows substitution of an AED at the point of sale**
- u Autonomy of prescriptions and free access of the patients to the prescribed treatments remain basic principle of medical practice**



# Biopharmaceutics Classification System (BCS)

	High Solubility	Low Solubility
High Permeability	<b>Class 1</b> High Solubility High Permeability (Rapid Dissolution for Biowaiver)	<b>Class 2</b> Low Solubility High Permeability
Low Permeability	<b>Class 3</b> High Solubility Low Permeability	<b>Class 4</b> Low Solubility Low Permeability

The **FDA** used the **BCS** system to allow **waiver** of bioavailability and **bioequivalence** testing of **Class 1** IR drug products

*Amidon et al, Pharm Res, 1995; FDA Guidelines for Industry, 2000*



# *BCS Classifications of AEDs*

- ☐ Most AEDs are BCS class I drugs, with the exception of:
  - ☐ BCS Class II: PHT, CBZ, OXC, felbamate & rufinamide
  - ☐ BCS Class III: GBP

## **BCS Class I drugs**

- ☐ Mainly eliminated by metabolism,
- ☐ Minimal transport effect on their disposition & minimal food effect

*Anderson, Ther Drug Monit, 2008; Wu & Benet, Pharm Res, 2005*