Ειδικές περιπτώσεις φαρμάκων που χρήζουν προσοχής από την άποψη της θεραπευτικής ισοδυναμίας με τα γενόσημα

Παναγιώτης Μαχαίρας

Εργαστήριο Βιοφαρμακευτικής - Φαρμακοκινητικής
Τμήμα Φαρμακευτικής
Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

21-23 Σεπτεμβριου 2012
(Πόρτο Χέλι)

Παρουσίαση

- Α. Εισαγωγή
- Β. Σχεδιασμός και Στατιστική ανάλυση Μελετών Βιοίσοδυναμίας
- Γ. Φάρμακα με στενό θεραπευτικό εύρος
- Δ. Κυκλοσπορίνη
- Ε. Αντιεπιληπτικά Φάρμακα
- ΣΤ. Πληθυσμιακή Φαρμακοκινητική

Α. Εισαγωγή

1960s- 1970s:

Pioneering work of:

Wagner J., Nelson E., Levy G., Riegelman S., Garret E., Gibaldi M. …

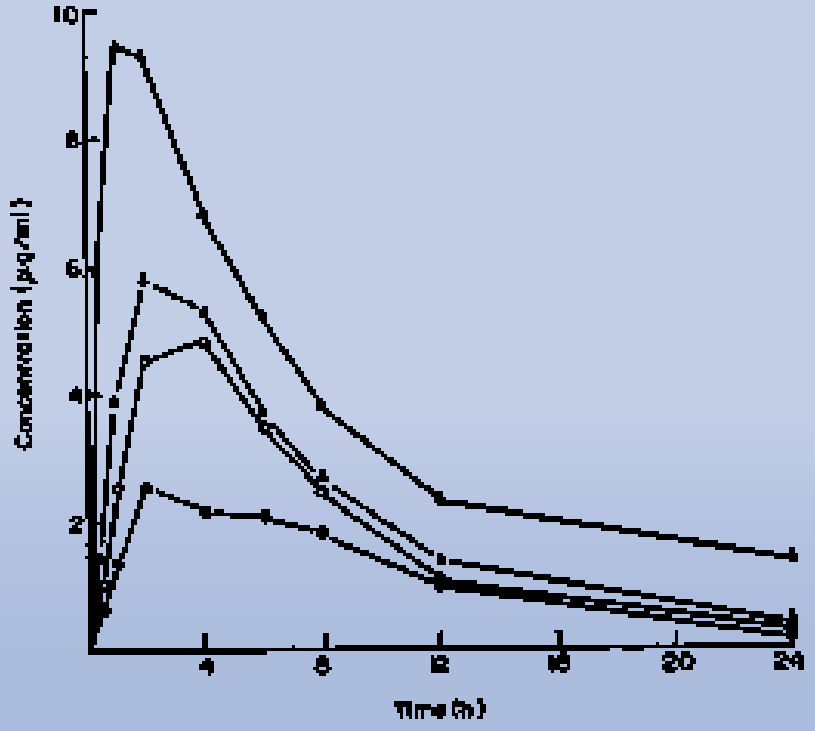
Generics *superior* to innovator

Melikian AP, Straughn AB, Slywka GW, Whyatt PL, Meyer MC. Bioavailability of 11 phenytoin products. *J. Pharmacokin. Biopharm*. 5(2):133-46 (1977).

Tannenbaum PJ, Rosen E, Flanagan T, Crosley AP. The influence of dosage form on the activity of a diuretic agent. *Clin Pharmacol Ther* 9(5):598-604 (1968).

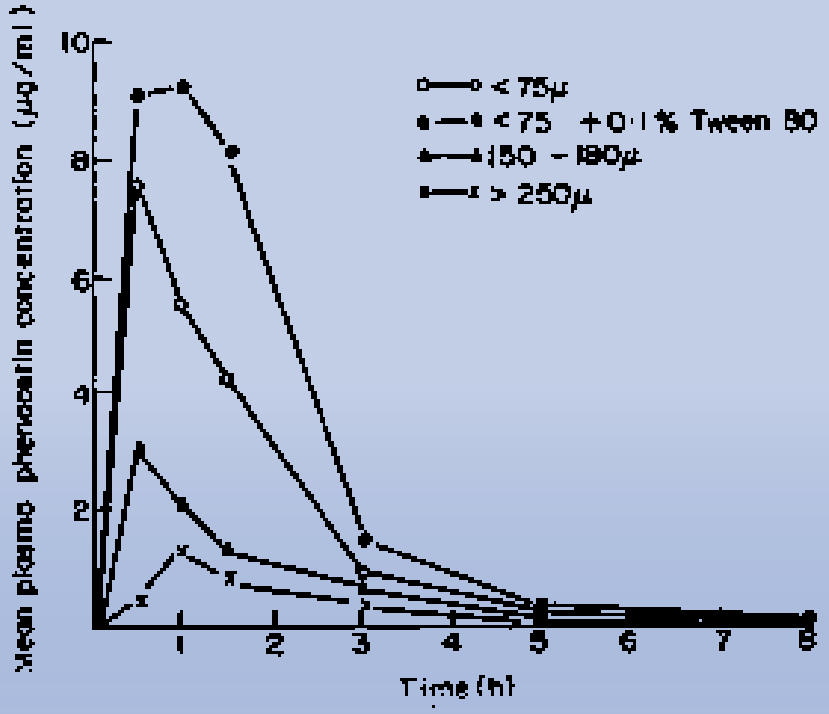
Generics *inferior* to innovator

Glazko AJ, Kinkel AW, Alegnani WC, Holmes EL. An evaluation of the absorption characteristics of different chloramphenicol preparations in normal human subjects. *Clin Pharmacol Ther*. 9(4):472-83 (1968).



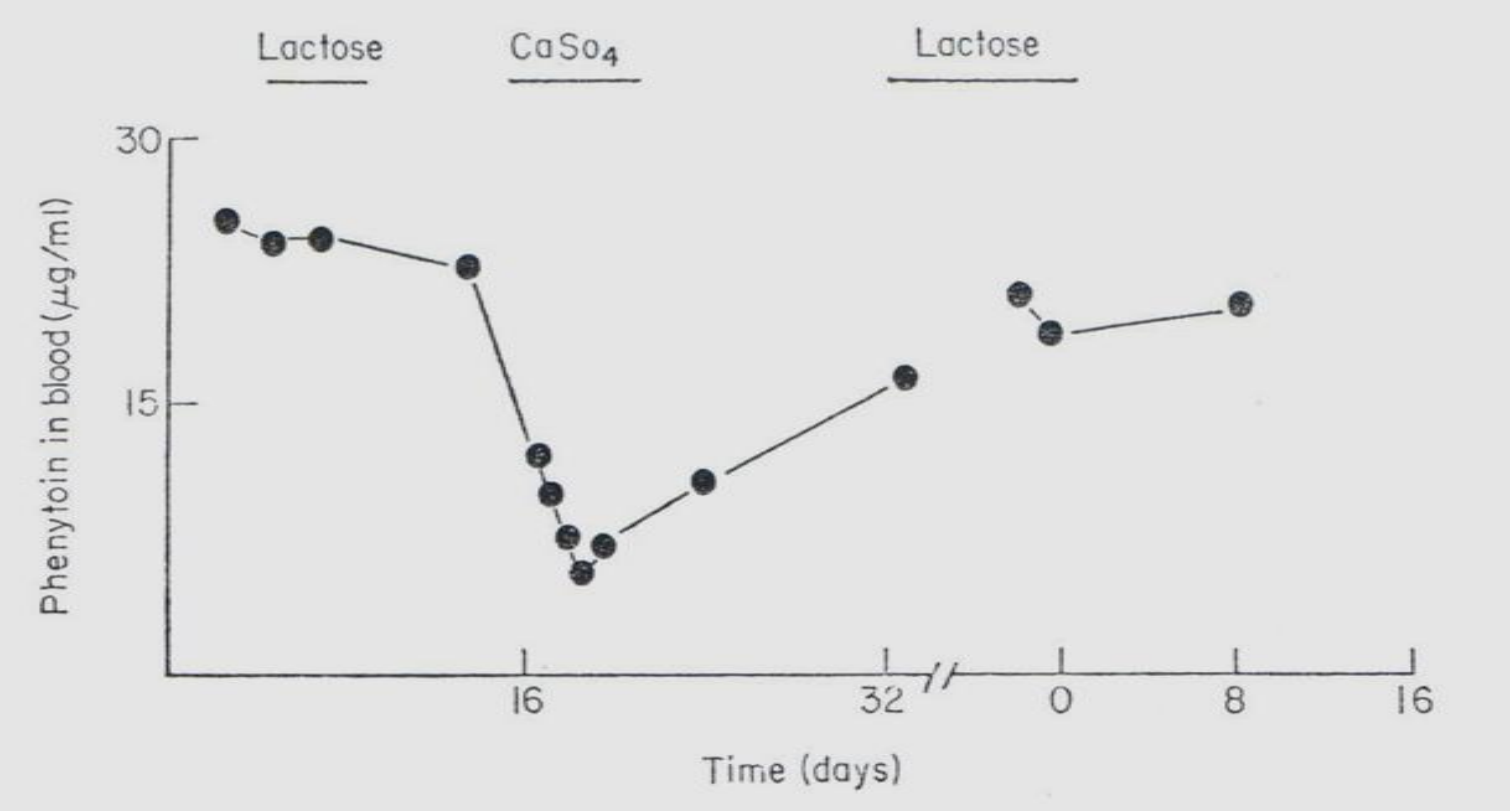
Mean plasma levels of chloramphenicol in ten human subjects following 0.5 g oral doses in various formulations.

Glazko AJ et al. *Clin Pharmacol Ther*. 9(4):472-83 (1968).



Mean plasma phenacetin concentrations in six human subjects after 1.5 g doses
In suspensions of different particle sizes.

Prescott LF, Steel RF, Ferrier WR. The effects of particle size on the absorption of phenacetin in man. A correlation between plasma concentration of phenacetin and effects on the central nervous system. *Clin Pharmacol Ther*. 11(4):496-504 (1970).



Influence of lactose and calcium sulphate as excipients on the concentration of phenytoin in blood in a patient taking 400 mg/day.

Tyrer JH, Eadie MJ, Sutherland JM, Hooper WD. *Br Med J* 4, 271 (1970).

Bioavailability

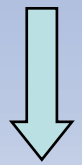
*The **rate** and **extent** to which the active drug ingredient or therapeutic moiety is absorbed and becomes available at the site of drug action*

Bioequivalence

Absence of a significant **difference in rate** *and* **extent of absorption** at the same molar dose of the therapeutic moiety under similar experimental conditions.

Bioequivalence Assumption

When a generic drug is claimed bioequivalent to a brand-name drug



it is assumed that they are therapeutically equivalent

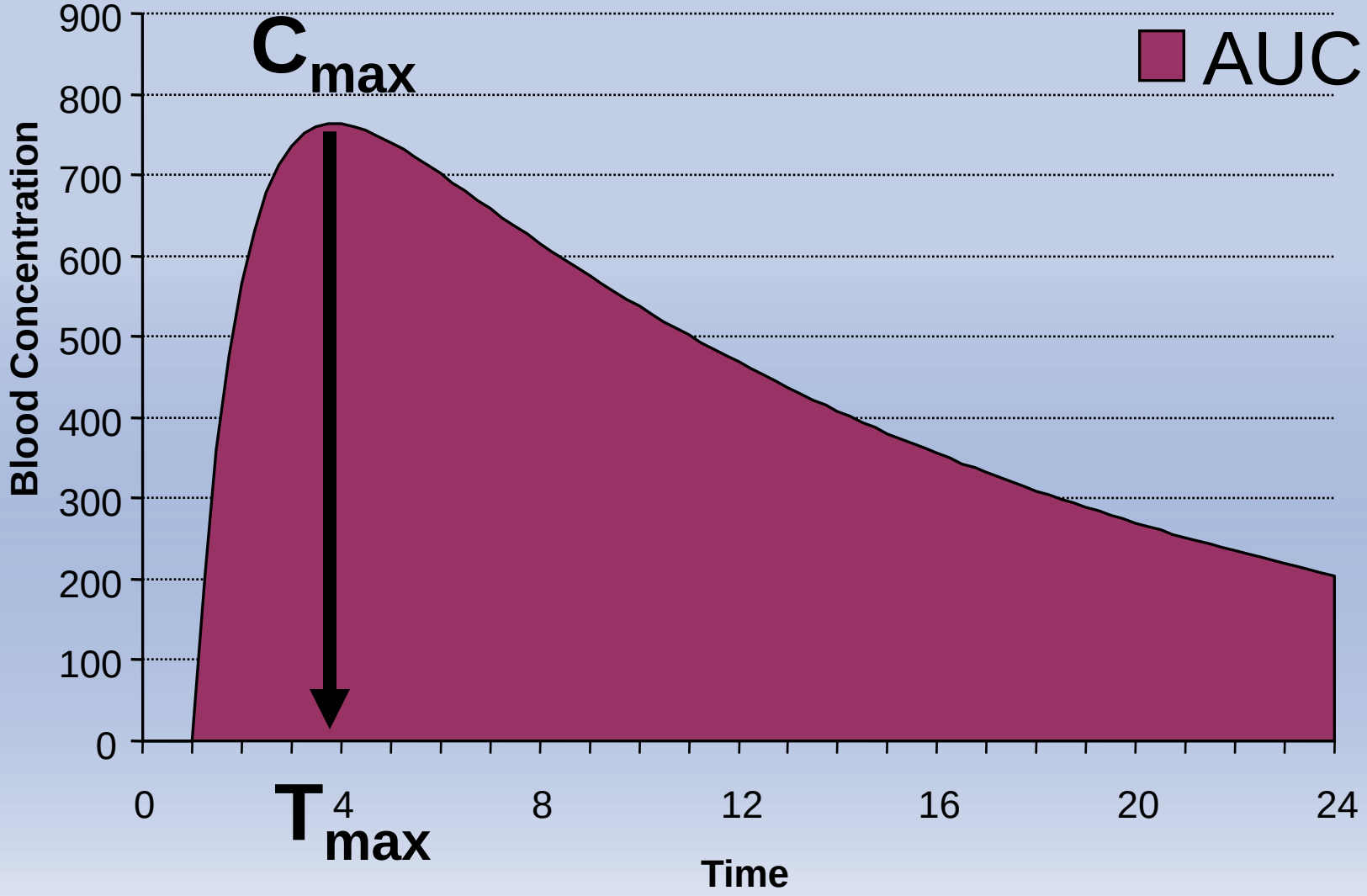
Pharmacokinetic Measures of Bioequivalence

Extent: $AUC_{(0\text{-}tlast)}$, $AUC_{(0\text{-}\infty)}$

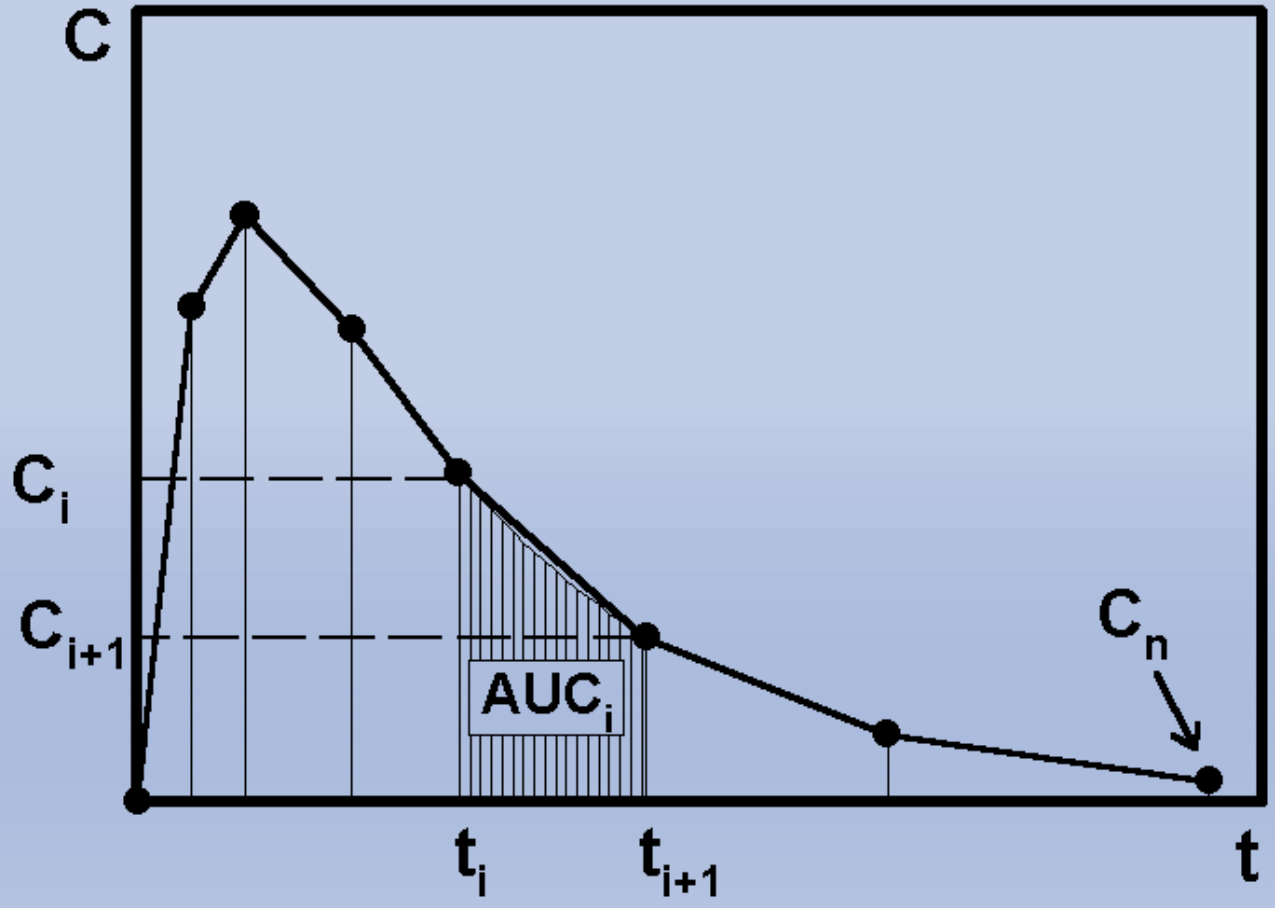
Rate: C_{max}

Other Measures: T_{max}, Half-life ($t^1/_2$), % fluctuation

Bioequivalence Parameters



AUC



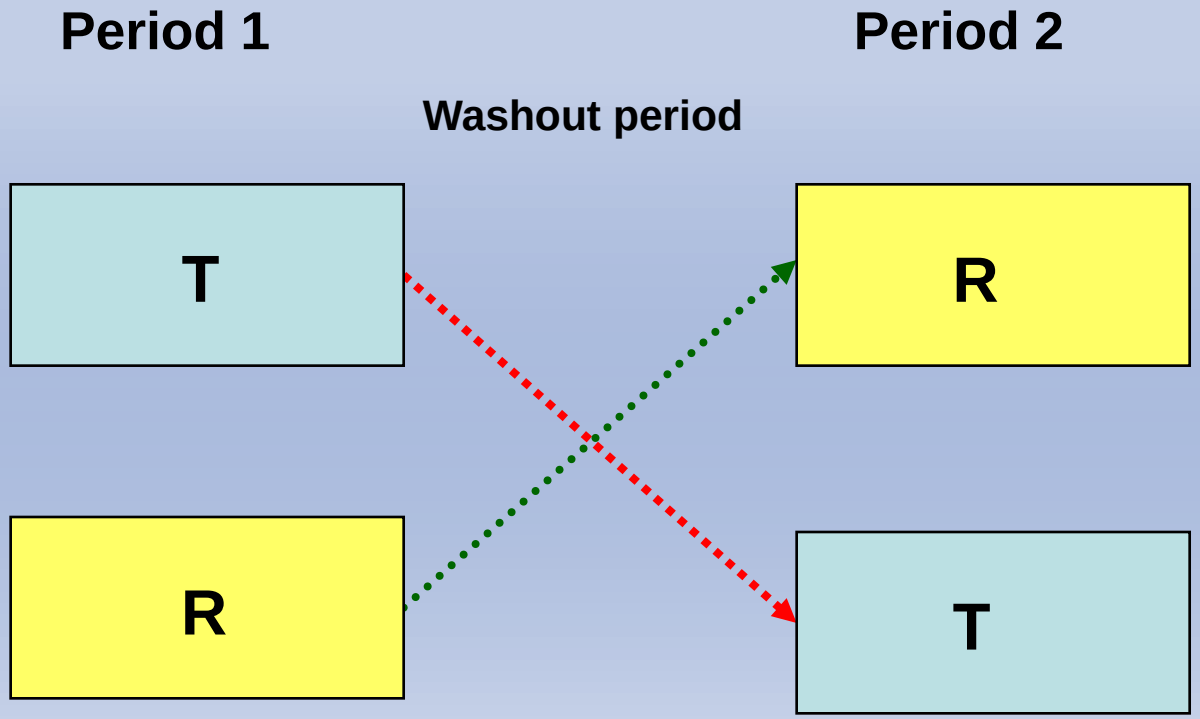
$$AUC = \sum_{i=1}^{n} AUC_i + \frac{C_n}{K_el}$$

$$AUC_i = \frac{(C_i + C_{i+1})}{2}(t_{i+1} - t_i)$$

Β. Σχεδιασμός και Στατιστική ανάλυση Μελετών Βιοίσοδυναμίας

Bioequivalence studies

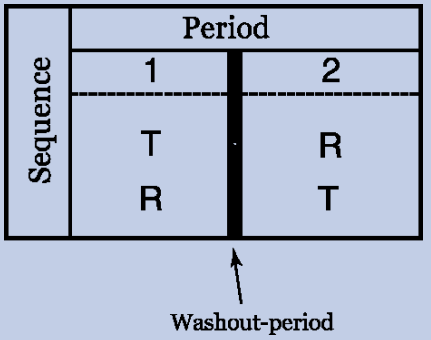
2 x 2 cross-over design



Current approach for BE

Two-period, two treatment crossover design

N: number of subjects



Average Bioequivalence criterion:

$$-\theta_A \le (\mu_T - \mu_R) \le \theta_A$$

where:

μ_T **:** population average response of the log-transformed measure for the Test formulation

μ_R **:** population average response of the log-transformed measure for the Reference formulation

θ_A **:** ln(1.25) $\Rightarrow$ ***predefined BE limits***

or equivalently: $0.80 \le T/R \le 1.25$

T/ R **:** Test to Reference geometric mean ratio ***(GMR)***

In practice:

Average BE of the two formulations is concluded if the 90% confidence intervals (CI) around the test to reference geometric mean ratio (GMR) for both C_{max} and AUC fall within the BE acceptance limits of 0.80 - 1.25.

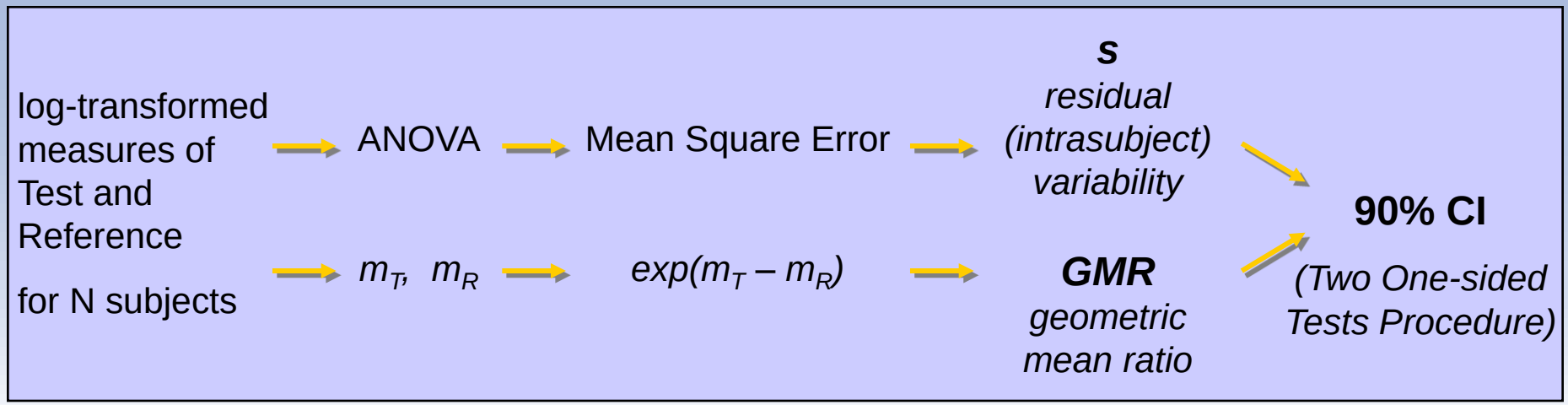
$$\text{Upper, Lower limits of the 90\% CI} = \exp\left[(m_T - m_R) \pm t_{0.05,N-2}\, s\sqrt{2/N}\right]$$

where:

m_T, m_R : *observed Test and Reference means of the log-transformed measures*

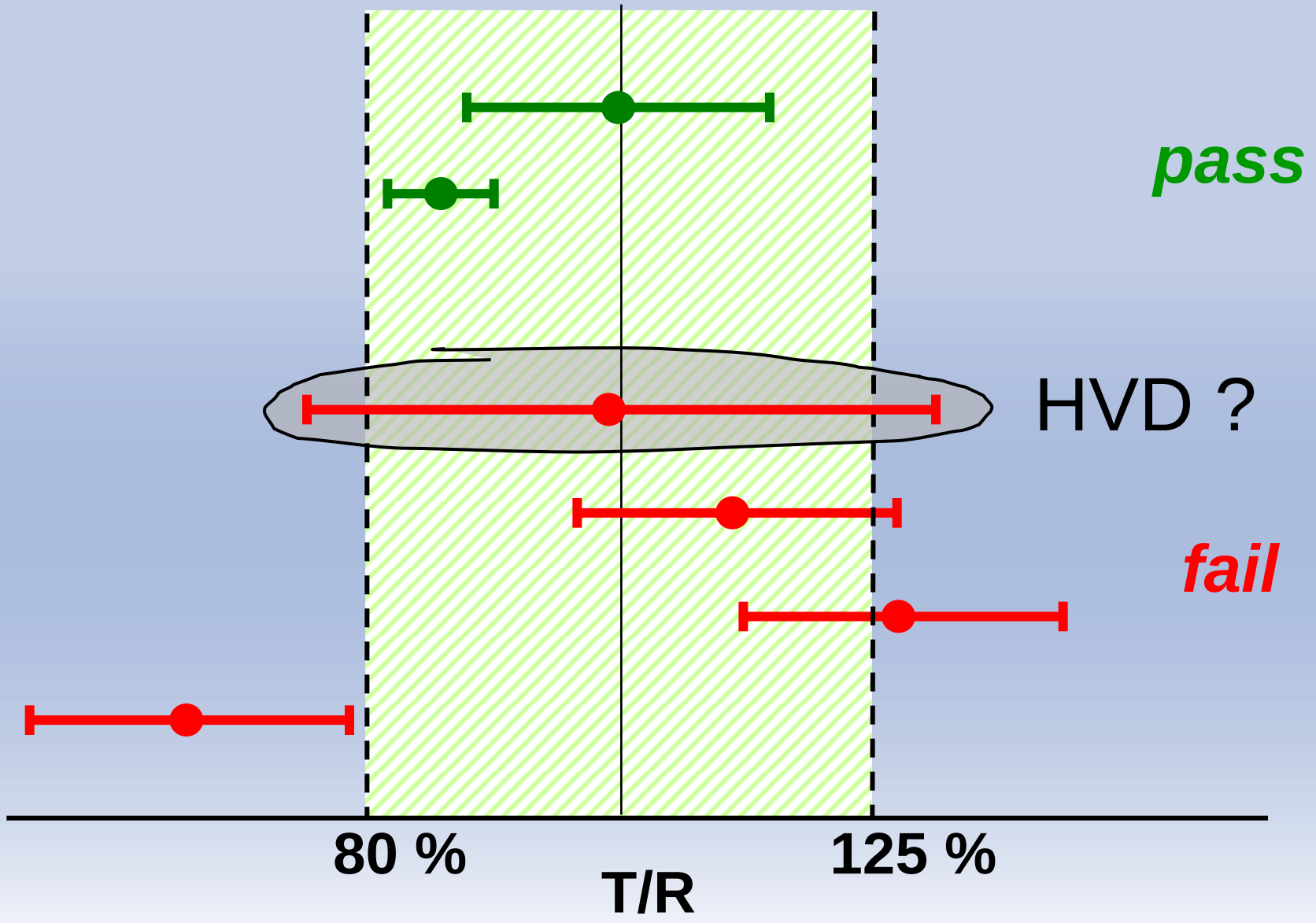
N : *number of subjects*

s : *intrasubject variability*



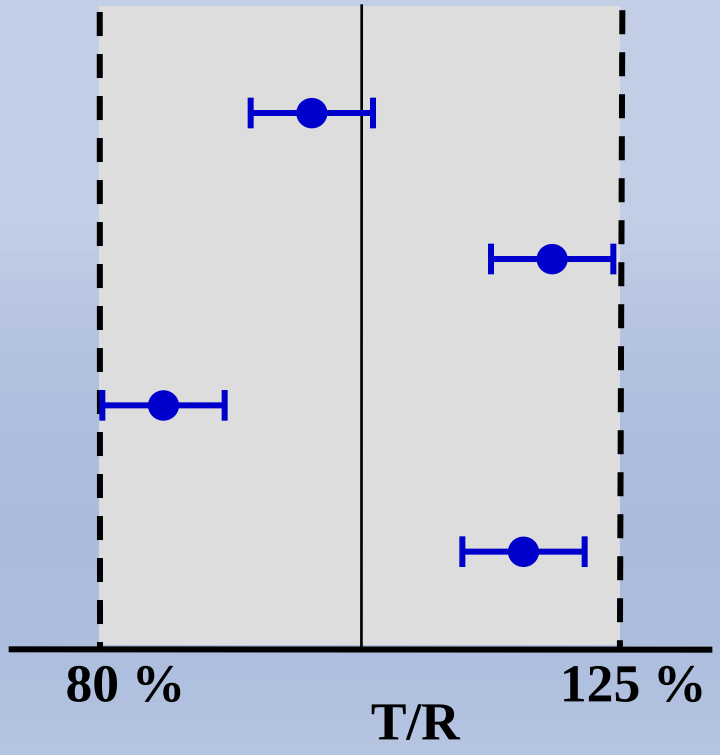
90% CI and BE limits

possible results

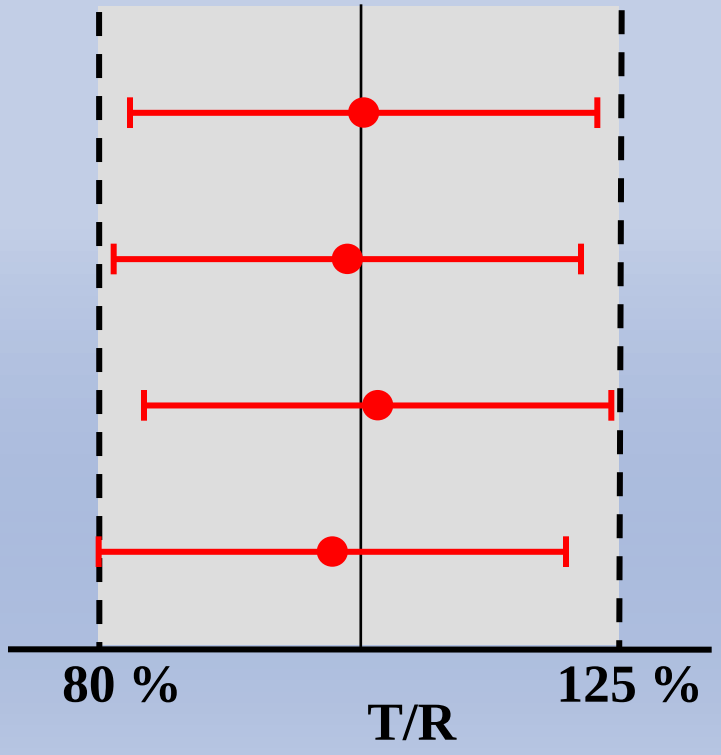


Intrasubject variability and GMR

Low variability



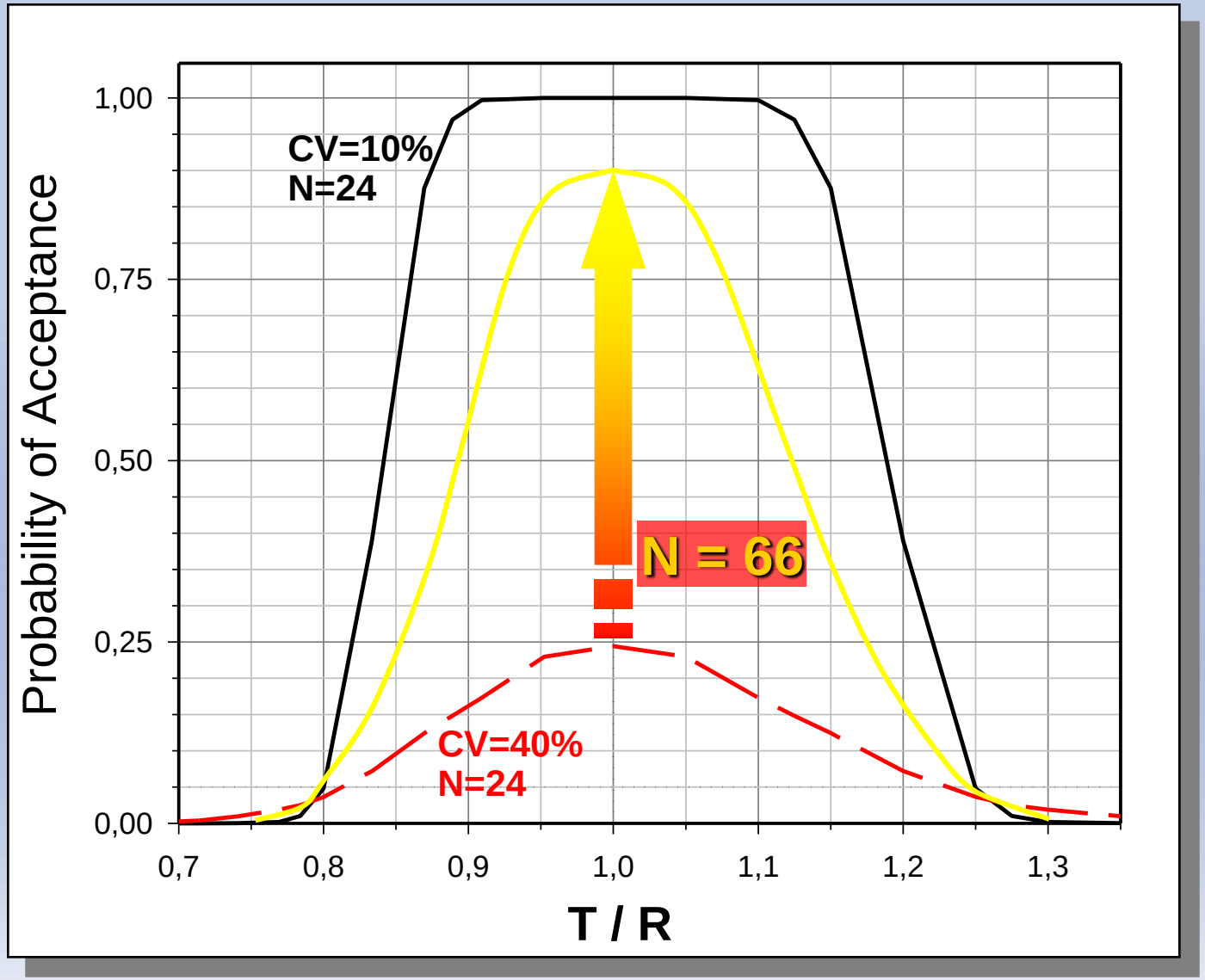
High variability



GMR: *Large deviations from 100% may be accepted*

GMR: *Must be closed to 100% to fit in BE limits*

Probability that 90%CI falls within 80 – 125% in a 2-way cross-over BE study for CV=10% and 40% with 24 subjects



European Medicines Agency

London, 20 January 2010
Doc. Ref.: CPMP/QWP/EWP/1401/98 Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

DISCUSSION IN THE JOINT EFFICACY AND QUALITY WORKING GROUP	December 1997 – October 1998
TRANSMISSION TO CPMP	July 1998
RELEASE FOR CONSULTATION	December 1998
DEADLINE FOR COMMENTS	June 1999
DISCUSSION IN THE DRAFTING GROUP	February – May 2000
TRANSMISSION TO CPMP	July – December 2000
RELEASE FOR CONSULTATION	December 2000
DEADLINE FOR COMMENTS	March 2001
DISCUSSION IN THE DRAFTING GROUP	March - May 2001
TRANSMISSION TO CPMP	July 2001
ADOPTION BY CPMP	July 2001
DATE FOR COMING INTO OPERATION	January 2002
DISCUSSION ON REV. 1 IN THE PK-GROUP OF THE EFFICACY WORKING PARTY	May 2007-July 2008
DISCUSSION ON REV. 1 BY THE QUALITY WORKING PARTY	June 2008
DRAFT REV. 1 AGREED BY THE EFFICACY WORKING PARTY	8 July 2008
ADOPTION REV. 1 BY CHMP FOR RELEASE FOR CONSULTATION	24 July 2008
END OF CONSULTATION REV. 1 (DEADLINE FOR COMMENTS)	31 January 2009

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@ema.europa.eu http://www.ema.europa.eu

4.1.10 Highly variable drugs or drug products

Highly variable drug products (HVDP) are those whose intra-subject variability for a parameter is larger than 30%. If an applicant suspects that a drug product can be considered as highly variable in its rate and/or extent of absorption, a replicate cross-over design study can be carried out.

Those HVDP for which a wider difference in C_{max} is considered clinically irrelevant based on a sound clinical justification can be assessed with a widened acceptance range. If this is the case the acceptance criteria for C_{max} can be widened to a maximum of 69.84 – 143.19%. For the acceptance interval to be widened the bioequivalence study must be of a replicate design where it has been demonstrated that the within-subject variability for C_{max} of the reference compound in the study is >30%. The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers. The request for widened interval must be prospectively specified in the protocol.

The extent of the widening is defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence according to $[U, L] = \exp[\pm k \cdot s_{WR}]$, where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and s_{WR} is the within-subject standard deviation of the log-transformed values of C_{max} of the reference product. The table below gives examples of how different levels of variability lead to different acceptance limits using this methodology.

Within-subject CV (%)*	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

$$* CV(\%) = 100\sqrt{e^{s_{WR}^2} - 1}$$

The geometric mean ratio (GMR) should lie within the conventional acceptance range 80.00-125.00%.

The possibility to widen the acceptance criteria based on high intra-subject variability does not apply to AUC where the acceptance range should remain at 80.00 – 125.00% regardless of variability.

It is acceptable to apply either a 3-period or a 4-period crossover scheme in the replicate design study.

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European Journal of Pharmaceutical Sciences 26 (2005) 54–61
EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES
www.elsevier.com/locate/ejps

Geometric mean ratio-dependent scaled bioequivalence limits with leveling-off properties

Vangelis Karalis, Panos Macheras, Mira Symillides *

Laboratory of Biopharmaceutics-Pharmacokinetics, School of Pharmacy, University of Athens, Panepistimiopolis, Athens 157 71, Greece

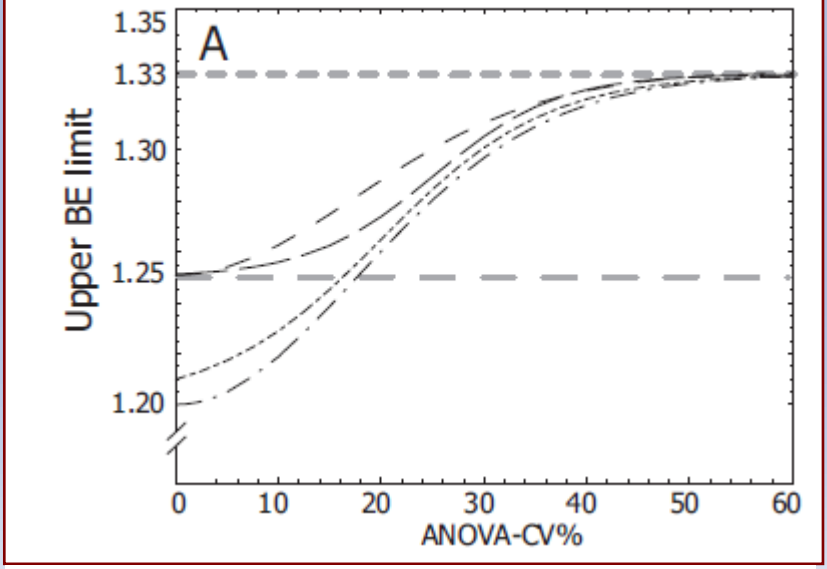
Received 7 December 2004; received in revised form 13 April 2005; accepted 18 April 2005
Available online 13 June 2005

Pharmaceutical Research, Vol. 23, No. 11, November 2006 (© 2006)
DOI: 10.1007/s11095-006-9107-1

Research Paper

Novel Scaled Bioequivalence Limits with Leveling-off Properties

John Kytariolos,[1] Vangelis Karalis,[1] Panos Macheras,[1] and Mira Symillides[1,2]



(A) Novel scaled BE limits as a function of intrasubject variability.

European Journal of Pharmaceutical Sciences 44 (2011) 497–505

Contents lists available at SciVerse ScienceDirect

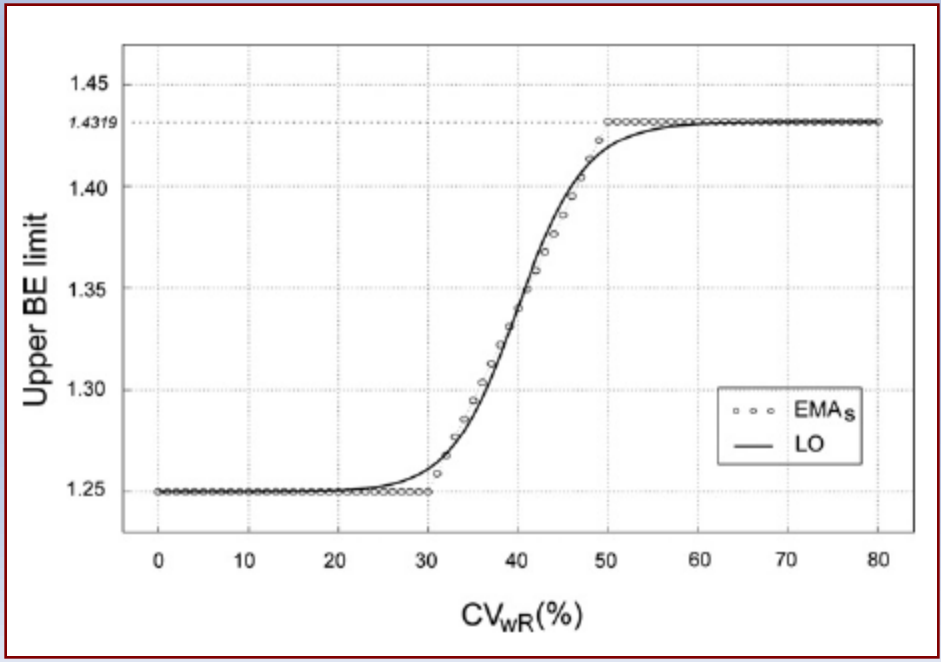
European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

On the leveling-off properties of the new bioequivalence limits for highly variable drugs of the EMA guideline

Vangelis Karalis, Mira Symillides, Panos Macheras

Laboratory of Biopharmaceutics-Pharmacokinetics, School of Pharmacy, University of Athens, Athens, Greece

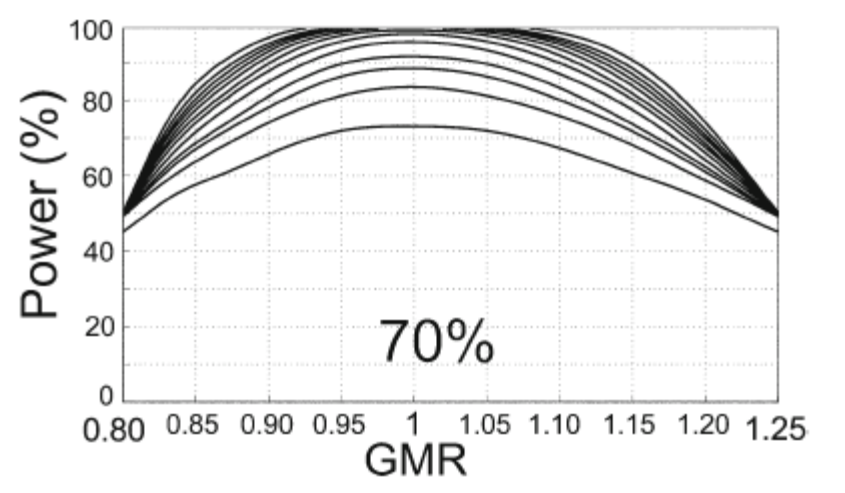


Pharm Res (2012) 29:1066–1077
DOI 10.1007/s11095-011-0651-y

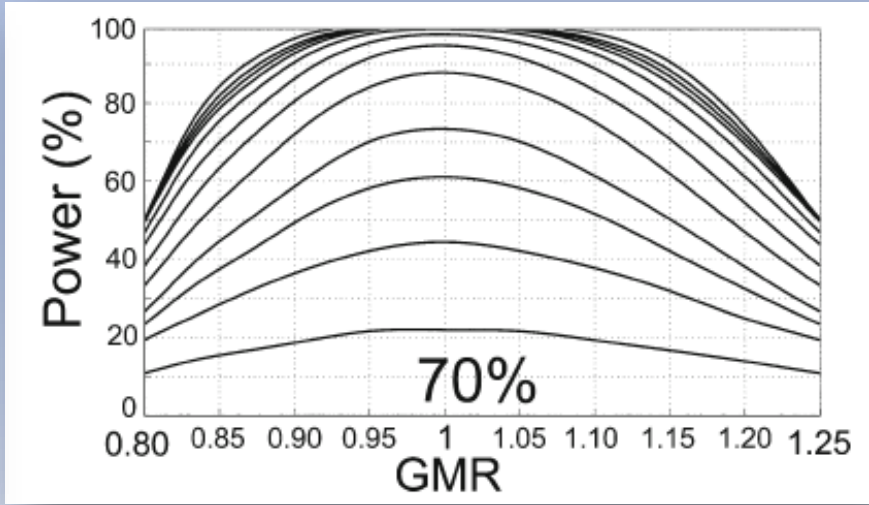
RESEARCH PAPER

Bioequivalence of Highly Variable Drugs: A Comparison of the Newly Proposed Regulatory Approaches by FDA and EMA

Vangelis Karalis • Mira Symillides • Panos Macheras



FDA



EMA

Γ. Φάρμακα με στενό θεραπευτικό εύρος

European Medicines Agency

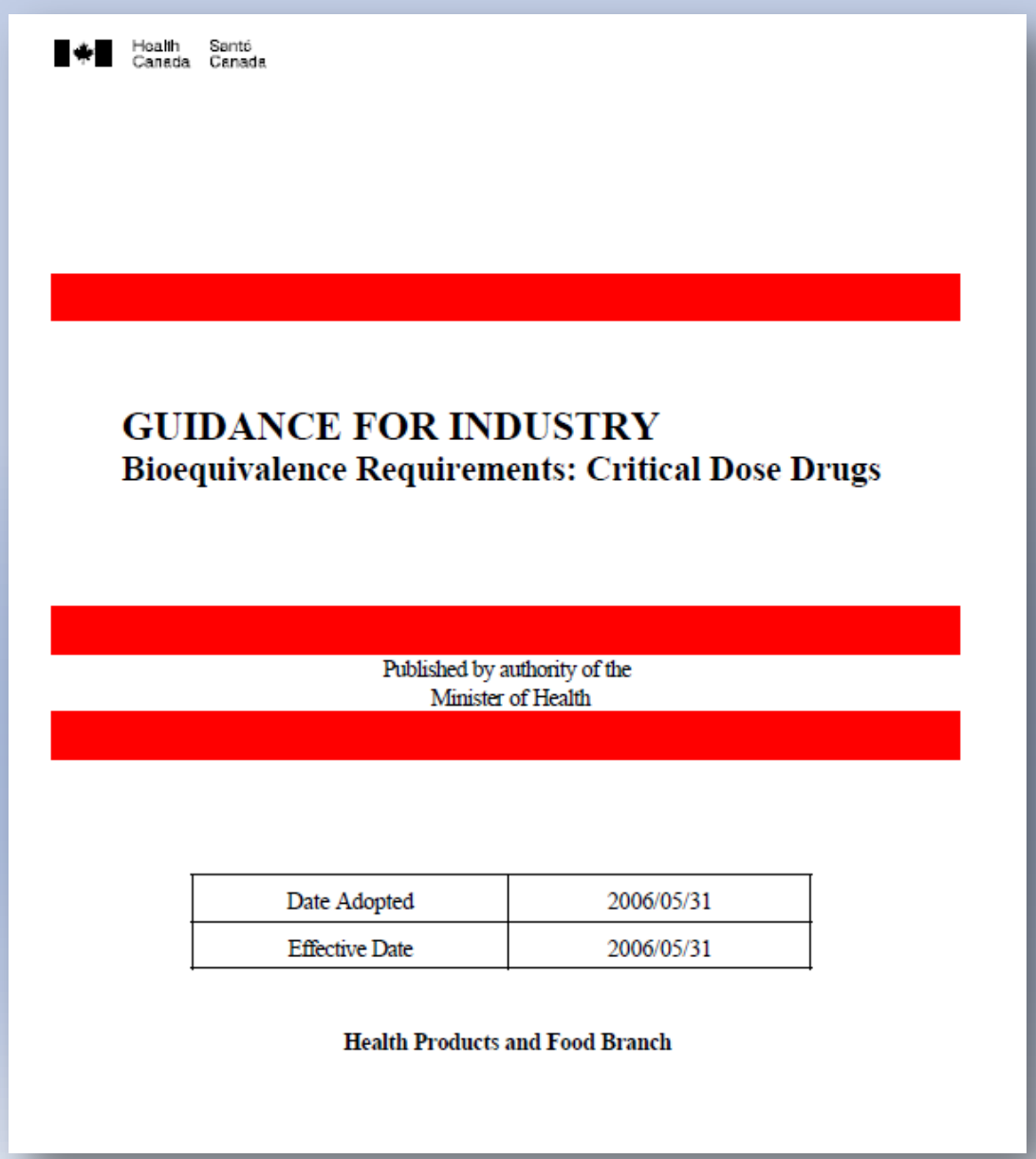
London, 20 January 2010
Doc. Ref.: CPMP/QWP/EWP/1401/98 Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

4.1.9 Narrow therapeutic index drugs

In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be tightened to 90.00-111.11%. Where Cmax is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter. It is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTID based on clinical considerations.



Cyclosporine

Digoxin

Flecainide

Lithium

Phenytoin

Sirolimus

Tacrolimus

Theophylline

Warfarin

발 간 등 록 번 호
11-1470000-001738-14

식의약품 종합정보서비스
KIFDA

Guidance Document for Bioequivalence Study

영문 생물학적동등성시험기준

2008

KFDA 식품의약품안전청 Korea Food & Drug Administration
의 약 품 안 전 국
생물학적동등성평가과

Active Ingredient Having a Narrow Therapeutic Range

(Related to the Article 2 Clause 13)

Number	Active ingredient
1	Aprindine
2	Carbamazepine
3	Clindamycin
4	Clonazepam
5	Clonidine
6	Cyclosporine
7	Digitoxin
8	Digoxin
9	Disopyramide
10	Ethinyl Estradiol
11	Ethosuximide
12	Glybuzole
13	Guanethidine
14	Isoetharine
15	Isoprenaline
16	Isoproterenol
17	Lithium
18	Metaproterenol
19	Methotrexate
20	Minoxidil

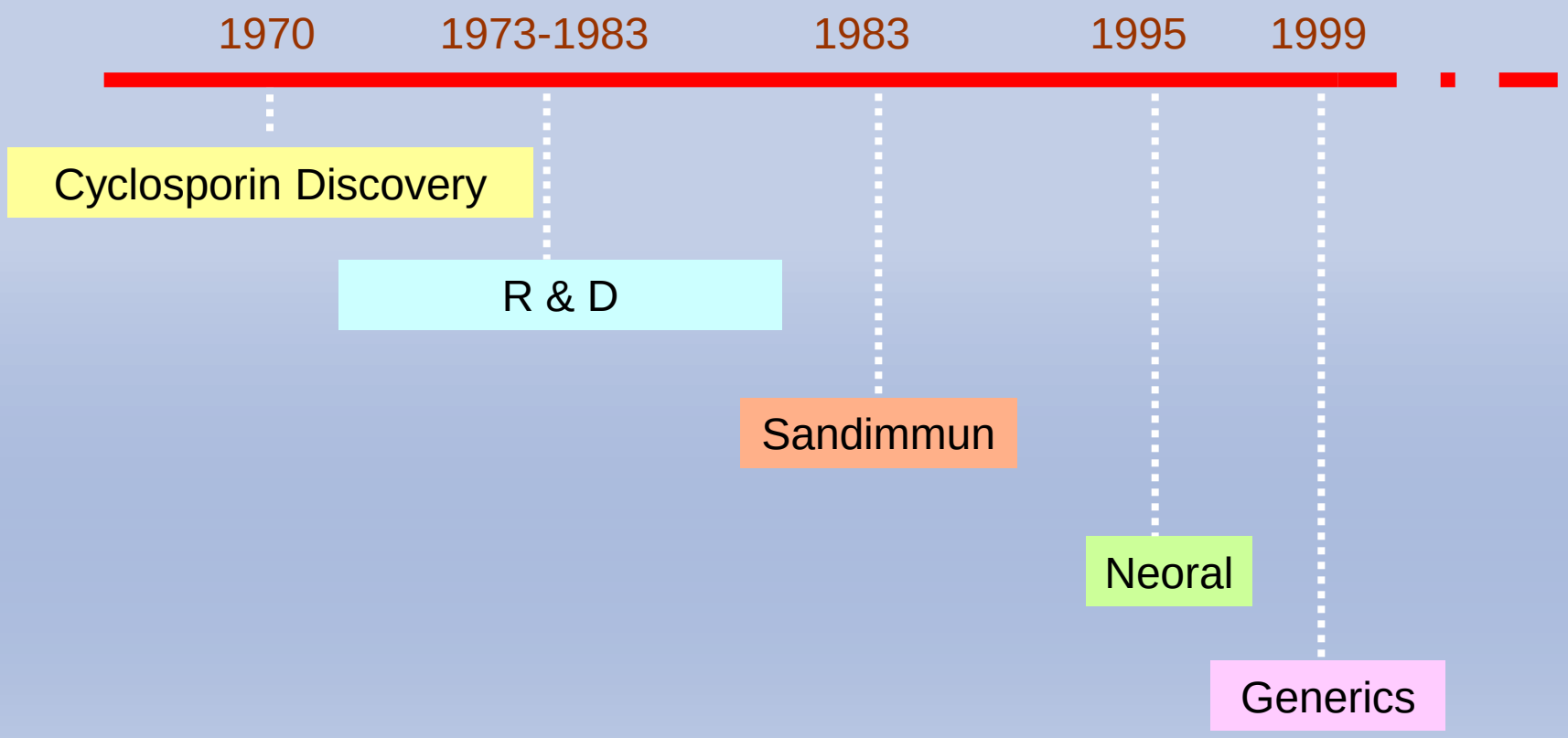
Number	Ingredient
21	Phenobarbital
22	Phenytoin
23	Prazosin
24	Primidone
25	Procainamide
26	Quinidine
27	Sulfonylurea compounds[1)]
28	Tacrolimus
29	Theophylline compounds[2)]
30	Valproic acid
31	Warfarin
32	Zonisamide

1) Acetohexamide, Glibenclamide, Gliclazide, Glyclopyramide, Tolazamide, Tolbutamide

2) Aminophylline, Oxitriphylline (Choline Theophylline), Diprophylline (Dyphylline), Proxyphylline, Theophylline

Δ. Κυκλοσπορίνη

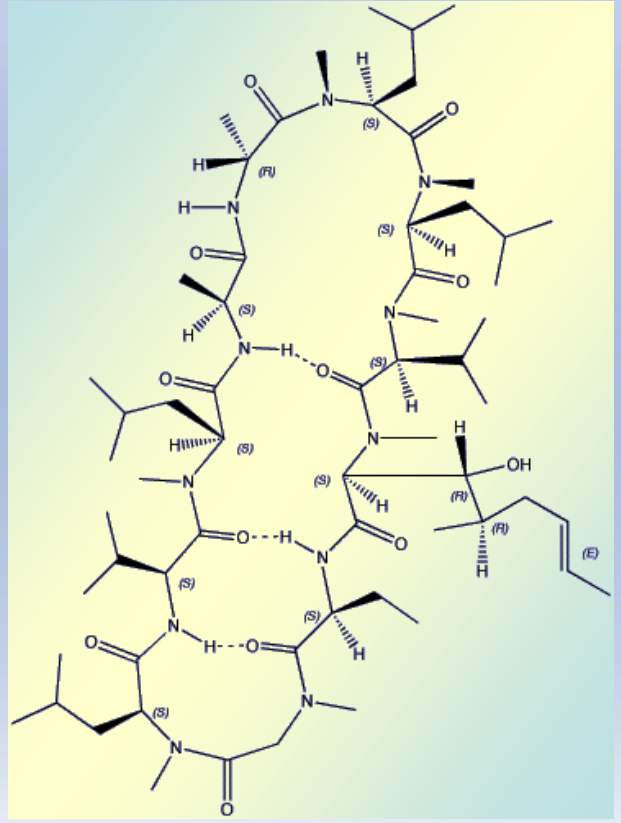
Outline: From the discovery to the market



1973-1976

- Determination of the exact structure of cyclosporin.

- Cyclosporin was found to be made up of 11 amino acids, 10 of which were known but the amino acid at position ‘1’ was unknown.



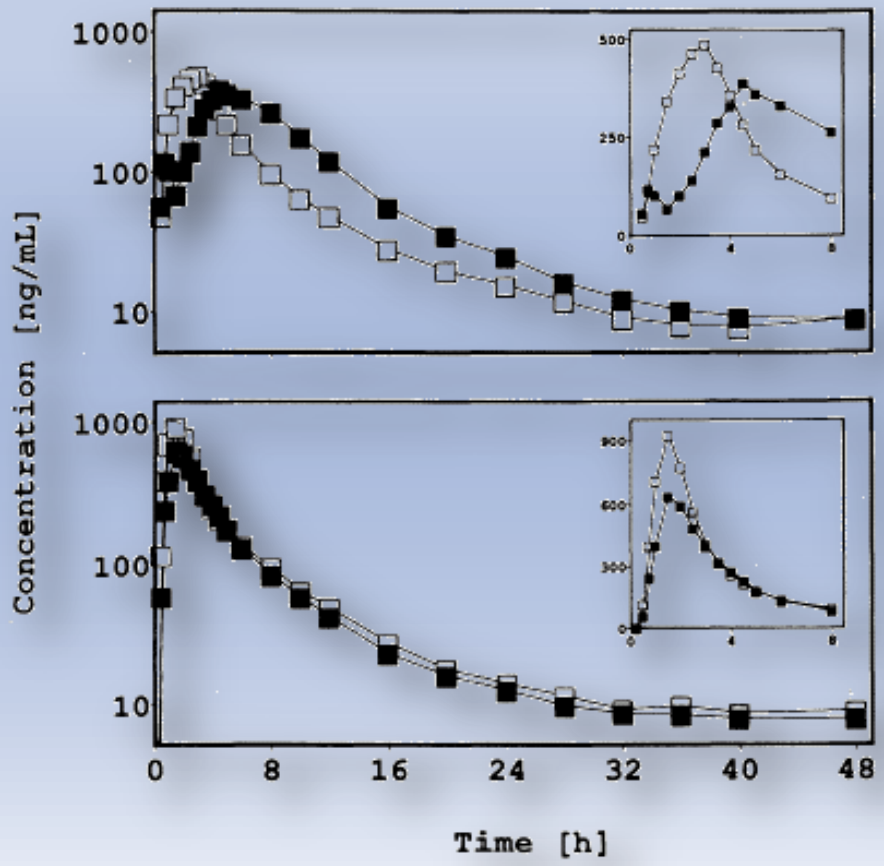
The structure
of cyclosporin

Neoral®

Influence of a Fat-Rich Meal on the Pharmacokinetics of a New Oral Formulation of Cyclosporine in a Crossover Comparison with the Market Formulation

Pharmaceutical Research, Vol. 11, No. 1, 1994

Edgar A. Mueller,[1] John M. Kovarik,[1,5] Johannes B. van Bree,[2] Joachim Grevel,[3] Peter W. Lücker,[4] and Klaus Kutz[1]

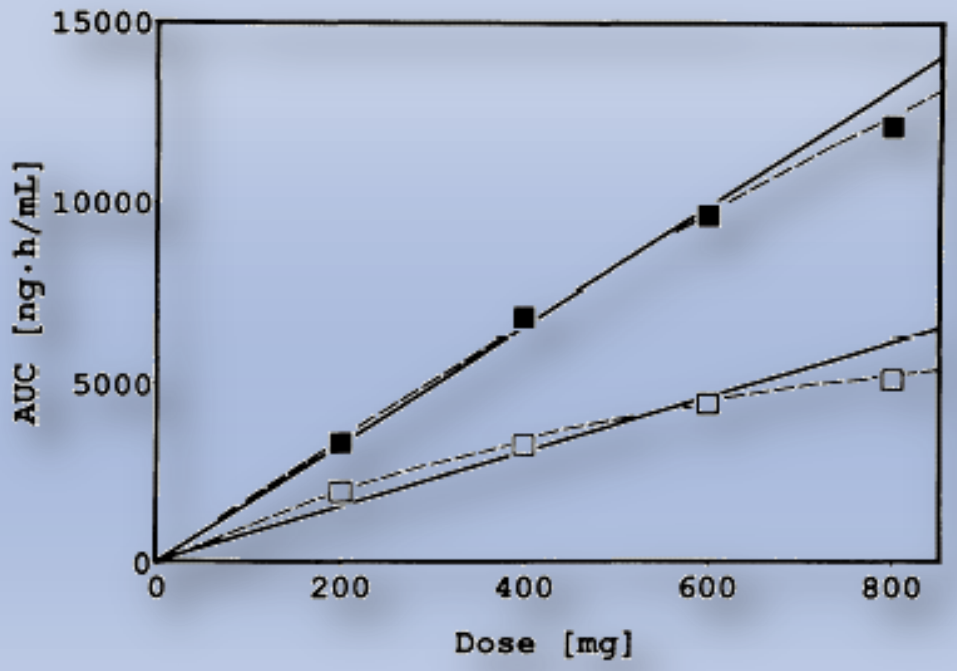


Geometric mean whole-blood cyclosporine concentration-time profiles following single oral administrations of the 300-mg reference formulation (top) and 180-mg test formulation (bottom) under fasting conditions (□) and with a fat-rich meal (■) to 24 healthy male volunteers.

Improved Dose Linearity of Cyclosporine Pharmacokinetics from a Microemulsion Formulation

Pharmaceutical Research, Vol. 11, No. 2, 1994

Edgar A. Mueller,[1] John M. Kovarik,[1,5] Johannes B. van Bree,[2] Wolfgang Tetzloff,[3] Joachim Grevel,[4] and Klaus Kutz[1]



Relationship between dose and cyclosporine AUC_b following single oral administrations of the reference (□) and test (■) formulations to healthy volunteers. Superimposed is the best fit of a straight line (——) and a hyperbolic function (--) regressed through the origin.

Γενόσημα

Γενόσημα προϊόντα κυκλοσπορίνης στην Ελλάδα: Imunofar®

Κοινοτική αποκεντρωμένη διαδικασία
Ηνωμένο Βασίλειο, Γερμανία, Ελλάδα, Τσεχία, Σλοβακία
Cyclosporin A – μαλακά καψάκια - 25mg, 50mg, 100 mg

Transplantation Proceedings, 40, 2245–2251 (2008)

Six-Month Clinical Outcome of Cyclosporine Microemulsion Formulation (Sigmasporin Microral) in Stable Renal Transplant Patients Previously Maintained on Sandimmun Neoral

J.S. Al Wakeel, F.A.M. Shaheen, M.C. Mathew, H.M. Abou Zeinab, A. Al Alfi, N.M. Tarif, M.S.A. Al Mousawi, T.S. Mahmoud, A.S. Alorrayed, E.A. Fagir, R.S. Dham, and D.S. Shaker

Transplantation Proceedings, 40, 2252–2257 (2008)

Therapeutic Equivalence and mg:mg Switch Ability of a Generic Cyclosporine Microemulsion Formulation (Sigmasporin Microral) in Stable Renal Transplant Patients Maintained on Sandimmun Neoral

J.S. Al Wakeel, F.A.M. Shaheen, M.C. Mathew, H.M. Abouzeinab, A. Al Alfi, N.M. Tarif, M.S.A. Al Mousawi, T.S. Mahmoud, A.S. Alorrayed, E.A. Fagir, R.S. Dham, and D.S. Shaker

Ε. Αντιεπιληπτικά Φάρμακα

Epilepsia, **48**(10):1825–1832, 2007
Blackwell Publishing, Inc.

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

Generic products of AEDs

Reason for switching to generics:

Pharmacoeconomic (generics are cheaper)

Raised concerns:

- Do generic AEDs work as well as brand AEDs in terms of their efficacy, safety and quality?
- Can generic AEDs be used as substitutions for brand AEDs?
- Can generic products of AEDs be used interchangeably?

Meir Bialer. *Epilepsia*, 48(10):1825–1832, 2007

Characteristics of epilepsy

- ✓ chronic disorder
- ✓ often requires lifelong treatment
- ✓ *primary goal*: avoidance of seizures **+** keep ADRs to a minimum
- ✓ if long-term remission has been achieved:

  - avoid even a single breakthrough seizure
  - just one seizure after a period of control can have major implications at the social level

Characteristics of AEDs

AEDs are *usually* considered to be treatments with a narrow therapeutic index (*NTI**) (e.g., phenytoin)

**NTI*: less than a 2-fold difference between:
the *minimum toxic concentration* and the *minimum effective concentration*

⇒ slight variations in drug absorption may result in significant negative health outcomes

⇒ careful titration and patient monitoring

However:

- some AEDs exhibit wide therapeutic range
  [e.g., carbamazepine, lamotrigine (2.5-15 mg/L)]

- breakthrough seizures or ADRs due to generic substitutions were reported for AEDs with a *linear* PK and a *wide therapeutic range*

Requirements for generic antiepileptic medicines: a clinical perspective

Eugen Trinka · Günter Krämer · Martin Graf

J Neurol (2011) 258:2128–2132

1. Do generic AEDs have the same efficacy, safety and quality?
2. Can generic AEDs be used as substitutions for brand AEDs?
3. Can generic products of AEDs be used interchangeably?
4. Does the generic AED manufacturer guarantee the long-term consistency of availability on the market?
5. Do generic AEDs reduce the costs, and—if so—are these costs worth any additional risk to patient's safety?

Information Regarding Anti-Epileptic Drugs

U.S. Food and Drug Administration

in Response to Requests in

Senate Report No. 111-39

and

House Agriculture Committee Report No. 111-279

FDA Approved Generic AEDs
(as of January 2010)

Generic Name	Number of Generic Products Marketed
Phenytoin	5
Carbamazepine	7
Carbamazepine ER	2
Divalproex Na – DR	13
Divalproex Na – ER	6
Lamotrigine	14
Gabapentin	11
Topiramate	16
Levetiracetam	17
Oxcarbazepine	8
Zonisamide	13

ER = Extended-release formulation
DR = Delayed-release formulation

Table II[10]
Bioequivalence Measures for Approved Generic AEDs
Mean (upper & Lower 90% Confidence Interval limits)

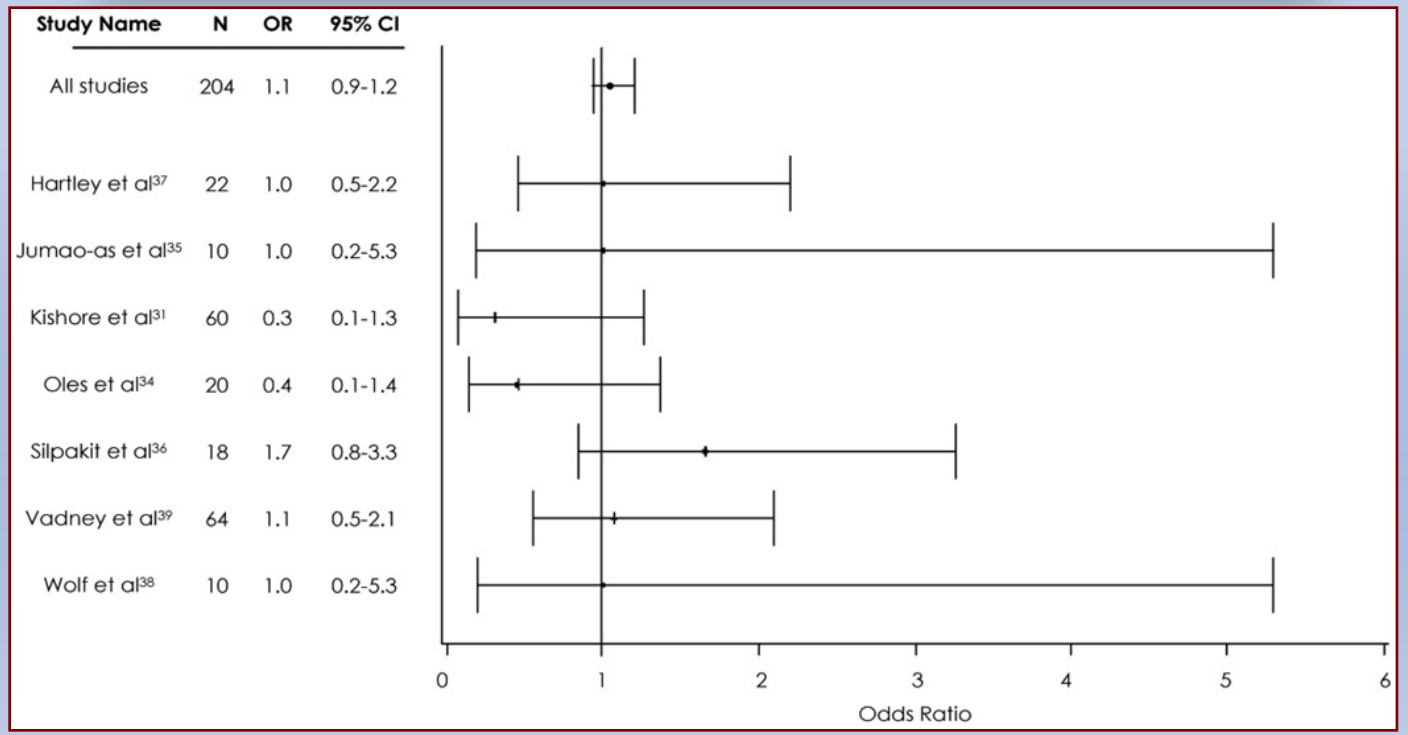
Drug	AUC Ratio	Cmax Ratio
Phenytoin	0.99 (0.95, 1.02)	1.09 (0.99, 1.20)
	0.88 (0.85, 0.92)	0.88 (0.83, 0.94)
Carbamazepine	1.18 (1.14, 1.22)	1.14 (1.10, 1.19)
	0.97 (0.90, 1.00)	0.90 (0.87, 0.94)
Lamotrigine	1.07 (1.02, 1.12)	1.10 (1.05, 1.15)
	1.00 (0.94, 1.04)	0.91 (0.85, 0.98)
Levetiracetam	1.02 (0.97, 1.04)	1.06 (1.02, 1.12)
	0.97 (0.95, 1.0)	0.92 (0.85, 1.00)
Zonisamide	1.08 (0.99, 1.19)	1.08 (1.01, 1.15)
	0.96 (0.89, 1.03)	0.96 (0.88, 1.05)
Topiramate	1.05 (1.00, 1.10)	1.09 (1.03, 1.15)
	0.95 (0.93, 0.98)	0.92 (0.82, 1.03)

[10] The two rows of data represent the highest and lowest point estimates and 90 percent confidence intervals for all approved generic formulations of the antiepileptic drug cited. For example, for phenytoin, there are five approved formulations. We compiled the 90 percent confidence intervals and point estimates from the test/reference AUC and C_{max} ratios from all the bioequivalence studies of these 5 phenytoin products and report the highest and lowest values from this group of studies.

Seizure Outcomes Following Use of Generic vs. Brand-Name Antiepileptic Drugs: A Systematic Review and Meta-Analysis

Aaron S. Kesselheim, M.D., J.D., M.P.H.[1], Margaret R. Stedman, Ph.D.[1], Ellen J. Bubrick, M.D.[2], Joshua J. Gagne, Pharm.D., M.S.[1], Alexander S. Misono, B.A.[1], Joy L. Lee, B.A.[1], M. Alan Brookhart, Ph.D.[3], Jerry Avorn, M.D.[1], and William H. Shrank, M.D., M.S.H.S.[1]

Drugs. 2010 March 26; 70(5): 605–621. doi:10.2165/10898530-000000000-00000.



Meta-analysis of randomized controlled trials comparing generic and brand-name antiepileptic drugs
Error bars represent 95% confidence intervals (CI). The Odds Ratio (OR) is odds of uncontrolled seizures after an AED switch. OR >1 suggests poor control for generic medications compared to brand name medications; OR <1 suggests lower odds of poor control for generic medications compared to brand-name medications. See Appendix for a breakdown of the number of patients who had uncontrolled seizures in the generic and brand-name groups.

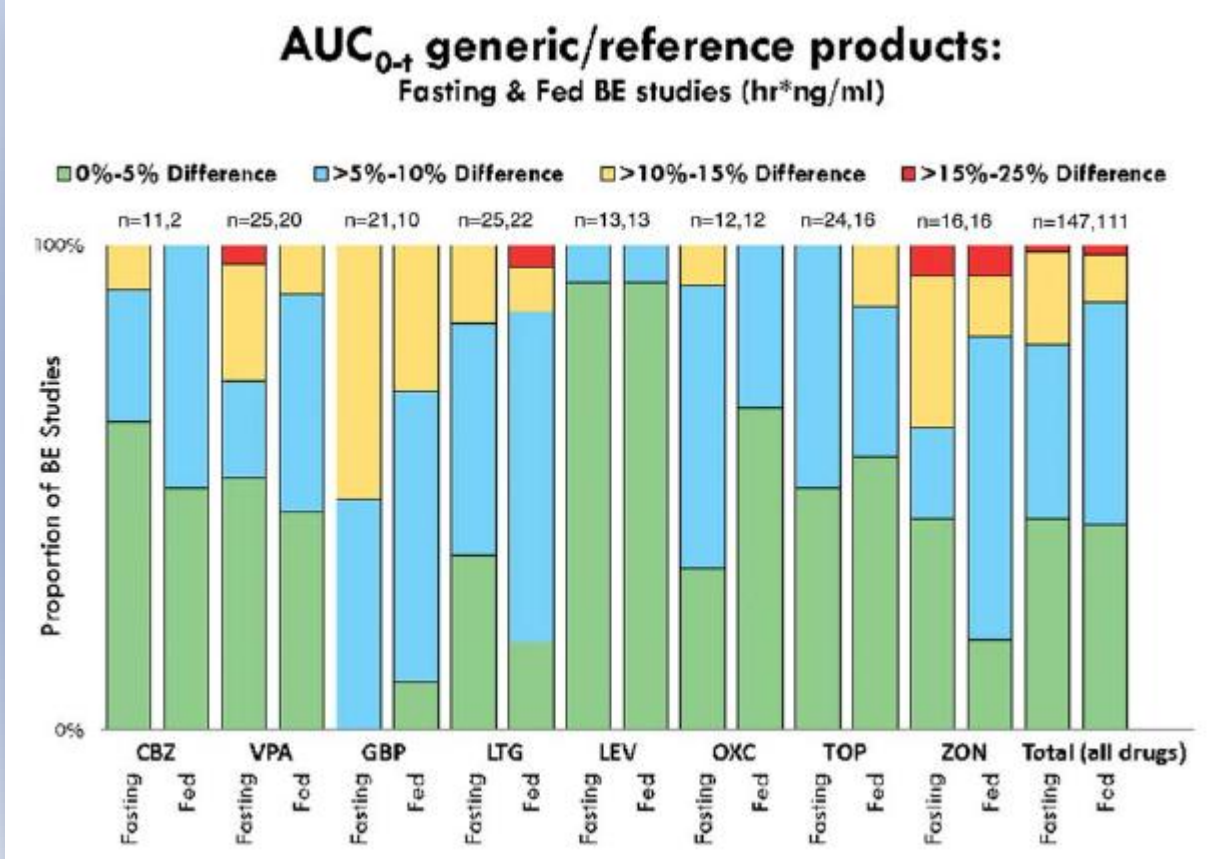
Conclusion

Though physicians may want to consider more intensive monitoring of high-risk patients taking AEDs when any medication change occurs, in the absence of better data, there is little evidenced-based rationale to challenge the implementation of generic substitution for AEDs in most cases.

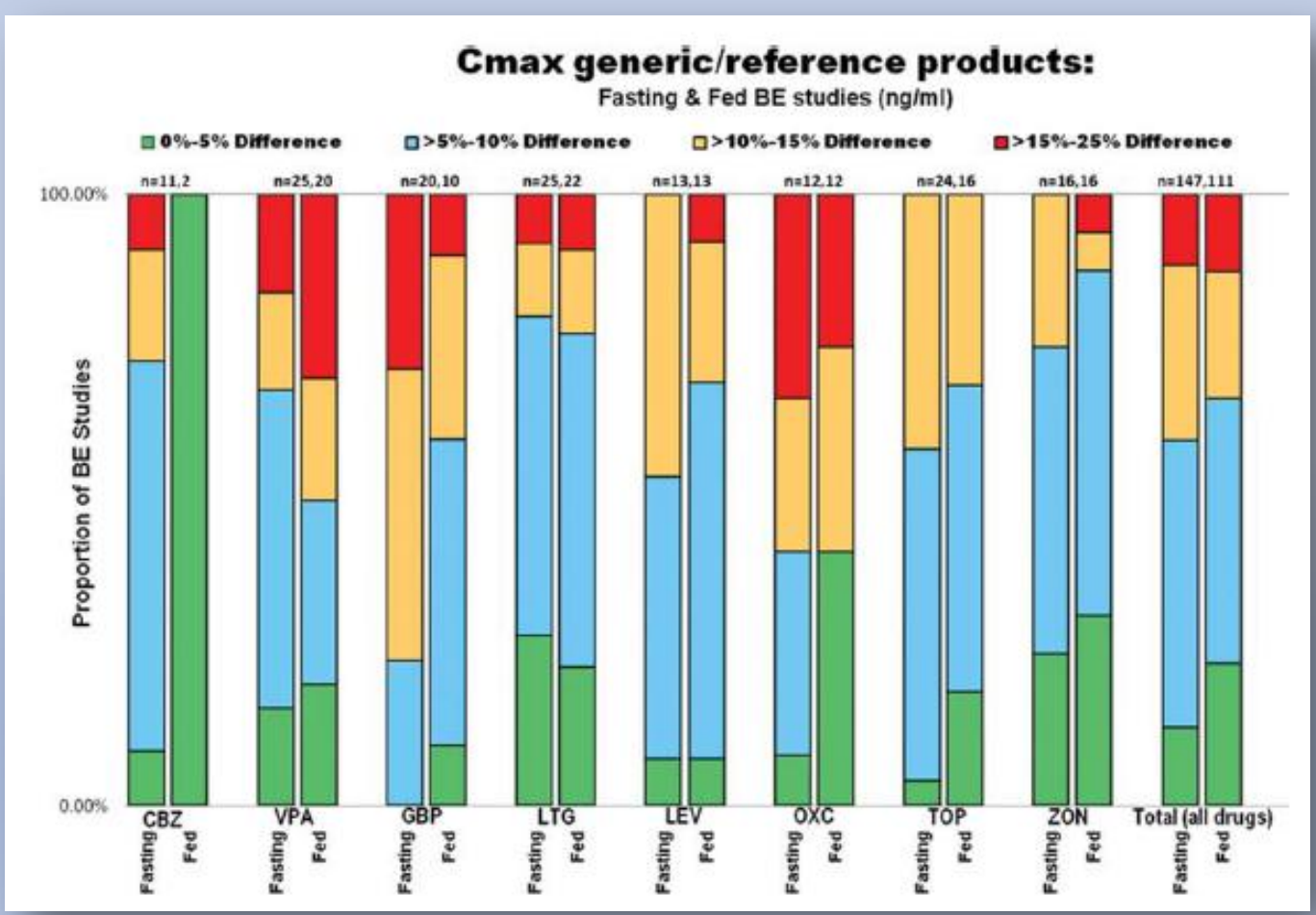
ANN NEUROL 2011;70:221–228

Assessing Bioequivalence of Generic Antiepilepsy Drugs

Gregory L. Krauss, MD,[1] Brian Caffo, PhD,[2] Yi-Ting Chang, MS,[2]
Craig W. Hendrix, MD,[3] and Kelly Chuang[1]



CBZ = carbamazepine; VPA = divalproex; GBP = gabapentin; LTG = lamotrigine; LEV = levetiracetam; OXC = oxcarbazepine; TOP = topiramate; ZON = zonisamide.



CBZ = carbamazepine; VPA = divalproex; GBP = gabapentin; LTG = lamotrigine; LEV = levetiracetam; OXC = oxcarbazepine; TOP = topiramate; ZON = zonisamide.

Epilepsia, 51(6):941–950, 2010
doi: 10.1111/j.1528-1167.2010.02573.x

CRITICAL REVIEW AND INVITED COMMENTARY

Generic products of antiepileptic drugs: A perspective on bioequivalence and interchangeability

*Meir Bialer and †Kamal K. Midha

Table 1. French League Against Epilepsy (LFCE) recommendations and considerations on the use of generic AEDs for the treatment of epilepsy

1. The LFCE considers AEDs as a particular class of drugs which are problematic in their substitution when they are used for the epilepsy indication.
2. The LFCE recommends avoiding substitution by generic AEDs (particularly from one generic by another) in the treatment of epilepsy without the agreement of the consulting physician and of the patients.
3. The LFCE is opposed to the practice that allows the substitution of an AED at the point of sale without the prior consent of the prescriber and the patient.
4. The LFCE considers that both the autonomy of prescription and the free access of the patients to the prescribed treatments remain basic principle of medical practice
5. The LFCE recommends, in case of break-through seizures or recurrence of seizures in seizure-free patients, to monitor systematically the AED blood-levels and to record the details related to compliance issues and substitution procedure.

Table 2. The American Academy of Neurology (AAN) and The American Epilepsy Society (AES) position statements on the coverage of AEDs for the treatment of epilepsy

The AAN position statement includes the following:

1. The AAN opposes generic substitution of AEDs without the attending physician's approval.
2. The AAN supports the use of new-generation AEDs.
3. The AAN opposes policies that would result in arbitrary switching among AEDs.

The AES supports the following principles concerning the continuity of AEDs for patients with epilepsy:

1. The AES opposes formulation substitution of AEDs for the treatment of epilepsy without physician and patient approval.
2. The AES opposes all state and federal legislations and formularies that limit the ability of physicians to determine which AED formulation to prescribe to patients with epilepsy.
3. The AES strongly supports the development of federal regulations validated in patients with epilepsy that ensure that the various generic AED formulations are therapeutically equivalent and can be used interchangeably without concern for safety or efficacy (American Epilepsy Society (AES), 2007).

ΣΤ. ***Ρύθμιση δοσολογικών σχημάτων για φάρμακα που χρήζουν προσοχής με βάση τις αρχές της Πληθυσμιακής Φαρμακοκινητικής***

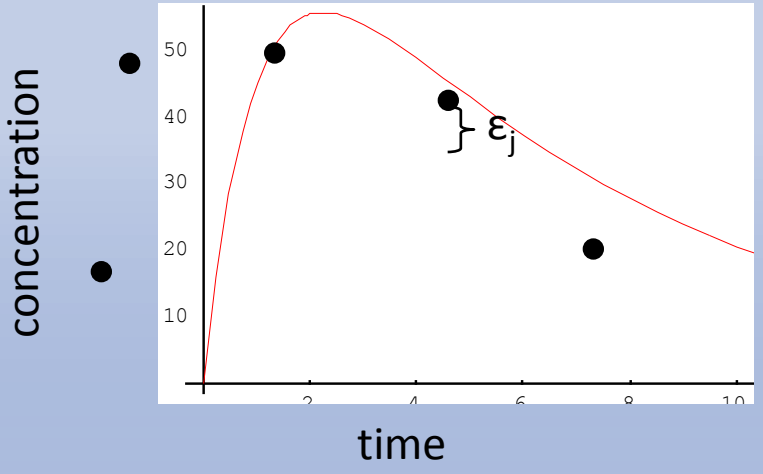
Individual pharmacokinetics

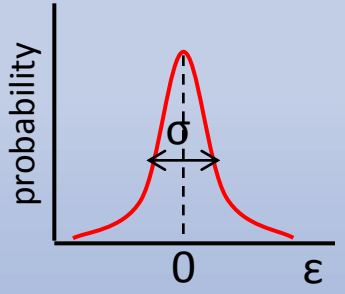
Fitting a model to data: $C_j = f(\theta, t_j) + \varepsilon_j$

Least squares

Maximum likelihood

$\varepsilon_j \sim N(0,\sigma)$

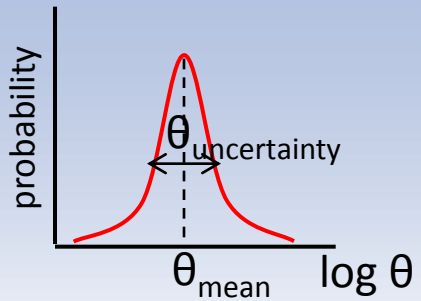


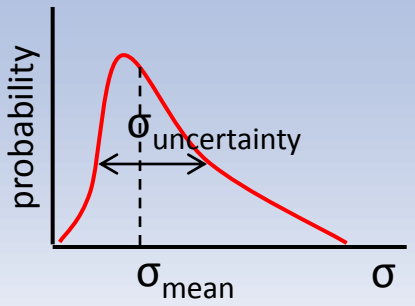


mean value: 0

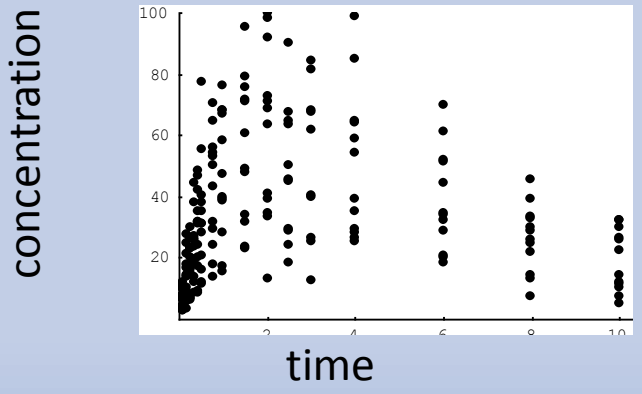
variance: σ

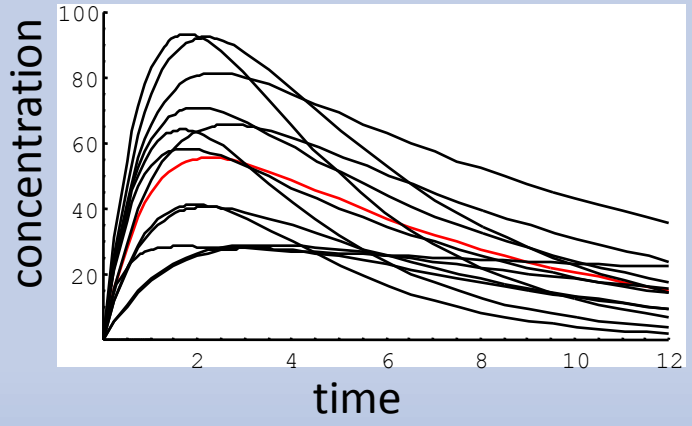
Uncertainty



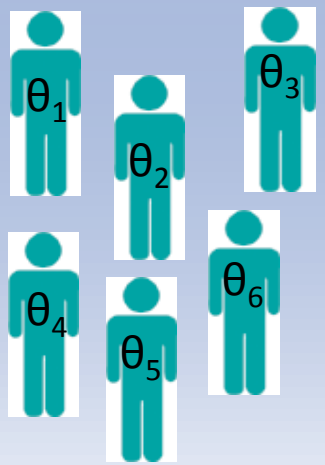


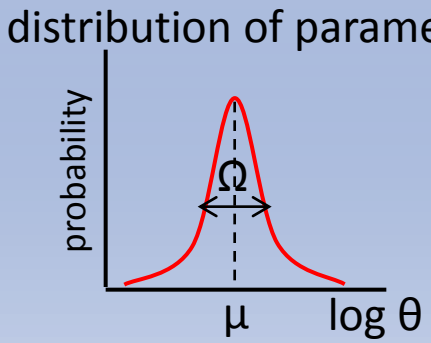
Parametric population pharmacokinetics





inter- individual variability



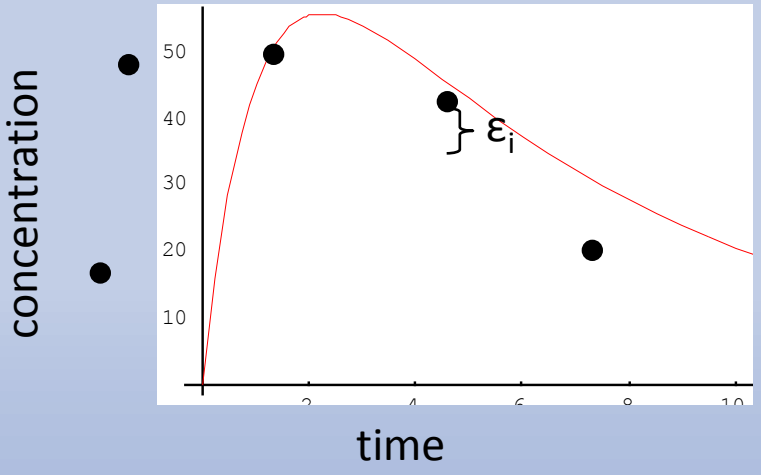


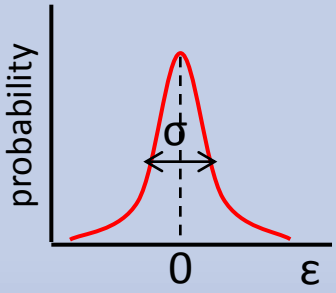
mean value: μ

variance: Ω

Residual variability

Variability that is not explained by Ω

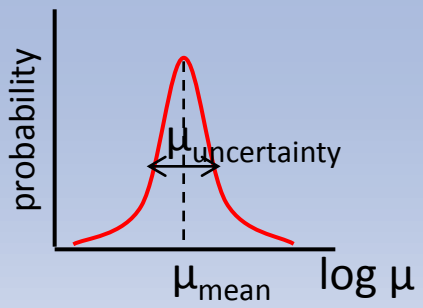


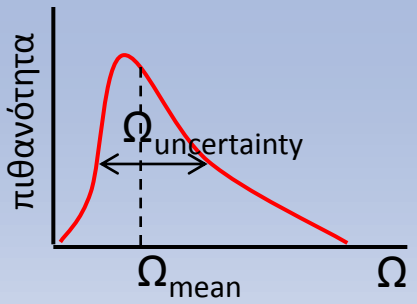


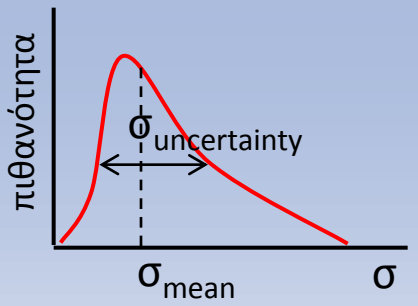
mean value: 0

variability: σ

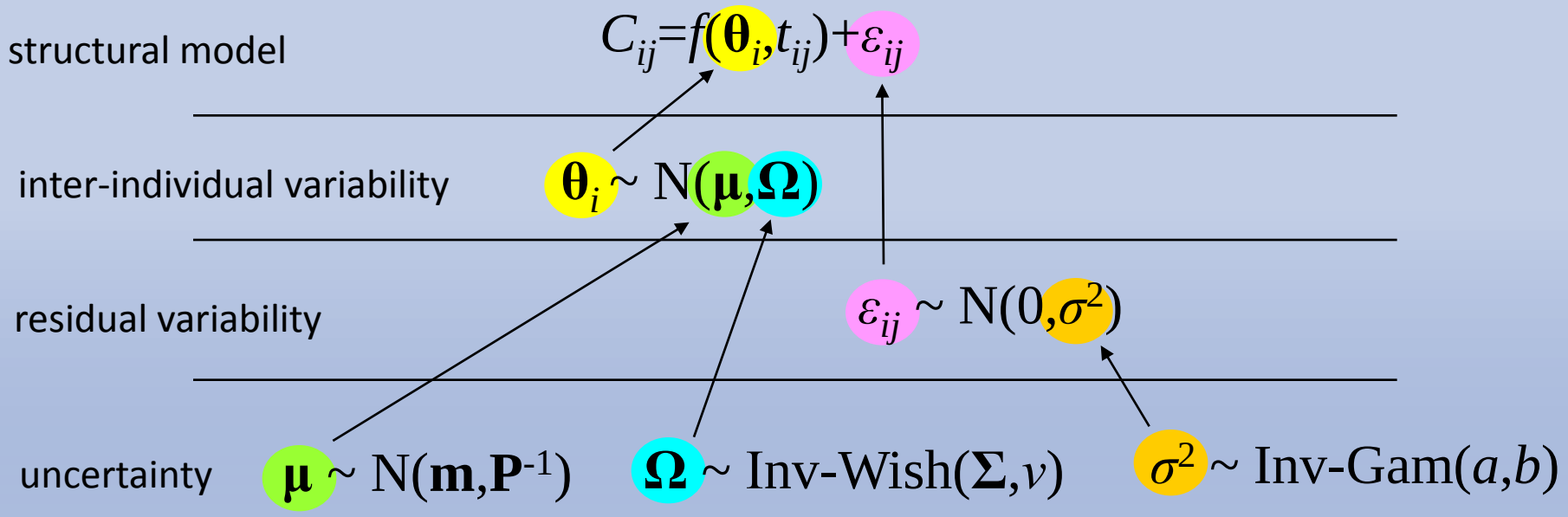
Uncertainty





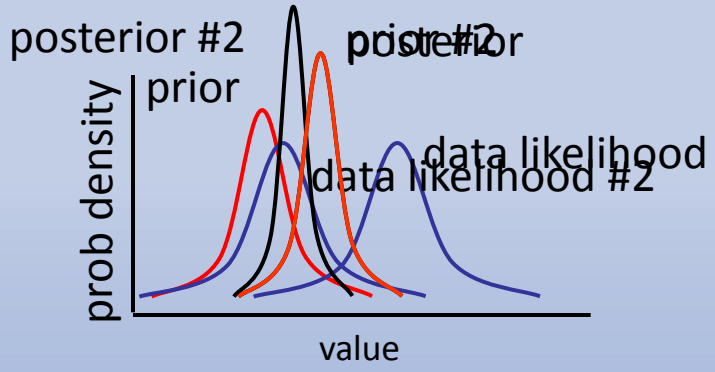


Hierarchical model (3 levels)



Bayes' theorem

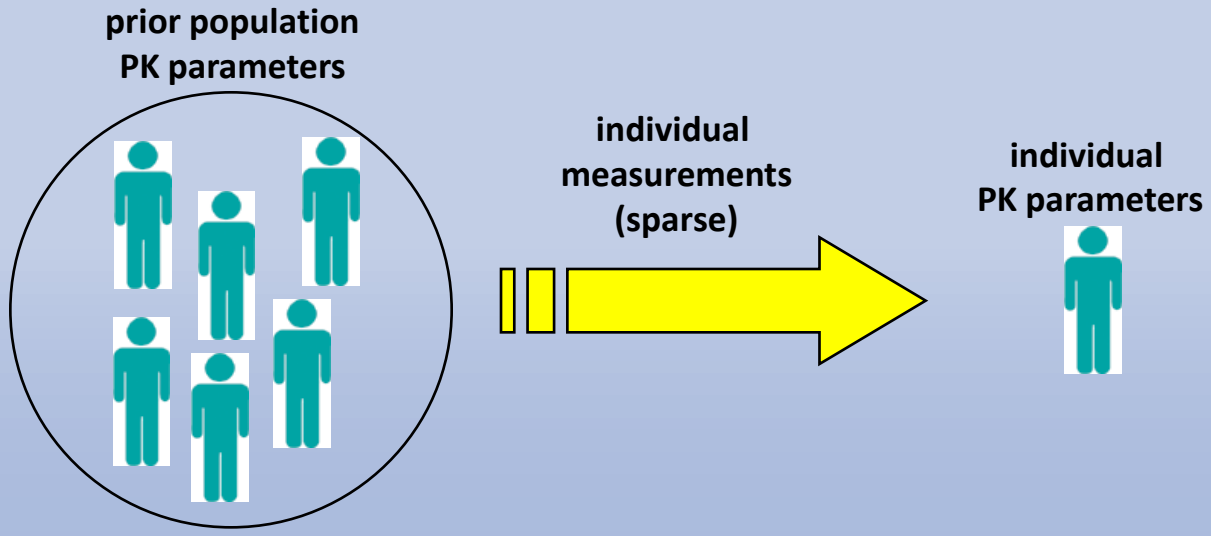
The product of the prior and the data likelihood normalised gives the **posterior distribution**



$$P(\theta|\mathbf{X}) = \frac{p(\theta)\ l(\mathbf{X}|\theta)}{\int p(\theta) l(\mathbf{X}|\theta) d\theta}$$

Sequential use of Bayes theorem

Bayesian individualization



Therapeutic Drug Monitoring

Individual PK parameters ⟶ Dose individualization

The Challenge of Achieving Target Drug Concentrations in Clinical Trials: Experience From the Symphony Study

(Transplantation 2009;87: 1360–1366)

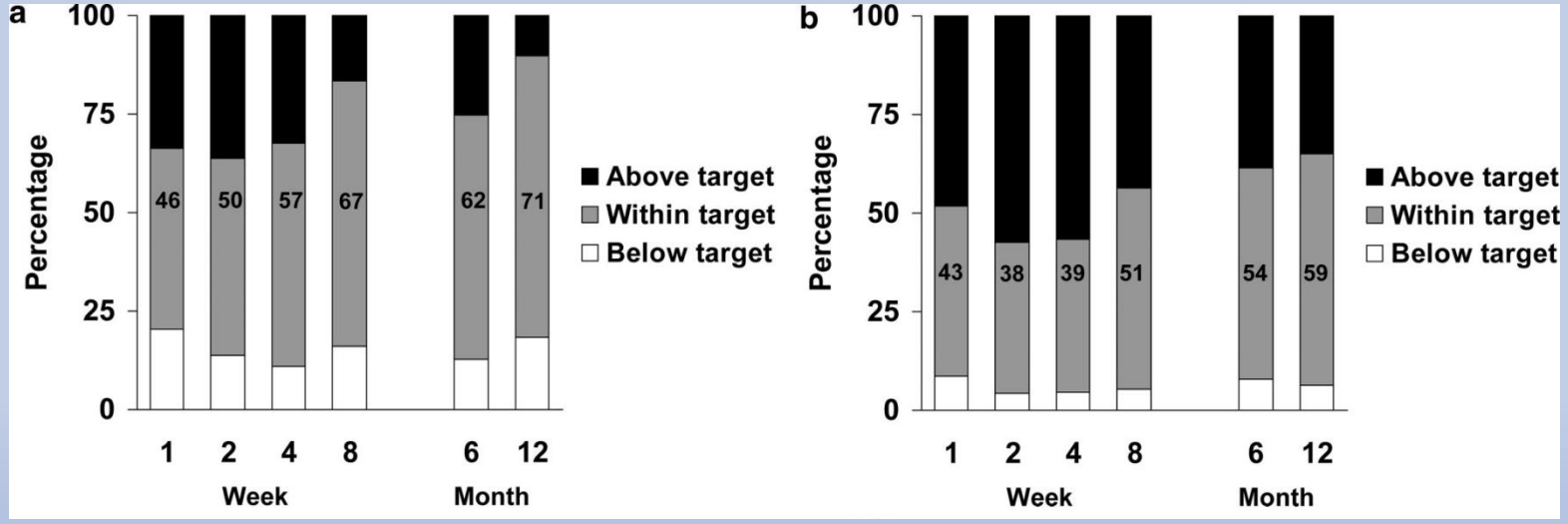
Henrik Ekberg,Richard D. Mamelok, Thomas C. Pearson,Flavio Vincenti,He´lio Tedesco-Silva,and Pierre Daloze

Background. The Symphony study compared four immunosuppressant regimens, defined by protocol-specified target drug concentrations. This subanalysis examines actual drug levels and the implications on the interpretation of results.

Methods. De novo renal transplant patients (n=1645) were randomized to receive mycophenolate mofetil (2 g/day) and corticosteroids in combination with standard-dose cyclosporine A or daclizumab induction and low-dose CsA ,low-dose tacrolimus,or low-dose sirolimus.

Results. Low-dose Tac was significantly superior for renal function, acute rejection, and graft survival at 12 months.
Median trough levels of CsA, Tac, or SRL were toward the high end of target ranges in all groups, and 50% to 60% were within target.

Conclusions. To replicate the Symphony study results in clinical practice, the protocol-defined drug concentration targets should be aimed for, but the concentrations actually achieved may be regarded as acceptable



Percent of patients above, within and below target range at weeks 1, 2, 4, and 8, and months 6 and 12. (a) Standard-dose cyclosporine; (b) Low-dose cyclosporine

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2011.04039.x

Dosing equation for tacrolimus using genetic variants and clinical factors

Chaitali Passey,[1] Angela K. Birnbaum,[1] Richard C. Brundage,[1] William S. Oetting,[2] Ajay K. Israni[3] & Pamala A. Jacobson[1]

[1]Department of Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, MN 55455, [2]Department of Experimental and Clinical Pharmacology and Institute of Human Genetics, University of Minnesota, Minneapolis, MN 55455 and [3]Department of Medicine, Nephrology Division, Hennepin County Medical Center, Minneapolis, MN 55415, USA

Correspondence
Dr Pamala A. Jacobson PharmD, Department of Experimental and Clinical Pharmacology, Weaver Densford Hall 7-151, 308 Harvard St SE, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, USA.
Tel.: +1 612 624 6118
Fax: +1 612 625 3927
E-mail: jacob117@umn.edu

The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Institute of Allergy and Infectious Disease or the National Institute of Health.

All authors approve the content and submission of this manuscript.

Keywords
CYP3A5, kidney transplantation, pharmacogenetics, pharmacogenomics, pharmacokinetics, tacrolimus

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2 December 2010
Accepted
1 June 2011
Accepted Article
14 June 2011

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Patients with low tacrolimus troughs are at a higher risk of rejection while those with high troughs are at an increased risk for toxicity. Therefore, achieving the therapeutic range is important.
- CYP3A5 genotype and days post transplant have been previously shown individually to be associated with tacrolimus troughs.

AIM

To develop a dosing equation for tacrolimus, using genetic and clinical factors

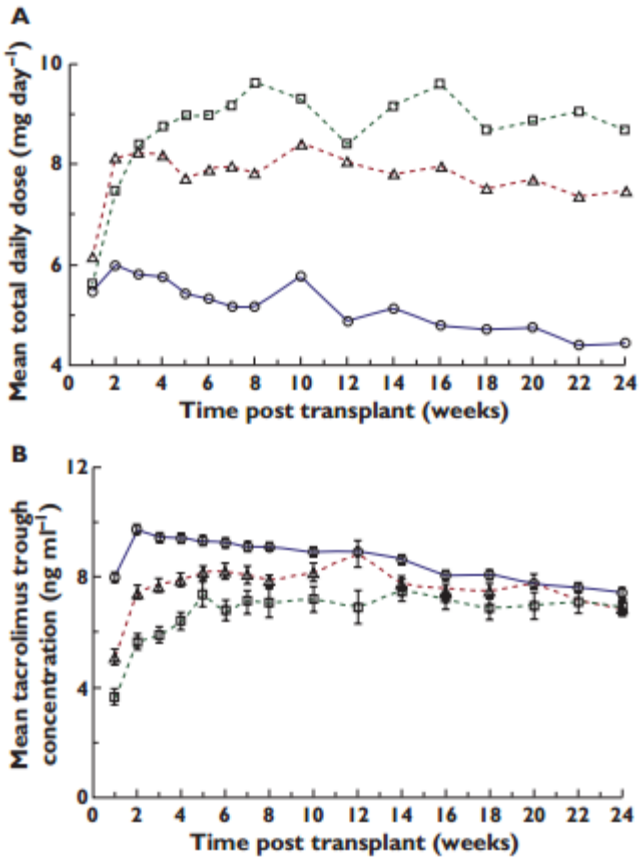

Figure 1

Tacrolimus doses and troughs by CYP3A5 genotype (○ CYP3A5*3/*3, △ CYP3A5*1/*3, □ CYP3A5*1/*1) over the first 6 months post transplant. (A) Total daily doses by CYP3A5 genotype. (B) Trough concentrations by CYP3A5 genotype (mean ± SE)

Ευχαριστώ

για την προσοχή σας!