The validity of the generic principle in drug regulation

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Concerns about generic drugs

Clin Kidney J (2014) 7: 151–155

Equivalence of generic medicines in general and immunosuppressants in particular – a regulatory opinion on switching of ciclosporin, tacrolimus and mycophenolate mofetil

Generics and Biosimilars Initiative Journal (GaBI Journal). 2013;2(2):86-90.
DOI: 10.5639/gabij.2013.0202.019

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Aims

- To investigate issues that may have an impact on the **interchangeability** of a **generic drug and its brand-name drug** from a regulatory and pharmacokinetic perspective;

- Also on the **interchangeability of generic drugs**;

- to provide **recommendations** for optimizing the **regulation** of generic drugs.

Interchangeability of generic and the brand-name drug

1. Intra-subject variability

(*Br J Clin Pharmacol* 81, 667-78 (2016))

2. Impact of post-marketing variations

(to be submitted)

1. The intrasubject variation of drug exposure

- Aims:
  - to investigate reason for difference in total and peak drug exposure in individuals that is observed upon switching to generic drugs
  - Clarify the role of intrasubject variability in pharmacokinetics in this effect.

- Design:
  - Retrospective reanalysis of existing studies;
  - Archived data from **replicate design bioequivalence** studies
  - Nine replicate design studies representing six drug classes, i.e. for **alendronate, atorvastatin, cyclosporine, ebastine, exemestane, mycophenolate mofetil, and ropinirole**.

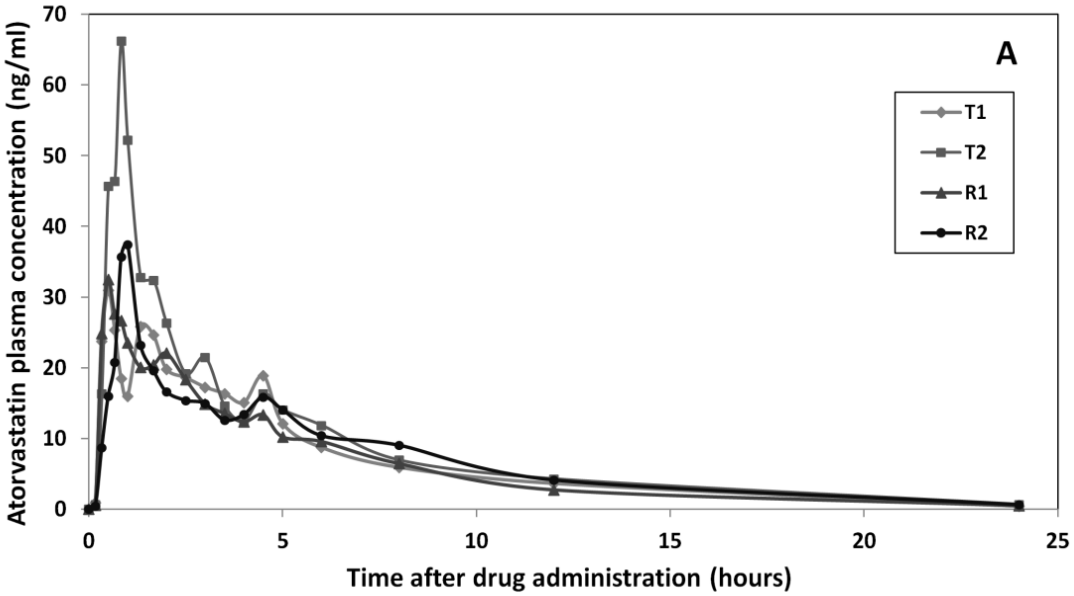
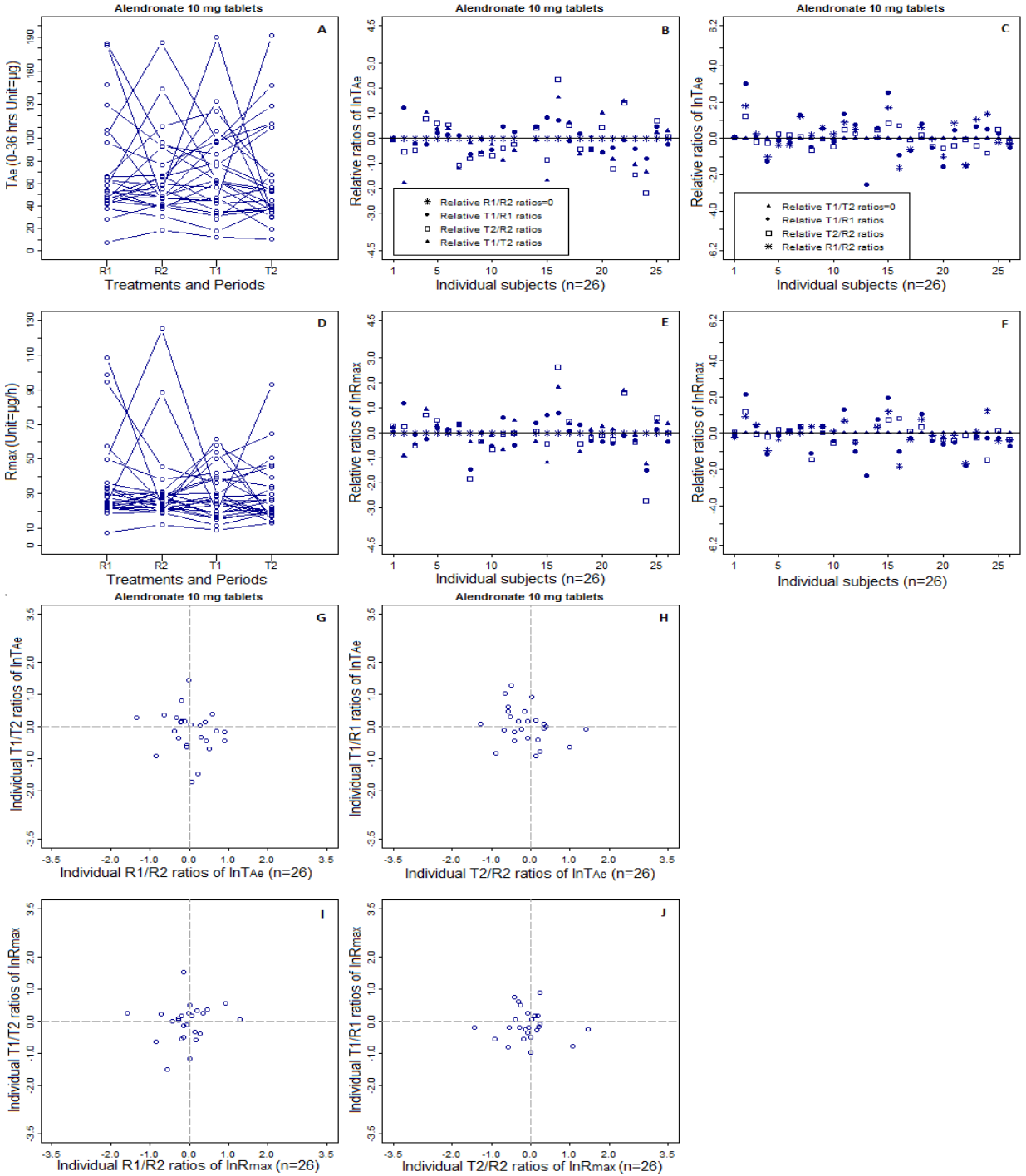


Figure 1 - 1. Individual illustrative atorvastatin plasma concentration-time curves for the brand-name and generic drugs in a single subject in the replicate design bioequivalence study (t=24 hours) in an arithmetic scale (A)


Alendronate 10 mg tablets
A
TAe (0-36 hrs Unit=µg)
Treatments and Periods
R1
R2
T1
T2
B
Relative ratios of lnTAe
Relative R1/R2 ratios=0
Relative T1/R1 ratios
Relative T2/R2 ratios
Relative T1/T2 ratios
Individual subjects (n=26)
C
Relative T1/T2 ratios=0
Relative T1/R1 ratios
Relative T2/R2 ratios
Relative R1/R2 ratios
D
Rmax (Unit=µg/h)
E
Relative ratios of lnRmax
F
G
Individual T1/T2 ratios of lnTAe
Individual R1/R2 ratios of lnTAe (n=26)
H
Individual T1/R1 ratios of lnTAe
Individual T2/R2 ratios of lnTAe (n=26)
I
Individual T1/T2 ratios of lnRmax
Individual R1/R2 ratios of lnRmax (n=26)
J
Individual T1/R1 ratios of lnRmax
Individual T2/R2 ratios of lnRmax (n=26)

Results

Table 1 - 1. Estimations of intrasubject variances, variance due to subject-by-formulation interaction, and the probability of exposure ratio beyond the borders of 80-125% range in individuals.

Active substances (Strength)	Ratios	N	AUC0-t (ln-scale)				Cmax (ln-scale)			
			Mean	Intrasubject variances	Variance of SbyF interaction (the upper boundary of 95% CI*)	Probability of ratio beyond 80-125% (%)	Mean	Intrasubject variances	Variance of SbyF interaction (the upper boundary of 95% CI*)	Probability of ratio beyond 80-125% (%)
Alendronate (10 mg)	R2-R1	25	0.023	0.140	-0.069 (0.033)	67.3	-0.069	0.155	-0.042 (0.057)	68.9
	T2-T1	26	-0.106	0.233		74.4	-0.014	0.181		71.1
	T-R	25	-0.039	0.118		72.8	-0.093	0.126		72.8
Alendronate (70 mg)	R2-R1	68	-0.042	0.237	0.047 (0.158)	74.6	-0.135	0.291	0.021 (0.147)	77.0
	T2-T1	67	0.006	0.223		73.9	0.010	0.269		76.1
	T-R	67	0.005	0.277		77.7	-0.039	0.301		79.1
Atorvastatin (40 mg)	R2-R1	54	0.098	0.051	-0.015 (0.007)	48.7	-0.057	0.176	-0.091 (0.003)	70.7
	T2-T1	58	0.126	0.062		52.6	0.216	0.332		78.4
	T-R	54	-0.043	0.042		52.7	0.022	0.163		75.5
Cyclosporin (100 mg)	R2-R1	133	0.015	0.037	-0.006 (0.003)	41.5	-0.019	0.170	-0.026 (0.019)	70.2
	T2-T1	134	0.022	0.034		39.3	0.034	0.161		69.5
	T-R	133	0.025	0.029		41.5	0.025	0.140		70.6
Exemestane (25 mg)	R2-R1	54	-0.016	0.020	-0.008 (-0.001)	26.2	-0.025	0.093	-0.007 (0.032)	60.6
	T2-T1	54	-0.001	0.020		26.2	0.069	0.080		57.7
	T-R	54	0.039	0.011		26.3	0.006	0.079		62.2
Mycophenolate mofetil (250 mg)	R2-R1	37	0.001	0.011	-0.003 (0.003)	12.8	0.051	0.135	-0.029 (0.026)	66.8
	T2-T1	37	-0.032	0.015		19.2	0.008	0.095		60.8
	T-R	37	-0.007	0.009		18.3	0.012	0.086		65.9
Mycophenolate Mofetil (500 mg)	R2-R1	41	-0.003	0.026	0.002 (0.013)	32.9	0.112	0.199	-0.038 (0.030)	72.4
	T2-T1	40	-0.041	0.009		9.3	-0.061	0.097		61.3
	T-R	40	-0.012	0.020		32.1	-0.014	0.110		69.6
Ropinirole (2 mg)	R2-R1	33	-0.006	0.014	0.000 (0.010)	18.5	0.042	0.022	0.009 (0.047)	29.3
	T2-T1	29	0.007	0.016		21.9	0.138	0.080		57.7
	T-R	28	-0.067	0.016		29.3	0.144	0.060		57.8

SbyF interaction, Subject-by-Formulation interation. * The upper boundary of 95% CI for the variance of SbyF interaction is used in the calculation of the probability of (T-R) ratio beyond the borders of 80-125% range.

Results

1. Variation in individual total and peak exposure seen when a patient is **switched** from a brand-name drug to a generic drug **is comparable** to the variation seen following **repeated administration** of the brand-name drug.

2. Only the **intrasubject variability** seems to play a crucial and decisive role in the variation in drug exposure seen.

3. **No additional formulation dependent variation** in exposure is observed upon switching

2. The cumulative impact of post-marketing quality variations

- Post-marketing changes of drugs
- Approved on an independent, case-by-case basis (unless multiple variations are submitted at once)
- Theoretically cumulative effect on the quality of a medicinal product

- The consequence : changes in the drug quality

  →the current drug may be different from the one that demonstrated bioequivalence with the brand-name drug.

Methods

- Critical post-marketing quality variations
- Ten active substances with a low solubility (BCS class II and IV)
- A risk assessment model → combines all critical variations applied to brand-name or generic drugs

Risk (R) =Hazard (H) x Exposure (E)

- Threshold = 40.5 (based on cases with a known risk)
- Validation

Table 2 - 1. Definitions of relative risk scores for hazard.

Hazard component	Categories		Relative risk score (1= no risk)
Log P	Ideal range: 1.56 - 3.34		2
	10%-90% percentile: -0.65 - 1.56; 3.34 - 5.36		3
	Outlier zone: < -0.65 or > 5.36		4
Therapeutic Index	Non-narrow therapeutic range		2
	Narrow therapeutic range		4
Dosage form	Oral solutions		2
	Standard coating tablets or capsules		2.5
	Enteric-coated or delayed-release tablets or capsules		3
	Controlled or sustained-release capsules		3
	Controlled or sustained-release tablets		3.25
Dose	> 10 mg		1.5
	≤ 10 mg		2.25
Absorption dynamics	Absorption mechanisms	Passive diffusion	1.5
		Known active transport mechanism	1.875
		Known CYP 3A4 or P-gp interaction	1.875
	Delivery conditions	Non site-specific absorption	1.5
		Site-specific absorption	2.25

Results

Table 2 - 2. Summary of selected medicinal products and risk assessment results.
– Naproxen as an example

						Risk assessments results[$]			
Active substances (ATC-5)	Generic medicinal products (n)	Selection of products[*] (n)		Time since registration[**$] (mean (the range), years)	Number of variations[$] (mean (the range))	Relative hazard (mean (median, the range))	Exposure (mean (median, the range))	Total risk (mean (median, the range))	Predicted positive cases[†] (n)
Naproxen (M01AE02)	23	16	Branded: 2	15.3; 21.3	1; 1	1.3; 1.3	4.2; 4.2	5.2; 5.2	0
			Generics: 14	13.2 (6.2-25.8)	1.5 (1-4)	1.3 (1.3, 1.3-1.5)	6.9 (3, 2-30.8)	8.8(4.2, 3-38.5)	0

Table 2 - 3. Evaluation of risk assessment results for the brand-name and generic drugs.

	Life time (mean (the range), years)	Selection of variations (mean (the range))	Predicted positive cases*	Predicted negative cases**
Brand-name drugs (n=16)	12.7 (2.6 - 21.9)	2.8 (1 - 6)	5 (31.3%)	11 (68.7%)
Generic drugs (n=99)	8.4 (0.6 - 32.8)	2.2 (1 - 9)	15 (15.2%)	84 (84.8%)
Total (n=115)	-	-	20 (17.4%)	95 (82.6%)
Predicted positive cases* (n=20)	14.7 (3 - 32.8)	4.6 (2 - 9)	-	-
Predicted negative cases** (n=95)	7.8 (0.6 - 25.8)	2 (1 - 6)	-	-

* the drugs of total risks above threshold (threshold = 40.5); ** the drugs of total risks below threshold (threshold = 40.5).

Results

- The totality of post-marketing variations would affect 17% of the drugs assessed (n= 20 out of 115)

  → 13% (15 out of 115) were generic drugs (n=99)

  → 4% (5 out of 115) were brand-name drugs (n=16)

A limited number of generic drugs and brand-name drugs is affected.

- Overestimation of the model + low number of critical variations (n=2 in average)

Our concerns can neither be relieved nor strengthened.

Although **Regulatory action** may **not be necessary** at the moment, the effect of critical variations on generic drugs should be **re-assessed** in the future, using an improved risk assessment model.

Interchangeability of generic and generic drug

3. A comparative bioavailability study of gabapentin
(*Clin Pharmacol Ther 94, 519-24 (2013))*

4. Inter-study comparison for immunosuppressants and a broad selection of medicines
(Eur J Clin Pharmacol 71:979–990 (2015))

Interchangeability of generic and generic drug

Eur J Clin Pharmacol. 2011 Oct;67(10):1007-16. Epub 2011 Apr 15.

Interchangeability of generic anti-epileptic drugs: a quantitative analysis of topiramate and gabapentin.

Maliepaard M, Banishki N, Gispen-de Wied CC, Teerenstra S, Elferink AJ.

Medicines Evaluation Board, MEB-CBG, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB, Nijmegen, The Netherlands. m.maliepaard@cbg-meb.nl

Generic drug A ⟷ Generic drug B

3. A comparative bioavailability study of gabapentin

A randomized, four-way crossover, comparative bio-availability study of branded (Neurontin®) and three generics 800 mg gabapentin tablets in healthy subjects under fasting conditions.

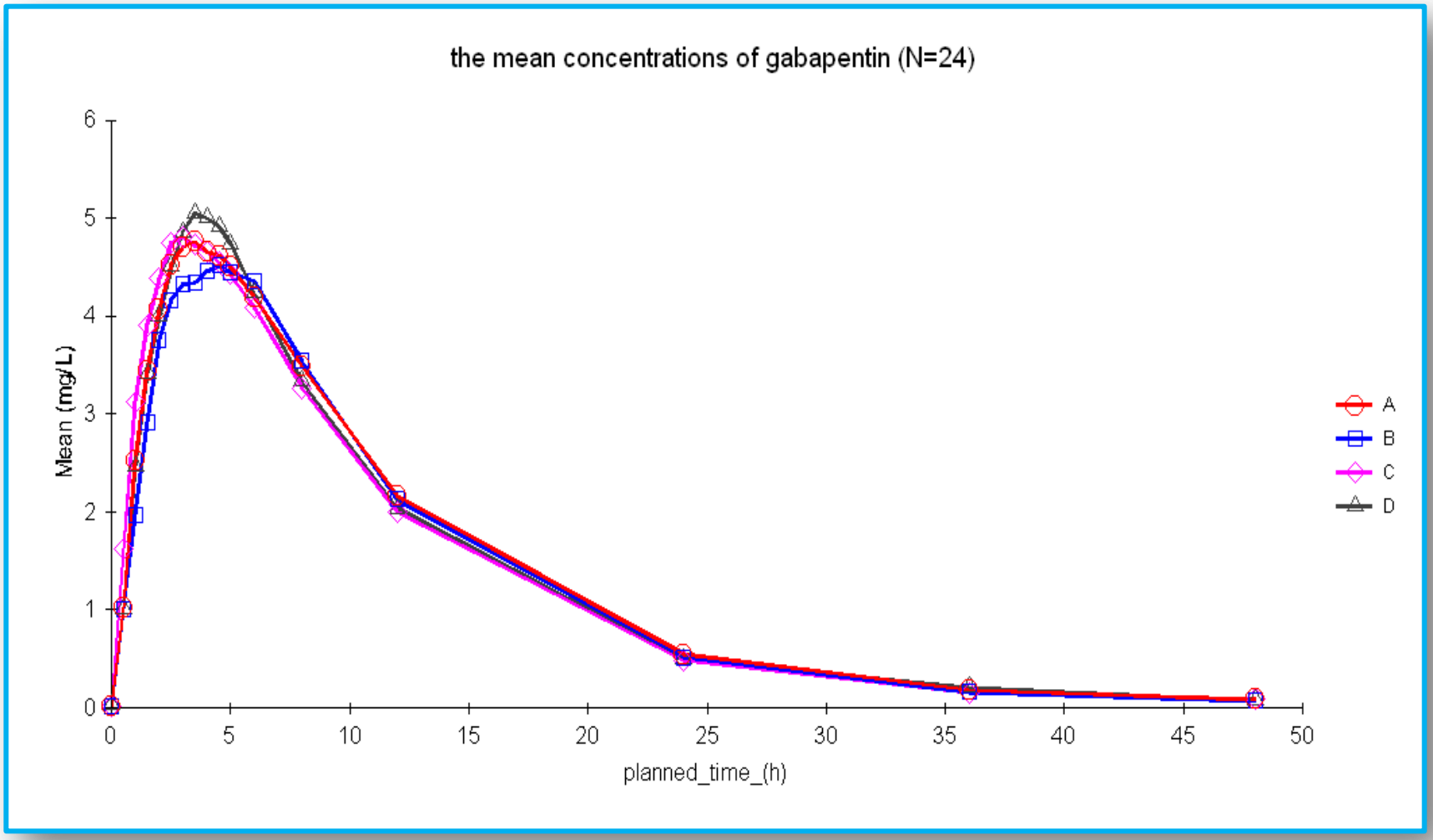
Protocol No.: CBG/Gaba2011/01

National Trial Register number: NTR2964

CRO Study No.: DRUM 11-GABA

- Objective
  To investigate the possible 'drifting effect' upon generic-generic exchange in vivo for gabapentin

Comparative Bio-availability Study



	C_{max}	AUC_{0-48}	AUC_{inf}
G1 vs Neurontin			
Ratio	100.7%	96.9%	96.5%
90% CI	91.4%—110.5%	89.5%—104.9%	89.1%—104.4%
G2 vs Neurontin			
Ratio	105.1%	98.7%	98.7%
90% CI	93.5%—118.3%	87.6%—111.2%	88.0%—110.7%
G3 vs Neurontin			
Ratio	106.1%	98.7%	98.3%
90% CI	97.1%—115.8%	91.6%—106.4%	91.4%—105.8%
G1 vs G2			
Ratio	95.8%	98.1%	97.7%
90% CI	84.1%—109.0%	87.3%—110.4%	87.2%—109.5%
G1 vs G3			
Ratio	94.9%	98.1%	98.1%
90% CI	86.9%—103.6%	91.0%—105.9%	91.2%—105.4%
G2 vs G3			
Ratio	99.1%	100%	99.6%
90% CI	89.9%—109.2%	91.7%—109.1%	92.3%—109.2%

3. Comparative Bio-availability Study - results

- I→G: 90% CI in line with results of BE studies in registration files at the CBG-MEB
- G→G: 90% CI all within the 80-125% criterion for bioequivalence
- 90% CI comparable with the simulated 90% CIs for C_{max} and AUC_t. (Maliepaard, 2011) ***– validation of the method***

4. Inter-study comparison for immunosuppressants and a broad selection of medicines

Dataset:

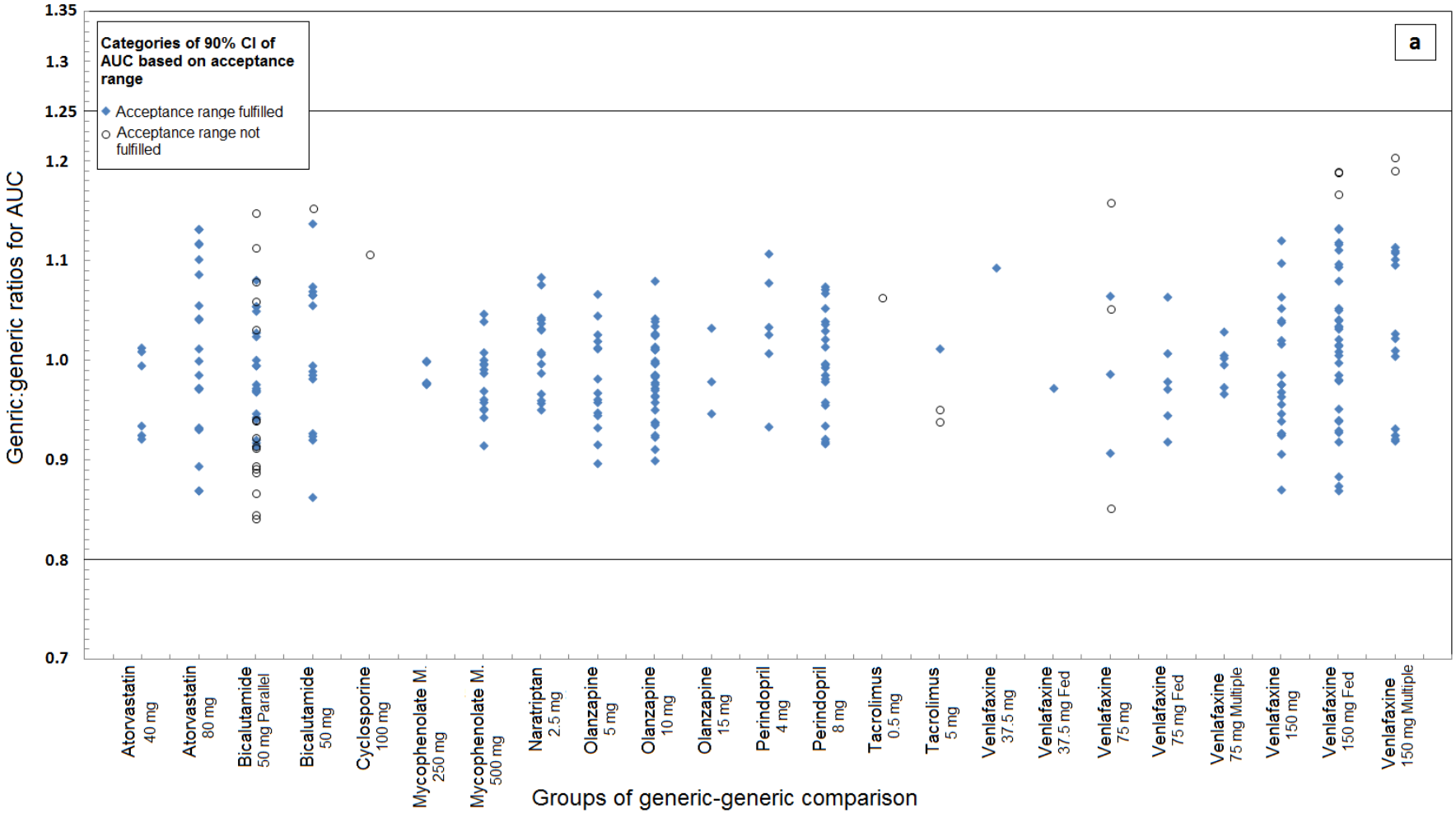
- 9 APIs, 115 brands of generic drugs were identified, which were registered based on 120 bioequivalence studies in total.
- The generic:innovator ratios:
  - AUC: (90.0% - 116.7%);
  - C_{max} : (87.7% - 118.5%).

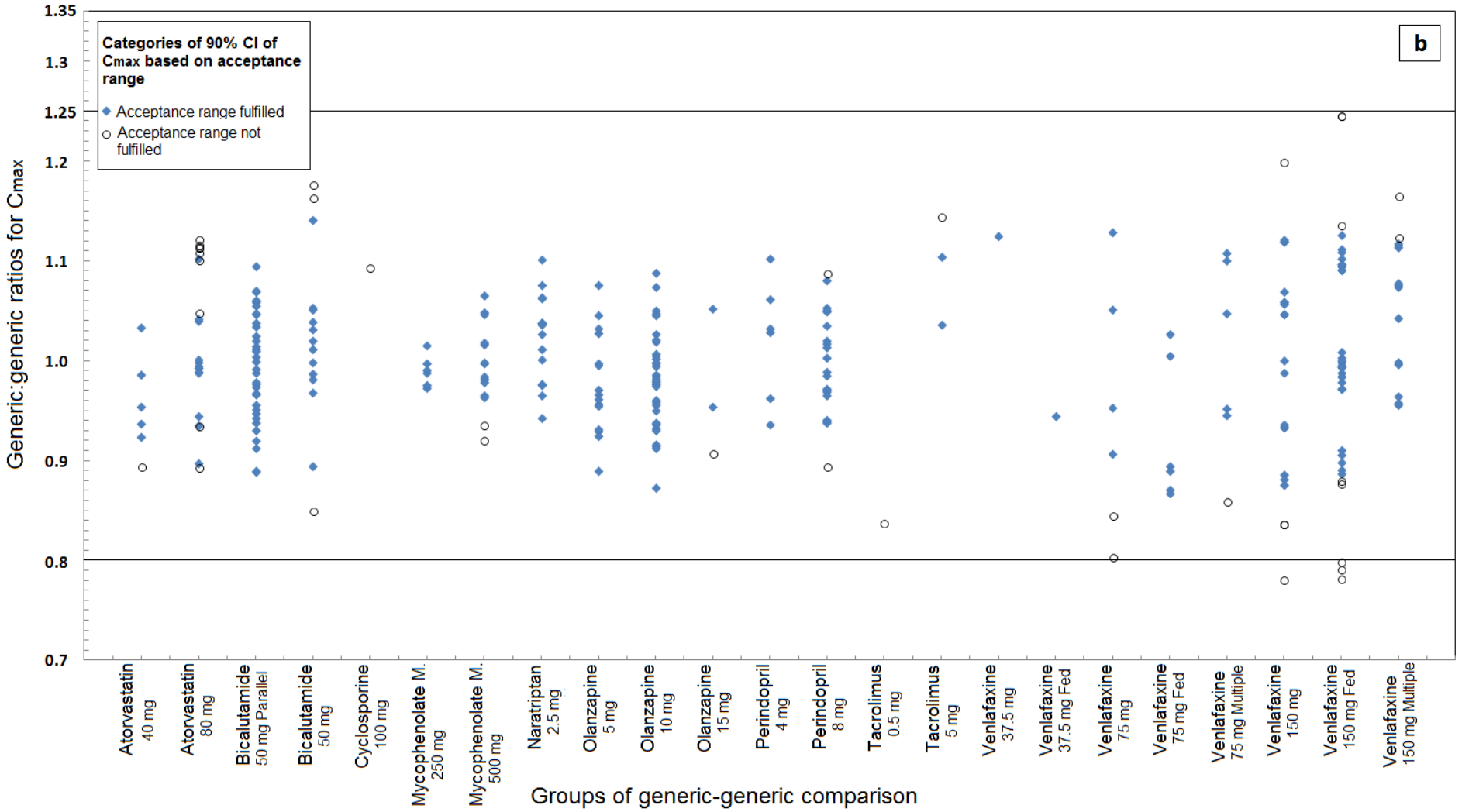
The mean absolute deviation of the ratios from 100% in this set of generics was 4.5% for AUC and 5.1% for C_{max}.

Table 4 - 1. A summary of selected generic drugs and bioequivalence studies (ranges of 90% CIs for AUC and C_{max}) in the study. – *Atorvastatin as an example*

APIs (dosage form)	Generic brands (n=115)	Strengths (mg)	Generics (n=354)	Year of studies	Study strength (mg)	BE studies (n=120)	Design			90% CI for AUC		90% CI for C_{max}	
										The range of LL (%)	The range of UL (%)	The range of LL (%)	The range of UL (%)
Atorvastatin (IR)	18	10	18	2006 - 2010	40	4	Crossover	Single-dose	Fasting	90.0-98.0	99.0-107.7	89.0-97.9	108.0-123.4
		20	18										
		30	2										
		40	18		80	7				94.5-112.2	106.3-121.5	88.3-104.6	107.1-123.6
		60	1										
		80	11										

Figure 4 -1. Ratios of generic-generic drug comparisons for (a) AUC and (b) C_{max} (n=292).




b
Categories of 90% CI of Cmax based on acceptance range
Acceptance range fulfilled
Acceptance range not fulfilled
Generic:generic ratios for Cmax
1.35
1.3
1.25
1.2
1.1
1.0
0.9
0.8
0.7
Atorvastatin 40 mg
Atorvastatin 80 mg
Bicalutamide 50 mg Parallel
Bicalutamide 50 mg
Cyclosporine 100 mg
Mycophenolate M. 250 mg
Mycophenolate M. 500 mg
Naratriptan 2.5 mg
Olanzapine 5 mg
Olanzapine 10 mg
Olanzapine 15 mg
Perindopril 4 mg
Perindopril 8 mg
Tacrolimus 0.5 mg
Tacrolimus 5 mg
Venlafaxine 37.5 mg
Venlafaxine 37.5 mg Fed
Venlafaxine 75 mg
Venlafaxine 75 mg Fed
Venlafaxine 75 mg Multiple
Venlafaxine 150 mg
Venlafaxine 150 mg Fed
Venlafaxine 150 mg Multiple
Groups of generic-generic comparison

Study results

- The estimated generic:generic ratios (Fig. 4-1).
  - AUC: (84.2% - 120.4%);
  - C_{max} : (78.1% - 124.5%)

  The mean absolute deviation of the ratios from 100% in this set of generic drugs was 5.4% for AUC and 6.1%.for C_{max}.

- The 90% CIs for both AUC_t and C_{max} **within** the bioequivalence criteria: **80.5%** (in **90.1% and 87.0%** at least for AUC_t and C_{max}, respectively).
- Not meeting the bioequivalence criteria:
  - in 26 (out of 29 cases) for AUC_t and in 29 (out of 38 cases) for C_{max}, a wider range of 75-133% (or 80-125%) was not exceeded in the indirect comparison.

- Thus, although the results are not fully reassuring, we consider **a pronounced risk** upon generic-generic exchange in clinical practice as **unlikely**.
- Overall, our study suggests that exposure-related risks associated with the exchange of different generic drugs in clinical practice is limited, and not much increased -if any- to the situation in which a generic is exchanged with the innovator.

Discussions

- Individual bioequivalence vs. average bioequivalence
- The impact of regulatory activities (post-marketing quality variations and guideline revision)

Eur J Clin Pharmacol (2015) 71:1083–1089
DOI 10.1007/s00228-015-1889-9

PHARMACOKINETICS AND DISPOSITION

Influence of point estimates and study power of bioequivalence studies on establishing bioequivalence between generics by adjusted indirect comparisons

Luther Gwaza[1,2] · John Gordon[3] · Henrike Potthast[4] · Jan Welink[5] · Hubert Leufkens[1] · Matthias Stahl[6] · Alfredo García-Arieta[7]

Conclusions

- Patients prescribed generic drugs should be able to trust that these drugs are as effective and safe as brand-name drugs or other generic drugs.

- While the interchangeability of generic and brand-name drugs has been extensively investigated, conclusions are far from unanimous.

- In general, confidence in generic drugs has increased considerably in recent years.

- Relatively little is known about the interchangeability of generic drugs.

Conclusion

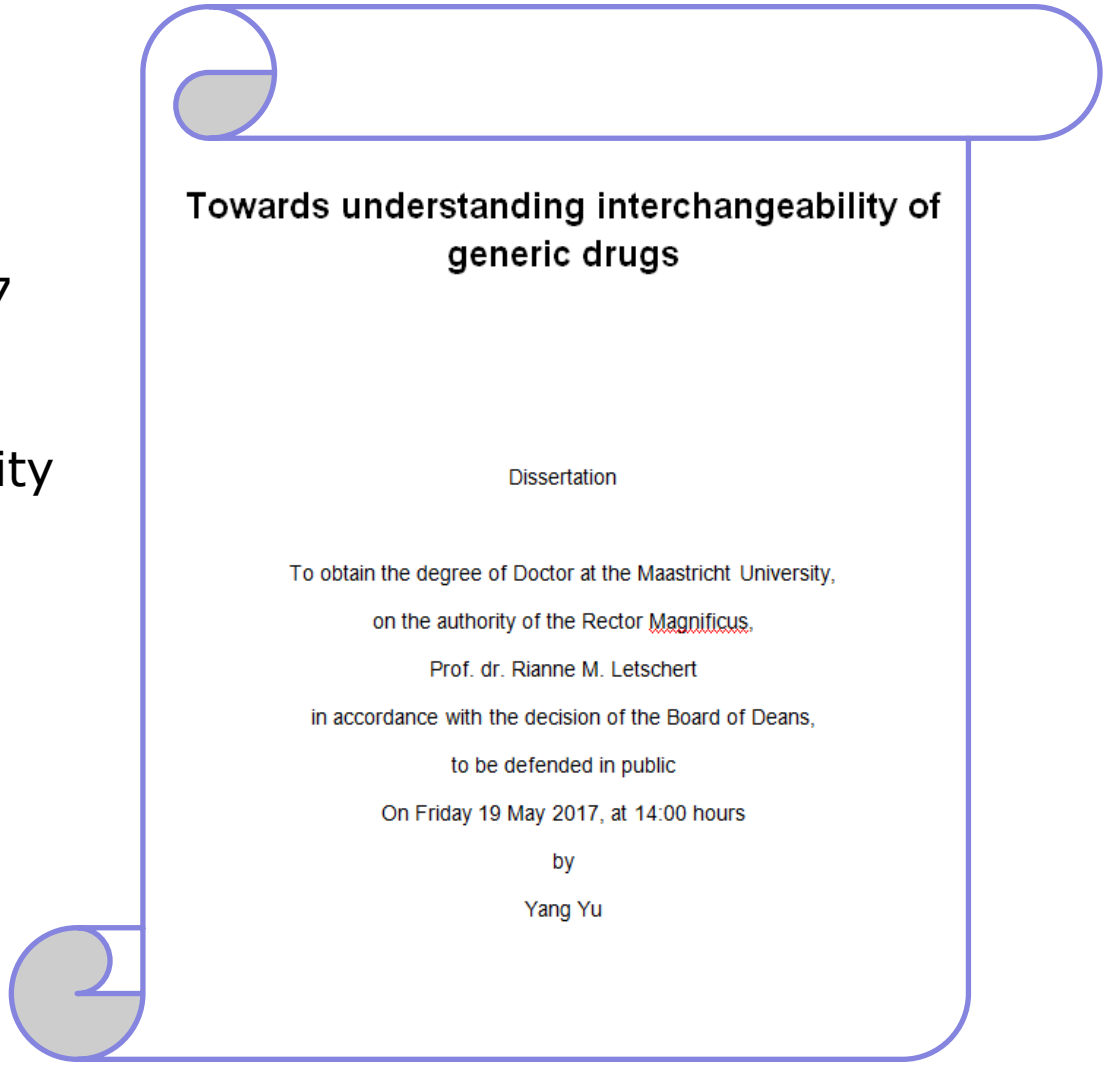
- Current regulation for registration of a generic drug in Europe is reasonably strict to ensure the bioequivalence of the generic drug with the brand-name drug.

- However, there are still rooms to improve the regulations, for example to update the bioequivalence acceptance criterion of 80-125%.

PhD defense

Time: Friday 19 May 2017 (14:00)

Place: Maastricht University



Towards understanding interchangeability of generic drugs

Dissertation

To obtain the degree of Doctor at the Maastricht University,

on the authority of the Rector Magnificus,

Prof. dr. Rianne M. Letschert

in accordance with the decision of the Board of Deans,

to be defended in public

On Friday 19 May 2017, at 14:00 hours

by

Yang Yu

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Back up slides – guideline revision

Box 1. EMA guidelines and PKWP Questions & Answers documents for bioequivalence studies for immediate-release oral dosage form medicines investigated.

Release date	BE guidelines and Q&A documents*	Index†
July 26, 2001	**Note for Guidance on the Investigation of Bioavailability and Bioequivalence** *(Doc Ref: CPMP/EWP/QWP/1401/98, not available online)*	NfG 2001
July 27, 2006	**Questions & Answers on the bioavailability and bioequivalence guideline** *(Doc Ref: EMEA/CHMP/EWP/40326/2006, not available online)*	Q&A 2006
January 22, 2009	**Question & Answers: Positions on Specific Questions Addressed to the EWP Therapeutic Subgroup on Pharmacokinetics** *(Doc Ref: EMEA/618604/2008, not available online)*	Q&A 2009
January 20, 2010	**Guideline on the Investigation of Bioequivalence** *(Doc Ref: CPMP/EMP/QWP/1401/98 Rev. 1/Corr**, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf)*	G BE 2010
July 22, 2010	**Question & Answers: Positions on Specific Questions Addressed to the EWP Therapeutic Subgroup on Pharmacokinetics** *(Doc Ref: EMEA/618604/2008 Rev. 2, not available online)*	Q&A 2010

Table 1. Specific requirements in the EMA guidelines for demonstration of bioequivalence for the generic drugs of selected medicines.

Guidance Medicines	NfG 2001	Q&A 2006	Q&A 2009	G BE 2010*	Q&A 2010*
Ciclosporine (micro-emulsion)	1. Single dose; 2. Fasting; 3. Narrowed acceptance range for AUC and C_{max} as an option.	3. Narrowed acceptance range for AUC and C_{max} as an option		1. Single dose; 2. Fasting & fed; 3. Narrowed acceptance range for AUC and C_{max} (90-111%)	
Paroxetine	1. Single dose or multiple-dose		1. Single dose & multiple-dose	1. Single dose	
Omeprazole (ER)	1. Single dose(fasting & fed) & multiple-dose		1. Single dose (fasting & fed) & multiple-dose	1. Single dose (fasting & fed)	1. Single dose (fasting & fed)
Clopidogrel	1. Parent compound or metabolite;				1. Parent compound
Simvastatin	1. Parent compound (Cmax and/or AUC) & metabolites (AUC)		1. Parent compound & metabolites	1. Parent compound	
Losartan	1. Parent compound (Cmax and/or AUC) & metabolites (AUC)			1. Parent compound	1. Parent compound
Levothyroxine				1. Baseline correction for drug exposure levels	

Figure 1. Illustration of evaluation outcome of registered generic drugs for test medicines (n=92).