REVIEW

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Evaluation of the pharmacokinetic parameters of standard oral antibiotics in a bioequivalence study of generic products

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Pharmacokinetic parameters were summarized in clinical bioequivalence studies in Japan to confirm the validity for the use of parameters obtained from the clinical studies. Pharmacokinetic parameters, including maximum plasma/serum concentrations (C_{max}), area under the plasma/serum drug concentration-time curve (AUC), time to achieve C_{max} (T_{max}), and half life ($t_{1/2}$), of the standard products (original drugs) after oral administration of antimicrobials, including respiratory quinolones, cephalosporins, macrolides, and penicillin-based antibiotics were investigated by use of interview forms and/or package inserts from the generic products and the relationship among the pharmacokinetic parameters such as C_{max}, AUC, T_{max}, and $t_{1/2}$ were estimated. In all the studies, the standard and generic products were administrated orally to healthy fasting subjects. Although there was more than a 1.5-fold difference in the C_{max} and $AUC_{0\text{-}24\ h}$, but not in the T_{max} and $t_{1/2}$ values for levofloxacin tablets and cefacrol tablets, these parameters for other antibiotics were similar in various studies. The obtained results suggested that the parameters obtained from recent bioequivalence studies would be useful in identifying pharmacokinetic behavior of the original drugs, especially early time release; however, the pharmacokinetic results obtained from the recently conducted bioequivalence studies may be superior to those obtained from studies conducted in the past.

1. Introduction

The pharmacokinetic parameters obtained during phase I clinical studies on healthy subjects are important for the simulation of efficacy based on pharmacokinetics/pharmacodynamics (PK/PD) and drug-drug interactions that lead to an improvement in the outcome by proper use of pharmaceutical products in patients and novel drug development. In addition, the pharmacokinetic parameters in healthy fasting subjects are important to investigate (1) the effect of the meal and (2) compare elderly subjects, patients with infectious diseases, and patients with renal and/or hepatic disorders. However, sometimes no phase I clinical study data are available for older products.

Recently, many generic products have become available on the market at off-patent of original products in the world including Japan because of the reduction in healthcare cost (Yomota 2012). Recommendations for the performance of comparative dissolution studies (for oral products) and bioequivalence studies between the generic and reference products are outlined in the "Guideline for Bioequivalence Studies of Generic Products" (PMDA web, 2012; NIHS web, 2012) to be launched in Japan. In many bioequivalence studies of generic products, the original drugs (innovator products) are used as reference products.

In the recent Japanese guideline, products are considered to be bioequivalent if the 90% confidence interval of the difference in the average values of the logarithmic parameters to be assessed between the test and reference products is within the acceptable range of log 0.80–1.25 (PMDA web, 2012; NIHS web, 2012). These parameters include the area under the blood (plasma, serum) concentration-time curve (AUC) and the maximum blood (plasma, serum) concentration (C_{max}) (PMDA web; NIHS web). Because the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) is accepting the study results, it can be assumed that the clinical studies including the dosing and sampling time, assay results of drug concentrations, and analytical methods for the pharmacokinetic analysis are scientifically validated. In addition, most of the bioequivalence studies were conducted in healthy subjects. The simulation of efficacy, pharmacokinetics, and drug-drug interactions based on PK/PD has been previously conducted using the results of clinical pharmacokinetic studies. However, there are often few reports on the pharmacokinetic parameters of the original drugs, especially for early time-release products. In addition, the assay methods for drug concentrations in plasma, serum, or blood have dramatically improved. Therefore, it would be useful to review the pharmacokinetic parameters of original products from numerous bioequivalence studies. However, few reports have focused on the approach that involves estimating pharmacokinetic profiles using results obtained from previous bioequivalence studies.

This review aimed to evaluate the significance of determining the pharmacokinetic parameters of original products from previous bioequivalence studies. The present review investigated nine generic products that are widely used in Japan, especially antibiotics such as respiratory quinolones, cephalosporins, macrolides, and penicillin-based antibiotics. Carbapenem antibiotics were not investigated, since most of the products, except faropenem sodium hydrate, launched by only one pharmaceutical company Farom®, were not orally administered but were used as injections.

2. Data collection and analytical methods

The timing of the appearance of original products and generic products in Japan, which were investigated in the present review, is listed in Table 1. The pharmacokinetic parameters of the corresponding original drugs were investigated using interview forms or package inserts or both of the generic products. The original drugs include three respiratory quinolones, three cephalosporins, two macrolides, and a penicillin-based antibiotic. In addition, the results obtained for the antibiotics were compared with those for drugs other than antibiotics such as etizolam, a psychotropic drug mainly eliminated by metabolism in the liver (generic products launched in the market after 1992) and tacrolimus, an immunosuppressant mainly eliminated by metabolism in the liver (generic products launched after December 2013).

Table 1: Investigated original and generic antibiotic products in Japan

Year	Original product launched	Generic products started launch	Standards for bioequivalence study
1960	Erythromycin stearate (Erythrocin®, 200 mg tablets)		
1975	Amoxicillin (Sawacillin®)		
1979	Amoxicillin (Pasetocin®)		
1980			"Division-Notification 718 of the Pharmaceutical and Food Safety Bureau, dated May 30, 1980"
1981		Erythromycin stearate	
1982	Cefaclor (Kefral®)		
1984	Etizolam (Depas®)		
1985	Ofloxacin (Tarivid®)		
1988	Ciprofloxacin (Ciproxan®)		
1990		Cefaclor	
1991	Cefdinir (Cefzon®) Clarithromycin (Clarith®)		
1992		Etizolam	
1993	Tacrolimus (Prograf®) Levofloxacin (Kravit®)		
1994	Voglibose (Basen®)		
1997	Cefcapene pivoxil hydrochloride hydrate (Flomox®)		
2001			"Division-Notification 786 of the Pharmaceutical and Food Safety Bureau, dated May 31, 2001"
2002		Ciprofloxacin	
2004	Voglibose (Basen® OD tablets)		
2006		Ofloxacin Clarithromycin	
2007		Voglibose (Tablets and OD tablets)	
2008	Tacrolimus (Graceptor®, once a day formulation)	Cefdinir	
2009	Levofloxacin (Cravit®, 250, 500 mg tablets)	Levofloxacin (100 mg tablets) Cefcapene pivoxil hydrochloride	
2011		Amoxicillin	
2012			"Division-Notification 0229-10 of the Pharmaceutical and Food Safety Bureau, dated February 29, 2012"
2013		Tacrolimus	

Names in parentheses are brand names. OD: orally disintegrating.

The interview forms and package inserts of the generic products were obtained from the PMDA website (PMDA web, 2012; NIHS web, 2012). The pharmacokinetic parameters, including C_{max}, AUC, time to achieve C_{max} (T_{max}), and half-life ($t_{1/2}$) values of the 12 reference drugs (original drugs) were determined in the bioequivalence study of generic products. The relationship between the parameters collected including the AUC, C_{max}, and $t_{1/2}$ were determined. The sampling time of the third last time point and the final point were investigated, because more than three time points (minimal) are usually required for an exact estimation of the $t_{1/2}$ during the elimination phase when estimated by non-parametric analysis as recommended by the guidelines of the clinical pharmacokinetic studies in pharmaceutics in Japan (Ministry of Health, Labour, and Welfare, 2001), i.e., the sampling time of the third last time point and the final point are important for $t_{1/2}$ estimation.

Additional pharmacokinetic parameters reported in the literature were investigated using MEDLINE (via PubMed). However, detailed data obtained in the bioequivalence studies for generic products are not always published in papers, but in reports generated by the company. Orally disintegrating (OD) products were excluded from this investigation because pharmaceutical formulations rather than the drug disposition have a larger effect on the pharmacokinetic parameters.

In all bioequivalence studies conducted, the generic and reference drugs were administered to healthy fasting subjects. The plasma/serum concentrations were measured; however, the blood concentration of tacrolimus was measured.

In general, bioequivalence studies of generic products launched before 2000, between 2001 and 2012, and after 2013 were conducted according to the standards for the bioequivalence study in the "Division-Notification 718 of the Pharmaceutical and Food Safety Bureau, dated May 30, 1980" (PMDA web, 2012), "Division-Notification 786 of the Pharmaceutical and Food Safety Bureau, dated May 31, 2001" (PMDA web, 2012), and "Division-Notification 0229-10 of the Pharmaceutical and Food Safety Bureau, dated February 29, 2012" (NIHS web, 2012; PMDA web, 2012;), respectively. Thus, the effects of the launching time of generic products on the variability of pharmacokinetic parameters among the bioequivalence studies were also discussed.

3. Respiratory quinolones

Although the levofloxacin 100-mg tablets were launched by the pharmaceutical company that produced the original product, the company discontinued them and released the 500-mg tablet (Cravit®) in 2012. This new tablet strength was released because the administration of levofloxacin at a dose of 100 mg thrice daily or 250 mg once or twice daily, did not achieve the target C_{max}/minimum inhibitory concentration (MIC) values against particular strains with a 1–2 μg/mL MIC (Kanda et al. 2009). This led to the

Table 2: Pharmacokinetic studies after a single oral administration of a film-coated tablet of levofloxacin hydrate (standard product, 100 mg tablet) to healthy, fasting, male volunteers

Studwy No.	No. of products	No. of subjects	Total points*	No. of sampling points* before		Sampling time of third last (h)	C_{max} (µg/mL)			$AUC_{0-12\,h}$ (µg · h/mL)			T_{max} (h)	$t_{1/2}$ (h)
				2 h	4 h		Mean	S.D.	C.V. (%)	Mean	S.D.	C.V. (%)		
A	4	10	9	4	6	6	0.988	0.173	17.5	6.808	0.743	10.9	1.0	6.39
B	1	20	9	4	6	8	1.10048	0.26256	23.9	7.61413	1.27299	16.7	0.89	6.4
C	1	20	10	6	7	6	1.15	0.31	27.0	7.8	0.94	12.1	1.1	6.6
D	4	22	9	4	6	6	1.07309	0.16752	15.6	7.898343	1.134923	14.4	1.0	7.018
E	2	20	10	5	6	8	1.13379	0.17353	15.3	8.04498	0.80968	10.1	1.13	7.71
F	1	20	9	5	6	6	1.102	0.2414	21.9	8.1702	1.2992	15.9	0.91	7.58
G	4	16	9	4	5	8	1.264	0.2527	20.0	8.5921	1.3574	15.8	1.0	6.3
H	2	10	9	5	6	6	1.4146	0.1203	8.5	8.2198	0.8529	10.4	0.87	6.18
I	1	18	9	5	6	6	1.3247	0.3273	24.7	8.961	1.346	15.0	1.083	7.511
J	3	20	8	4	5	6	1.39	0.36	25.9	8.67	1.21	14.0	0.9	7.3
K	3	12	11	5	7	8	1.400	0.420	30.0	9.093	1.744	19.18	1.24	7.5
L	2	22	11	6	8	6	1.61	0.44	27.3	10.42	1.55	14.9	1.0	6.7
M	2	14	9	4	6	6	1.55	0.35	22.6	10.82	2.52	23.3	0.9	5.9
Mean	-	17.2	9.4	4.7	6.2	6.6	1.27	0.28	21.6	8.55	1.29	14.8	1.0	6.9
Median	-	20	9	5	6	6	1.264	0.26	22.6	8.22	1.27	14.9	1.0	6.7
Max	-	22	11	6	8	8	1.61	0.44	30.0	10.82	2.52	23.3	1.24	7.71
Min	-	10	8	4	5	6	0.988	0.12	8.5	6.808	0.743	10.1	0.87	5.9

*Sampling point before oral dose is not included.
Coefficient of variation (C.V.) was calculated as reported, standard deviation (S.D.) divided by mean.

Table 3: Pharmacokinetic studies after a single oral administration of ciprofloxacin (standard product, 100 or 200 mg tablet) to healthy, fasting, male volunteers

Tablet (mg)	Study No.	No. of products	No. of subjects	Total points[1]	No. of sampling points* before 2 h	Sampling time of third last (h)	C_{max} (µg/mL)			$AUC_{0-24\,h}$ (µg · h/mL)[2]			T_{max} (h)	$t_{1/2}$ (h)
							Mean	S.D.[3]	C.V. (%)[4]	Mean	S.D.[3]	C.V. (%)[4]		
100	100-A	5	20	9	5	6	0.597	0.148	24.8	1.987 ($AUC_{0-10\,h}$)	0.414	20.8	1.11	2.79
200	200-A*	3	18	9	5	7	1.2296	0.2585	21.0	5.0929	0.9920	19.5	0.86	5.08
	200-B	1	10	9	5	8	1.321	0.249	18.8	5.286	0.681	12.9	0.93	5.14
	200-C	1	10	10	4	8	1.34	0.02 (SE)	–	6.11	0.20 (SE)	–	1.1	3.7
	200-D*	1	24	10	5	6	1.39	0.32	23.0	4.95 ($AUC_{0-12\,h}$)	1.02	20.6	1.0	4.3
	200-E*	1	28	10	5	8	1.4299	0.3181	22.2	5.9576	1.2637	21.2	1.018	3.8993
	Mean	–	18.0	9.6	4.8	7.4	1.34	0.29	21.3	5.61	0.99	18.5	1.0	4.4
	Median	–	18.0	10.0	5.0	8.0	1.34	0.29	21.6	5.62	1.01	20.0	1.0	4.3
	Max	–	28	10	5	8	1.4299	0.32	23.0	6.11	1.2637	21.2	1.1	5.14
	Min	–	10	9	4	6	1.2296	0.2490	18.8	5.0929	0.6810	12.9	0.86	3.7
100	Ciproxacin®-PI**	1	8	6	3	4	0.56	0.06 (SE)	–	2.08	0.17 (SE)	–	1.18	3.02
200	Ciproxacin®-PI**	1	21	9	4	8	1.21	0.08 (SE)	–	4.59	0.18 (SE)	–	1.08	3.68

Plasma concentrations were measured by HPLC* or bioassay**. BE: bioequivalence study, Ciproxan®-P1: phase I study of original product (Ciproxan®).
1) Sampling point before oral dose is not included. 2) $AUC_{0-24\,h}$ unless otherwise noted in parentheses.
3) S.D.: standard deviation unless otherwise noted in parentheses as standard error (S.E.).
4) Coefficient of variation (C.V.) was calculated as reported S.D. divided by mean.

development of resistant strains with $^1/_8$–$^1/_2$ of the antimicrobial sensitivity against levofloxacin (Kanda et al. 2009). Since then, 30 companies conducted 13 types of bioequivalence studies for levofloxacin 100-mg tablets (Table 2). The generic products were launched after 2012, and therefore, the bioequivalence studies were conducted according to the standards for bioequivalence studies in the "Division-Notification 786 of the Pharmaceutical and Food Safety Bureau, dated May 31, 2001" (PMDA web, 2012). In all the studies, 10–22 healthy, fasting male subjects received a single dose of a levofloxacin 100-mg tablet, and a crossover design with two phases was conducted. The sampling time point until 2 h after dosing, which is close to the T_{max} (approximately 1 h), was 4–6 and the third and last sampling time point, which is important for the $t_{1/2}$ estimation, was 6–8 h. Therefore, the mean T_{max} and $t_{1/2}$ were 0.87–1.24 and 5.9–7.71 h, respectively, indicating that there were no marked differences between the bioequivalence studies. In contrast, 1.6-fold difference in the mean C_{max} and $AUC_{0\text{-}24\ h}$ between the studies was observed, although the coefficient of variation for the mean C_{max} and $AUC_{0\text{-}24\ h}$ within each study was less than 30%. The AUC is usually affected by C_{max} or $t_{1/2}$ or both. Therefore, the relationship between the $AUC_{0\text{-}24\ h}$ and these parameters was investigated (Fig. 1). The results showed a good correlation between the $AUC_{0\text{-}24\ h}$ and C_{max} but not the $t_{1/2}$. Levofloxacin is predominantly eliminated by renal excretion, and its $t_{1/2}$ is prolonged in patients with renal dysfunction (Cravit Tablets packing insert, 2013). Because all the evaluated bioequivalence studies were conducted in healthy male subjects, the renal function appears to play a minor role in the pharmacokinetic parameters. Therefore, $t_{1/2}$ was almost constant between the bioequivalence studies and independent of the $AUC_{0\text{-}24h}$ (Fig. 1). For ciprofloxacin 100-mg and 200-mg tablets (Table 3), seven companies conducted one type (for 100-mg tablets) and five types (for 200-mg tablets) of bioequivalence studies. For ofloxacin 100-mg tablets (Table 4), seven companies conducted seven types of bioequivalence studies. These generic products were launched in 2002 and 2006, respectively, and therefore, the bioequivalence studies were conducted according to the standards for bioequivalence studies in the "Division-Notification 786 of the Pharmaceutical and Food Safety Bureau, dated May 31, 2001" (PMDA web, 2012). In all the studies, 10–24 healthy, fasting male subjects received a single dose of a ciprofloxacin 100-mg or 200-mg tablets or ofloxacin 100-mg tablets, and a crossover design with two phases was conducted. The sampling time point until 2 h after dosing, which is close to the T_{max} (approximately 1 h), was 4–5 h and 3–4 h, and the third and last sampling time point was 6–8 h. Thus, the mean T_{max} and $t_{1/2}$ for ciprofloxacin were 0.86–1.1 and 3.7–5.14 h, respectively, while the same for ofloxacin were 1.042–2 h and 2.7–7.0 h, respectively, thereby indicating that there were no marked differences between the bioequivalence studies, except for $t_{1/2}$ obtained in a study on ofloxacin (study no. BE-G), for which the last sampling time was 12 h, although that in other studies was 24 h. C_{max} and $AUC_{0\text{-}24\ h}$ for ciprofloxacin and ofloxacin were similar between

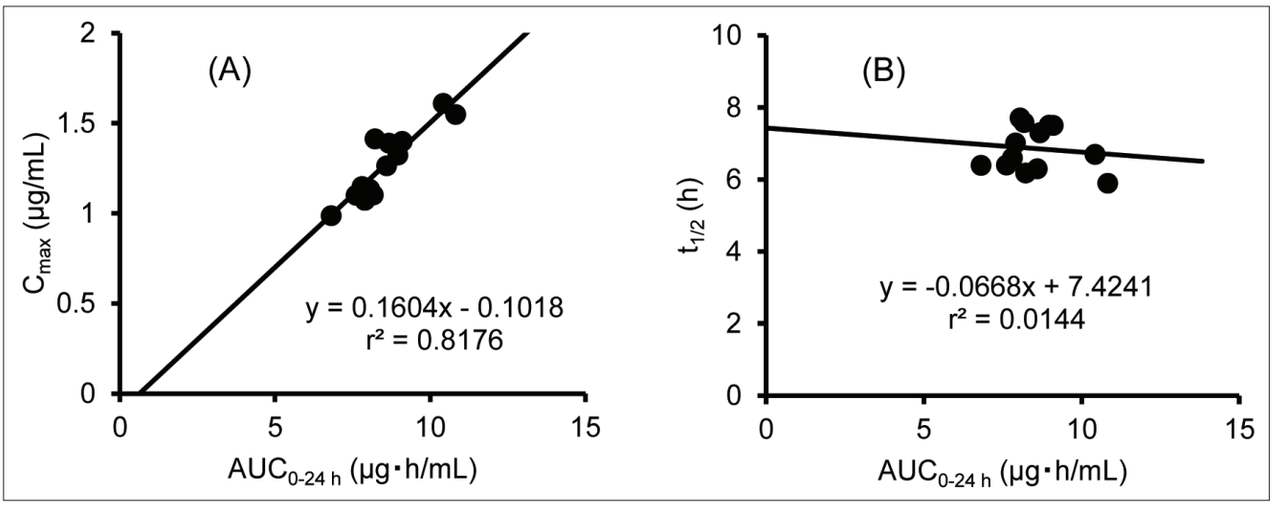

Fig. 1: Relationship between $AUC_{0\text{-}24\ h}$ and C_{max} (A) or $t_{1/2}$ (B) using the standard product, levofloxacin, in a bioequivalence study.

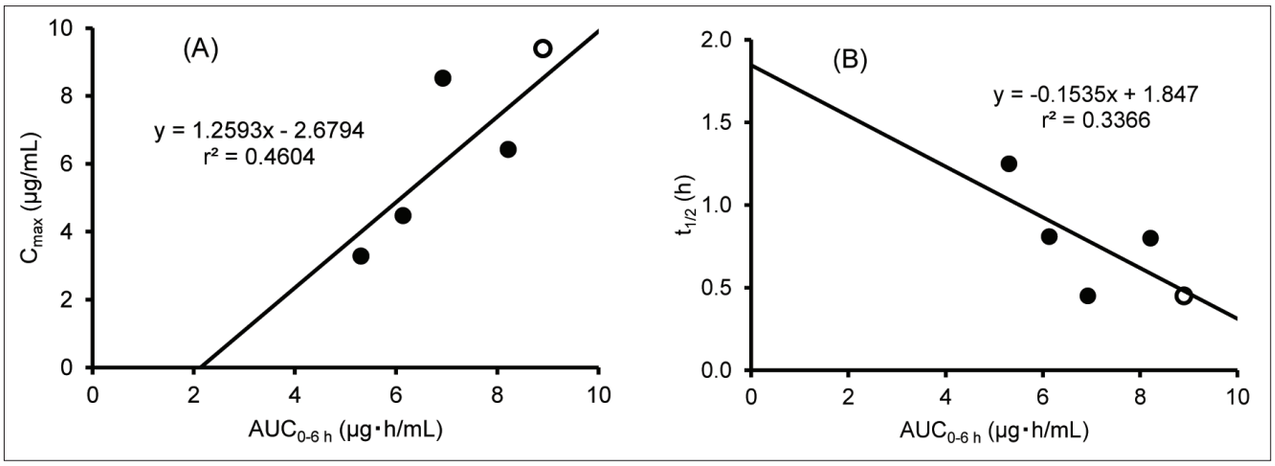

Fig. 2: Relationship between $AUC_{0\text{-}6\ h}$ and C_{max} (A) or $t_{1/2}$ (B) using the standard product, cefaclor, in a bioequivalence study.
Open circle: phase I study for the original product (Kefral®).

Table 4: Pharmacokinetic studies after a single oral administration of ofloxacin (standard product, 100 mg tablet) to healthy, fasting, male volunteers

Study No.	No. of products	No. of subjects	Total points[1]	No. of sampling points* before 2 h	Sampling time of third last (h)	C_{max} (µg/mL) Mean	S.D.[3]	C.V. (%)[4]	$AUC_{0\text{-}24\ h}$ (µg · h/mL)[2] Mean	S.D.[3]	C.V. (%)[4]	T_{max} (h)	$t_{1/2}$ (h)
BE-A	1	10	10	3	8	0.67	0.16	23.9	4.37	1.73	39.6	1.1	6.9
BE-B	1	10	10	4	8	1.117	0.056 (SE)	–	7.244	0.370 (SE)	–	1.3	5.2
BE-C*	1	24	9	4	6	1.124	0.230	20.5	7.881	0.941	11.9	1.042	6.592
BE-D*	1	14	9	4	6	1.17	0.20	17.1	7.64	1.30	17.0	1.6	7.0
BE-E	1	20	9	3	8	1.1760	0.2526	21.5	7.5624	1.3206	17.5	1.2	5.8
BE-F*	1	14	9	4	7	1.61	0.30	18.6	8.99	0.98	10.9	1.11	5.46
BE-G	1	12	9	4	6	0.97	0.17	17.5	4.90 ($AUC_{0\text{-}12\ h}$)	0.67	13.7	2.00	2.71
Mean	–	14.9	9.3	3.7	7.0	1.1	0.2	19.8	7.3	1.2	18.4	1.3	5.7
Median	–	14.0	9.0	4.0	7.0	1.1	0.2	19.5	7.6	1.1	15.3	1.2	5.8
Max	–	24	10	4	8	1.61	0.3	23.88	8.99	1.73	39.6	2	7.0
Min	–	10	9	3	6	0.67	0.16	17.09	4.37	0.67	10.9	1.042	2.7
Tarivit®-PI*	1	5	6	2	4	1.00	–	–	6.02	1.05	17.4	2	3.59

* Plasma concentrations were measured by HPLC. BE: bioequivalence study, Travit®-P1: phase I study of original product (Travit®).
1) Sampling point before oral dose is not included.
2) $AUC_{0\text{-}24\ h}$ unless otherwise noted in parentheses.
3) S.D.: standard deviation unless otherwise noted in parentheses as standard error (S.E.).
4) Coefficient of variation (C.V.) was calculated as reported S.D. divided by mean.

Table 5: Pharmacokinetic studies after a single oral administration of cefaclor (standard product, 250 mg capsule) to healthy, fasting, male volunteers

Study No.	No. of products	No. of subjects	Total points[1]	No. of sampling points* before 1 h	Sampling time of third last (h)	C_{max} (µg/mL) Mean	S.D.[3]	C.V. (%)[4]	$AUC_{0\text{-}6\ h}$ (µg · h/mL)[2] Mean	S.D.[3]	C.V. (%)[4]	T_{max} (h)	$t_{1/2}$ (h)
BE-A	1	14	7	3	2	3.289	0.442	13.4	5.300	0.752	14.2	0.96	1.25
BE-B	1	14	9	4	3	4.48	1.85	41.3	6.13	1.81	29.5	1.07	0.81
BE-C	1	12	8	4	2	8.53	2.47	29.0	6.92	1.30	18.8	0.69	0.45
BE-D*	1	12	7	3	2	6.43	0.86	13.4	8.21	1.71	20.8	0.9	0.8
BE-E*	1	14	7	3	2	6.69	1.13	16.9	6.03 ($AUC_{0\text{-}3\ h}$)	0.91	15.1	0.62	0.58
BE-F	2	10	12	4	6	8.2	0.4 (SE)	–	9.6 ($AUC_{0\text{-}24\ h}$)	0.4 (SE)	–	0.7	1.2
BE-G	1	10	12	3	6	8.38	0.54 (SE)	–	9.32 ($AUC_{0\text{-}24\ h}$)	0.25 (SE)	–	0.73	–
Mean	–	12.3	8.9	3.4	3.3	6.6	1.4	22.8	6.6	1.3	19.7	0.81	0.85
Median	–	12.0	8.0	3.0	2.0	6.7	1.1	16.9	6.5	1.3	18.8	0.73	0.81
Max	–	14	12	4	6	8.53	2.47	41.3	8.21	1.81	29.5	1.07	1.25
Min	–	10	7	3	2	3.289	0.442	13.4	5.3	0.752	14.2	0.62	0.45
Kefral®-PI*	1	14	7	2	2	9.4	–	–	8.9	–	–	0.72	0.45

Plasma concentrations were measured by bioassay*. BE: bioequivalence study, Kefral®-P1: phase I study of original product (Kefral®).
1) Sampling point before oral dose is not included.
2) $AUC_{0\text{-}24\ h}$ unless otherwise noted in parentheses.
3) S.D.: standard deviation unless otherwise noted in parentheses as standard error (S.E.).
4) Coefficient of variation (C.V.) was calculated as reported S.D. divided by mean.

the studies, although the parameters for ofloxacin obtained by a study (study no. BE-A) were approximately 60% of other reported values. In addition, C_{max}, $AUC_{0\text{-}24\ h}$, $T_{max,}$ and $t_{1/2}$ of these products obtained in bioequivalence studies were similar to those obtained in other phase I studies with original drugs (Tarivit®).

4. Cephalosporins

For cefaclor 250 mg-capsule (Table 5), eight companies conducted seven types of bioequivalence studies. The generic products were launched in 1990, and therefore, the bioequivalence studies were conducted according to the standards for bioequivalence studies in the "Division-Notification 718 of the Pharmaceutical and Food Safety Bureau, dated May 30, 1980" (PMDA web, 2012). The sampling time point until 1 h after dosing, which is close to the T_{max} (approximately 1 h), was 3–4 h. The third and last sampling time points were 2–6 h and 3–24 h, respectively. Although the mean T_{max} was 0.62–1.07 h, $t_{1/2}$ was 0.45–1.25 h and was dependent on the last sampling time. In addition, a 2.6- and 1.5-fold difference in the mean C_{max} and $AUC_{0\text{-}6\ h}$, respectively, between the studies was observed, although the coefficient of variation for the mean C_{max} and $AUC_{0\text{-}6\ h}$ within each study was less than 30%. The relationship between the $AUC_{0\text{-}6\ h}$ and these parameters (Fig. 2) indicated a good correlation between the $AUC_{0\text{-}6\ h}$ and C_{max} but not the $t_{1/2}$. The estimated $AUC_{0\text{-}6\ h}$ and C_{max} in the phase I study for the original product (Kefral®) were larger than those in all bioequivalent studies.

For cefdinil 50- or 100 mg-tablet (Table 6), five or ten companies conducted two or four types of bioequivalence studies, respectively. The generic products were launched in 2008, and therefore, the bioequivalence studies were conducted according to the standards for bioequivalence studies in the "Division-Notification 786 of the Pharmaceutical and Food Safety Bureau, dated May 31, 2001" (PMDA web, 2012). No marked differences in the mean C_{max} and $AUC_{0\text{-}24\ h,}$ T_{max}, and $t_{1/2}$ values were observed between bioequivalence studies. In addition, the parameters estimated in the phase I study for the original product (Cefzon®) were similar to those in all bioequivalent studies.

For cefcapene pivoxil hydrochloride 75- or 100 mg-tablet (Table 7), five or eight companies conducted two types of bioequivalence studies. The generic products were launched in 2009, and therefore, the bioequivalence studies were conducted according to the standards for bioequivalence studies in the "Division-Notification 786 of the Pharmaceutical and Food Safety Bureau, dated May 31, 2001" (PMDA web, 2012). Similar mean C_{max}, $AUC_{0\text{-}24\ h,}$ T_{max}, and $t_{1/2}$ were demonstrated between bioequivalence studies because the phase I study for original product (Flomox®) was conducted using healthy male volunteers administered Flomox® at 30 min after meals. In addition, the plasma concentrations in bioequivalence studies were measured by high-performance liquid chromatography (HPLC) or LC/mass spectrometry (LC/MS), which is a relatively new technology and has higher specificity than the bioassay, which was used for the Flomox® phase I study. Therefore, the parameters obtained in the bioequivalence studies are important to determine the basic and reliable pharmacokinetic parameters.

Thus, it seems that pharmacokinetic parameters obtained for the newer generic products by the bioequivalence studies conducted under the newer guidelines are more acute than those of older products are, although the sample size was small.

5. Macrolides

For clarithromycin 200 mg-tablets (Table 8), 23 companies conducted 14 types of bioequivalence studies. The generic products were launched after 2006, and therefore, the bioequivalence studies were conducted according to the standards for bioequivalence studies in the "Division-Notification 786 of the Pharmaceutical and Food Safety Bureau, dated May 31, 2001" (PMDA web, 2012). Clarithromycin is predominantly metabolized by cytochrome P450 (CYP) 3A4 to 14-hydroxylclarithromicin, an active metabolite (Rodrigues et al. 1997). The plasma/serum concentrations of both clarithromycin and 14-hydroxylclarithromicin were measured using the bioassay (9-11 Clarith interview form, 2015; Suwa et al. 1988a, b). The concentrations measured by HPLC or LC/MS/MS in the bioequivalence studies are more accurate than those obtained using the bioassay for the original product. However, the demonstrated data in the packing insert of the original product (Clarith®) was based on the serum concentrations determined by the bioassay, although the data in the interview form were based on information obtained by both the bioassay and using HPLC. The estimated C_{max} and AUC values measured by HPLC were 50% of those obtained using a bioassay.

For erythromycin stearate 200 mg-tablet (Table 9), only one company conducted one type of bioequivalence study. The generic product was launched in 1981, and therefore, the bioequivalence studies were conducted according to the standards for bioequivalence studies in the "Division-Notification 718 of the Pharmaceutical and Food Safety Bureau, dated May 30, 1980" (PMDA web, 2012). Although no detailed information, except for the mean C_{max}, AUC, T_{max}, and $t_{1/2}$ values were stated on the package insert and on the interview form of the original product Erithrocin®, pharmacokinetic parameters of the original product of erythromycin stearate were estimated in the bioequivalent study using the generic product. Because the original azithromycin product was launched in 2000, and reliable pharmacokinetic parameters from phase I studies, including a dose-proportionality study and repeated dose study, were demonstrated, bioequivalence studies of the generic products were not investigated.

6. Penicillin-based antibiotics

Amoxicillin was the most frequently used oral product, although other penicillin-based antibiotics, including ampicillin and piperacillin, were products for injection. Therefore, only amoxicillin was investigated for this review. For amoxicillin 125 mg-tablet (Table 10), four companies conducted two types of bioequivalence studies. The generic products were launched in 2011, and therefore, the bioequivalence studies were conducted according to the standards for bioequivalence studies in the "Division-Notification 786 of the Pharmaceutical and Food Safety Bureau, dated May 31, 2001" (PMDA web, 2012). The mean C_{max}, $AUC_{0\text{-}24\ h,}$ T_{max}, and $t_{1/2}$ values differed slightly between the two studies. No bioequivalence studies were conducted for the amoxicillin 250 mg-tablet.

7. Comparison with drugs other than antibiotics

Similar to products other than antibiotics, we reviewed the results obtained in bioequivalence studies on etizolam and tacrolimus, which were launched after 1992 and 2013, respectively. Alternatively, bioequivalence studies for voglibose were not conducted because the plasma concentrations of voglibose were extremely low in the phase I study of the original product owing to poor absorption. The original etizolam product (Depas®) was launched in Japan in 1984. The dosage and administration recommendations for the drug before or after meals are not described on the package insert (Depas Tablets packing insert, 2012). For etizolam 0.5-mg tablets (Table 11), 20 companies conducted 14 types of bioequivalence studies. The generic products were launched after 1992, and therefore, the bioequivalence studies were conducted according to the standards for bioequivalence study "Division-Notification 718 of the Pharmaceutical and Food Safety Bureau, dated May 30, 1980" (PMDA web, 2012). The number of tablets administered to subjects differed between the bioequivalence studies and included one, two, or four tablets (one study used two different tablet numbers). In addition, the last time point for plasma sampling was different between the studies and ranged from 13–48 h. However, the sampling time point until 2 h after dosing, which is close to the T_{max} (1–2 h), was 2–5, suggesting that there was sufficient to estimate the T_{max} and C_{max}. The sampling time of the third last time point was later than 4 h. Therefore, the mean T_{max} and $t_{1/2}$ were 0.79–3.5 and 4.39–8.56 h, respectively. The relationships between C_{max}, $AUC_{0\text{-}24h}$, and the dose (tablet number) are shown in Fig. 2. The C_{max} and $AUC_{0\text{-}24\ h}$ of the two studies following dosing with two tablets (studies 1-A and 1-D), were far from the lines. Approximately, a five-fold difference in the C_{max} and $AUC_{0\text{-}24h}$ was observed between studies 1-A and 1-D.

Table 6: Pharmacokinetic studies after a single oral administration of cefdinir (standard product, 50 or 100 mg tablet) to healthy, fasting, male volunteers

Tablet (mg)	Study No.	No. of products	No. of subjects	Total points[1)]	No. of sampling points* before 4 h	Sampling time of third last (h)	C_{max} (µg/mL)			$AUC_{0\text{-}24\,h}$ (µg · h/mL)[2)]			T_{max} (h)	$t_{1/2}$ (h)
							Mean	S.D.[3)]	C.V. (%)[4)]	Mean	S.D.[3)]	C.V. (%)[4)]		
50	50-A*	3	19	9	4	8	0.55	0.19	34.5	2.97	0.96	32.3	3.9	1.63
	50-B	2	16	9	4	8	0.52	0.14	26.9	2.48 ($AUC_{0\text{-}12\,h}$)	0.64	25.8	3.7	1.5
100	100-A*	3	10	9	4	8	0.81	0.20	24.7	4.51	1.16	25.7	4.5	2.99
	100-B	2	15	9	4	8	0.90	0.27	30.0	4.30 ($AUC_{0\text{-}12\,h}$)	1.04	24.2	3.8	1.5
	100-C*	4	20	8	4	6	0.9764	0.1112	11.4	4.6643 ($AUC_{0\text{-}10\,h}$)	0.7763	16.6	3.9	2.0
	100-D	1	12	10	4	10	1.0983	0.2896	26.4	5.6423	1.7775	31.5	4.3	1.4880
	Mean	–	14.3	9.0	4.0	8.0	0.95	0.22	23.1	5.08	1.19	24.5	4.13	1.99
	Median	–	13.5	9.0	4.0	8.0	0.94	0.24	25.5	5.08	1.10	25.0	4.10	1.75
	Max	–	20	10	4	10	1.0983	0.2896	30.0	5.6423	1.7775	31.5	4.5	2.99
	Min	–	10	8	4	6	0.81	0.1112	11.4	4.51	0.7763	16.6	3.8	1.4880
50	Cefzon®-PI**	1	6	9	4	8	0.64	0.20	31.3	3.40 ($AUC_{0\text{-}inf}$)	1.12	32.9	4.3	1.75
100	Cefzon®-PI**	1	6	9	4	8	1.11	0.31	27.9	5.78 ($AUC_{0\text{-}inf}$)	1.62	28.0	3.8	1.59

Plasma concentrations were measured by HPLC* or bioassay**. Cefzon®-P1: phase I study of original product (Cefzon®).
1) Sampling point before oral dose is not included.
2) AUC0-24 h unless otherwise noted in parentheses.
3) S.D.: standard deviation.

4) Coefficient of variation (C.V.) was calculated as reported S.D. divided by mean.

Table 7: Pharmacokinetic studies after a single oral administration of cefcapene pivoxil hydrochloride (standard product, 75 or 100 mg tablet) to healthy, fasting, male volunteers

Tablet (mg)	Study No.	No. of products	No. of subjects	Total points[1)]	No. of sampling points* before 2 h	Sampling time of third last (h)	C_{max} (µg/mL)			$AUC_{0\text{-}10\,h}$ (µg · h/mL)[2)]			T_{max} (h)	$t_{1/2}$ (h)
							Mean	S.D.[3)]	C.V. (%)[4)]	Mean	S.D.[3)]	C.V. (%)[4)]		
75	75-A*	6	20	10	4	6	0.60706	0.14280	23.5	2.04378	0.46037	22.5	1.83	1.89
	75-B**	1	19	10	5	4	0.76	0.25	32.9	2.48	0.93	37.5	1.9	1.3
	Mean	–	19.5	10.0	4.5	5.0	0.68	0.20	28.2	2.26	0.70	30.0	1.87	1.60
100	100-A*	7	19	10	4	6	0.81821	0.21883	26.7	2.70911	0.58801	21.7	2.13	1.53
	100-B**	1	20	10	5	4	0.92	0.25	27.2	3.00	0.71	23.7	1.8	1.3
	Mean	–	19.5	10.0	4.5	5.0	0.87	0.23	27.0	2.85	0.65	22.7	1.97	1.42
75[5)]	Flomox®-PI***	1	6	11	3	6	1.04	0.21	20.2	3.00	0.38	12.7	2.1	0.88
100[5)]	Flomox®-PI***	1	6	8	2	6	1.28	0.33	25.8	3.86 ($AUC_{0\text{-}12}$ h)	0.52	13.5	1.3	1.01

Cefcapene concentrations in plasma or serum (for only Flomox® 100 mg) were measured by HPLC*, LC/ LC/mass spectrometry** or bioassay***.
1) Sampling point before oral dose is not included.
2) $AUC_{0\text{-}24\,h}$ unless otherwise noted in parentheses.
3) S.D.: standard deviation.
4) Coefficient of variation (C.V.) was calculated as reported S.D. divided by mean.
5) Flomox®-P1: phase I study of original product (Flomox®). Flomox was administered to healthy male volunteers at 30 min after meal.

Table 8: Pharmacokinetic studies after a single oral administration of clarithromycin (standard product, 200 mg tablet) to healthy, fasting, male volunteers

Study No.	No. of products	No. of subjects	Total points[1]	No. of sampling points* before 1 h	Sampling time of third last (h)	C_{max} (µg/mL)			$AUC_{0\text{-}24\,h}$ (µg · h/mL)[2]			T_{max} (h)	$t_{1/2}$ (h)
						Mean	S.D.[3]	C.V. (%)[4]	Mean	S.D.[3]	C.V. (%)[4]		
BE-A	2	9	11	4	8	0.48766	0.22406	45.9	3.03946	1.64607	54.2	1.89	3.09
BE-B***	2	24	11	4	8	0.58406	0.31123	53.3	3.50602	1.64020	46.8	1.94	3.42
BE-C	1	20	9	3	8	0.5312	0.1468	27.6	3.5383	0.8676	24.5	1.8	4.2
BE-D	2	12	11	4	8	0.5600	0.1162	20.8	3.5866	0.7458	20.8	2.08	3.09
BE-E***	2	14	9	4	8	0.548	0.238	43.4	3.602	1.237	34.3	2.1	2.3
BE-F	1	30	7	2	8	0.5433	0.2673	49.2	3.7145	1.7284	46.5	2.9	4.9 (±6.5)
BE-G	1	20	10	5	8	0.6211	0.1609	25.9	3.8693	1.1984	31.0	1.83	2.96
BE-H	1	19	9	3	8	0.547	0.249	45.5	3.883	1.270	32.7	2.10	8.97 (±14.10)
BE-I	1	17	11	4	8	0.75	0.25	33.3	4.12	1.60	38.8	1.56	3.13
BE-J	1	20	10	5	8	0.81	0.36	44.4	4.33	1.23	28.4	1.3	2.9
BE-K***	1	30	8	3	6	0.6701	0.3701	55.2	4.4675	2.1711	48.6	1.9	3.0
BE-L	1	20	9	4	8	0.720	0.236	32.8	4.934	1.273	25.8	1.75	5.28
BE-M**	6	20	9	3	6	0.490	0.165	33.7	2.947 ($AUC_{0\text{-}12\,h}$)	1.179	40.0	2.03	3.51
BE-N***	1	22	10	4	6	0.8589	0.3579	41.7	5.057 ($AUC_{0\text{-}12\,h}$)	2.045	40.4	1.95	3.1860
Mean	–	19.8	9.6	3.7	7.6	0.62	0.25	39.49	3.88	1.38	36.04	1.94	3.85
Median	–	20.0	9.5	4.0	8.0	0.57	0.24	42.55	3.79	1.27	33.52	1.90	3.16
Max	–	30	11.0	5.0	8.0	0.86	0.37	55.23	4.93	2.17	54.16	2.90	8.97
Min	–	9	7.0	2.0	6.0	0.49	0.12	20.75	3.04	0.75	20.79	1.30	2.30
Clarith®-P1*[5]	–	8	11	4	8	1.16	0.10 (S.E.)	–	8.98 ($AUC_{0\text{-}\infty}$)	0.64 (S.E.)	–	1.93	4.04
Clarith®-P1*	–	8	11	4	8	1.27	0.11 (S.E.)	–	8.98 ($AUC_{0\text{-}\infty}$)	0.64 (S.E.)	–	1.6	4.42
Clarith®-P1**	–	8	11	4	8	0.65	0.07 (S.E.)	–	4.54 ($AUC_{0\text{-}\infty}$)	0.42 (S.E.)	–	1.8	3.83
Clarith®-P1 (14-Hydroxylated metabolite)	–	8	11	4	8	0.48	0.03 (S.E.)	–	5.69 ($AUC_{0\text{-}\infty}$)	0.26 (S.E.)	–	2.1	7.99

Plasma/serum concentrations were measured by bioassay*, HPLC**, or LC/MS/MS***. BE: bioequivalence study, Clarith®-P1: phase I study of original product Clarith®, Clarith interview form, 2015).
1) Sampling point before oral dose is not included.
2) $AUC_{0\text{-}24\,h}$ unless otherwise noted in parentheses.
3) S.D.: standard deviation unless otherwise noted in parentheses as standard error (S.E.).
4) Coefficient of variation (C.V.) was calculated as reported S.D. divided by mean.
5) Pharmacokinetic parameters were calculated by one-compartment model fitting instead of model independent analysis.

Table 9: Pharmacokinetic studies after a single oral administration of erithromycin stearate (standard product, 200 mg tablet) to healthy, fasting, male volunteers

No. of Tablets	Study No.	No. of products	No. of subjects	Total points[1)]	No. of sampling points* before 4 h	Sampling time of third last (h)	C_{max} (µg/mL)			$AUC_{0-9\,h}$ (µg · h/mL)[2)]			T_{max} (h)	$t_{1/2}$ (h)
							Mean	S.D.[3)]	C.V. (%)[4)]	Mean	S.D.[3)]	C.V. (%)[4)]		
2	BE-A*	1	11	5	3	5	1.27	0.28	22.0	4.36	1.10	25.2	3.7	2.8
1	Erithrocin®-P1	–	?	?	?	?	0.82	–	–	–	–	–	2.8	No data
2	Erithromycin stearate®-IF*[5)] [Saito et al., 1988]	–	6	7	4	6	1.88	–	–	6.05 ($AUC_{0-12\,h}$ or $AUC_{0-\infty}$?)	–	–	2.2	1.78

Plasma/serum concentrations were measured by bioassay*. Erithrocin®-P1: phase I study of original product Erithrocin®).
1) Sampling point before oral dose is not included.
2) $AUC_{0-12\,h}$ unless otherwise noted in parentheses.
3) S.D.: standard deviation unless otherwise noted in parentheses as standard error (S.E.).
4) Coefficient of variation (C.V.) was calculated as reported S.D. divided by mean.
5) Pharmacokinetic parameters were calculated by one-compartment model fitting instead of model independent analysis.

Table 10: Pharmacokinetic studies after a single oral administration of amoxicillin (standard product, 125 or 250 mg capsule) to healthy, fasting, male volunteers

Capsule (mg)	Study No.	No. of products	No. of subjects	Total points[1)]	No. of sampling points* before 2 h	Sampling time of third last (h)	C_{max} (µg/mL)			$AUC_{0-6\,h}$ (µg · h/mL)[2)]			T_{max} (h)	$t_{1/2}$ (h)
							Mean	S.D.[3)]	C.V. (%)[4)]	Mean	S.D.[3)]	C.V. (%)[4)]		
125	125-A*	2	16	9	4	4	2.76	0.84	30.4	6.58	1.16	17.6	1.66	0.97
	125-B**	2	14	8	4	4	1.6517	0.3958	24.0	3.9099 ($AUC_{0-8\,h}$)	0.6177	15.8	1.32	1.18
	Mean	–	15	8.5	4	4	2.21	0.62	27.2	6.58	–	–	1.5	1.1
	Median	–	15	8.5	4	4	2.21	0.62	27.2	6.58	–	–	1.5	1.1
	Max	–	16	9	4	4	2.76	0.84	30.4	6.58	–	–	1.66	1.18
	Min	–	14	8	4	4	1.6517	0.3958	24.0	6.58	–	–	1.32	0.97
250	(No bioequivalence studies)													
125	Sawacillin®-PI**	(No phase I studies)												
	Pasetocin®-PI**	(No phase I studies)												
250	Sawacillin®-PI**	1	(46-54)	5	3	3	(3.68)	–	–	–	–	–	(2)	–
	Pasetocin®-PI**	1	56	5	2	2	(3.82)	–	–	–	–	–	(2)	–

1) Sampling point before oral dose is not included.
2) $AUC_{0-24\,h}$ unless otherwise noted in parentheses.
3) S.D.: standard deviation.
4) Coefficient of variation (C.V.) was calculated as reported S.D. divided by mean.
Plasma concentrations were measured by LC/mass spectrometry* or HPLC**. Sawacillin®-P1, Pacetocin-P1: phase I study of original product (Sawacillin®, Pacetocin®).
Values in parentheses were tentatively described in the table.

Table 11: Pharmacokinetic studies after a single oral administration of etizolam (standard product, 0.5 mg tablet) to healthy, fasting, male volunteers

No. of Tablet	Study No.	No. of products	No. of subjects	Total points[a]	No. of sampling points[a] before 2 h	No. of sampling points[a] before 4 h	Sampling time of third last (h)	C_{max} (ng/mL) Mean	C_{max} (ng/mL) S.D. [2]	C_{max} (ng/mL) C.V. (%)	$AUC_{0\text{-}24\ h}$ [1] (ng · h/mL) Mean	$AUC_{0\text{-}24\ h}$ [1] (ng · h/mL) S.D. [2]	$AUC_{0\text{-}24\ h}$ [1] (ng · h/mL) C.V. (%)	T_{max} (h)	$t_{1/2}$ (h)
1	1-A	1	19	8	4	5	6	8.462	1.647	19.5	60.753	21.220	34.9	0.79	6.25
	1-B	1	44	12	5	8	8	11.30	3.46	30.6	63.69	19.87	31.2	0.81	6.71
	1-C	2	12	8	2	4	8	8.4	1.1	13.1	64.2	10.5	16.4	2.0	6.2
	1-D	1	12	8	5	6	4	10.858	2.011	18.5	59.856 ($AUC_{0\text{-}13\ h}$)	12.917	21.6	1.00	4.91
	1-E	1	10	7	4	5	4	10.7	2.4	22.4	60.34 ($AUC_{0\text{-}13\ h}$)	12.19	20.2	0.83	4.39
	1-F	1	10	7	4	5	4	9.9	2.3	23.2	62.6 ($AUC_{0\text{-}13\ h}$)	13.6	21.7	0.97	5.54
2	2-A	3	16	8	3	4	7	9.62	1.81	18.8	47.37	10.87	22.9	1.3	6.5
	2-B	1	14	9	5	6	8	16.4	1.2 (S.E.)	-	114.6	13.0 (S.E.)	-	0.8	5.7
	2-C	1	20	9	4	6	6	18.04	3.68	20.4	149.35	43.70	29.3	1.1	6.9
	2-D	2	12	11	4	7	8	35.67	3.72	10.4	259.47	32.17	12.4	2.08	8.56
4	4-A	2	12	12	2	4	24	28.18	1.44 (S.E.)	-	296.39 ($AUC_{0\text{-}48\ h}$)	13.95 (S.E.)	-	3.5	☒
	4-B	1	12	8	4	5	5	35.2	8.8	25.0	242.9	59.7	24.6	0.94	4.5
	4-C	1	12	9	3	5	6	26.2	1.0 (S.E.)	-	280.3	9.0 (S.E.)	-	3.0	7.0
	4-D	2	12	8	4	5	6	32.03	7.16	22.4	344.66	110.25	32.0	1.38	7.69
Mean		–	15.5	8.9	3.8	5.4	7.4	–	–	20.4	–	–	24.3	1.5	6.2
Median		–	12.0	8.0	4.0	5.0	6.0	–	–	20.4	–	–	22.9	1.1	6.3
Max		–	44	12	5	8	24	–	–	30.6	–	–	34.9	3.5	8.56
Min		–	10	7	2	4	4	–	–	10.4	–	–	12.4	0.79	4.39

[a]Sampling point before oral dose is not included.
Coefficient of variation (C.V.) was calculated as reported, standard deviation (S.D.) divided by mean.
1) $AUC_{0\text{-}24\ h}$ unless otherwise noted in parentheses.
2) S.D. unless otherwise noted in parentheses as standard error (S.E.).

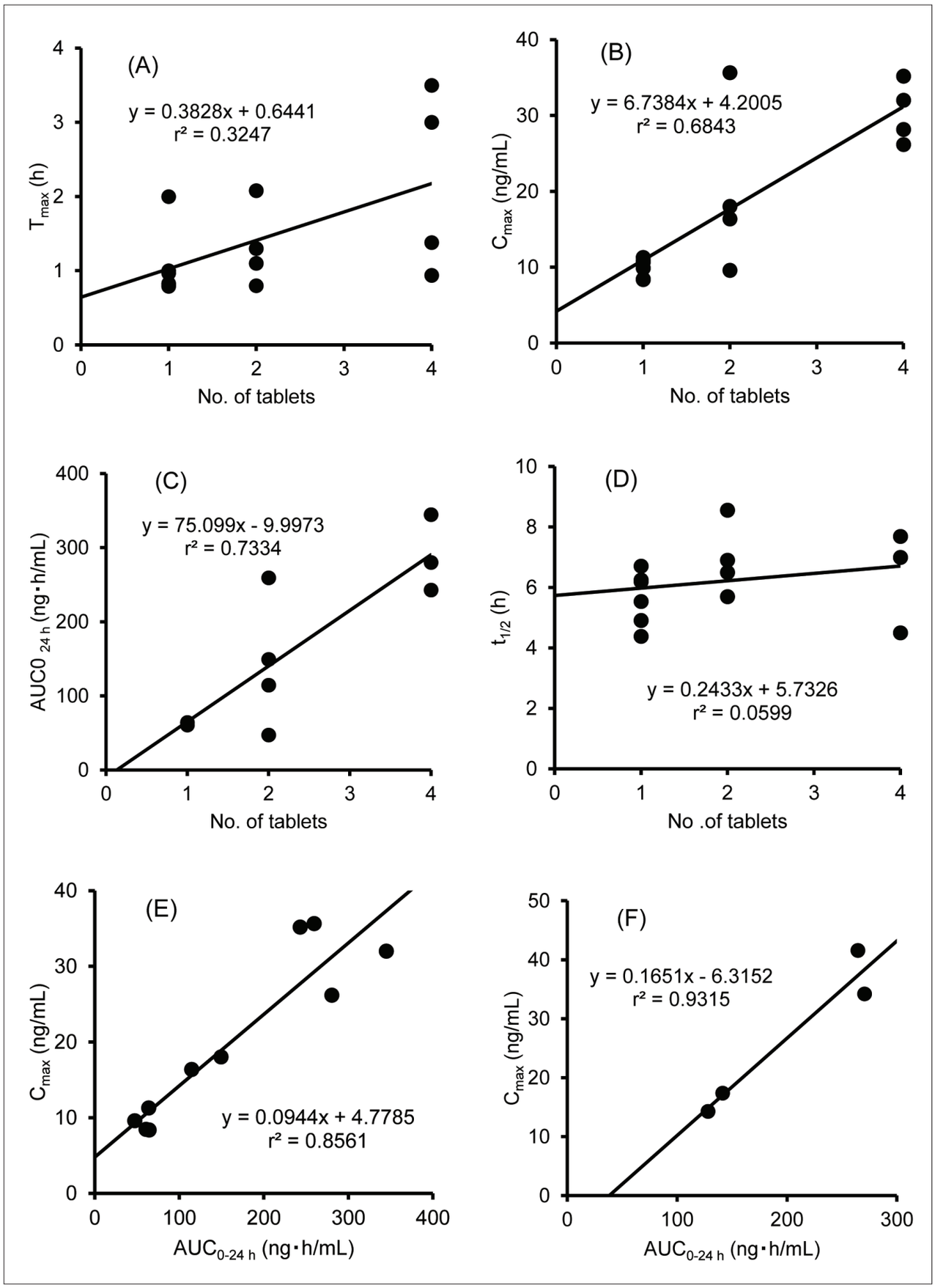

Fig. 3: Relationship between number of tablets and T_{max} (A), C_{max} (B), $AUC_{0\text{-}24\ h}$ (C), or $t_{1/2}$ (D) and between $AUC_{0\text{-}24\ h}$ and C_{max} (E, F) using the standard product, etizolam, in a bioequivalence study.
A-E: 0.5 mg tablets, F: 1 mg tablets.

Table 12: Pharmacokinetic studies after a single oral administration of etizolam (standard product, 1 mg tablet) to healthy, fasting, male volunteers

No. of Tablet	Study No.	No. of products	No. of subjects	Total points*	No. of sampling points* before		Sampling time of third last (h)	C_{max} (ng/mL)			$AUC_{0\text{-}24\,h}$ [1] (ng · h/mL)			T_{max}	$t_{1/2}$
					2 h	4 h		Mean	S.D. [2]	C.V. (%)	Mean	S.D. [2]	C.V. (%)	(h)	(h)
1	1-A	1	12	8	5	6	4	20.433	3.429	16.8	113.75 ($AUC_{0\text{-}13\,h}$)	23.010	20.2	1.00	4.89
	1-B	1	10	7	4	5	4	21.6	4.1	19.0	122.22 ($AUC_{0\text{-}13\,h}$)	26.29	21.5	0.77	4.98
	1-C	1	12	8	2	4	8	14.3	2.3	16.1	128.0	33.0	25.8	1.8	8.2
	1-D	1	10	7	4	5	4	19.8	3.7	18.7	122.9 ($AUC_{0\text{-}13\,h}$)	28.4	23.1	0.80	5.62
	1-E	1	20	9	4	6	6	17.39	3.89	22.4	141.41	42.02	29.7	1.0	6.5
	1-F	7	12	11	4	7	8	41.58	6.48	15.6	264.37	44.72	16.9	1.46	16.38
	1-G	1	12	8	4	5	5	34.2	5.2	15.2	270.4	56.3	20.8	0.78	5.99
2	2-A	2	12	12	2	4	24	28.10	1.49 (S.E.)	-	299.50 ($AUC_{0\text{-}48\,h}$)	10.14 (S.E.)	-	3.33	–
Mean		–	12.5	8.8	3.6	5.3	7.9	–	–	17.7	–	–	22.6	1.4	7.5
Median		–	12.0	8.0	4.0	5.0	5.5	–	–	16.8	–	–	21.5	1.0	6.0
Max		–	20	12	5	7	24	–	–	22.4	–	–	29.7	3.33	16.38
Min		–	10	7	2	4	4	–	–	15.2	–	–	16.9	0.77	4.89

*Sampling point before oral dose is not included.
Coefficient of variation (C.V.) was calculated as reported standard deviation (S.D.) divided by mean.
1) $AUC_{0\text{-}24\,h}$ unless otherwise noted in parentheses.
2) S.D. unless otherwise noted in parentheses as standard error (S.E.).

Table 13: Pharmacokinetic studies after a single oral administration of etizolam (standard product, 0.5 or 1 mg tablet) to healthy, fasting volunteers reported using interview form from Depas and several journals

Reference	Tablets and no. of tablets	Subject[1] and no. of subjects	Mean body weight (kg)	Total points*	No. of sampling points* before		Sampling time of third last (h)	C_{max} (ng/mL)			$AUC_{0\text{-}24\,h}$ [2] (ng · h/mL)			T_{max}	$t_{1/2}$
					2 h	4 h		Mean	S.D. [2]	C.V. (%)	Mean	S.D. [3]	C.V. (%)	(h)	(h)
Depas IF(2012)	1 mg, 2	M, 10 (After)	–	8	2	3	12	25	1.5 (SE)	–	284.3 ($AUC_{0\text{-}36\,h}$)	40.4 (SE)	–	3.3	6.3
Fracasso *et al.*(1991)	0.5 mg, 1	M, 6	72	10	4	5	9	8.3	1.7	20.5	–	–	–	0.9	3.4
Araki *et al.* (2004)	1 mg, 1	M, 12	73.5	11	4	6	10	17.7	4.0	22.6	154	52	33.8	1.1	12.0
Kondo *et al.* (2005)	1 mg, 1	M, 11	73	11	4	6	10	17.5	4.1	23.4	–	–	–	1.0	11.1
Fukusawa	1 mg, 1	M/F, EM, 12	69.4	11	4	6	10	17.3	6.8	39.3	105	58	55.2	1.0	10.5
et.al. (2005)	1 mg, 1	M/F, PM, 9		11	4	6	10	20.7	6.7	32.4	158	52	32.9	1.1	14.8
	1 mg, 1	M/F, A, 5		11	4	6	10	15.4	5.9	38.3	59	41	69.5	0.7	8.3
	1 mg, 1	M/F, B, 7		11	4	6	10	18.7	7.5	40.1	138	44	31.9	1.1	12.0

*Sampling point before oral dose is not included.
Coefficient of variation (C.V.) was calculated as reported, standard deviation (S.D.) divided by mean. IF: interview form.
1) M: Male, F: female, (After): Etizolam was administered at 30 min after meal. EM: Extensive metabolizer (*CYP2C19*1/*1*, **1/*2*, or **1/*3*), PM: Poor metabolizer (*CYP2C19*2/*2*, **2/3*, or **3/*3*), A: *CYP2C19*1/*1*, B: *CYP2C19*1/*2*, or **1/*3*)
2) $AUC_{0\text{-}24\,h}$ unless otherwise noted in parentheses.
3) S.D. unless otherwise noted in parentheses as standard error (S.E.).

Table 14: Pharmacokinetic studies after a single oral administration of tacrolimus (standard product, 0.5, 1, or 5 mg capsule) to healthy, fasting, male volunteers

Tacrolimus (mg)	Study No.	No. of products	No. of subjects	Total points*	Sampling time of third last (h)	C_{max} (μg/mL)			Final point (h)	AUC_{0t} (μg · h/mL)			T_{max} (h)	$t_{1/2}$ (h)
						Mean	S.D.	C.V. (%)		Mean	S.D.	C.V. (%)		
0.5	A	2	48	13	24	3.1958	1.3563	42.4	72	25.30	13.50	53.4	1.45	31.95
1	A	2	48	13	24	5.7603	2.2964	39.9	72	48.3	23.1	47.8	1.67	30.66
	B	1	59	?	24	5.93	2.38	40.1	48	44.21	26.26	59.4	1.54	24.52
5	A	2	32	13	24	31.579	10.363	32.8	72	240.6	91.9	38.2	1.53	30.31

*Sampling point before oral dose is not included.
Coefficient of variation (C.V.) was calculated as reported standard deviation (S.D.) divided by mean. Study A: 0.5, 1, and 5 mg tacrolimus was conducted for the estimation of the bioequivalence of the generic products in the same company.

For the etizolam 1-mg tablets (Table 12), 15 companies conducted eight types of bioequivalence studies because one company did not manufacture 1-mg tablets, and three companies conducted only dissolution test but not bioequivalence studies. In one study, two tablets were administered while one tablet was administered in the other seven studies. The last time point for the plasma sampling differed between the studies and was 13–48 h. Therefore, the conditions were different between the studies. In contrast, the sampling time point until 2 h after dosing was 2–5 h and the sampling time of the third and last time point, which is important for the $t_{1/2}$ estimation, was later than 4 h. The mean T_{max} and $t_{1/2}$ were 0.77–1.46 and 4.89–16.38 h, respectively. Although the coefficient of variation for the mean C_{max} and $AUC_{0\text{-}24\ h}$ within each study was less than 30%, a 2.9- and 2.1-fold difference was observed, respectively, between the studies. In addition, a good correlation was observed between the $AUC_{0\text{-}24\ h}$ and C_{max} for the 1- and 0.5-mg tablets (Fig. 2).

For the original drug product of etizolam (Depas®), only the pharmacokinetic parameters determined after a single administration 30 min after a meal, but not under fasting conditions, were included in the interview form and on the package insert (Table 13) (Depas Tablets interview form, 2012). In contrast, the clinical studies of various functions were assessed in healthy fasting subjects (Table 13). Because the bioequivalence studies were conducted in fasting subjects, these results are not comparable with the pharmacokinetic parameters of the original product. There were no marked differences between the T_{max} and $t_{1/2}$ of original drug and those obtained in the bioequivalence studies of the generic products. However, the C_{max} and $AUC_{0\text{-}24\ h}$ obtained in two studies after a dose of two tablets were far from the lines; the differences in the C_{max} and $AUC_{0\text{-}24h}$ between the two studies were approximately five-fold. Etizolam is predominantly metabolized in the liver to 8-ethyl hydroxylated and 1-methyl hydroxylated metabolites by CYP2C9 and CYP3A4, respectively (Depas Tablets interview form, 2012; Niwa et al. 2005). Although the CYP2C9 is polymorphic, the frequency of PMs in the Japanese population is assumed to be <0.1% (Kurose et al. 2012). Thus, the contribution of the effect of CYP2C9 polymorphism to the differences observed was considered negligible. In contrast, Fukasawa et al. (2005) administered one tablet of etizolam (1 mg) to healthy Japanese subjects who were poor metabolizers (PMs) and homozygous or heterozygous for the *cytochrome P450 (P450* or *CYP) 2C19*2 or CYP2C19*3* alleles following overnight fasting. They demonstrated that the AUC and $t_{1/2}$ for these subjects were 1.5- and 1.4-fold lower, respectively, than those in subjects with more than one *CYP2C19*1* (wild type) allele (Table 3). The frequency of PMs the in Japanese population is assumed to be approximately 20% (Kurose et al. 2012). Furthermore, Araki et al. (2004) reported that itraconazole, a potent inhibitor of CYP3A4, increased the AUC and $t_{1/2}$ of etizolam. In addition, Kondo et al. (2005) showed that carbamazepine, an inducer of P450s including CYP1A2 and CYP3A4, decreased the AUC and $t_{1/2}$ of etizolam. Although the contribution of CYP3A4 to the metabolism of etizolam was discussed, no explanation was provided for the effects of CYP2C19 polymorphism on the pharmacokinetic parameters of etizolam (Fukasawa et al. 2005). The $AUC_{0\text{-}12\ h}$ and $t_{1/2}$ values in these studies were 154 ng·h/mL and 11.1–12.0 h, respectively. The reported values were similar to those of the reference products reported in the bioequivalence studies of the generic etizolam (Table 12). It is well known that there are marked individual differences in the CYP3A4 content of the liver and intestine (Tateishi et al. 1999; von Richter et al. 2004). Although these individual differences could account for the variations in the pharmacokinetic parameters between the bioequivalence studies, other reasons might be involved because the coefficient of variation in each study was less than 34.9%.

For the tacrolimus capsules (Table 14), three companies conducted two kinds of bioequivalence studies. The generic products were launched after 2013, and therefore, the bioequivalence studies were conducted according to the standards for bioequivalence studies in the "Division-Notification 0229-10 of the Pharmaceutical and Food Safety Bureau, dated February 29, 2012" (PMDA web, 2012; NIHS web, 2012). The number of healthy subjects that

were enrolled (32–59) in the tacrolimus study was larger than the number of subjects in other studies. Although the coefficient of variation for the mean C_{max} and $AUC_{0\text{-}24\ h}$ values within each study was 32.8–59.4%, no marked differences were demonstrated. The last time point for plasma sampling differed between the studies and ranged from 48–72 h while the sampling time for the third last time point was 24 h. The mean T_{max} and $t_{1/2}$ were 1.45–1.67 and 24.52–31.95 h, respectively. Because the safety margin of tacrolimus is narrow, this immunosuppressant is administered under therapeutic drug monitoring (TDM), especially in patients who have undergone transplants (Graceptor capsule packing insert and interview form, 2014; Prograf capsule packing insert, 2014; Shiraga et al. 1994). Because tacrolimus is eliminated through metabolism by CYP3A4/5 in the liver and intestine (Graceptor capsule packing insert and interview form, 2014; Prograf capsule packing insert, 2014; Shiraga et al. 1994; Shiraga et al. 1999; Niwa et al. 2006), which leads to individual differences in the pharmacokinetics, dose adjustment with TDM is necessary. The number of healthy subjects (32–59) enrolled in these studies was larger than the number for the studies on other products. Therefore, there were no marked differences in the mean C_{max}, $AUC_{0\text{-}t}$, T_{max}, and $t_{1/2}$ between the bioequivalence studies despite a coefficient of variation of 32.8–59.4% within each study.

The pharmacokinetic study of the original tacrolimus capsule product (Prograf®) was not conducted in healthy subjects during the development of the product, and only pharmacokinetic parameters in patients who underwent transplants were published (Prograf capsule packing insert, 2014). The pharmacokinetic study of Prograf® (twice daily dosage) in healthy subjects was conducted during the development of the once-daily product, Graceptor® an extended-release capsule to compare the pharmacokinetics of both products (Graceptor capsule packing insert and interview form, 2014). In the interview form of Graceptor® (Graceptor capsule packing insert and interview form, 2014), the C_{max} values after single doses of Prograf® including 1.5 mg (three 0.5-mg capsules), 3 mg (three 1-mg capsules), or 5 mg (one 5-mg capsule) administered to healthy male subjects were reported to be 7.431, 17.5, and 26.7 ng/mL, respectively. In addition, the $AUC_{0\text{-}\infty}$ values were 74.28, 175, and 297 ng·h/mL. The T_{max} and $t_{1/2}$ values were 1.03–2.00 and 34.0–37.5 h, respectively. The pharmacokinetic parameters such as the C_{max}, AUC, T_{max}, and $t_{1/2}$ for the bioequivalence studies (Table 14) were comparable with the reported values (Graceptor capsule packing insert and interview form, 2014).

Thus, it seems that the quality of bioequivalence studies of pharmaceutical products other than antibiotics studies has also improved with respect to development of the standards of bioequivalence studies, although the summarized samples were limited.

8. Discussion

Most of the bioequivalence studies of antibiotics evaluated in the present paper were conducted according to the guidelines dated 1980, 2001, and 2012 (PMDA web, 2012; NIHS web, 2012). The interview form of the generic products specify that drug concentrations and pharmacokinetic parameters including the AUC and C_{max} may vary, depending on the selection of subjects and study conditions such as the number of sampling points and sampling time of body fluids. Marked differences were observed in the studies, especially for those on etizolam, followed by levofloxacin and cefaclor.

Variations in the C_{max} and AUC values between the bioequivalence studies of some drugs, including levofloxacin, cefaclor, and etizolam, can be attributed to differences in some factors. These factors include body weight of the participating subjects, absorption rates, measured drug concentrations, and the lots of the original products. However, it appears to be difficult to determine the specific reasons for the differences in each study. The body weights of subjects were not described in the package insert and interview form of the generic products. However, the value for healthy male subjects in Japan is around 60–70 kg as reported in other Japanese clinical studies for etizolam, and is not expected to vary between the bioequivalence studies (Table 13). The bioequivalence studies including the measurement of drug concentrations should be conducted under Good Clinical Practice guidelines, as well as reviewed and approved by the PMDA. In addition, the original products should be manufactured under Good Manufacturing Practice guidelines. Thus, the variation in absorption was expected to be minimal with minimal difference in the conditions of the clinical studies, although individual variations in the absorption of the products in humans were not demonstrated. Numerous plasma concentration evaluations of etizolam in the 1990s were determined using gas chromatography or high-performance liquid chromatography (HPLC) as described in the interview form of Depas® (Depas Tablets packing insert, 2012) and by Fracasso et al. (1991). However, plasma concentrations of most of products have been measured using HPLC and/or liquid chromatography-tandem mass spectrometry (LC/MS/MS) since the year 2000. Therefore, analytical methods and instruments have dramatically improved, and the skill and knowledge of individuals engaged in applying these techniques are expected to improve. Because the variation between the bioequivalence studies was the most with etizolam, followed by levofloxacin and cefaclor, compared to other products including tacrolimus, these analytical improvements may contribute to the minor differences between the studies.

The pharmacokinetic parameters determined in Phase I studies are frequently used to predict human *in vivo* pharmacokinetics from *in vitro* experimental studies (Yamazaki 2000; Ito et al. 2010) as well as to estimate the efficacy of antibiotics using C_{max}/MIC and AUC/MIC (Rybak 2006). The data collected in the present study would be useful for obtaining accurate pharmacokinetic information about original drugs especially the early time-release products because the parameters are obtained from multiple studies. However, the results obtained from bioequivalence study conducted recently may be superior to those obtained from earlier studies. A limitation of the present study is that we only estimated a limited number of drugs, and therefore, further investigations involving a larger number of drugs would be required. Although this investigation was conducted only for Japanese generic products, we expect that the results obtained in Japan can be used in the United States and Europe for harmonization.

Conflicts of interest: The authors declare that they have no conflict of interest.

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