June 2000 Volume 22 Number 3

A Journal Devoted to Therapeutic Drug Monitoring and Clinical Drug Toxicology

THERAPEUTIC DRUG MONITORING

Official Journal of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology

LIPPINCOTT WILLIAMS & WILKINS

Therapeutic Drug Monitoring
22:330–345 © 2000 Lippincott Williams & Wilkins, Inc., Philadelphia

Recommendations for Bioequivalence Testing of Cyclosporine Generics Revisited

Uwe Christians,* M. Roy First,† and Leslie Z. Benet,*

**Department of Biopharmaceutical Sciences, School of Pharmacy, University of California, San Francisco, CA; †University of Cincinnati Medical Center, Cincinnati, OH*

Summary: The immunosuppressant cyclosporine is generally considered a critical-dose drug. The validity of standard criteria to establish bioequivalence between cyclosporine formulations has recently been challenged. Recommendations included establishment of individual bioequivalence rather than average bioequivalence, establishment of bioequivalence in transplant patients and in subgroups known to be poor absorbers, as well as long-term efficacy and safety studies in transplant patients. However, at the moment individual bioequivalence is a theoretical concept, the practical benefits of which have not statistically been proven. The proposed patient pharmacodynamic studies can be expected to require an unrealistically high number of subjects to achieve sufficient statistical power. It is well established that the common practice of blood-concentration–guided dosing of cyclosporine efficiently compensates for interindividual and intraindividual variability and allows for safely switching cyclosporine formulations as bioinequivalent as Sandimmune and Neoral. Recent studies comparing the generic cyclosporine formulation SangCya with Neoral, including individual bioequivalence, bioequivalence in transplant patients, and long-term safety after switching from Sandimmune to SangCya, confirmed that it was valid to conclude bioequivalence of both cyclosporine formulations based on standard average bioequivalence criteria. Present FDA guidelines for approving bioequivalence can be considered adequate and sufficient for generic cyclosporine formulations. **Key Words:** Cyclosporine—Cyclosporine generics—Bioequivalence—Individual bioequivalence—Therapeutic drug monitoring.

Mostly as a result of the introduction of the undecapeptide cyclosporine as immunosuppressant, graft and patient survival have significantly improved during the last two decades and transplantation is an established standard procedure at most large medical centers. However, there are considerable costs for immunosuppressive therapy requiring life-long maintenance to prevent the transplant organ from being rejected (1,2). In the United States and Europe there are more than 200,000 transplant recipients requiring daily immunosuppressive therapy for the rest of their lives, the majority of whom are receiving immunosuppressive drug regimens based on cyclosporine. Worldwide sales of the innovator's cyclosporine formulations Sandimmune and Neoral (Novartis Pharma, Basel, Switzerland) were estimated at US$ 1.3 billion in 1997. In the United States, the innovator's patent protection expires after 17–20 years and other companies are then free to manufacture interchangeable generic products. Novartis' composition of matter patent on cyclosporine expired in the United States in September 1995. One generic cyclosporine formulation, SangCya (SangStat Medical, San Mateo, CA, USA), has recently been approved by the United States Food and Drug Administration (FDA). Others have filed for approval.

In 1984, the Drug Price Competition and Term Restoration Act (3) allowed the FDA to use a simplified approval process for generic drug products, the so-called

Received June 10, 1999; accepted December 30, 1999.
Address correspondence and reprint requests to Leslie Z. Benet, Ph.D., Professor, Department of Biopharmaceutical Sciences, School of Pharmacy, University of California, San Francisco, 533 Parnassus Ave, Room U-68, San Francisco, CA 94143-0446

abbreviated new drug application (ANDA) (4). The FDA's approval process of generic drugs evaluates chemistry, manufacturing and controls, in vivo bioequivalence, labeling, in vitro dissolution if applicable, and includes inspection and auditing of all facilities (5). Because the efficacy and safety of an innovator's drug has already been established, the FDA regulations are promulgated based on the belief that there is no reason to repeat the same studies with the generic version of the drug that contains exactly the same molecular entity as the innovator's product. Because of the lower costs of development and competition in the market, generic drugs usually sell for significantly less than the price of the innovator's product before the availability of generics. It is generally agreed that the prescribing and use of generic drugs lead to considerably reduced cost. Generic drugs also have the potential to improve the quality of care. Lower-cost alternatives may improve adherence to therapies for patients who cannot afford innovator drugs, and these alternatives provide an increased duration of therapy for patients with capped medical benefits. During the last 27 years, the FDA has approved more than 5,000 generic drugs for marketing in the United States (5). To date, the FDA is not aware of any validated study of an FDA-designated equivalent generic product that met FDA specifications but that was not equivalent to the corresponding innovator's product (6,7). In addition, the FDA's investigation of single cases of decreased efficacy or increased toxicity never revealed problems attributed to substitution of one approved product for another therapeutically equivalent product (7). In spite of this excellent safety record, there is a great reluctance by many clinicians to use generic equivalents for so-called "critical-dose drugs." Although there is no official definition for "critical-dose" or "narrow-therapeutic-index" drugs, and no general consensus as to which drugs fall within this category (8), bioequivalence-related issues of critical-dose drugs have been discussed intensively. Benet and Goyan (9) defined narrow-therapeutic-index drugs as "those for which small changes in pharmacokinetic response lead to marked changes in pharmacodynamic response." Accordingly, cyclosporine is generally regarded as a typical critical-dose drug (10–15). Bioequivalence testing procedures, especially in the case of critical-dose drugs, have been criticized in the past for many reasons, most of which potentially apply to cyclosporin (9,10,12,13). A fundamental problem is the definition of bioequivalence, which is based on the assumption that bioavailability (rate and extent) is a valid surrogate for efficacy and safety (16,17). This requires a clinically significant association between blood/plasma concentrations and pharmacodynamic effects that is not necessarily always the case. However, for cyclosporine the relationship between pharmacokinetics and safety has been extensively studied and provides the basis for the generally accepted blood-level–guided dosing regimens. Several other potential issues regarding the interchangeability of cyclosporine formulations are of concern to clinicians. There is doubt that the results of pivotal bioequivalence studies that are conducted in healthy volunteers are extrapolatable to transplant patients who exhibit several factors affecting cyclosporine pharmacokinetics that are not present in healthy volunteers (see below and Fig. 1). This applies especially for subpopulations of patients who are known poor absorbers. Intraindividual variability of cyclosporine is a critical clinical issue that has been associated with acute and chronic rejection (18,19) and cannot be addressed by pivotal healthy volunteer trials. This translates into suspicion that standard bioequivalence testing may not be a valid approach to establishing long-term safety and efficacy in transplant patients.

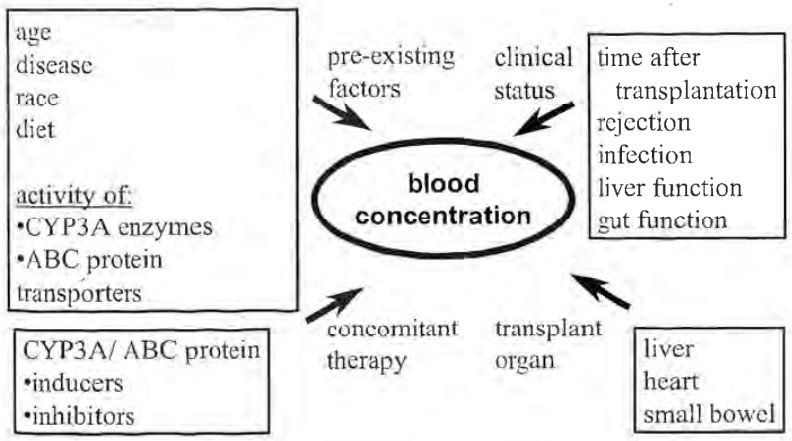

FIG. 1. Factors potentially affecting cyclosporine pharmacokinetics in transplant patients.

TABLE 1. *Comparison of guidelines and recommendations to establish bioequivalence and to switch between cyclosporine formulations*

Recommendation	Johnston et al., 1997[10]	Sabatini et al., 1999[13]	Kahan, 1999[14,21]
Average/individual bioequivalence	Validity of average bioequivalence questionable	Demonstration of individual bioequivalence should be mandatory for FDA approval	Average bioequivalence is a valid approach to establish interchangeability, individual bioequivalence should be demonstrated for the first CsA generic approved
Bioequivalence studies in patients after transplantation	Should be required for all CsA generics	Should be required for FDA approval of all CsA generics	Recommended for first CsA generic approved
Bioequivalence studies in subpopulations that are poor absorbers	Should be required for all CsA generics	Should be required for FDA approval of all CsA generics	Recommended for first CsA generic approved
Long-term efficacy and safety studies in transplant patients	Should be required (study period >3 months)	Not addressed	6-months pre-marketing follow-up
Physicians and patients must approve switch of CsA formulations even if bioequivalent	Not addressed	Yes	Not required

CsA, cyclosporine.

The question has been raised by several authors (10, 12,14,20) as to what extent the standard bioequivalence criteria used by the FDA and most drug agencies in other countries address these concerns and the sufficiency of these criteria to establish the safety of substituting cyclosporine formulations. This has also been discussed in recent meetings (13,21*). This has resulted in several different and sometimes contradictory guidelines and recommendations (Table 1). It was our goal to critically review cyclosporine bioequivalence issues and the discussed recommendations in light of bioequivalence and clinical data that is presently available for several generic cyclosporine formulations and in light of the extensive experience with switching transplant patients between the innovator's bioequivalent cyclosporine formulations as well as between the bioinequivalent Sandimmune and Neoral formulations.

CYCLOSPORINE FORMULATIONS

Recognizing the limitations of the original cyclosporine formulation Sandimmune, a crude oil-in-water droplet mixture (22), the innovator (Novartis Pharma, Basel, Switzerland) developed a microemulsion preconcentrate, Neoral, that improved emulsification and dispersion of cyclosporine in the small intestine and resulted in better and more reproducible absorption (23,25). From the beginning, Neoral was developed to increase cyclosporine bioavailability and, therefore, to be bioinequivalent (i.e., suprabioavailable) to Sandimmune (10,20,24). In fact, Sandimmune and Neoral should be considered different drug products (20).

In healthy volunteer studies (25,26) as well as in clinical studies in transplant patients (23–25,27) and psoriasis patients (28,29), Neoral cyclosporine pharmacokinetics differed from those of Sandimmune, yielding increased maximum blood concentration (C_{max}), decreased time to reach C_{max} (t_{max}), and increased area-under-the-time–concentration curve (AUC) (23). Depending on the dose, the relative bioavailability of Neoral in healthy volunteers was 1.7-fold to 2.4-fold and the C_{max} 1.9-fold to 2.1-fold higher than after the same Sandimmune cyclosporine dose (26). In de novo recipients of kidney transplants, depending on the time after transplantation, dose-normalized AUCs were 32–63% higher than in Sandimmune-treated patients (27). The mean increases of AUC and C_{max} of 39% and 15%, respectively, in stable recipients of kidney transplants after switching from Sandimmune to Neoral (30) were smaller than in the healthy volunteer studies (26). Although based on healthy volunteer studies, a conversion factor of 0.6 (Neoral:Sandimmune) was estimated, transplant patients were switched 1:1(25). In a clinical study in 55 stable recipients of kidney transplant, switching from Sandimmune to Neoral on a 1:1 basis resulted in 22% higher cyclosporine trough blood concentrations (31). However, patients with higher cyclosporine doses before conversion from Sandimmune to Neoral are more likely to require dose reduction in the postconversion course. When switched from Sandimmune to Neoral, good absorbers remain good absorbers whereas poor absorbers become good absorbers (32). The higher bioavailability and different

*Generic Immunosuppressants: Should you be worried? Transplantation Society sponsored symposium. Montreal, Canada, July 12. Presentations were published in Transplant Proc 1999; 31[supplement].

pharmacokinetic pattern of Neoral raised several safety concerns that required clarification in clinical studies (23–25). The high cyclosporine C_{max} after Neoral was of special concern because high cyclosporine C_{max} values have been related to short-term renal vasoconstriction and possibly chronic cyclosporine nephropathy (33). Another concern was the higher total exposure of patients during conversion from Sandimmune to Neoral (23). The conversion protocol recommends starting Neoral at the preconversion dose (1:1 conversion) with subsequent dose adjustments according to cyclosporine trough blood concentrations. It was necessary to assume that the greater exposure to cyclosporine from the microemulsion formulation might increase the nephrotoxic risk. In fact, adverse events such as hypertension, nephrotoxicity, and acute rejection have been reported after conversion (30). However, as of today, despite the two products' significant pharmacokinetic differences, clinical studies have established a safety and tolerability profile of Neoral comparable to that of Sandimmune (24). Long-term studies did not show any statistically significant differences between recipients of kidney transplants treated with Sandimmune and those treated with Neoral in terms of safety, including creatinine concentrations, patient and graft survival, as well as the incidence of acute rejection (23,24,27,34,35). This is not surprising: because of the drug's highly intraindividually and interindividually variable pharmacokinetics and narrow therapeutic index, cyclosporine doses must be adjusted according to cyclosporine blood concentrations (36). Regular therapeutic drug monitoring is required, and the cyclosporine concentrations are kept in a narrow target concentration range that is independent of the cyclosporine formulation. However, because of its improved dose linearity and lower intraindividual pharmacokinetic variability, Neoral is generally considered to have proven benefits to patient care over Sandimmune (2,10,24,27).

In October 1998, the FDA approved SangCya (Sangstat Medical, Menlo Park, CA, USA) as the first generic cyclosporine formulation in the United States. SangCya is a nano-dispersion formulation based upon Sangstat's CPLF formulation technology (37). Bioequivalence with Neoral was not only established in pivotal healthy volunteer studies (38), but also in recipients of kidney and liver transplants (39,40) (Table 2, Fig. 2). In addition, individual bioequivalence between SangCya and Neoral was demonstrated (41) (Table 3, see below) following the draft FDA procedures (11,42). Safety and efficacy of SangCya was established in patients with kidney grafts during a 9-month observation period (43).

Healthy volunteer studies demonstrating bioequivalence with Neoral (Table 2) have been published for two other generic cyclosporine formulations, Neoplanta (Hanmi Pharmaceutical, Seoul, Korea) (44,45) and Cipol-NR (Chong Kun Dang, Seoul, Korea) (46). Like Neoral, both are microemulsion formulations (46,47). The difference between Neoplanta and Neoral is that Neoplanta uses dimethyl isosorbide instead of ethanol as the solvent (48). In de novo recipients of renal transplants, Neoplanta and Neoral (n = 20 for each group) showed similar efficacy in preventing graft rejection and similar tolerability (48).

VARIABILITY OF CYCLOSPORINE PHARMACOKINETICS

The significantly lower pharmacokinetic variability of cyclosporine after administration of Neoral compared to Sandimmune is commonly regarded as the major im-

TABLE 2. *Comparison of the results of bioequivalence studies in healthy volunteers and patients who have had a transplantation with cyclosporine formulations (test) bioequivalent to Neoral (reference)**

			C_{max} ratio (%)		AUC ratio (%)		
Cyclosporine	Subjects	n	Point Estimate	90% CI	Point Estimate	90% CI	Ref.
Test Formulation							
SangCya	Fasted male healthy volunteers	36	99	97–104	99	97–103	38
SangCya†	Fasted male and female healthy volunteers	20	95	90–101	97	92–102	41
SangCya	Fasted/fed male healthy volunteers	24	97	91–104	100	96–105	38
SandCya	Fasted female healthy volunteers	28	92	87–100	95	92–102	38
SangCya	Fasted male African-American volunteers	10	96	81–108	90	83–96	38
Neoplanta	Fasted male Korean healthy volunteers	24	97	90–101	99	94–102	45
Cipol-N	Fasted male Korean healthy volunteers	24	103	100–106	100	96–104	46
SangCya	Kidney transplant patients	32	90	84–102	94	86–106	39
SangCya	Liver transplant patients	26	86	81–106	95	89–109	40

* The AUC ratio in healthy volunteer studies is based upon the $AUC_{0-\infty}$, the AUC ratio studies on the $AUC_{0-\tau}$ in patients after transplant. Neoplanta[45] and Cipol-N[46], like Neoral[22], are microemulsion cyclosporine formulations, whereas SangCya is a nano-dispersion formulation based upon Sangstat's CPLF formulation technology[37].

† Analysis of individual bioequivalence see Table 3.

CI, confidence interval.

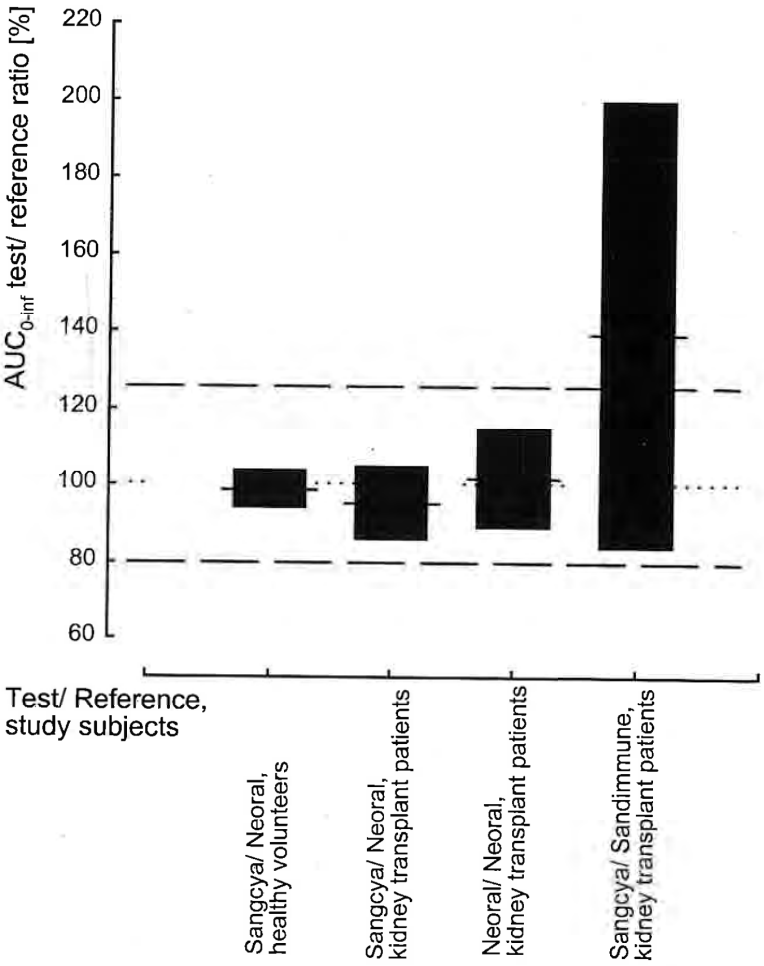

FIG. 2. Comparison of biocquivalence of different cyclosporine formulations in healthy volunteers and stable kidney transplant patients. The bars represent the 90% confidence intervals of the $AUC_{0-\infty}$ test/reference ratio and the lines across the bars represent the point estimates. The dotted line represents complete equivalence (100%), whereas the dashed lines are at 125% and 80%, the bioequivalence acceptance limits. Data is taken from references 38,39.

TABLE 3. *Comparison of intrasubject variability* and individual bioequivalence of SangCya (test) and Neoral (reference)*[41]

Parameter	SangCya	Neoral	Ratio (95% confidence interval)	p-value	Upper 95% confidence interval for θ_i†
C_{max} [$\mu g \cdot L^{-1}$]	0.0235	0.0327	0.72	0.50	1.277
CV	15.4%	18.2%	(0.22–1.76)		
$AUC_{0-24\,h}$ [$\mu g \cdot L^{-1} \cdot h$]	0.0111	0.0124	0.89	0.84	1.009
CV	10.5%	11.2%	(0.36–2.20)		
$AUC_{0-\infty}$ [$\mu g \cdot L^{-1} \cdot h$]	0.0127	0.0081	1.56	0.43	0.935
CV	11.3%	9.0%	(0.36–3.83)		

* Intrasubject variability was calculated following the procedure described by Liu. Intrasubject variability between SangCya (test) and Neoral (reference) was compared using the likelihood ratio χ^2 test. Intrasubject variability is based on the logarithmic scale.

† Bioequivalence was accepted when the upper 95% confidence interval was ≤ the individual bioequivalence limit θ_i, which was calculated at 2.245 using a bootstrap method (2000 samples).

CV, coefficient of intrasubject variability; C_{max}, maximum blood concentration.

provement of Neoral over Sandimmune (10,13,14). Fluctuating cyclosporine blood concentrations have been associated with chronic and acute rejection (18,19,49). In comparison to Sandimmune, the more consistent absorption from the Neoral formulation may result in a reduced incidence of chronic rejection (18) and toxicity, it is expected to make clinical management easier and safer (50), and it will reduce costs after transplantation (2). Demonstration of equivalent pharmacokinetic variability of generic cyclosporine formulations and Neoral has been a major concern (10,13,14,21).

Factors that play a major role in the low and variable oral bioavailability of cyclosporine include solubility, emulsification, countertransport of the drug by P170-glycoprotein and other ATP-binding cassette (ABC) protein transporters from the gut mucosa back into the gut lumen, and first-pass metabolism in the small intestine and liver.

After administration of cyclosporine as the original Sandimmune formulation, absorption of cyclosporine requires the following subsequent steps: formation of an oil-in-water droplet mixture with gastrointestinal fluids, emulsification of this mixture by bile salts, digestion of the oil droplet, and solubilization of cyclosporine in monoglycerides and bile salts resulting in a mixed micellar phase from which cyclosporine is absorbed (22,25). Emulsification by bile salts has been identified as the step that causes most of the variability in intestinal absorption of cyclosporine after Sandimmune administration. This step is dependent on food intake, bile flow, and gastrointestinal motility (51). Microemulsion and nano-dispersion cyclosporine formulations are hypothesized to shortcut the critical emulsification step. In the Neoral microemulsion, cyclosporine is dissolved in a mixture of corn oil mono-, di- and triglycerides, the hydrophilic solvent propylene glycol, the surfactant polyoxyl-40 hydrogenated castor oil, and the antioxidant DL-tocopherol (22). Upon contact with gastrointestinal fluid, a monophasic microemulsion is formed that has properties similar to the putative mixed micellar phase from which cyclosporine is absorbed.

Cyclosporine is a substrate of cytochrome P450 3A enzymes and the ATP-binding cassette transporter P170-glycoprotein (52–55). It is metabolized by CYP3A enzymes in the small intestine to its major metabolites (56). In patients, metabolites were found to account for as much as 50% of the measurable cyclosporine derivatives in portal vein blood after cyclosporine instillation into the small intestine (57). In microsomes isolated from the duodenum of patients, cyclosporine metabolism varied 10-fold (56,58). A clinical study using intubation techniques to deliver cyclosporine to different parts of the gastrointestinal tract established a significant inverse correlation between cyclosporine absorption and P170-glycoprotein messenger RNA at the administration site (59), suggesting that P170-glycoprotein–mediated intestinal countertransport significantly contributes to the incomplete absorption of cyclosporine. In a recent clinical study in stable recipients of kidney grafts (58), it was found that hepatic metabolism was responsible for 56% of the interpatient variability in apparent oral cyclosporine clearance and 32% of the variability in C_{max}. After the liver effect was taken into account, the only other parameter significantly contributing to cyclosporine pharmacokinetic variability was intestinal P170-glycoprotein, which was estimated to explain 17% of the variability in apparent oral clearance and 30% of the variability in C_{max} (58). In the same study, cytochrome P450 3A enzyme activities in the liver varied 3-fold and P170-glycoprotein in the small intestine 10-fold among patients. These studies demonstrate that cytochrome P4503A-dependent intestinal and hepatic first-pass metabolism as well as P170-glycoprotein–mediated intestinal countertransport reduce the oral bioavailability of cyclosporine whereas hepatic metabolism and intestinal countertransport also contribute to its pharmacokinetic variability.

AVERAGE BIOEQUIVALENCE TESTING

In the 1970s it was recognized that, even when two drug products contained the same active component at the same dose, small changes in the product formulation could result in significant differences in oral bioavailability. Several cases of lack of effect or intoxication after administration of pharmaceutically equivalent generic drug products were reported (60). Pharmaceutical equivalents contain the same active ingredient, are administered by the same route in the same dosage form, and are of identical strength and concentration (61). These experiences triggered an international effort to develop clinical and statistical procedures to establish bioequivalence between pharmaceutical equivalents. Today, drug regulatory authorities in the United States (62), the European Community (17), and most other countries require demonstration of average bioequivalence between the marketed and a generic drug product as the basis of approval. The rules to establish bioequivalence are basically similar in most countries with only minor differences. Bioequivalence studies typically aim to demonstrate that two pharmaceutical equivalents have similar pharmacokinetics (63). The standard bioequivalence trial is conducted according to a randomized 2-period crossover design and includes from 12–36 healthy normal male adults with an appropriate wash-out between study

periods. The key issue in bioequivalence testing is to demonstrate similar oral bioavailability. Because the pharmaceutical equivalents are orally administered, absolute bioavailability cannot be directly determined. Area-under-the curve (AUC) measurements serve as a surrogate for the extent of absorption; the maximum plasma concentration (C_{max}) and the time of its occurrence (t_{max}) together characterize the rate of absorption (64). Pharmacokinetic parameters used to establish bioequivalence in the FDA and European Committee for Proprietary Medicinal Products (CPMP) guidelines are shown in Table 4. Test and reference product are considered equivalent when the 90% confidence interval for the true formulation means ($\mu_{test}/\mu_{reference}$) falls within the acceptance limits of 0.8–1.25 (17,62). In practice, the confidence interval approach is carried out using log-transformed data (65). The 0.8–1.25 bioequivalence acceptance range translates into a difference in rate and extent of absorption between the two drug products of −20% to +25%. These acceptance limits are based on the medical decision that a −20%/+25% difference in the concentration of the active ingredient in blood will not be clinically significant (61). It is important to recognize that it is the upper and lower limit of the 90% confidence interval for the true mean ratios and not only the mean ratio (point estimate) that must be within the bioequivalence acceptance limits (61). The 90%-confidence interval is a measure of total variability, which is influenced by both interindividual and intraindividual variability (11,66). Variability is a factor that has a significant impact on acceptance or rejection in average bioequivalence testing.

TABLE 4. *Pharamacokinetic parameters in the United States and European guidelines for bioequivalence testing*[95]

Recommended pharmacokinetic parameters	United States and Canada*	Europe†
Single dose	C_{max}	C_{max}
	t_{max}	t_{max}
	AUC_{0-t}	AUC_{0-t}
	$AUC_{0-\infty}$	$AUC_{0-\infty}$
	$t_{1/2}$	$t_{1/2}$‡
		MRT‡
		Ae
		$Ae_{0-\infty}$
		dAe/dt
Multiple dose	C_{max}	Css_{max}
	C_{min}	Css_{min}
	AUC_{τ}	AUC_{τ}
	$AUC_{0-\infty}$	
	t_{max}	
	C_{av}	
	DF	

* Food and Drug Administration

† Committee for Proprietary Medicinal Products

‡ Mentioned in the CPMP guideline[17] as optional parameters.

Ae, cumulative urinary excretion from administration to the time point of the last measured concentration; $Ae_{0-\infty}$, cumulative urinary excretion extrapolated to infinity; dAe/dt, urinary excretion rate; AUC_{0-t}, area under the concentration time curve from administration to the time of the last measured concentration; $AUC_{0-\infty}$, AUC extrapolated to infinity; AUC_{τ}, AUC during a dosing interval; C_{max}, maximal blood/plasma concentration; Css_{max}, maximum blood/plasma concentration at steady state; C_{min}, minimum blood/plasma concentration; C_{av}, average blood/plasma concentration; Css_{min}, minimum blood/plasma concentration at steady state; DF, degree of fluctuation; MRT, mean residence time; $t_{1/2}$, blood/plasma concentration half-life; t_{max}, time from administration to C_{max}.

It has been suggested that the standard procedures to establish bioequivalence may not be adequate for all drugs and that modified procedures and additional data may be necessary (9,60,63,67). Drugs for which the validity of the standard approach for establishing bioequivalence must be assessed and if necessary modified, are (1) those with a narrow therapeutic index, (2) those with high interindividual and intraindividual pharmacokinetic variability, (3) those for which pharmacokinetics does not correlate with pharmacodynamic effects, and (4) those with nonlinear pharmacokinetics and/or controlled modified-release formulations (60). The validity of standard average bioequivalence procedures to establish bioequivalence of cyclosporine generics has been challenged (10,13), mostly because cyclosporine has been classified as a narrow-therapeutic-index, highly variable drug (11–14). A drug is commonly regarded as highly variable when it exhibits an intrasubject coefficient of variance ≥30% as estimated by analysis of variance (66,67). This criterion was clearly met by cyclosporine pharmacokinetics after oral administration of the original Sandimmune formulation. However, intrasubject variability of cyclosporine pharmacokinetics is formulation-dependent. Estimates of intrasubject variability in cyclosporine AUCs of 8% (68), 7% (69), 20% (70), and 9–21% (71) after Neoral administration have been reported in patients with kidney transplants.

The validity of average bioequivalence and the 0.8–1.25 acceptance range for narrow-therapeutic-index drugs has repeatedly been questioned. Tighter acceptance criteria, such as an acceptance range of 0.9–1.1 or the use of 95%- instead of the 90%-confidence intervals, have been proposed for narrow-therapeutic-index drugs (9) and are required by some drug regulatory agencies such as Canada's (72). In the United States it is believed that the present requirements to prove bioequivalence are already rigorous enough to prevent the possibility that dosage forms meeting regulatory criteria could lead to therapeutic problems, even for narrow-therapeutic-index drugs (9,21,61). Benet and Goyan (9) hypothesized that narrow-therapeutic-index drugs will have little difficulty in being proven bioequivalent even when the acceptance

criteria is narrowed, because by defininition such drugs are also agents with low intrasubject variability. If this were not true patients would routinely experience cycles of toxicity and lack of efficacy, and even therapeutic drug monitoring would be useless (8). Indeed, although in general the opposite is believed (10–13), cyclosporine given as Neoral or equivalent formulations does not seem to be an exception. So far, all pivotal healthy volunteer studies (38,41,45,46) reported for cyclosporine formulations shown to be bioequivalent to Neoral would also meet a 0.9–1.1 bioequivalence acceptance range (Table 2).

Current bioequivalence guidelines require comparison of the novel product with the corresponding form of a well-established innovator product. Accordingly, Sandimmune as well as Neoral qualify as reference formulations for bioequivalence studies. In Canada, cyclosporine generics bioequivalent to Sandimmune are acceptable, although the innovator discontinued marketing of the original Sandimmune formulation (72). Studies with generic cyclosporine formulations bioequivalent to Sandimmune have not yet been reported.

Johnston et al (10) reviewed the study procedures used to establish bioequivalence and clinical studies comparing Sandimmune and Neoral. The authors concluded that standard bioequivalence criteria are not sufficient to establish safety and efficacy of novel oral cyclosporine formulations and recommended extensive healthy volunteer and clinical studies "that should be carried out to establish therapeutic equivalence of any new oral form of cyclosporine" (10). However, as discussed by Castañeda-Hernández et al (20), these recommendations are based on several misconceptions. Johnston et al (10) based their discussion of the validity of average bioequivalence criteria and their recommendations on Neoral/Sandimmune data. This is misleading because Sandimmune and Neoral are not bioequivalent and were never meant to be bioequivalent (20). In contrast, all generic cyclosporine formulations reported (38,45,46) to date have been developed and shown to be bioequivalent to Neoral. Although Johnston et al (10) recommended that only oral formulations bioequivalent to Neoral should be acceptable, the rationale of several of the recommended studies is obviously based on Sandimmune data.

The discussion of bioequivalence guidelines for narrow-therapeutic-index drugs or critical-dose drugs is neither new nor cyclosporine-specific (9). In the past, the current bioequivalence guidelines have been sufficient for narrow-therapeutic-index drugs (9) and, from a regulatory point of view, are also adequate for cyclosporine (8,20,21).

Individual Bioequivalence Testing and Intraindividual Variability

Interchangeability of two drug products can be considered in terms of prescribability and switchability. Prescribability refers to the choice of two products when therapy is started in a drug-naïve patient (73). For recipients of transplants, prescribability is of relatively minor interest (21). During the initial period after transplantation, cyclosporine concentrations are closely monitored and cyclosporine doses are adjusted to maintain cyclosporine blood trough concentrations or cyclosporine AUCs in the target range. Because of the common practice of blood-level–guided dosing regimens, de novo transplant patients can safely be treated with cyclosporine even if a cyclosporine formulation is inequivalent to the innovator's formulation such as Sandimmune and Neoral. Switchability (73), when a patient stabilized on the innovator's product is switched to a generic cyclosporine formulation, is of greater clinical impact (14,21). Average bioequivalence testing, which is as discussed earlier the basis of approval of generic drugs in the United States and most other countries, measures prescribability rather than switchability. Therefore, the concept of individual bioequivalence has been introduced (74). Individual bioequivalence takes a possible subject-by-formulation interaction into account in the computation of the metric. The subject-by-formulation interaction is important when one formulation is more bioequivalent than the other in one or more subsets of the study population. A large subject-by-formulation interaction is an indicator for a lack of switchability between the test and the reference formulation in some individuals (66). Individual bioequivalence studies require a replicate design, where each subject receives the generic formulation twice and the innovator formulation twice. This study design allows also for estimation of interindividual and intraindividual variances. The FDA has recently published a Draft Guidance on the introduction of individual and population bioequivalence (11,42).

Because intraindividual variability of cyclosporine pharmacokinetics is an important clinical issue in patients with transplant (as stated earlier), several authors (12,13) strongly advocate the establishment of individual bioequivalence rather than average bioequivalence as the basis of FDA approval of generic cyclosporine formulations. They are confident that the current FDA draft guideline would satisfy these requirements. At the moment, however, the individual bioequivalence approach has not been statistically validated (61,66,75). So far, the FDA has retrospectively studied and presented 34 data sets from 12 4-period cross-over studies. None of these

studies was designed to establish individual bioequivalence. At present, the data does not appear to provide sufficient evidence of the prevalence of subject-by-formulation interaction to support the introduction of individual bioequivalence (75). In addition, only two prospective studies designed as individual bioequivalence studies have been reported (75). In one of these studies (76), one of the drugs studied was found to be bioequivalent to the reference product using individual bioequivalence criteria but was not bioequivalent using average bioequivalence criteria. Another drug was found bioequivalent according to average but not according to individual bioequivalence criteria. Another problem is that the behavioral characteristics of the individual bioequivalence metrics are not yet fully understood (66). It has been demonstrated that, because the scaled criterion of bioequivalence declares the equivalence of two formulations very liberally (75), two formulations were bioequivalent although the differences between their means exceeded 25% (66). The statistical model for individual bioequivalence has substantially more parameters than the model used for average bioequivalence (75). It can be expected that the estimated parameters have significantly larger uncertainties and undesirable correlations under certain conditions that have not yet completely been evaluated (75). Additional uncertainties arise from the use of the bootstrap method, which is used to estimate the one-sided confidence interval. The result is different in each calculation and may give rise to manipulations in borderline cases (75). Most importantly, as of today the consideration of individual bioequivalence is all theoretical. There is no evidence of a clinical problem with average bioequivalence testing; neither is there a safety or an efficacy issue. Furthermore, there is no evidence that individual bioequivalence would solve the problem if it existed (61,75). Because of the unsolved methodologic problems, it seems unlikely that the proposed individual bioequivalence guideline (42) will be implemented in its present form (66,75). Evaluation of the benefits of individual bioequivalence will require a database of prospective replicate design studies that will provide the FDA and drug companies with the necessary information to make a reasoned consensus judgment as to the appropriate criteria for individual bioequivalence (11,61,66,75).

Meanwhile, although not required by the FDA for approval, individual bioequivalence between SangCya and Neoral has been established in a replicated, four-period cross-over design study in healthy volunteers following the FDA draft guidelines (42) (Table 3). The results confirmed those found in the pivotal bioequivalence studies (38). Both cyclosporine formulations were also bioequivalent when data were analyzed using average bioequivalence metrics (Table 2). It is interesting to note that intraindividual variability in the healthy volunteers was similar to that reported in recipients of kidney transplants (68–71).

Benet (61) recently summarized the status of individual bioequivalence: "Currently, individual bioequivalence is a theoretical solution to solve a theoretical clinical problem." Generic drugs are approved on the basis of average bioequivalence studies. Although the FDA encourages companies to submit replicate design studies, approval decisions will be made on the basis of average bioequivalence metrics. Because it is unlikely that individual bioequivalence will be implemented in the near future, if at all, guidelines and recommendations for the approval of generic cyclosporine formulations mandating individual bioequivalence as a basis of FDA approval (12,13) seem to be of limited practical relevance.

Bioequivalence Testing in Recipients of Transplants and Special Patient Subpopulations

It has become obvious from discussions, recommendations, and consensus documents (10,13,14,21) that there are substantial worries in the transplant community about the extent to which pharmacokinetic comparisons of test and reference cyclosporine formulations in healthy volunteers, as required for approval by the FDA and other drug agencies, reflect safety and efficacy in transplant patients. Bioequivalence studies in the target population are favored by the nonregulatory guidelines and recommendations to establish bioequivalence of generic cyclosporine formulations (10,13,14) (Table 1). In comparison to healthy volunteers, a multitude of additional factors impacts cyclosporine pharmacokinetics in transplant patients (Figure 1), resulting in a higher interindividual and intraindividual variability. Patient subpopulations that are known poor absorbers and usually exhibit greater pharmacokinetic variability than the average stable transplant patient are of special concern (10,12–14,20,21). However, none of the guidelines defines specifically which subpopulations should be studied. Curtis et al (32) found that approximately one third of the recipients of kidney grafts included in their study were poor absorbers of cyclosporine after Sandimmune administration. These patients required the most extensive dose adjustments after being switched to Neoral. Other populations of poor absorbers include cystic fibrosis lung transplant recipients (77), pediatric patients (78), African-Americans (18,79), patients with impaired bile production (80,81), and diabetes patients (79,82). Again,

it is important to differentiate between Sandimmune and Neoral data. Subpopulations have been identified mostly on the basis of cyclosporine pharmacokinetics after Sandimmune administration. However, after switching to Neoral, cyclosporine bioavailability and pharmacokinetic variability significantly improved in most patients in these subpopulations (32,77,78,80,81), and poor absorbers of cyclosporine after Sandimmune administration turned into good absorbers after Neoral (32). At the moment, it is unclear whether a problem really exists with transplant patient subpopulations and generic cyclosporine formulations bioequivalent with Neoral. However, the situation will be different with generic cyclosporine formulations bioequivalent to Sandimmune.

Patients are often receiving individualized therapy including coadministration of several drugs. This is especially true in subpopulations such as patients with liver function impairment, diabetes, or cystic fibrosis. These patients require individualized treatment and it seems impossible and unethical to expose these patients to the controlled and congruent conditions usually required for bioequivalence studies. It can be expected that this introduces a significant study-center effect into bioequivalence analysis.

Transplant recipients, especially subpopulations of poor absorbers, are heterogenous and in most cases can be expected to exhibit significantly higher variability of cyclosporine pharmacokinetics within the subpopulation than those in the general population. The expected high pharmacokinetic variability will require much larger numbers of subjects than studies of healthy volunteers or stable transplant patients to yield bioequivalence with sufficient statistical power. Because several of these subpopulations represent small groups, recruitment may become a limiting factor.

In clinical studies, bioequivalence between the generic cyclosporine formulation SangCya and Neoral in kidney and liver transplant recipients has been evaluated (39,40). As shown in Table 2 and depicted in Figure 2, the studies confirmed the results of the pivotal healthy volunteer studies (38) and established bioequivalence between the test and reference formulation in the target population. Interestingly, the 90%-confidence intervals when SangCya and Neoral were compared in patients with kidney transplant were similar to those when Neoral was compared with itself in a replicate design study in the same patient population (Figure 2). In the Neoral-to-Neoral comparison, the 90%-confidence interval for the mean ratio was even slightly wider than in the SangCya-to-Neoral comparison.

ESTABLISHING LONG-TERM SAFETY IN TRANSPLANT PATIENTS

By design, bioequivalence studies do not have a clinical endpoint. Similar plasma concentration time-profiles are taken as a surrogate for therapeutic efficacy and safety (64). All recommendations to establish bioequivalence of generic cyclosporine formulations (10,13,14) discuss that a therapeutic rather than a pharmacokinetic endpoint would be desirable. Johnston et al (10) and Kahan (14) recommend long-term safety and efficacy studies in transplant patients. Although there is reasonable consensus about the length of the study period, the authors do not address the more important question of the desired clinical effect, the sensitivity, the statistical power and, depending on those, the number of subjects required for such studies. Assuming the test product has demonstrated bioequivalence, the objective may be to demonstrate that the test product is at least as good as the reference product in the stable patient population or in de novo patients. The objective of the study will have enormous impact on sample size. This issue has been addressed by McGilveray and Gallicano (72). Because, as discussed earlier, switching stable patients between cyclosporine formulations rather than starting de novo patients on a generic cyclosporine formulation is the important safety issue, stable transplant recipients should be included in safety and efficacy studies. The patients should randomly be assigned to two study groups. One group of patients will be switched to the novel generic cyclosporine formulation, the other group will continue to receive the reference product. Parameters included in the analysis would be the incidence and severity of side-effects, transplant function, and the incidence of rejection episodes. An acceptable sensitivity would probably be $\leq$10% difference between the study group receiving the test formulation and the one receiving the reference formulation. Considering that two bioequivalent cyclosporine formulations will be compared, the number of study subjects required to result in reasonable statistical power ($\geq$80%) will easily exceed those of phase III clinical trials and would be prohibitive in terms of time and costs required for the development of generic drug formulations. This does not take into account that cyclosporine doses, if necessary, will be adjusted in individual patients to maintain cyclosporine blood concentrations within the target concentration range. The efficacy and safety of Neoral has been compared with Sandimmune in a study in which 466 renal transplant patients were enrolled (34). Although Sandimmune and Neoral are not bioequivalent, the overall incidence of adverse events was similar, despite the increased exposure of patients to

cyclosporine in the test group after a 1:1 switch to Neoral. In addition there was no difference in kidney function. The results of this study comparing two bioinequivalent cyclosporine formulations indicate that, if the same number of patients were included, it would be practically impossible to detect or exclude differences in safety and efficacy of two bioequivalent cyclosporine formulations with reasonable sensitivity and statistical power.

Long-term safety data have been reported for SangCya (43) and Neoplanta (48). Considering the facts discussed earlier and that in each study fewer than 50 subjects were enrolled, the studies were statistically underpowered. Therefore, it is no surprise that both cyclosporine formulations, which are bioequivalent to Neoral (38,44), showed efficacy and safety similar to cyclosporine. These studies may help to boost confidence of transplant physicians and patients in the novel drug products, but they can hardly be regarded as a valid approach for detecting or excluding potential efficacy and safety differences between the test and reference formulations.

CLINICAL EXPERIENCE WITH SWITCHING BETWEEN BIOEQUIVALENT CYCLOSPORINE FORMULATIONS

Most of the guidelines and recommendations to establish bioequivalence of generic cyclosporine formulations and to switch between cyclosporine formulations (10,12, 13,21) are based on the experience with switching patients between the bioinequivalent Sandimmune and Neoral formulations. The prospect of the availability of bioequivalent generic cyclosporine formulations has triggered an intense discussion about the validity of standard bioequivalence procedures to establish safety and efficacy of cyclosporine generic products. These discussions ignore the fact that there is already considerable experience with switching patients between bioequivalent cyclosporine formulations. It is interesting to note that this discussion did not emerge when the first novel cyclosporine formulation, Sandimmune soft gelatin capsules, was introduced by the innovator as a follow-up to the oral solution more than 10 years ago. The original oral solution contained 100 mg cyclosporine in 50 mL olive oil, Labrafil M 1944 Cs, and ethanol (12.5%) as a vehicle (83). The rationale for the development of the soft gelatin capsule, in addition to increased convenience, was to mask the unpleasant taste of the oral solution and to avoid the variability introduced by the need to measure the oral solution and to dispense it in milk or fruit juice (83,84). The soft gelatin capsule formulation differed from the oral solution and contained corn oil, gelatin, glycerol, Labrafil M 2125 Cs, ethanol (12.7%), red iron oxide, sorbitol, titanium oxide, and other ingredients (83). Because these evaluations were carried out before 1992, none of the pharmacokinetic studies published used the bioequivalence metric that is in effect today to compare test (capsule) and reference (oral solution) formulations (85–89). In all studies, average oral bioavailability of the gelatin capsules was almost consistently 9–11% higher than that of the oral solution, but did not reach statistical significance (85–89). However, a recent study failed to establish bioequivalence between the Sandimmune oral solution and soft gelatin capsule in patients who had been identified as poor absorbers with higher C_{max} and AUC after administration of the soft gelatin capsule (12). Most long-term transplant patients were switched from the oral solution to the capsule, and few problems have been reported. In some countries, control of the blood concentration after switching from oral solution to capsule was required (21). The practice of blood-level–guided dose adjustments, which has been shown to efficiently compensate for differences in bioavailability, may have been one of the reasons that no serious problems were reported with switching between oral solution and capsule. However, because no difference in efficacy and safety were found in 466 renal transplant patients between the bioinequivalent formulations of Sandimmune and Neoral (34) as discussed earlier, the lack of problems with switching between the bioequivalent Sandimmune oral solution and capsule is not surprising.

Neoral is marketed as both capsule and oral solution. A single bioequivalence study has been reported that established bioequivalence between Neoral oral solution and capsules in healthy volunteers (90). C_{max} (point estimate, 1.04; 90%-confidence interval, 0.98–1.12%) and AUC (point estimate, 1.02%; 90%-confidence interval, 0.97–1.06%) were in the bioequivalence acceptance range. Based on their study, the authors concluded that in conjunction with routine concentration monitoring, the microemulsion soft gelatin capsule and the microemulsion oral solution can be interchanged without a need for dose adjustment and without alteration in cyclosporine blood concentration profiles (90). Indeed no problems have been reported with switching between oral solution and soft gelatin microemulsion formulation in transplant patients, although the authors' conclusion was exclusively based on healthy volunteer data (90). It can be concluded that transplant physicians and patients already have substantial experience with switching between bioequivalent cyclosporine formulations. As discussed earlier, the innovator used the same procedures to establish bioequivalence between its different cyclosporine formu-

lations as those used to establish bioequivalence between generic and the innovator's cyclosporine formulations. The experience with the innovator's bioequivalent formulations (oral solution/soft gelatin capsule) has shown that switching between bioequivalent cyclosporine formulations can generally be considered safe. Based on this data, there is no reason to believe that switching between the innovator's formulation and bioequivalent generic cyclosporine formulations is less safe than switching between the innovator's bioequivalent cyclosporine formulations.

BIOINEQUIVALENCE AND THERAPEUTIC DRUG MONITORING

Changes of oral bioavailability and bioinequivalence have always played an important role in the clinical management of cyclosporine-treated transplant recipients. Patients are switched from Sandimmune to Neoral, cyclosporine formulations that are not bioequivalent. It has recently been shown that many drugs interacting with the metabolism and intestinal countertransport of cyclosporine have a more significant impact on the drug's oral bioavailability than on its systemic elimination (91). Several drugs that are commonly used after transplantation, such as azole antifungals and calcium antagonists, are known inhibitors of cyclosporine metabolism and transport and increase its oral bioavailability whereas other drugs such as many corticosteroids and antiepileptics induce cyclosporine transport and metabolism and reduce its oral bioavailability. Because of their cyclosporine-sparing effect, calcium channel blockers and azole antifungals have been intentionally coadministered to improve cyclosporine bioavailability (92,93). Although cyclosporine doses were reduced by as much as 88% to maintain cyclosporine concentrations in the target range, kidney function was not different from that of the control group during the observation period of 3 years (93) (Table 5). Because of the drug's pharmacokinetic variability in combination with its narrow therapeutic index, cyclosporine blood trough concentrations or, as proposed recently AUC values, are regularly monitored and cyclosporine doses are adjusted to keep cyclosporine blood concentrations in the target range (36). This dosing strategy efficiently compensates for variability in cyclosporine oral bioavailability and elimination. It is well documented that because of blood-level–guided dosing adjustments, even bioinequivalence as great as that between Sandimmune and Neoral or that created when ketoconazole is intentionally coadministered (because of its cyclosporine-sparing effect) did not cause an increased incidence of cyclosporine toxicity (34,35,93).

Therapeutic drug monitoring and the generally accepted blood-level–guided dosing regimens have not been taken into account in most recommendations and guidelines to establish bioequivalence of generic cyclosporine formulations (10,12,13). Although we believe that all previous experience suggests that extra monitoring is not needed when patients are switched between bioequivalent cyclosporine formulations, it can be expected that most patients will have their cyclosporine blood concentrations checked within a short time after being switched from the innovator's to a generic cyclosporine formulation and cyclosporine doses will be adjusted as necessary. This will especially be the case with patients who are known to have fluctuating cyclosporine blood concentrations. If individual patients exist in whom the switch between two cyclosporine formulations of established bioequivalence causes a shift in blood trough concentrations, the common practice of therapeutic drug monitoring in combination with blood-level–guided dose adjustment can be expected to provide an efficient safety net.

CONCLUSIONS

From a theoretical point of view, many of the recommendations for establishing bioequivalence and safety of generic cyclosporine formulations by Johnston et al (10), Sabatini et al (13), and Kahan (14), seem desirable.

TABLE 5. *Long-term safety of the cyclosporine-sparing effect of ketoconazole in patients who are stable after kidney tansplantation*[93]

Parameter	Pre-study	Months					
		1	3	6	12	24	36
Cyclosporine dose [mg · kg^{-1} · d^{-1}]	5.6	1.3	1.2	1.1	0.9	0.8	0.7
Dose reduction [%]		77	79	84	86	86	87
Trough blood concentration [μg · L^{-1}]*	140	159	144	147	188	153	124
Creatinine in serum [mg · dL^{-1}]	1.8	1.8	1.8	1.7	1.7	1.7	1.8
Urea in serum [mg · dL^{-1}]	27	23	23	24	23	25	29

* Measured by high-performance liquid chromatography.

These include establishment of individual bioequivalence, establishment of bioequivalence in various transplant patient subpopulations, and long-term safety and efficacy studies. However, as discussed earlier, from a regulatory, practical, and/or statistical point of view, some of these recommendations will be difficult or even impossible to follow or, based on the extensive experience that already exists with the innovator's bioequivalent formulations as well as studies recently reported for generic cyclosporine formulations, must be considered unnecessary. Especially the recommendations by Johnston et al (10) and Sabatini et al (13) have several problems that undermine their practical relevance. Based on bioequivalence considerations of Sandimmune and Neoral, two formulations that are bioinequivalent, Johnston et al (10) proposed healthy volunteer and clinical studies that are close to what is required for clinical development of a new drug. This was appropriate for Neoral which, because it is more bioavailable than Sandimmune, had to be considered a new drug development (21). Because of both the higher cyclosporine C_{max} and the greater exposure (AUC), several safety issues had to be addressed in clinical studies. Most of the studies recommended by Johnston et al (10) will not be necessary for generic cyclosporine formulations that are bioequivalent to Neoral. A critical part of the recommendations by Sabatini et al (13) focuses on the requirement to demonstrate individual rather than average bioequivalence for FDA approval of generic cyclosporine formulations. As discussed earlier, the individual bioequivalence metrics have not been sufficiently evaluated and, because of a lack of data, the practical value of the subject-by-formulation interaction is unclear. Although an interesting theoretical concept, it seems unlikely that individual bioequivalence will be implemented in the near future because of many as yet unsolved problems (61,66,75). All guidelines recommend studying bioequivalence in subpopulations of patients who are known to be poor absorbers and to exhibit great pharmacokinetic variability. Again, it is important to differentiate between Sandimmune and Neoral. All studies that have described problems with subgroups of patients such as erratic oral bioavailability and fluctuating cyclosporine blood concentrations were based on Sandimmune. It is well established that these subgroups in particular benefitted from being switched to Neoral, resulting in significantly improved and less variable bioavailability. At the moment, it is unclear whether a bioavailability and variability problem in these subgroups with Neoral or bioequivalent formulations exists. Such a study needs to be conducted to answer this question for Neoral and one of the bioequivalent formulations, but as of this writing there is no reason to suspect that a formulation that is bioequivalent in healthy volunteers will not also be equivalent in these subgroups. The recommendations by Johnston et al (10) and Kahan (14) include long-term safety and efficacy studies in transplant patients. As discussed earlier, the number of patients that must be enrolled in such studies to result in sufficient sensitivity and statistical power to detect or exclude differences between two bioequivalent cyclosporine formulations will exceed those required for phase III multicenter trials during development of new drugs. This seems prohibitive. The recommendations by Kahan et al (14), and the roundtable discussion (21) upon which these recommendations are based, consider the standard bioequivalence procedure a valid approach to establish bioequivalence between generic cyclosporine formulations and the innovator's respective reference product. To strengthen clinicians' confidence in bioequivalent cyclosporine generics, it is recommended that the first approved generic cyclosporine formulation demonstrate that approved bioequivalent products behave identically in various patient populations as well as in distinct patient subgroups, and that it demonstrate individual bioequivalence. Some of these data are already available. Bioequivalence between SangCya and Neoral has successfully been established in kidney and liver graft recipients (39,40), and in African-American subjects (38), a known subpopulation of poor absorbers (Table 1). In addition, individual bioequivalence of SangCya and Neoral has been demonstrated in a healthy volunteer study. All studies available for generic cyclosporine formulations to date confirm the validity of pivotal bioequivalence trials.

Generic substitution is no novelty in transplantation medicine. Generic immunosuppressants include corticosteroids and azathioprine (40). Since the introduction of the original Sandimmune oral solution, Sandimmune capsules and the microemulsion Neoral became available. Patients were switched between the bioequivalent capsules and Sandimmune oral solution with little concern, although similar potential safety issues as discussed for generic substitution in recent consensus documents (13,15) may have applied (12).

It is understandable that, because of the high price of losing a graft, transplant physicians are worried about individual patients when switching from the innovator's to a generic cyclosporine formulation (21). However, there is extensive experience with safely switching patients between the innovator's bioequivalent and even bioinequivalent formulations, and blood-level–guided dosing adjustments are proven to efficiently compensate for potential changes in oral bioavailability of cyclosporine. It is likely that common problems in the manage-

ment of cyclosporine-treated transplant recipients, such as changes in pharmacokinetics caused by drug interactions, diet, disease and transplant function, will create more significant risks than switching between bioequivalent cyclosporine formulations (21).

Considering the practical shortcomings of most recent recommendations to establish bioequivalence of generic cyclosporine formulations, the fact that thousands of transplant patients have safely been switched between the innovator's bioequivalent and even bioinequivalent cyclosporine formulations for more than a decade, and that bioequivalence data of generic cyclosporine formulations in healthy volunteers and transplant patients is available, the present FDA guidelines for approving bioequivalence can be considered adequate and sufficient for generic cyclosporine formulations.

Acknowledgment: Preparation of this report was supported by the Deutsche Forschungsgemeinschaft grant Ch 95/6-2.

REFERENCES

1. Bennett WM, Olayei AJ. Pharmacoeconomics of immunosuppressive agents in renal transplant patients. *Transplant Proc* 1999;31 (suppl. 3A):6S.
2. Coukell AJ, Plosker GL. Cyclosporin microemulsion (Neoral). Pharmacoeconomic review of its use compared with standard cyclosporin in renal and hepatic transplantation. *Pharmacoeconomics* 1998;14:692–708.
3. Drug Price Competition and Patent Term Restoration Act. Public law 98-417, 98, Stat. 1585–1605, 1984.
4. Code of Federal Regulations, 21, Food and Drugs, Part 314.94, Content and format of an abbreviated application, pp. 134, 1995.
5. Dighe SV. A review of the safety of generic drugs. *Transplant Proc* 1999;31 (suppl. 3A):23S–24S.
6. Nightingale SL, Morrison JC. Generic drugs and the prescribing physician. *JAMA* 1987;258:1200–1204.
7. Nightingale SL. From the Food and Drug Administration: Generic substitution. *JAMA* 1998;279:645.
8. Benet LZ. Relevance of pharmacokinetics in narrow therapeutic index drugs. *Transplant Proc* 1999;31:1642–1644.
9. Benet LZ, Goyan JE. Bioequivalence and narrow therapeutic index drugs. *Pharmacotherapy* 1995;15:433–440.
10. Johnston A, Keown PA, Holt DW. Simple bioequivalence criteria: are they relevant to critical dose drugs? Experience gained from cyclosporine. *Ther Drug Monit* 1997;19:375–381.
11. Patnaik RN, Lesko LJ, Chen ML, Williams RL, FDA Individual Bioequivalence Working Group. Individual Bioequivalence: New concepts in the statistical assessment of bioequivalence metrics. *Clin Pharmacokinet* 1997;33:1–6.
12. Barr WH. The case for expanding bioequivalence criteria to include measures of individual bioequivalence in relevant population subsets. *Transplant Proc* 1999;31 (suppl. 3A):25S–30S.
13. Sabatini S, Ferguson RM, Helderman HJ, Hull AR, Kirkpatrick BS, Barr WH. Drug substitution in transplantation: A National Kidney Foundation white paper. *Am J Kidney Dis* 1999;33:389–397.
14. Kahan BD. Recommendations concerning the introduction of generic formulations of cyclosporine. *Transplant Proc* 1999;31: 1634.
15. Kahan BD, Welsh M, Rutzky LP. Challenges in cyclosporine therapy: the role of therapeutic drug monitoring by area under the curve monitoring. *Ther Drug Monit* 1995;17;621–624.
16. Food and Drug Administration (FDA), Division of Biopharmaceutics. Bioavailability and bioequivalence requirements. *Fed Regist* 1977;42:1624–1653.
17. CPMP (Committee for Proprietary Medicinal Products) Working Party in the Efficacy of Medicinal Products. Note for guidance: Investigation of bioavailability and bioequivalence. The Rule Governing Medicinal Products in the European Community. 1991;3: 149–167.
18. Kahan BD, Welsh M, Schoenberg L, et al. Variable oral absorption of cyclosporine. *Transplantation* 1996;62:599–606.
19. Inoue S, Beck Y, Nagao T, Uchida H. Early fluctuation in cyclosporine A trough levels affects long-term outcome of kidney transplants. *Transplant Proc* 1994;26:2571–2573.
20. Castañeda-Hernández G, Perez-Urizar J, Medeiros M. Current bioequivalence criteria are adequate for oral cyclosporin A formulations. *Ther Drug Monit* 1998;20:722–723.
21. Kahan BD. Discussion of recommendations concerning the introduction of generic formulations of cyclosporine. *Transplant Proc* 1999;31:1675–1684 .
22. Vonderscher J, Meinzer A. Rationale for the development of Sandimmune Neoral. *Transplant Proc* 1994;26:2925–2927.
23. Olyaei AJ, deMattos AM, Bennett WM. Switching between cyclosporin formulations. What are the risks? *Drug Saf* 1997;16:366–373.
24. Kovarik JM, Mueller EA, Niese D. Clinical development of a cyclosporine microemulsion in transplantation. *Ther Drug Monit* 1996;18:429–434.
25. Noble S, Markham A. Cyclosporin. A review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (Neoral). *Drugs* 1995;50:924–941.
26. Mueller EA, Kovarik JM, Van Bree JB, Tetzloff W, Grevel J, Kutz K. Improved dose linearity of cyclosporine pharmacokinetics from a microemulsion formulation. *Pharm Res* 1994;11:301–304.
27. Keown P, Niese D. Cyclosporine microemulsion increases drug exposure and reduces acute rejection without incremental toxicity in de novo renal transplantation. *Kidney Int* 1998;54:938–944.
28. Elder CA, Moore M, Chang CT, et al. Efficacy and pharmacokinetics of two formulations of cyclosporine A in patients with psoriasis. *J Clin Pharmacol* 1995;35:865–875.
29. Erkko P, Granlund H, Nuutinen M, Reitamo S. Comparison of cyclosporin A pharmacokinetics of a new microemulsion formation and standard oil preparation in patients with psoriasis. *Br J Dermatol* 1997;136:82–88.
30. Mueller EA, Kovarik JM, Van Bree JB, Lison AE, Kutz K. Pharmacokinetics and tolerability of a microemulsion formulation of cyclosporine in renal allograft recipients: A concentration-controlled comparison with the commercial formulation. *Transplantation* 1994;57:1178–1182.
31. Kovarik JM, Mueller EA, Van Bree JB, et al. Cyclosporine pharmacokinetics and variability from a microemulsion formulation. A multicenter investigation in kidney transplant patients. *Transplantation* 1994;58:658–663.
32. Curtis JJ, Lynn M, Jones PA. Neoral conversion from Sandimmune in maintenance renal transplant patients: an individual approach. *J Am Soc Nephrol* 1998;9:1293–1300.
33. Ruggenenti P, Perico N, Mosconi L, et al. Calcium channel blockers protect transplant patients from cyclosporine-induced daily renal hypoperfusion. *Kidney Int* 1993;43:706–711.
34. Taesch S, Niese D. Safety and tolerability of a new oral formulation of cyclosporin A, Sandimmun Neoral, in renal transplant patients. *Transplant Int* 1994;7:S263–S266, 1994.
35. Niese D. A double-blind randomized study of Sandimmun Neoral versus Sandimmun in new renal transplant recipients: results after 12 months. The International Sandimmun Neoral Study Group. *Transplant Proc* 1995;27:1849–1856.
36. Oellerich M, Armstrong VW, Kahan BD, et al. Lake Louise consensus conference on cyclosporin monitoring in organ transplan-

tation: Report of the consensus panel. *Ther Drug Monit* 1995;17: 642–654.
37. United States Patent and Trademark Office. Patent No. 5,766,629.
38. Schroeder TJ, Cho MJ, Pollack GM, et al. Comparison of two cyclosporine formulations in healthy volunteers: Bioequivalence of the new Sang-35 formulation and Neoral. *J Clin Pharmacol* 1998;38:807–814.
39. First MR, Alloway R, Schroeder TJ. Development of Sang-35: a cyclosporine formulation bioequivalent to Neoral. *Clin Transplant* 1998;12:318–324.
40. Alloway RR. Generic immunosuppressants used in solid organ transplantation. *Transplant Proc* 1999;31 (suppl. 3A):2S–5S.
41. Canafax DM, Irish DM, Berger Moran H, et al. An individual bioequivalence approach to compare the intrasubject variability of two ciclosporin formulations, SangCya and Neoral. *Pharmacology* 1999;59:78–88.
42. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Draft Guidance for Industry: In vivo bioequivalence studies based on population and individual bioequivalence approaches. Rockville, MD, October 1997.
43. First MR, Weiskittel P, Burton ML, et al. 9-Months safety and efficacy of Sang-35 in kidney transplant patients after conversion from Sandimmune. *Transplant Proc* 1998;30:1701–1705.
44. Lee YJ, Chung SJ, Shim CK. Bioequivalence of Neoplanta capsule to Sandimmune Neoral, microemulsion formulations of cyclosporin A in human subjects. *Int J Clin Pharmacol Ther* 1998;36:210–215.
45. Lee YJ, Chung SJ, Shim CK. Decreased oral availability of cyclosporin A at second administration. *Br J Clin Pharmacol* 1997; 44:343–345.
46. Park MS, Yu NC, Lee HK, Kim KH. Bioequivalence study of Cipol-N (cyclosporine microemulsion preparation) in healthy adults. *Transplant Proc* 1998;30:3541–3546.
47. United States Patent and Trademark Office. Cyclosporin-containing soft capsule composition. Patent No. 5,603,951.
48. Kim SC, Han DJ. Neoplanta as a new microemulsion formula of cyclosporine in renal transplantation: Comparative study with Neoral for efficacy and safety. *Transplant Proc* 1998;30:3547–3548.
49. Best NG, Trull AK, Tan KKC, et al. Blood cyclosporin concentrations and the short-term risk of lung rejection following heart lung transplantation. *Br J Clin Pharmacol* 1992;34:513–520.
50. Wahlberg J, Wilczek HE, Fauchald P, et al. Consistent absorption of cyclosporine from a microemulsion formulation assessed in stable renal transplant recipients over a one-year study period. *Transplantation* 1995;60:648–652.
51. Fahr A. Cyclosporin clinical pharmacokinetics. *Clin Pharmacokinet* 1993;24:472–495.
52. Christians U, Sewing KF. Ciclosporin metabolism in transplant patients. *Pharmacol Ther* 1993;57:291–345.
53. Wu C-Y, Benet LZ, Hebert MF, et al. Differentiation of absorption and first-pass gut and hepatic metabolism in humans: Studies with cyclosporine. *Clin Pharmacol Ther* 1995;58:492–497.
54. Wacher VJ, Wu CY, Benet LZ. Overlapping substrate specificities and tissue distribution of cytochrome P450 3A and p-glycoprotein: Implications for drug delivery and activity in cancer chemotherapy. *Mol Carcinog* 1995;13:129–134.
55. Wacher VJ, Silverman JA, Zhang Y, Benet LZ. Role of p-glycoprotein and cytochrome P450 3A in limiting oral absorption of peptides and peptidomimetics. *J Pharm Sci* 1998;87:1322–1330.
56. Lampen A, Christians U, Bader A, Hackbarth I, Sewing KF. Drug interactions and interindividual variability of ciclosporin metabolism in the small intestine. *Pharmacology* 1996;52:159–168.
57. Kolars JC, Awni WM, Merion RM, Watkins PB. First-pass metabolism of cyclosporine by the gut. *Lancet* 1991;331:1488–1490.
58. Lown KS, Mayo RR, Leichtmann AB, et al. Role of intestinal p-glycoprotein (mdr1) in interpatient variation in the oral bioavailability of cyclosporine. *Clin Pharmacol Ther* 1997;62:248–260.
59. Fricker G, Drewe J, Huwyler J, Gutmann H, Beglinger C. Relevance of p-glycoprotein for the enteral absorption of cyclosporin A, in vitro- in vivo correlation. *Br J Pharmacol* 1996;118:1841–1847.
60. Gleiter CH, Gundert-Remy U. Bioinequivalence and drug toxicity: How great is the problem and what can be done? *Drug Saf* 1994; 11:1–6.
61. Benet LZ. Understanding bioequivalence testing. *Transplant Proc* 1999;31 (suppl. 3A):7S–9S.
62. Food and Drug Administration (FDA). Bioavailability and bioequivalence requirements. *Fed Regist* 1992;57:17997–18001.
63. Schall R, Luus HG. On population and individual bioequivalence. *Stat Med* 1993;12:1109–1124.
64. Garbe E, Röhmel J, Gundert-Remy U. Clinical and statistical issues in therapeutic equivalence trials. *Eur J Clin Pharmacol* 1993; 45:1–7.
65. Sauter R, Steinijans VW, Diletti E, Böhm A, Schulz HU. Presentation of results from bioequivalence studies. *Int J Clin Pharmacol Ther Toxicol* 1992;30:233–256.
66. Midha KK, Rawson MJ, Hubbard JW. Individual and average bioequivalence of highly variable drugs and drug products. *J Pharm Sci* 1997;86:1193–1197.
67. Blume HH, McGilveray IJ, Midha KK. BIO-international 94, Conference on Bioavailability, Bioequivalence and Pharmacokinetic Studies. *Eur J Pharm Sci* 1995;3:113–124.
68. Sallas WM, Nedelman JR, Sheiner LB, Meligeni JA, Robinson WT. A non-linear mixed effect model comparing two formulations of cyclosporine in stable renal patients. *J Pharmacokinet Biopharm* 1995;23:495–514.
69. Ohashi Y, Izumo T. Comparison of intra-subject variability of different formulations by cross-over trials. In: Midha KK, Nagai K, eds. *Bioavailability, Bioequivalence and Pharmacokinetic Studies.* Tokyo: Business Center for Academic Societies 1996;113–118.
70. Keown P, Landsberg D, Halloran P, et al. A randomized, prospective multicenter pharmacoepidemiologic study of cyclosporine microemulsion in stable renal graft recipients. *Transplantation* 1996; 12:1744–1752.
71. Neoral. Physician's Desk Reference, ed. 52. Montvale: Medical Economics Data Production Co. 1998:1882–1889.
72. McGilveray IJ, Gallicano K. Generic drugs: the Canadian perspective. *Transplant Proc* 1999;31 (suppl. 3A):16S–18S.
73. Hauck WW, Anderson S. Measuring switchability and prescribability: when is average bioequivalence sufficient? *J Pharmacokinet Biopharm* 1994;22:551–565.
74. Anderson S, Hauck WW. Consideration of individual bioequivalence. *J Pharmacokinet Biopharm* 1990;18:259–273.
75. Endrenyi L, Amidon GL, Midha KK, Skelly JP. Individual bioequivalence: attractive in principle, difficult in practice. *Pharm Res* 1998;15:1321–1325.
76. Laganière S, Lalonde RL, Potvin D, Kimanani EK. Comparison between individual (IB) and average bioequivalence (AB) for 3 highly variable drugs. *Clin Pharmacol Ther* 1998;63:145.
77. Kesten S, Scavuzzo M, Chaparro C, Szalai JP. Pharmacokinetic profile and variability of cyclosporine versus Neoral in patients with cystic fibrosis after lung transplantation. *Pharmacotherapy* 1998;18:847–850.
78. Cooney GF, Habucky K, Hoppu K. Cyclosporin pharmacokinetics in pediatric transplant recipients. *Clin Pharmacokinet* 1997;32: 481–495.
79. Schroeder TJ, Hariharan S, First MR. Variations in bioavailability of cyclosporine and relationship to clinical outcome in renal transplant subpopulations. *Transplant Proc* 1995;27:837–839.
80. Trull AK, Tan KKC, Tan L, Alexander GJM, Jamieson NV. Absorption of cyclosporine from conventional and new microemulsion oral formulations in liver transplant recipients with external biliary diversion. *Br J Clin Pharmacol* 1995;39:627–631.
81. Winkler M, Haller G, Oldhafer K, et al. Cyclosporin new oral

formulation for early oral immunosuppressive therapy in liver transplant recipients. *Transplantation* 1996;62:1063–1068.
82. Serafinowicz A, Gaciong Z, Baczkowska T, Majchrzak J, Durlik M, Lao M. Cyclosporine (Sandimmun) pharmacokinetics in renal allograft recipients with diabetes mellitus. *Polish J Immunol* 1995; 20:437–439.
83. Yee GC. Dosage forms of cyclosporine. *Pharmacotherapy* 1991; 11:149S–152S.
84. Cavanak T, Sucker H. Formulation of dosage forms. *Prog Allergy* 1986;38:65–72.
85. Min DI, Hwang GC, Bergstrom S, et al. Bioavailability and patient acceptance of cyclosporine soft gealtin capsules in renal allograft recipients. *Ann Pharmacother* 1992;26:175–179.
86. Zehender C, Beveridge T, Nüesch E, Abisch A, Thiel G. Cyclosporin A capsules: bioavailability and clinical acceptance study in renal transplant patients. *Transplant Proc* 1988;20:641–643.
87. Bleck JS, Nashan B, Christians U, Schottmann R, Wonigeit K, Sewing KF. Single dose pharmacokinetics of cyclosporine and its main metabolites after oral cyclosporine as oily solution or capsule. *Arzneimittelforschung* 1990;40:62–64.
88. Nashan B, Bleck J, Wonigeit K, et al. Effect of application form of cyclosporine on blood levels: comparison of oral solution and capsules. *Transplant Proc* 1988;20:637–639.
89. Hildebrands LB, Hoitsma AJ, van den Berg JWO, Koene RAP. Cyclosporin A blood levels during use of cyclosporin as oral solution or in capsules: comparison of pharmacokinetic parameters. *Transplant Int* 1991;4:125–127.
90. Kovarik JM, Mueller EA, Johnston A, Hitzenberger G, Kutz K. Bioequivalence of soft gelatin capsules and oral solution new cyclosporine formulation. *Pharmacotherapy* 1993;13:613–617.
91. Benet LZ, Wu CY, Hebert MF, Wacher VJ. Intestinal drug metabolism and antitransport processes: A potential paradigm shift in oral drug delivery. *J Controlled Release* 1996;39:139–143.
92. Sridhar N, Schroeder TJ, Hariharan S, Pesce AJ, First MR. Influence of concomitant medication on cyclosporine dosage and blood concentrations in renal allograft patients. *Clin Transplant* 1991;6: 134–141.
93. First RM, Schroeder TJ, Michael A, Hariharan S, Weiskittel P, Alexander JW. Cyclosporine-ketoconazole interaction. Long-term follow-up and preliminary results of a randomized trial. *Transplantation* 1993;55:1000–1004.
94. Liu JP. Use of the repeated cross-over designs in assessing bioequivalence. *Stat Med* 1995;14:1067–1078.
95. Pidgen A. Bioequivalence and generic prescribing: an industrial view. *J Pharm Pharmacol* 1996;48:11–16.