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REVIEW

Methods, strengths, weaknesses, and limitations of bioequivalence tests with special regard to immunosuppressive drugs

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Summary

Within the field of solid organ transplantation, the patents for a number of immunosuppressive drugs have expired in the last few years. Tacrolimus, cyclosporine, and mycophenolate mofetil are now available as generic drugs. In some countries, the market penetration of these generic formulations is as high as 70%, whereas in some other countries, this figure is below 10%. Several professional societies have published position papers on the risks and benefits of generic substitution of immunosuppressive drugs. It often appears that transplant professionals are not fully aware of the requirements for registration of generic drugs. This article describes the registration requirements with a focus on bioequivalence testing, the strengths and weaknesses in this process, and the differences between Europe and the US.

Introduction

Drug development is a costly business. The cost of bringing a new drug to the market is close to 1 billion Euros. Following registration, the pharmaceutical company needs to earn back the investment within the remaining duration of the drug patent, i.e. a period of about 10 years in most cases. Generic products are available once the patent protection afforded to the original developer has expired. Generic manufacturers do not incur the cost of drug discovery, nor do they have to bear the burden of proving the safety and efficacy of the drugs through clinical trials, since these trials have already been conducted by the brand name drug company. Recent trends in the US prescription drug market have continued to show slow growth and a shift toward the predominance of generic alternatives. Generic medications make up close to 75% of all drugs dispensed in the US [1].

For registration of the generic formulation, demonstration of bioequivalence with the original brand name product is sufficient. The availability of the much cheaper generic versions will lead to price competition and results in substantially lower prices for both the original brand name product and the generic formulation. An analysis completed in the United States (US) demonstrated that

when a generic drug is manufactured by one to four pharmaceutical companies, the generic retail price averages about 40% of the innovator product price. When more than 10 generic manufacturers enter the market, the average retail price generally falls to less than 25% of the innovator product price [2]. In these times of economical recession, the short-term gain of governmental institutions in reducing drug-related expenses by promoting generics may have implications for pharmaceutical industry and might compromise future drug development with companies only focusing on fast transition (development) molecules (e.g., oncology products) aimed at important markets. Consequently, smaller markets will be neglected.

Within the field of solid organ transplantation, the patents for a number of immunosuppressive drugs have expired in the last few years. Tacrolimus, cyclosporine, and mycophenolate mofetil are now available as generic drugs. In some countries, the market penetration of these generic formulations is as high as 70%, whereas in some other countries, this figure is below 10%. In 2011, the Danish Medicines Agency decided that generic substitution should no longer be possible for tacrolimus and cyclosporine. Several professional societies have published position papers on the risks and benefits of generic substitution of immunosuppressive drugs [3–9]. It often appears that transplant professionals are not fully aware of the requirements for registration of generic drugs. This article describes the registration requirements with a focus on bioequivalence testing, the strengths and weaknesses in this process, and the differences between Europe and the US.

Bioequivalence

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards [10]. Bioequivalence studies are typically single-dose studies performed in a small number (typically 24–48) of healthy volunteers. If two formulations are compared, a randomized, two-period, two-sequence single-dose cross-over design is recommended. Single-dose studies are generally more sensitive than multiple-dose studies in assessing release of the drug from the formulation into the systemic circulation. Each volunteer takes one dose of the reference product and after a wash-out period, one dose of the generic formulation (for half of the volunteers in the reverse order). Serum/plasma samples are obtained at regular intervals and assayed for the parent drug (or occasionally metabolite) concentration. The concentration data are used to assess key pharmacokinetic parameters such as the drug concentration versus time curves (AUC) and the peak concentration (C-max). The regulatory limits applied are that the 90% confidence intervals of the geometric means for the ratios (test:reference) of the AUC values and the C-max values must fall between 80% and 125%. (The confidence limits are asymmetrical because log-transformed data are used in the comparison.) For an illustration of possible bioequivalence study outcomes, see Fig. 1. These requirements for similarity between the two products are therefore in both the extent of absorption (AUC ratio) and the rate of absorption (C-max ratio). In the US, only the highest dose strength of an available drug product undergoes *in vivo* bioequivalence testing, whereas lower dose strengths undergo *in vitro* testing [11]. If a test product constitutes several strengths, it is sufficient to establish bioequivalence with only one strength, provided that linear pharmacokinetics for this drug has been demonstrated, i.e. a proportional increase in AUC and C-max with increased dose, over the therapeutic dose range. As an example: tacrolimus 5-mg capsules were studied in human bioequivalence studies under fasting and fed conditions, whereas the 0.5-mg and 1-mg capsules underwent *in vitro* dissolution testing only.

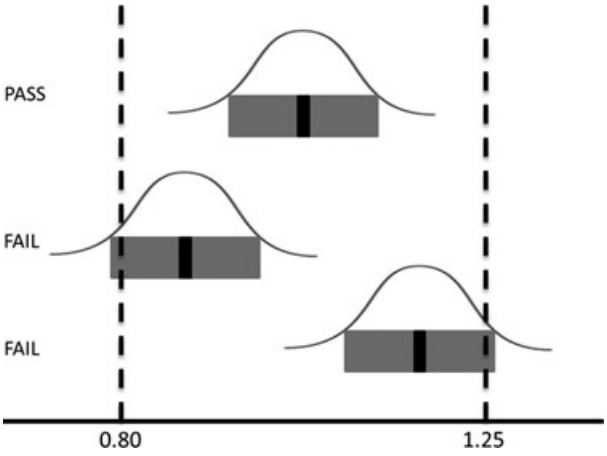

Figure 1 Illustration of possible bioequivalence study outcomes.

After Canada had done so already in 2006, also EMA has changed its policy for narrow therapeutic index drugs in 2010. For products with a narrow therapeutic index, the acceptance interval for AUC is now tightened to 90–111% [12]. Unfortunately, EMA indicates that they cannot define a set of criteria to categorize drugs as narrow therapeutic index drugs and it must be decided case by case if an active substance is a narrow therapeutic index drug based on clinical considerations. For the calcineurin inhibitors tacrolimus and cyclosporine, there is not much discussion that they do qualify as narrow therapeutic index drug, but for mycophen-

olate mofetil, this qualification is not granted. In the near future, also for mTOR-inhibitors patents will expire, and we assume also that for these drugs generic formulations will need to fulfill the stricter criteria. Remarkably, the United States Food and Drug Administration (FDA) has not changed its policy, and the 80–125% criteria are also applied to narrow therapeutic index drugs, including all immunosuppressive drugs. However, the FDA is considering tightening its approval criteria, especially for narrow therapeutic index (NTI), or critical dose, drugs. In April 2010, in an 11-to-2 vote, members of the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology suggested that the agency's confidence intervals for bioequivalence should be narrowed to a range of 90%–111% from the current range of 80%–125%, saying that the current intervals were not sufficient for generic NTI drugs [13]. The FDA is currently taking this recommendation under advisement.

Parent drug or metabolites

Evaluation of bioequivalence should be based upon measured concentrations of the parent compound. Also for inactive prodrugs, demonstration of bioequivalence for the parent compound is recommended. The reason is that C-max of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than C-max of a metabolite. Given the availability of sensitive bioanalytical assays, it is unusual that parent drug cannot be measured accurately and precisely. Mycophenolate mofetil (MMF), however, is subject to extensive presystemic metabolism to the active metabolite mycophenolic acid (MPA). MMF also has a short half life (less than 1 h). Plasma concentrations of MPA are 1000-fold higher compared with MMF. As a consequence, reliable estimation of C-max and AUC for MMF would be difficult. Therefore, for MMF, an exception was made. Demonstration of bioequivalence for the main active metabolite MPA without measurement of the parent compound MMF is allowed.

Trough, C-max, and AUC

In daily practice for several immunosuppressive drugs, therapeutic drug monitoring (TDM) is performed. The predose (generally referred to as trough) concentrations are the marker for drug exposure, and doses are adjusted based on these troughs. As stated above, for bioequivalence C-max and AUC are the parameters tested. Trough concentrations are not looked at in bioequivalence studies, and a statistical evaluation of the time to maximal concentration (t-max) is not required. There is no requirement for manufacturers of generic formulations to demonstrate that the relationship between trough concentrations and AUC is identical with the innovator drug, and that the same trough concentrations can be used as targets. For drugs where TDM is based on abbreviated AUC measurement, using so-called limited sampling strategies to predict AUC, differences in t-max or changes in the shape of the pharmacokinetic profile may lead to false predictions. For valid comparison between formulations, such data need to be provided, to allow regular drug monitoring to be performed under valid assumptions.

Fed or fasting conditions?

EMA asks that bioequivalence studies are conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations. For products where the Summary of Product Characteristics (SmPC) recommends intake of the reference product on an empty stomach or irrespective of food intake, the bioequivalence study should be conducted under fasting conditions. For products where the SmPC recommends intake of the reference product only in the fed state, the bioequivalence study should generally be conducted under fed conditions.

However, for products with specific formulation characteristics (e.g., microemulsions, solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required unless the product must be taken only in the fasted state or only in the fed state.

In cases where information is required in both the fed and fasted states, it is acceptable to conduct either two separate two-way cross-over studies or a four-way cross-over study.

The FDA requires all medications where food is known to affect absorption, to have bioequivalence studies performed in both fasted and fed state [14]. In 2000, the FDA announced that SangStat Medical Corporation had agreed to recall all lots of SangCya (cyclosporine) oral solution because of clinical evidence that the generic drug is not bioequivalent to Novartis AG's Neoral oral solution when mixed with apple juice as recommended in its labeling.

An example of a bioequivalence study in fasted and fed state is given in Table 1. This table shows the results from a bioequivalence study comparing innovator cyclosporine

Table 1. Results from bioequivalence studies comparing innovator cyclosporine (Sandimmune Optoral 25-mg capsules) and generic cyclosporine (producer: International Drug Licensing).

	Fasted Ratio (%) for test/reference product (90% CI)	Fed Ratio (%) for test/reference product (90% CI)
AUC (0–inf), ng/h/ml	95.1 (92.2; 97.9)	109.6 (103.2; 116.3)
C-max, ng/ml	88.2 (84.1; 92.4)	122.5 (108.9; 137.8)

and generic cyclosporine. The data show that the AUC ratio for test/reference product (92.2; 97.9) is within the 90–111% range for the study performed under fasted conditions, but that in fed state, the upper value of the confidence interval exceeds the upper limit (103.2; 116.3). The confidence interval for the C-max ratio under fed conditions was even outside of the 80–125% limit (108.9; 137.8). Based on these studies in 2009, the Committee for Medicinal Products for Human Use (CHMP) concluded that the data were not adequate to confirm the bioequivalence of this medicine with the reference medicine, and marketing authorization was not granted [15].

Comparison with innovator drug only

When a patent expires, there are usually several generic manufacturers that develop a generic formulation. All these companies are required to test their drug against the innovator drug. There is no requirement to demonstrate bioequivalence with the other generic formulations, and all generics are considered interchangeable. It is argued that although the generic formulations have not been directly compared in a formal bioequivalence study, it would be unlikely that they would fail if directly compared [16]. This is a shortcoming of the registration process. If generic formulation A has 90% confidence intervals for the ratios (test:reference) of the AUC and the C-max that fall close to the upper limit of the range of 80–125%, and generic B is close to the lower limit of this range, then it may very well be that A and B are not bioequivalent. Regulators argue that it would be practically and financially very difficult to require each brand to be compared with every other brand in formal bioequivalence studies. For the second and third generic formulation, we do not think this would be a real hurdle. Instead of only one bioequivalence study with the innovator drug, the generic manufacturer would have to do two or three bioequivalence studies, also comparing their generic with the already available generic formulations. By the time the sixth or seventh generic formulation is being developed, the number of required bioequivalence studies indeed exceeds the realistic situation. But why would we need six or seven different formulations? Having just 2 or 3 or 4 seems like enough. As substitution from one generic formulation to another will almost certainly happen, often under uncontrolled conditions, this requirement should be added to the registration process.

Healthy volunteers or transplant recipients?

Registration authorities ask for bioequivalence studies in healthy volunteers only, unless the drug carries safety concerns that make this unethical. Healthy volunteers are regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the reference medicinal product is approved (the elderly, children, patients with renal or liver impairment, etc.). We do agree that requiring bioequivalence studies in transplanted patients is not realistic [17]. Compared with healthy volunteers in patients there is a higher degree of intra-subject variability. This variability will make it more difficult to demonstrate bioequivalence, and studies would have to include substantially more subjects to bring the 90% confidence intervals for the ratios within the bioequivalence limits. We would not want to advocate a plethora of studies in all sorts of subgroups (ethnicity, children, elderly, cystic fibrosis patient, liver, lung, heart, etc.). In some cases, to fulfill the perceived need for bioequivalence studies in patient populations, generic manufacturers have sponsored studies in transplanted patients [18–21]. These studies were not required by the registration authorities. The main goal was to convince transplant physicians that the generic product was also bioequivalent with the innovator drug in the target patient groups. The information generated in these studies is very helpful and manufactures should be encouraged to support such investigations.

It has been argued that although the innovator and generic formulation contain the same active substance, difference in excipients may impact on the disposition of co-administered drugs. An example of such a phenomenon is the study by Kovarik *et al.* [22], where sirolimus pharmacokinetics were different in the presence of generic versus innovator cyclosporine.

Shape and color of the tablets and capsules

The regulatory agencies do not require that generic formulations have the same shape and color as the innovator drug. Differences in shape or color between the generic and innovator drug may result in confusion of the patient. Changes in the purchase policy of either the pharmacist or the health insurance company will lead to dispensing of numerous generic formulations from various origins over time. Most patients will be able to figure out that these generic tablets and capsules that look different are in boxes with different print and are labeled with different brand names in fact contain the same active substance. However, a proportion of patients will be confused and make mistakes. They may not realize it is the same drug, and take doses from different manufacturers at the same time, leading to over-exposure, potentially with severe toxicity as an outcome. Or they are so confused that they decide not to take the drugs at all, and show them to their transplant physician at the next outpatient visit and discuss with him or her what to do. This may lead to under-exposure, potentially leading to serious acute rejections that may result in graft loss. Besides the personal drama, the financial cost of such complications may outweigh the potential savings associated with generic sub-

stitution. Dispensing pharmacists of course should take care of informing the patient on any substitutions, and ensure that the patient can identify the different formulations correctly [23]. In the US, transplant centers are required to have a dedicated clinical pharmacist in their team, and this pharmacist would be well equipped to take care of patient education and medication reconciliation. In Europe, however, the multidisciplinary transplant teams typically do not have a pharmacist. We strongly would recommend that following a first substitution from the innovator drug to a generic formulation, there should be no subsequent generic–generic substitution. To avoid such subsequent substitutions, the prescription of a so-called branded generic is recommended, as for the dispensing pharmacist, it shows that not just any generic formulation is okay. Dispensing of immunosuppressive drugs through one or more designated pharmacies may be a solution to achieve better control over what product is handed to the patient.

Clinical outcome or bioequivalence only?

EMA and FDA do not ask for clinical outcome data for registration of generic drugs. Therapeutic equivalence is assumed on the basis of bioequivalence. We do agree that with the same molecular entity, it is unlikely that a difference in drug exposure that is less than 20% will result in a difference in clinical outcome. The currently used combination of induction therapy followed by a calcineurin inhibitor, MPA, and steroids results in incidences of acute rejection that have reached percentages below 10%. To demonstrate noninferiority, one would need to study large numbers of patients, and it is not realistic to expect this will be done. There are published papers of studies investigating clinical outcome in innovator versus generic drug in transplanted patients, but these studies are underpowered [24–26]. In the transplant field, there have been numerous studies comparing standard dose immunosuppressive treatment with reduced dose regimens. Despite differences in drug exposure that were considerably higher than 20%, many of these studies did not show a difference in the incidence of acute rejections [27–29]. One could also argue that a formal head-to-head trial comparing the innovator drug with one specific generic formulation in newly transplanted patients would not reflect the way these generics will be used in clinical practice. In the clinical trial setting, all patients randomized for generic drug will be supplied with the same formulation of the drug throughout the duration of the study. In real life, patients will be faced with repetitive switches from one generic to the other, or even worse with dispensing of different strengths of the same drug from different manufacturers at the same time. Often such substitutions will be made on the initiative of the pharmacist or insurance company, without informing the prescribing physician, who then is unable to monitor drug exposure following these substitutions.

The perspective of the patient

Patients often suspect that cost-driven substitutions may compromise their quality of care. They have been treated with the originator drug for considerable time, with good experience, and they feel uncertain to switch to another formulation, even with their doctor's consent. A survey in the UK showed that 84% of renal transplant patients felt that generics are not equivalent or only equivalent sometimes and that they were uncertain that generics had the same quality as branded medicines [30]. In the US, a survey among 255 transplant recipients showed that 81 patients (32%) had been converted to a generic immunosuppressant, but 25% of converted patients did not believe that there was equivalence between generic and brand products [31]. When patients are not allowed to choose freely, this may affect their adherence to medication, intentional, or unintentional, potentially influencing clinical outcome. For epilepsy patients, it was shown that adherence to medication in the course of time may change, sometimes as a consequence of receiving a generic that is not trusted [32]. Forcing generic substitution upon patients seems incompatible with a patient-centered medicine [33].

Pharmaceutical quality

A large portion of medications approved for use in the United States and European Union are either fully manufactured in foreign countries or manufactured domestically using foreign-made ingredients, which has raised the question about the importance of pharmaceutical quality. In the US, the number of foreign-made pharmaceuticals doubled between 2004 and 2009 [34]. Given these concerns, the FDA has instituted a policy that it will inspect domestic and foreign establishments prior to approving any new drug product. The FDA has inspectors located in China, India, Africa, Australia, New Zealand, the Middle East, Europe, and Latin America. The FDA also collaborates with foreign regulatory agencies to discuss relevant information about pharmaceutical products. After initial inspection prior to FDA approval, the agency is charged with inspecting each manufacturer every 2 years for compliance with Good Manufacturing Practice (GMP); however, given the limited resources to accomplish this, the FDA has developed a risk-based process to select manufacturers for inspection. This process results in inspecting only a small percentage of foreign manufactures. For example, in 2007, the agency inspected fewer than 11% of approved foreign manufacturing facilities [35]. The Generic Pharmaceutical Association supports measures to strengthen the foreign drug inspection system by increasing funding for FDA inspections through registration or inspection fees paid by the manufacturer; establishment of one uniform, high-

quality inspection system for both domestic and foreign facilities; and implementing a better "risk-based" approach to inspections, so that more attention is focused on those facilities at greatest risk [36].

Also, EMA provides guidance regarding GMP for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. The guidance is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess [37].

Conclusion

Concerns continue to exist among practitioners and patients regarding generic formulations of narrow therapeutic index drugs. These concerns stem from, among other reasons, the need for only bioequivalence testing in healthy volunteers to receiving regulatory approval and marketing. Although in Europe and Canada, more stringent criteria to attain bioequivalence are used compared with the United States, generic drugs have not been introduced into transplant medicine in higher proportions of patients. Especially the fear for subsequent uncontrolled substitutions, following a first substitution from innovator drug to a generic formulation, causes prescribers to choose for innovator drug. Generic substitution in organ transplantation should be done in a consistent manner, utilizing TDM to maximize outcomes. Avoiding confusion and mistakes by patients can only be reached if subsequent generic –generic substitution is not done. Substitution of the brand name drug for a generic formulation should only be initiated by the transplant physician. Only when the initiative for generic substitution comes from the prescriber, can appropriate monitoring of the drug blood concentrations be ensured. Pharmacists and health insurance providers should refrain from forcing generic substitution. Prescription of a so-called branded generic may help to avoid such subsequent substitutions.

References

1. Generic Pharmaceutical Association. 2010. Annual report: www.gphaonline.org.
2. Frank RG. The ongoing regulation of generic drugs. *New Engl J Med* 2007; **357**: 1993.
3. Pollard S, Nashan B, Johnston A, *et al.* CONSENT: Consensus on Substitution in European Transplantation. A pharmacokinetic and clinical review of the potential clinical impact of using different formulations of cyclosporin A. *Clin Ther* 2003; **25**: 1654.
4. Uber PA, Ross HJ, Zuckermann AO, *et al.* Generic drug immunosuppression in thoracic transplantation: an ISHLT educational advisory. *J Heart Lung Transplant* 2009; **28**: 655.
5. KDIGO clinical practice guideline for the care of kidney transplant recipients. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. *Am J Transplant* 2009; (9 Suppl 3): S1.
6. Christians U, Klawitter J, Clavijo CF. Bioequivalence testing of immunosuppressants: concepts and misconceptions. *Kidney Int Suppl* 2010; **115**: S1.
7. Van Gelder T. ESOT Advisory Committee on Generic Substitution. European Society for Organ Transplantation Advisory Committee recommendations on generic substitution of immunosuppressive drugs. *Transpl Int* 2011; **24**: 1135.
8. Klintmalm GB. Immunosuppression, generic drugs and the FDA. *Am J Transplant* 2011; **11**: 1765.
9. Harrison JJ, Schiff JR, Coursol CJ, *et al.* Generic immunosuppression in solid organ transplantation: a Canadian perspective. *Transplantation* 2012; **93**: 657.
10. Birkett DJ. Generics: equal or not? *Aust Prescr* 2003; **26**: 85.
11. Davit BM, Nwakama PE, Buehler GJ, *et al.* Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. *Ann Pharmacother* 2009; **43**: 1583.
12. Guideline on the investigation of bioequivalence. EMA. http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf (last accessed 9 October 2011).
13. U.S. FDA. Summary Minutes of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM210930.pdf (last accessed 2 December 2012).
14. U.S. FDA. Guidance for Industry. Food-effect bioavailability and fed bioequivalence studies. http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126833.pdf (last accessed 22 October 2009).
15. EMA. Doc. Ref. EMEA/CHMP/466894/2009 http://www.emea.europa.eu/docs/en_GB/document_library/Referrals_document/Ciclosporin_IDL_29/WC500014145.pdf (last accessed 30 July 2009).
16. Maliepaard M, Hekster YA, Kappelle A, *et al.* Requirements for generic anti-epileptic medicines: a regulatory perspective. *J Neurol* 2009; **256**: 1966.
17. Latran M. Response to Klintmalm on the use of generic immunosuppression. *Am J Transplant* 2012; **12**: 791; author reply 794.
18. Vítko S, Ferkl M. Interchangeability of ciclosporin formulations in stable adult renal transplant recipients: comparison of Equoral and Neoral capsules in an international, multicenter, randomized, open-label trial. *Kidney Int Suppl* 2010; **115**: S12.
19. Momper JD, Ridenour TA, Schonder KS, Shapiro R, Humar A, Venkataramanan R. The impact of conversion from prograf to generic tacrolimus in liver and kidney transplant

recipients with stable graft function. *Am J Transplant* 2011; **11**: 1861.
20. Sunder-Plassmann G, Reinke P, Rath T, *et al.* Comparative pharmacokinetic study of two mycophenolate mofetil formulations in stable kidney transplant recipients. *Transpl Int* 2012; **25**: 680.
21. Alloway RR, Sadaka B, Trofe-Clark J, Wiland A, Bloom RD. A randomized pharmacokinetic study of generic tacrolimus versus reference tacrolimus in kidney transplant recipients. *Am J Transplant* 2012; **12**: 2825.
22. Kovarik JM, Noe A, Wang Y, Mueller I, DeNucci G, Schmouder RL. Differentiation of innovator versus generic cyclosporine via a drug interaction on sirolimus. *Eur J Clin Pharmacol* 2006; **62**: 361.
23. Greene JA. The substance of the brand. *Lancet* 2011; **378**: 120.
24. Roza A, Tomlanovich S, Merion R, *et al.* Conversion of stable renal allograft recipients to a bioequivalent cyclosporine formulation. *Transplantation* 2002; **74**: 1013.
25. Hibberd AD, Trevillian PR, Roger SD, *et al.* Assessment of the bioequivalence of a generic cyclosporine A by a randomized controlled trial in stable renal recipients. *Transplantation* 2006; **81**: 711.
26. Rutkowski B, Bzoma B, Dębska-Ślizień A, Chamienia A. Immunosuppressive regimens containing generic mycophenolate mofetil (Myfenax) in de novo renal transplant recipients–preliminary results of 6-month observation. *Ann Transplant* 2011; **16**: 74.
27. Ekberg H, Tedesco-Silva H, Demirbas A, *et al.* ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007; **357**: 2562.
28. Nashan B, Saliba F, Durand F, *et al.* Pharmacokinetics, efficacy, and safety of mycophenolate mofetil in combination with standard-dose or reduced-dose tacrolimus in liver transplant recipients. *Liver Transpl* 2009; **15**: 136.
29. Lehmkuhl HB, Arizon J, Viganò M, *et al.*; 2411 Study Investigators. Everolimus with reduced cyclosporine versus MMF with standard cyclosporine in de novo heart transplant recipients. *Transplantation* 2009; **88**: 115.
30. Al Ameri MN, Whittaker C, Tucker A, Yaqoob M, Johnston A. A survey to determine the views of renal transplant patients on generic substitution in the UK. *Transpl Int* 2011; **24**: 770.
31. Hulbert AL, Pilch NA, Taber DJ, Chavin KD, Baliga PK. Generic immunosuppression: deciphering the message our patients are receiving. *Ann Pharmacother* 2012; **46**: 671.
32. Cramer JA, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. *Epilepsy Behav* 2002; **3**: 338.
33. Al Ameri MN, Epstein M, Johnston A. Generic and therapeutic substitutions: are they always ethical in their own terms? *Pharm World Sci* 2010; **32**: 691.
34. FDA. How does FDA oversee domestic and foreign drug manufacturing? http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194989.htm (last accessed 1 December 2012).
35. FDA. Drug Safety. http://www.gao.gov/assets/120/119754.pdf (last accessed 1 December 2012).
36. Generic Pharmaceutical Association. http://www.gphaonline.org/issues/foreign-inspectionsreimportation (last accessed 2 December 2012).
37. EMA. ICH Topic Q 7. Good Manufacturing Practice for Active Pharmaceutical Ingredients. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002825.pdf (last accessed 1 December 2012).