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EDUCATIONAL REVIEW

# Generic immunosuppressants

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**Abstract** Immunosuppressive drugs for solid organ transplantation are critical dose drugs with a narrow therapeutic index. Many of the most commonly used innovator drugs are off patent and have been replicated by generic counterparts, often at substantial cost-savings to the patient. However, serious adverse events caused by the transition from innovator to generic medications, specifically in pediatric solid organ transplant recipients, have questioned these autosubstitutions. The purpose of this review is to summarize the criteria set forth by the regulatory bodies, and to examine how major immunosuppressive drugs conform to these recommendations. Regulatory bodies have established inconsistent criteria to demonstrate bioequivalence between innovator and generic medications, causing approved generic variations to have varying levels of equivalence with the innovator drugs. In order to minimize the risk for under-immunosuppression, the following recommendations have been concluded. Brand prescribing of cyclosporine and tacrolimus are recommended due to evidence of adverse events after conversion to generic formulations and differences in dissolution parameters. Mycophenolate mofetil (MMF) shows better bioequivalence between innovator and generic formulations, however caution should be advised when switching between formulations. The institution of 'innovator only' policies may be appropriate at this time in order to minimize the risk of under-immunosuppressing patients until the evidence of more stringent bioequivalence has been established.

**Keywords** Calcineurin inhibitors · mTOR inhibitors · Antimetabolites · MMF · Tacrolimus · Sirolimus

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## Introduction

The substitution of brand name drugs with their generic equivalents is often performed without hesitation. It is believed that these drugs offer similar efficacy at a fraction of the price of their innovator counterparts. With so many health care systems struggling to balance the needs of their patients with financial realities, the choice appears self-evident. Unfortunately, in the world of pediatric transplantation, the

quick substitution of immunosuppressants requires careful consideration.

The enactment of the 1984 Hatch–Waxman Act, which generated the Abbreviated New Drug Application (ANDA), enticed generics manufacturers to target drugs with weaker patents in the legal realm [1]. This has resulted in the rapid availability of generic drugs, including immunosuppressants. Not surprisingly, generic drug producers disproportionately target drugs with the highest profit margin [2], leading to healthy competition, thereby reducing the overall price for consumers [3]. This reduction in drug costs has been very advantageous, having resulted in a savings of approximately $1 trillion for the US Health care system from 2002 to 2011 [4]. While on paper this appears to be a win for all but "Big Pharma", its success hinges on one assumption; that generic drugs are equivalent to their brand name counterparts when used chronically in the intended patient population.

There is considerable variability among licensing organizations in the world. According to the Food and Drug Administration (FDA), generic medications are expected to be bioequivalent to the corresponding reference originator. Two formulations are considered bioequivalent when the 90% confidence interval ratio of the test-to-reference formulation for a bioavailability measure is within 80 and 125%, arising from a bioequivalence study. While this may be an acceptable level for most generic medications, there exists a subset known as critical dose drugs (CDD). The FDA does not make special provisions for CDDs. By contrast, Health Canada has much more stringent criteria and defines CDD as "drugs where comparatively small differences in dose or concentration lead to serious dose- and concentration-dependent therapeutic failures and/or serious adverse drug reactions." Health Canada recognizes only nine critical dose drugs, three of which are commonly used in renal transplantation: cyclosporine, tacrolimus, and sirolimus. In fact, unfavorable outcomes associated with the substitution of innovator drugs with imitator drugs have been reported in pediatric transplant recipients [5–8]. With such a narrow therapeutic index, and the fact that many generic drugs are not tested for bioequivalence in children or in renal transplant patients [9], there is warranted concern. The most important antirejection drugs, calcineurin inhibitors (cyclosporine and tacrolimus), antimetabolites (mycophenolate mofetil (MMF), and enteric coated mycophenolate sodium (ECMPS)) are now off patent and generic equivalents have entered the market. Predictably, uptake has been swift in clinical practice, often with pharmacy substitution unbeknownst to the patient or physician [10]. While the system and patients are able to save money through decreased medication costs, there is the question of whether we can afford to gamble with the significant consequences, including acute rejection episodes or even graft loss and death. We therefore reviewed the available literature on the topic of generic immunosuppressants in pediatric transplantation to develop general recommendations about generic immunosuppressant use in the pediatric transplantation setting.

## What are the requirements for licensing generic immunosuppressants?

For this educational review, we will list some of the data available in the literature meeting American, European and/or Canadian guidelines regarding generic pharmaceutical licensing. Unfortunately, there exists much variability between each guideline. Special considerations will be given to discussions regarding narrow therapeutic index drugs.

## Food and Drug Administration (FDA) criteria

The FDA requirements for generic immunosuppressants are identical to those of all other generic drugs—no consideration is given to the fact that they are CDDs. Rather than requiring preclinical and clinical data to establish safety and effectiveness, the FDA assumes a similar safety profile as long as the generic drug is shown to be bioequivalent to the existing innovator drug in normal healthy subjects [11]. This requires that the generic drugs have the same amount and same type of active principle, the same route of administration, and the same therapeutic effectiveness as the original drug (United States Food and Drug Administration. Code of Federal Regulation, Title 21, Part 320 B. (IDRAC N°8425): URL https://cortellis.thomsonreuterslifesciences.com/ngg/report/ri/regulatory/8425 (08/Jan/2014). However, bioequivalence and therapeutic effectiveness are not necessarily the same. Ultimately, the clinician wants the same efficacy with no rejection and minimal toxicity. According to the FDA, if two drug products with the same qualitative and quantitative active ingredient are shown to be bioequivalent with a 90% confidence interval (CI) and an acceptance range of 80–125%, it is assumed that their in vivo performance, safety, and efficacy are comparable as well [12].

This criterion may be insufficient for CDDs (cyclosporine, tacrolimus, sirolimus), and MMF and for most immunosuppressants [13]. As such, this concept may be particularly important in transplant settings.

## European Medicines Agency (EMA) and Health Canada criteria

The main difference between the FDA criteria in the US and EMA criteria is the fact that the European Union has special considerations for pharmaceuticals with a narrow therapeutic index. The EMA gives a limit of 90.00 to 111.11%, which is a much narrower acceptance range (Committee for Medicinal

Products for Human Use. Guideline on the investigation of bioequivalence. CPMP/EWP/QWP/1401/98 Rev.1/ Corr**.2010. (IDRAC N°120,848): URL https://cortellis.thomsonreuterslifesciences.com/ngg/report/ri/regulatory/120848 (14/Jan/2014)). Similarly, Canada has stricter guidelines with an AUC acceptance interval from 90 to 112% (Health Canada. Guidance document-comparative bioavailability standards: formulations used for systemic effects. 2012. www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/gd_standards_ld_normes-eng.php-a2.1.).

## COFEPRIS criteria

In Mexico, COFEPRIS (Comisión para la Protección de Riesgos Sanitarios) authorizes the drug formulation of both innovator and generic drugs. Prior to 2013, bioequivalence for narrow therapeutic index drugs was deemed true if the 90% confidence intervals of the geometric mean $C_{max}$ and AUC test/reference ratios were within the limits of 80 to 125%, allowing a variation in bioequivalence of –20% to +20% between formulations. However, on May 6, 2013, the limits were tightened to align more similarly with the EMA and Health Canada. Currently, bioequivalence for CDDs is only considered true if the $C_{max}$ and AUC test/reference ratios fall within the limits of 90 to 110% (http://dof.gob.mx/nota_detalle.php?codigo=5314833&fecha=20%2f09%2f2013). Nevertheless, most of the generics of the triple therapy used in Mexico in transplant recipients (tacrolimus, mycophenolate, and prednisone) were approved before 2013, and thus not subject to these stricter regulations.

**Key points:**

The guidelines for licensing generics vary widely by country.

The FDA does not provide for special considerations for critical dose drugs.

Special considerations should be given to critical dose drugs.

The strict European guidelines should be adopted and monitored world-wide.

## Arguments in favor of using generic immunosuppressants

The main argument in favor of using generic immunosuppressants is cost. In the United States of America, considered to be the largest pharmaceutical market in the world, the use of generic medications increased from 19% of all prescribed drugs in 1984 to 75% in 2009, with an estimated savings of 70–80% of the cost compared to the innovator [14]. Transplant recipients are prescribed immunosuppressive drugs for as long as they have a functioning graft, and with the number of transplant recipients increasing constantly, it is attractive to any health system to have a low cost option for treatment and medications.

## Arguments against the use of generic immunosuppressants

An increasing number of generic immunosuppressive drugs have been made available for use in patients with solid organ transplants. These CDDs have been approved by agencies using standards that either do not appreciate the sensitive nature of these drugs or are now based on outdated bioequivalence standards [8, 15]. Given the potential for organ rejection with inadequate immunosuppression, there is growing concern that the current criteria for approval are not rigorous enough. Unfortunately, there is a lack of high-quality data supporting bioequivalence between generic and innovator immunosuppressive drugs, especially in children, with most bioequivalence studies being demonstrated in healthy adult volunteers (European Medicines Agency.

Guideline on the investigation of bioequivalence [homepage on the Internet]. 2010 [cited 2013 Mar 27]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf.). Data in real patients would be more appropriate due to drug interactions, altered intestinal transit times, altered renal and hepatic function, metabolizer status, ethnic background, and many other factors that may alter the bioequivalence and overall effect.

It could be argued that there may be significant differences with regards to generic immunosuppressants. Whereas some from industrialized nations may have higher standards, they may be lower in developing nations. Unfortunately, there are no good data about this perception. The following recommendations for each drug are based on the available data at the time of the publication of this review.

In the following three sections, we review the scant data available in patients for the three most important immunosuppressants, namely cyclosporine, tacrolimus, and MMF. Unfortunately, the data are largely from adult patients.

## Cyclosporine

Cyclosporine is the first calcineurin inhibitor to come off patent. It was introduced by Borel and Feurer in 1977 [16]. The introduction of this drug has revolutionized transplant medicine and dramatically improved the 1-year graft survival [17]. At the time of the patent expiry, the manufacturer used an unprecedented tool to maintain the profit of this blockbuster drug: a different, micoremulsified formulation (Neoral®) with more reliable pharmacokinetics was introduced. Unfortunately, the bioequivalence was not well studied, and many problems occurred after a one-to-one conversion, including rejections and graft loss [18]. Since Neoral® came off patent, a number of studies have compared the bioavailability of generic cyclosporine, namely 28 studies in kidney transplant recipients, one in liver transplant recipients, and three in heart transplant recipients [15]. Of these, 12 were randomized controlled clinical trials, with the majority in renal transplantation [15]. Ten studies reported 90% confidence intervals for the area under the time concentration curve (AUC) and maximum concentration ($C_{max}$) [19–27]. Molnar et al. pooled these studies to a meta-analysis and systematic review [15] and found that among the randomized controlled trials comparing the mean AUC ratio, the pooled estimate of the 90% confidence interval was 0.93 (0.89 to 0.98), which met the FDA criteria, but failed to meet the EMA and Health Canada requirement. For the maximum concentration, the pooled estimate of the 90% confidence interval was 0.90 (0.85 to 1.02) in the randomized controlled clinical trials, which met the FDA and Health Canada requirements, but again failed the EMA criteria. The meta-analysis of acute rejection between Neoral® and generic immunosuppressive cyclosporine formulations in both randomized controlled clinical trials and observational studies favored the innovator drug with a Peto odds ratio of 0.66 [15, 28].

Unfortunately, the pediatric literature is scant. Riva et al. performed a conversion study from innovator to generic cyclosporine, and observed a 16.7% drop of the AUC and a 13.1% drop of the 2-h concentration. In some patients, a drop of the AUC of as much as 56.7% was observed. They concluded the need for very close monitoring [29]. Based on the meta-analysis and the scant pediatric studies, a switch from innovator to imitator microemulsified cyclosporine will require very close monitoring and may lead to unfavorable outcomes. The authors suggest that such a conversion should not be recommended.

**Key points:**

The risk for under-immunosuppression with cyclosporine must be minimized.

Brand prescribing and dispensing of cyclosporine is necessary except for perhaps some de-novo patients that remain on the same generic cyclosporine throughout.

A generic cyclosporine adhering to the strict European guidelines would be preferred.

It is important not to switch formulation except on the advice of the transplant physician.

Therapeutic drug monitoring of cyclosporine therapy is essential.

## Tacrolimus

Tacrolimus is also a macrolide calcineurin inhibitor, obtained from *Streptomyces tsukubaensis* in Japan in 1984 by T. Goto, T. Kino, and H. Hatanka, and approved by FDA for use in solid organ transplantation in 1994 [30]. After a randomized controlled trial demonstrating superior outcome and fewer cosmetic adverse events [31–33], tacrolimus rapidly became the predominantly used calcineurin inhibitor in pediatric transplantation. The 2014 North American Renal Transplant Collaborative Study (NAPRTCS) Annual Report demonstrated an increase of the utilization of tacrolimus at 3 years post kidney transplantation from 43% in the era 1996–2001 to 82% in the era 2008–2013, while cyclosporine utilization decreased from 50% to 1.1% in the same period of time. https://web.emmes.com/study/ped/annlrept/annualrept2014.pdf.

Tacrolimus is considered a class II drug in the biopharmaceutical classification system, meaning that it has low solubility and high permeability. Therefore its dissolution in the gastrointestinal tract is a rate-controlling step for absorption [34, 35]. Several non-innovator tacrolimus formulations from different countries (Tenacrine®, Framebin®, and Talgraf®) exhibit inferior dissolution parameters with regard to the innovator, Prograf®. They exhibited slower and incomplete dissolution releasing 21–51% of tacrolimus at 2 h whereas the innovator Prograf® had complete dissolution [36]. Another generic tacrolimus available in Mexico, Limustin®, yields similar trough levels as Prograf® in pediatric patients but has lower AUC and $C_{max}$, explained by its lower dissolution profile [5]. In the aforementioned adult meta-analysis [15], three randomized controlled clinical trials were included that reported the primary pharmacokinetic outcome of the AUC and $C_{max}$. The 90% confidence intervals for both parameters mean ratios of the pooled data did not meet FDA, EMA, or Health Canada bioequivalence criteria [15]. Fortunately, there were no significant differences with regards to rejection episodes and graft loss or serum creatinine observed [15]. In pediatric renal transplant recipients in the USA, lower tacrolimus trough levels have been reported when patients were switched to generics, requiring dose adjustments and close follow-up [37]. In a population pharmacokinetic study of tacrolimus in pediatric patients, the *CYP3A5* gene polymorphism and formulation type were the most important variables for the population model [38]. Taken together, the substitution of brand-name tacrolimus with generics cannot be recommended.

**Key points:**

The risk for under-immunosuppression with tacrolimus must be minimized.

Brand prescribing and dispensing of tacrolimus is mandatory.

It is important not to switch formulation.

Therapeutic drug monitoring of tacrolimus therapy is essential.

## MMF

Within a short time after the introduction of mycophenolate mofetil (MMF), it had almost completely replaced azathioprine, which was the most widely used antimetabolite antirejection drug until the mid 1990s [39]. MMF is now the most widely used antirejection drug in pediatric renal transplantation [40, 41]. The drug is also frequently used in hematopoietic stem cell transplants, liver and intestinal transplantation [42], and in pediatric heart transplantation [43]. This drug was not considered a CDD, although recent evidence suggests a need for therapeutic drug monitoring of MMF and maintaining a minimum exposure to avoid rejection [44]. There is strong evidence that underexposure with an AUC of less than 30 mg*h/l early after renal transplantation may cause rejection [45, 46]. International consensus guidelines recommend monitoring for both adults [47] and children [48]. There is also emerging evidence that underexposure of mycophenolic acid

(MPA) over time may be associated with the formation of donor-specific antibodies [49].

Generic MMF was first developed in 2004 [50]. A well-conducted, single-dose, two-way crossover, bioequivalence study of mycophenolate mofetil 500 mg tablet under fasting conditions in healthy male subjects demonstrated agreement with the strict European regulatory criteria [51].

In the aforementioned meta-analysis on generic immunosuppressants by Dr. Greg Knoll's group [15], six studies used MMF, including two RCTs in kidney transplant recipients. One study (crossover trial in kidney transplants) reported the AUC and $C_{max}$ mean ratios and 90% confidence intervals as 0.959 (0.899 to 1.023) and 0.873 (0.787 to 0.968), respectively [52]. These values did not fulfill any of the FDA, EMA, or Health Canada requirements for bioequivalence. The authors also pooled acute rejection for the observational studies (6-month outcomes) and found no significant difference for rejection (Peto odds ratio 0.49, but 95% confidence interval from 0.09 to 2.56) [15]. Pediatric studies are also scant. One study that included a few heart transplant children suggested that there was no difference in the tacrolimus trough levels of the concomitantly given calcineurin inhibitor between the two MMF formulations [53]. Unfortunately, this study was not very helpful because only trough levels were compared. By contrast, a study by Gonzalez-Ramirez et al. that measured MPA pharmacokinetic profiles in a small and heterogeneous group of transplant recipients found no difference in the exposure, expressed as AUC, between Tevacept® and the innovator drug [54]. There seem to be no other data available and the limitations of the Tevacept® study have been highlighted [8]. On the other hand, based on some case reports, Teun van Gelder et al. are warning against careless switching between different formulations. They state: "MMF and EC-MPS are therapeutically equivalent. Although neither is considered to be a narrow therapeutic index drug, this should not lead to careless switching between the innovator drug and generic formulations, or between one generic formulation and another." [55].

Since the current data is so incomplete, the authors of this educational review really must advocate for additional prospective studies. It does appear that conversion to generic MMF is much less problematic than conversion to generic calcineurin inhibitors, however caution should be advised when switching between formulations.

**Key points:**

The risk for under-immunosuppression with MMF must be minimized.

A generic MMF adhering to the strict European guidelines would be preferred.

Brand prescribing and dispensing of MMF may not be necessary, but the same formulation should be used throughout.

It is important not to switch formulation except on the advice of the transplant physician.

The role of therapeutic drug monitoring of MMF therapy requires further evaluation.

## Additional considerations

The general take-away from this is that the risk for under-immunosuppression must be minimized. A transplant organ is a scarce resource and its long-term survival relies importantly on the quality of immunosuppression and organ rejection prevention. Several governments and societies have discussed the matter and offered thoughtful evaluations. As a rule, the generic replacement of the innovator drugs have a lower bioavailability [15]. The Canadian Society of Transplantation (CST) conducted a thorough review of the available literature and recommended extreme caution as the organization felt that the use of generic immunosuppressants posed a significant patient safety risk because of the lack of

safety evidence and the absence of structural safeguards to prevent uncontrolled substitutions [56]. The CST recommended the demonstration of bioequivalence in transplant recipients and in subpopulations known to have a high variability in blood concentration rather than only in healthy young subjects [56]. Subsequently, many institutions have implemented innovator-only policies [57]. The institution of GF (London Health Sciences Centre) implemented an innovator-only policy for cyclosporine, tacrolimus, and mycophenolate products that is similar to that of many other Canadian tertiary care institutions. This was prompted after serious complications due to the unknown conversion from brand name MMF to generic MMF in a child. An extract of the briefing note is listed below. The final decision was to have only brand name cyclosporine, tacrolimus, and mycophenolate products on formulary for all patients. The final decision reads:

## Generic oral Immunosuppressants – Conversion to brand name products

There are presently numerous generic forms of oral immunosuppressants (such as seven different generic forms of mycophenolate). Clinical experts at LHSC have recommended that patients on generic forms of immunosuppressants be converted to the brand name product on admission and continued on the brand name product after discharge, eventually converting our transplant population to brand name. Consensus statements in this field discourage brand substitution (see Canadian statement), so maintaining everyone on the brand name would reduce switches when patients are admitted to hospital.

In order to achieve this, the following steps will be taken by the pharmacy department:

1. Pharmacy will only stock the BRAND name product for cyclosporine, mycophenolate mofetil, mycophenolate sodium, and tacrolimus.
2. Any patient admitted to LHSC on generic versions of these immunosuppressants will be switched to the brand name version.
3. The clinical pharmacist, in conjunction with the team, will reinforce the importance of continuing on the same brand of therapy on discharge from LHSC.
4. Non-transplant patients will also be switched to the brand name version of these drugs.
5. **Exception:** In select patients being *initiated* on cyclosporine therapy, consideration may be given to supplying a generic brand of cyclosporine when drug coverage or cost dictates use of the generic product after discharge. (In addition to the brand name products mentioned above, a generic cyclosporine will be available at LHSC.)

EFFECTIVE: Immediately.

## Recommendations

Based on the lack of evidence that bioequivalence is proven in real patients and the evidence provided above, the authors of this educational review cannot recommend the substitution of brand name tacrolimus in pediatric renal transplant recipients. For cyclosporine, there may be the option of starting de novo patients on generic cyclosporine, especially those that have demonstrated bioequivalence in patients, while precautions must be in place to avoid mixing of various formulations. For the CDDs belonging to the mTOR class, there is insufficient data to make any recommendations. The undersigned recommend implementing innovator-only policies for all critical dose immunosuppressants, i.e., calcineurin inhibitors and mTOR inhibitors. For MMF, substitution should be safe and brand prescribing and dispensing of MMF may not be necessary, but the same formulation should be used throughout.

## Conclusions

While it is acknowledged that generic immunosuppressants, especially for calcineurin and mTOR inhibitors, may offer significant cost savings for the drug therapy, there is insufficient data to recommend their use in confidence. Generics must be approved after testing in real patients, preferably using the strict European guidelines. Switching among different formulations, unbeknownst to the treating transplant specialist, must be avoided to prevent underexposure and rejection. For MMF, the issue may be less critical.

## Questions (answers are provided following the reference list)

1. Which regulatory authority has the weakest guidelines for the registration of "critical dose drug" generics:
   a) Food and Drug Administration (FDA)
   b) European Medicines Agency (EMA)
   c) Mexican Drug Regulatory Agency (Coferis)
   d) Health Canada Food and Drug Administration

2. Which immunosuppressant is not a "critical dose drug":
   a) Sirolimus
   b) Tacrolimus
   c) Cyclosporine
   d) Mycophenolate mofetil

3. Which aspect of generic immunosuppressants has the greatest unintended impact on patient safety:
   a) Uncontrolled switch between different formulations
   b) Lower $C_{max}$ of non-innovator drug

c) Different dissolution
d) Ontogeny of drug disposition

4. The generic formulations for which drug do not meet any of the bioequivalence recommendations of the FDA, EMA or Health Canada:
   a) Cyclosporine
   b) Everolimus
   c) Sirolimus
   d) Tacrolimus

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**Compliance with ethical standards**

**Competing interests** Mara Medeiros, Julia Lumini, Noah Stern, Gilberto Castañeda, and Guido Filler have no competing interests.

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## Answers

1. a; 2. d; 3. a; 4. d