

# Critical Dose Drug Considerations for Post-Transplant Patients

## Authors

**Transplant Specialist:** Ramesh Prasad, MBBS, MSc, MA, PhD, FRCPC, FACP, FASN, FASH, FAST (Ontario)

**Pharmacists:** Jennifer Harrison (lead), BPharm, MSc (Ontario)

Christian Coursol, BPharm, MSc (Québec)

Élisabeth Gélinas-Lemay, BPharm, MSc (Québec)

## Learning Objectives

Upon completion of the program, participants will be able to:

- Define critical dose drugs, also known as narrow therapeutic index drugs
- Identify considerations for substitutions between different immunosuppressant drug formulations based on pharmacokinetic data and patient outcomes, including brand name, subsequent entry formulations, and immediate- vs. extended-release formulations
- Outline the key considerations and appropriate steps for managing potential switches in immunosuppressant drug formulation after transplant

## Introduction

The purpose of this newsletter is to provide Canadian pharmacists with the knowledge and tools to make informed decisions when considering substitutions for critical dose drugs, also known as narrow therapeutic index drugs, for a patient post-transplant. The content of this newsletter focuses on the following topics:

### Critical Dose Immunosuppressant Drugs

- Narrow therapeutic index
- Interpatient and inpatient variability
- Therapeutic drug monitoring to balance efficacy and toxicity

### Alternative Formulations

- Bioavailability and bioequivalence
- 'Prescribability' vs. 'switchability'
- Factors influencing pharmacokinetics of immunosuppressant drugs in transplant recipients
- Immediate- vs. extended-release formulations

### Considerations for Switching

- Product monograph cautions
- Summary of clinical data of generic immunosuppressants in transplant recipients
- *Canadian Society of Transplantation Recommendations on Generic Immunosuppression in Transplant Recipients*

### Pharmacist Role in Drug Product Substitutions and Patient Education

- The changing paradigm in management of post-transplant patients and the role of the pharmacist
- Factors contributing to medication non-adherence and the unique role for pharmacists
- A systematic and structured approach to dispensing critical dose immunosuppressant drugs

## Terminology

- Critical dose drugs, also referred to as narrow therapeutic index (NTI) drugs
- Innovator drug, also referred to as brand name drug
- Subsequent entry drugs, also referred to as generics or alternative formulations



The Canadian Council on Continuing Education in Pharmacy has accredited this program for 1 CEU.  
CCCEP File #: 1480-2019-2661-L-P. (Accreditation period: December 12, 2018 – December 12, 2019)

# Test Your Knowledge of Critical Dose Drugs for Post-Transplant Patients

## 1. Which of the following is not considered a critical dose drug by Health Canada?

- A. Cyclosporine
- B. Mycophenolate mofetil
- C. Sirolimus
- D. Tacrolimus

## 2. Which of the following statements is true regarding critical dose drugs?

- A. Critical dose drugs have a relatively large therapeutic index
- B. Critical dose drugs are drugs for which comparatively large differences in dose or concentration can lead to therapeutic failures
- C. Critical dose drugs are drugs for which comparatively small differences in dose or concentration can lead to potentially serious adverse reactions or therapeutic failures
- D. Critical dose drugs are biologic medical products that are almost an identical copy of the original innovator product

## 3. Which of the following statements from the *Canadian Society of Transplantation Recommendations on Generic Immunosuppression in Solid Organ Transplant Recipients* is false?

- A. Generic immunosuppression use should be approached with caution
- B. Close monitoring is essential when initiating therapy and with any change in drug product
- C. Patient education regarding generic medications and generic substitution is essential
- D. Generic immunosuppressive formulations in pediatric solid organ transplant recipients is recommended

## 4. Which of the following statements is true regarding bioequivalence or alternative formulations (generics)?

- A. Bioequivalence needs to be shown from a single generic to the innovator formulation, but not from one generic to another generic
- B. Bioequivalence needs to be shown from a single generic to the innovator formulation, and also from one generic to another generic
- C. For critical dose drugs, the ratio of area under the curve (AUC) for generic vs. innovator formulations should be within the limits of 80% to 125% in order to be deemed bioequivalent
- D. Bioequivalence is based on the rate and extent of absorption of a drug into the systemic circulation

## 5. Which of the following statements is false regarding inpatient variability (IPV) in pharmacokinetics?

- A. Inpatient variability refers to variability within an individual over time
- B. Inpatient variability refers to variability from one individual to another individual
- C. High inpatient variability with critical dose immunosuppressant drugs may put a patient at risk of over- or under-immunosuppression
- D. High inpatient variability in immunosuppressant drug exposure is associated with poorer outcomes in solid organ transplant recipients

## 6. Which of the following is not considered a key factor in specific target concentrations for therapeutic drug monitoring, for narrow therapeutic index drugs?

- A. Transplanted organ
- B. Perceived risk of rejection (immunologic risk)
- C. Gender
- D. Time post-transplant

## 7. Which of the following statements regarding prescribability and switchability of alternative formulations is false?

- A. Prescribability refers to the confidence in safety/efficacy of bioequivalence when prescribing a drug to a naïve patient
- B. Switchability refers to the appropriate transfer of a patient from one drug product formulation to another and may require dose adjustment
- C. Switchability refers to the confidence in safety/efficacy of bioequivalence when prescribing a drug to a naïve patient
- D. Switchability is not currently part of Health Canada requirements for generic interchangeability

## What Are Critical Dose Drugs?

Critical dose drugs, also known as narrow therapeutic index (NTI) drugs, are those for which comparatively small differences in dose or concentration can lead to potentially serious adverse reactions or therapeutic failures.<sup>1</sup> Adverse reactions may be persistent, irreversible, slowly reversible, or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death.<sup>1</sup>

### Critical dose drug examples

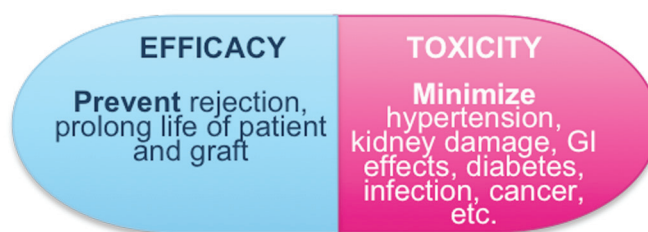
- |  |  |
|--|--|
| <ul style="list-style-type: none"><li>• <b>Cyclosporine</b></li><li>• Digoxin</li><li>• Flecainide</li><li>• Lithium</li><li>• Phenytoin</li></ul> | <ul style="list-style-type: none"><li>• <b>Sirolimus</b></li><li>• <b>Tacrolimus</b></li><li>• Theophylline</li><li>• Warfarin</li></ul> |
|--|--|

Critical dose drug examples from Health Canada.<sup>1</sup>  
Bolded drugs are immunosuppressant drugs

## Narrow Therapeutic Index and Therapeutic Drug Monitoring

Clinicians rely on tools such as therapeutic drug monitoring (TDM) to determine a balance between the need for immunosuppression to prevent rejection vs. an increased risk of infection, malignancy, and toxicities.<sup>2,3</sup> TDM involves blood sampling and dose adjustments to reach the therapeutic window in order to optimize the balance between efficacy and toxicity.<sup>2,3</sup> TDM involves:

- Maintaining serum drug concentration/level within a limited defined 'therapeutic' window
- Determining a range of values with the greatest probability of therapeutic success



Goal of immunosuppressive therapy:  
Optimize balance between efficacy and toxicity

Specific target concentrations may differ depending on:<sup>2</sup>

- Transplanted organ
- Perceived risk of rejection (known as "immunologic risk") or previous rejection
- Other immunosuppressant drugs used in the regimen
- Time post-transplant
- Possible toxicity/adverse reactions
- Transplant centre's protocol



## Critical Dose Drugs: Immunosuppressants

Health Canada has designated several immunosuppressant transplant drugs as critical dose drugs, including cyclosporine, tacrolimus, and sirolimus.

### Cyclosporine (or ciclosporine)

- Calcineurin inhibitor (CNI) used in combination with an antiproliferative agent, with or without corticosteroids as maintenance therapy<sup>4-6</sup>

### Tacrolimus

- Potent CNI recommended as the first-line CNI immunosuppressant agent, in combination with an antiproliferative agent, with or without corticosteroids as maintenance therapy<sup>4,5</sup>
- Available in immediate-release (twice-daily) and extended release (once-daily) formulations<sup>7-9</sup>

### Sirolimus

- A mammalian target of rapamycin inhibitor (mTORi), it is initially used in combination with cyclosporine and corticosteroids, with cyclosporine withdrawn at 2–4 months post-kidney transplant<sup>\*4,5,10</sup>
- Optimal place in therapy is not established but it is available as a second-line option for selected patients

\*In low to moderate immunological risk patients; In high immunological risk patients, it should continue to be used with cyclosporine and corticosteroids for the first year following transplantation and any adjustments thereafter on the basis of the clinical status of the patient.

Drug & standard oral starting dose (per product monographs) <sup>6–10</sup>	Therapeutic target range (per product monographs) <sup>6–10</sup>
<b>Cyclosporine</b> 10–15 mg/kg/day	$C_0 = 100\text{--}400\text{ ng/mL}$
<b>Tacrolimus</b> 0.1–0.3 mg/kg/day	<b>Month 1–3:</b> $C_0 = 7\text{--}20\text{ ng/mL}$ <b>Month 4–12:</b> $C_0 = 5\text{--}15\text{ ng/mL}$ Long-term post-transplant patients often are maintained at the low end of this target range
<b>Sirolimus</b> 6 mg loading dose, then 2 mg daily	<b>Low-to-moderate immunologic risk where cyclosporine is to be withdrawn:</b> $C_0 = 16\text{--}24\text{ ng/mL}$ within first year <b>Thereafter:</b> $C_0 = 12\text{--}20\text{ ng/mL}$ <b>High immunologic risk:</b> $C_0 = 10\text{--}15\text{ ng/mL}$

*Note: Target ranges suggested for tacrolimus and sirolimus in product monographs are generally higher than what is used in clinical practice. Target ranges should be individualized to the patient. Pharmacists may consult the prescriber to determine the desired target for any given patient.*

## Interpatient and Inpatient Variability

In addition to being critical dose/narrow therapeutic index drugs, calcineurin inhibitors also have highly variable pharmacokinetics. High inpatient variability (IPV) in concentration over time often seen with cyclosporine, tacrolimus, and sirolimus may put the patient at risk of over- or under-immunosuppression.<sup>11</sup> Serious consequences in solid organ transplant recipients include:<sup>12–15</sup>

- **Under-immunosuppression** resulting in increased rates of rejection and graft loss
- **Over-immunosuppression** resulting in increased rates of nephrotoxicity and neurotoxicity

**Interpatient variability**  
(from one individual to the next)



**Inpatient variability**  
(in any given patient)



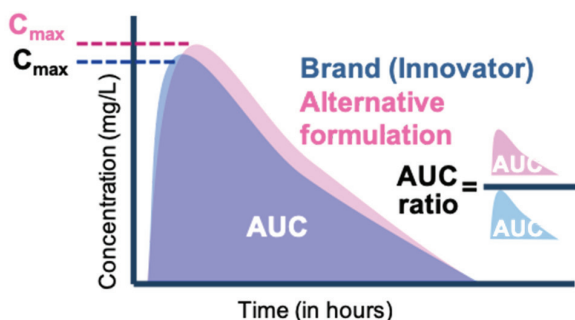
## Alternative Formulations

All subsequent entry drugs, also known as generics or alternative formulations, are approved by Health Canada based on bioequivalence to an innovator, or reference product.<sup>16</sup> The bioavailability of the alternative formulation should be very similar to the innovator product. Bioavailability is the rate and extent of absorption of a drug into the systemic circulation. It is assessed using pharmacokinetic variables:

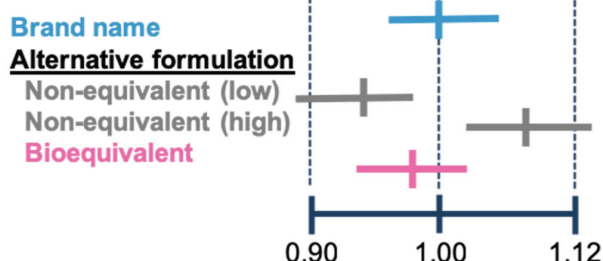
- **AUC:** Area under the curve – reflects extent of absorption
- **$C_{max}$ :** Maximum blood concentration – reflects rate of absorption

To be deemed 'bioequivalent,' the 90% confidence interval (CI) of the relative area under the curve (AUC) of the test to reference formulation should be within 90% to 112% inclusive (for non-critical dose drugs, this range is normally 80% to 125%).<sup>16</sup> In addition, the 90% CI of maximum blood concentration, or  $C_{max}$ , should be contained within the limits of 80% to 125%. Bioequivalence studies are a surrogate marker for clinical effectiveness and safety data.<sup>17</sup> While bioequivalence must be shown from an alternative formulation to an innovator product, bioequivalence does not need to be shown from one alternative formulation to another.<sup>18</sup>

Simulation of drug concentration vs. time curve for two drug products







Criteria for acceptance for AUC ratio



## Factors Influencing Pharmacokinetics of Immunosuppressant Drugs in SOTR

There are numerous factors that may influence the pharmacokinetics of immunosuppressant drugs that bioequivalence studies or alternative formulations do not always take into account.<sup>11</sup>

Factors	Relevance for approval of generic formulations <sup>11</sup>	
Disease state	<ul style="list-style-type: none"> <li>Bioequivalence studies conducted in healthy volunteers receiving a single dose of the medication do not capture the potential impact of co-morbidities nor the longitudinal variability that may occur with chronic use</li> </ul>	
Drug-drug interactions	<ul style="list-style-type: none"> <li>Bioequivalence studies are not conducted in the presence of commonly co-administered medications, which may have clinically relevant implications for SOTR</li> </ul>	
Drug-food interactions	<ul style="list-style-type: none"> <li>Bioequivalence testing in both the fed and fasted state is required for critical dose drugs</li> <li>Unique formulation-specific dietary interactions with branded or generic products are not likely to be captured with current regulatory approval processes</li> </ul>	
High-risk populations	<ul style="list-style-type: none"> <li>Bioequivalence studies are not conducted in pediatrics</li> <li>Populations with potentially altered immunosuppression absorption patterns or polymorphisms are under-represented in bioequivalence studies</li> </ul>	

### ‘Prescribability’ vs. ‘Switchability’

There is a difference between the ‘prescribability’ and ‘switchability’ of an alternative formulation.<sup>11</sup> ‘Prescribability’ refers to the willingness of a health care practitioner to prescribe an alternate formulation to a naïve patient because confidence in efficacy and safety of the formulation has been assured by the population bioequivalence studies required by Health Canada. In contrast, ‘switchability’ refers to the ability to appropriately transfer a given patient from branded to bioequivalent alternative formulation (or vice versa), or from one alternate (bioequivalent) formulation to another. Current Health Canada licensing requirements for alternate formulations do not test for ‘switchability.’

**A significant proportion of patients (~20-40%) may require dose adjustment when switching formulations**

### Immediate-Release vs. Extended-Release Formulations

One critical dose immunosuppressant drug, tacrolimus, is available in both an immediate-release (IR) twice-daily formulation and an extended-release (ER) once-daily formulation.<sup>7-9</sup> Both have similar efficacy and tolerability profiles in adult *de novo* kidney and liver transplant recipients.<sup>19-21</sup> Stable kidney or liver transplant patients may be converted from IR to ER tacrolimus, in combination with adrenal corticosteroids and MMF, based on equivalent tacrolimus whole blood trough concentrations, but switching is recommended to be done under supervision of a transplant specialist.<sup>7-9</sup> There are many factors which determine dose adjustment requirements, an important one being ethnicity.<sup>22</sup> Roughly 10% to 20% of patients need dose adjustment upon switching.<sup>22</sup>

**Mistaken interchangeability** of ER tacrolimus for IR tacrolimus in kidney transplant patients refilling prescriptions at a community pharmacy identified some common themes for error reports:<sup>23</sup>

- Practitioners believed that IR and ER tacrolimus were completely interchangeable, dose for dose
- Orders using the generic name “tacrolimus,” without the appropriate brand name, led to misinterpretation during dispensing
- Some computerized pharmacy order screens listing these medications by the generic name tacrolimus placed the brand names for IR and ER tacrolimus on the same selection screen
- Many of the errors that have been detected were caught by the patients, who noticed a difference in the appearance of the capsule and questioned a health care practitioner





## Provincial Differences in Drug Interchangeability

Drug interchangeability is determined by the individual province or territory. Pharmacists may be legally required to dispense an interchangeable generic product where they exist. In addition, hospital formularies often restrict medication product selection to one formulation that may not necessarily reflect the choices available in the community.<sup>11</sup>

For provinces where there is mandatory interchangeability, these provinces require that the interchangeable product dispensed be the lowest priced product available. A patient may still choose to pay the difference between the brand name and alternative formulation. In provinces with optional interchangeability, pharmacists may substitute a prescribed drug with an interchangeable drug, but it is not mandatory.<sup>24</sup> Again the patient should be informed and have the option to pay the difference in price if they prefer.<sup>25–36</sup>

Interchangeability		
Province	Mandatory	Optional
Manitoba	✓	
Newfoundland & Labrador	✓	
Ontario	✓	
PEI	✓	
Québec	✓	
Saskatchewan	✓	
Alberta		✓
British Columbia		✓
New Brunswick		✓
Nova Scotia		✓

*Mandatory vs. optional interchangeability is not a legal obligation, but rather deals with reimbursement issues.*

There are exceptions to these rules in some provinces. For example, in Québec, the innovator formulation of cyclosporine is listed in Appendix V of the *List of Medications* for which the lowest price method does not apply and therefore can not be substituted.<sup>37</sup> In Ontario, the innovator formulation of cyclosporine is provided free of charge to the patient under the Special Drugs Program when dispensed by a specially designated facility (i.e., transplant centre hospital pharmacy).

## Considerations for Switching

Product monographs for critical dose immunosuppressant drugs all provide cautions on switching between formulations, including informing physicians responsible for maintenance therapy in order to initiate therapeutic drug monitoring to achieve target concentrations in individual patients.<sup>6–9</sup>

The Canadian Society of Transplantation has also provided a number of recommendations on generic immunosuppression in solid organ transplant recipients based on available clinical research.<sup>11</sup>

## Canadian Society of Transplantation Recommendations on Generic Immunosuppression in Transplant Recipients

**Generic immunosuppression use should be approached with caution.**

**The intended drug product formulation should be explicitly stated on all prescriptions.**

- Consistency of drug products in the immunosuppressive regimen should be maintained
- Switching formulations and the use of more than one preparation in the same patient should be avoided

**Close monitoring is essential when initiating therapy and with any change in drug product.**

Because of known differences in pharmacokinetics and insufficient data, the **routine use of generic immunosuppressive formulations in pediatric transplant recipients is not recommended.**

**Patient education regarding generic medications and generic substitution is essential.**

**More extensive data should be made available** regarding the efficacy and safety of generic immunosuppressive therapy for proper use and monitoring.

## Changing Paradigm in Management of Post-Transplant Patients: Pharmacist Role

Graft rejection remains a major barrier to successful transplantation and is largely attributed to:

- Chronic immunologic processes leading to destruction of graft<sup>38</sup>
- Non-adherence to immunosuppression
  - Meta-analysis of 10 studies demonstrated that odds of graft failure increased 7-fold in non-adherent vs. adherent subjects following kidney transplantation<sup>39</sup>

A “one-size-fits-all” approach to post-transplant management fails to address individual needs of patients and may be contributing to the lack of improvement in long-term outcomes.<sup>38</sup> The changing paradigm in management of post-transplant patients involves consideration of four patient-specific domains (predictive, preventive, personalized, and participatory medicine) when caring for transplant patients.<sup>38</sup> In particular, pharmacists can play key roles in improving participatory and personalized domains.

Domain	Pharmacist role
<b>Personalized</b> Immunosuppression regimens and post-transplant monitoring	<b>Communicate</b> with transplant centre before initiating any change in treatment
<b>Participatory</b> medicine catered to individual transplant recipients	<b>Reinforce</b> the importance of adherence and address any questions the patient may have

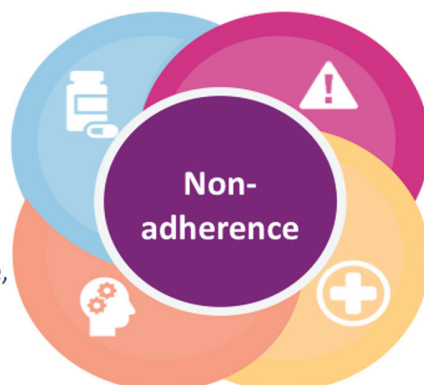
## Factors Contributing to Non-Adherence After Transplantation<sup>40, 41</sup>

### Polypharmacy

Recipients take multiple immunosuppressants and other medications for comorbidities

### Inadvertent forgetfulness

Medications interfere with lifestyle, patients become preoccupied and forget OR patient does not recognize their medication



### Side effects

Diarrhea, sleeplessness, weight gain, fatigue, hair loss, skin cancer, and others

### Health services

Patients may find it difficult to attend all medical appointments, access pharmacies, or afford their medications

## Strategies for Promoting Immunosuppressant Therapy Adherence<sup>42, 43</sup>

### Medication-taking

- ☐ Assess for barriers to appropriate medication-taking
- ☐ Develop system of reminder cues; use reminder devices
- ☐ Implement behaviour-changing strategies
- ☐ Simplify immunosuppression regimens (reduce the number and frequencies of medications, where possible, with appropriate follow-up)
- ☐ Provide medication organizational tools such as dosettes, blister packaging
- ☐ Provide individualized patient education via a variety of methods
- ☐ Modify regimen to decrease adverse effects, where possible
- ☐ Monitor compliance with surveys, laboratory work, and prescription refills
- ☐ Use a non-judgmental approach to the discussion of adherence



### Social support

- ☐ Involve family members and friends as a support system
- ☐ Urge care team members to develop rapport with patient
- ☐ Team work with the transplant specialist



# Proposed Model for Dispensing of Critical Dose Immunosuppressant Drugs

1

## Collect information

- Patient insurance and other drug coverage information
- Available drug product options (i.e., innovator vs. alternate formulations)
- Is this a continuation of therapy? If yes, determine which drug product patient has been receiving.

2

## Assess options

- Mandatory vs. optional interchangeability
- Out-of-pocket cost to patient for each option
- Patient preferences, if applicable
- Product monograph cautions on switching

3

## Select and dispense product

- If dispensing consistent formulation, no further actions required
- If dispensing alternate formulation, proceed to Step 4
- Ideally, substitution of an alternate formulation should occur in consultation with prescriber

4

## Actions if dispensing alternate formulation

- Notify: Patient and prescriber of drug product switch
- Monitor: Recommend monitoring of blood concentration post-switch
- Educate: Patient on drug product and reinforce directions for use
- Document: In patient's file

### Accreditation Criteria

This program is accredited as an Independent Study Program for 1.0 CEUs. To complete this course adequately and obtain your credits, please go to [www.NTICHE.com](http://www.NTICHE.com) and follow the steps below to complete the online post-test and obtain your certificate.

- Register and follow the instructions to access the program
- Complete the online post-test and the evaluation form to provide your feedback, and print/download your letter of attendance for your files

Should you encounter any problems and/or questions about this program, please contact the program provider, ICPDHM, at 1-877-685-1888, ext. 207.

References: 1. Health Canada Guidance Document Revised June 2018. [https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt\\_formats/pdf/prodpharma/applic-demande/guide-ld/bio/comparative-bioavailability-standards-formulations-used-systemic-effects.pdf](https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/bio/comparative-bioavailability-standards-formulations-used-systemic-effects.pdf); 2. Andrews LM, et al. *Expert Opin Drug Metab Toxicol*. 2015;11(6):921-36; 3. Ericson JE, et al. *Ther Drug Monit*. 2017;39(1):13-20; 4. KDIGO Transplant Work Group. *Am J Transplant*. 2009;9(suppl 3):S1-S157; 5. Knoll GA, et al. *Am J Kidney Dis*. 2010 Aug;56(2):219-46; 6. <sup>Pr</sup>Neoral® and <sup>Pr</sup>Sandimmune<sup>®IV</sup> Product Monograph revised Jan 2015, accessed Sept 2018; 7. <sup>Pr</sup>Sandoz® Tacrolimus Product Monograph revised Jan 2016, accessed Sept 2018; 8. <sup>Pr</sup>Prograf® Product Monograph revised Nov 2016, accessed Sept 2018; 9. Advagraf® Product Monograph revised July 2015, accessed Sept 2018; 10. <sup>Pr</sup>Rapamune® Product Monograph revised Oct 2017, accessed Sept 2018; 11. Harrison JJ *Transplantation*. 2012;93:657-65; 12. Shuker N, et al. *Transpl Int*. 2016;29(11):1158-67; 13. Pollock-BarZiv SM, et al. *Pediatr Transplant*. 2010; 14:968; 14. Savoldi S, et al. *Transplant Proc*. 1997;29:288; 15. Borra LCP, et al. *Nephrol Dial Transplant*. 2010;25:2757; 16. Health Canada. Available from [https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt\\_formats/pdf/prodpharma/applic-demande/guide-ld/bio/comparative-bioavailability-standards-formulations-used-systemic-effects.pdf](https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/bio/comparative-bioavailability-standards-formulations-used-systemic-effects.pdf); 17. CADTH 2012 [https://www.cadth.ca/sites/default/files/pdf/What\\_Are\\_Bioavailability\\_and\\_Bioequivalence\\_e.pdf](https://www.cadth.ca/sites/default/files/pdf/What_Are_Bioavailability_and_Bioequivalence_e.pdf); 18. El Hajj, et al. *Expert Rev Clin Immunol*. 2015;11(5):659-72; 19. Saengram W, et al. *Eur J Clin Pharmacol*. 2018 Oct;74(10):1249-60; 20. McCormack PL, *Drugs* 2014;74:2053-64; 21. Weiler N, et al. *Transplant Proc*. 2013; 45(6):2321-5; 22. Glick L, et al. *Transp Res*. 2014;3:7; 23. ISMP Canada Safety Bulletin 2009;9(5); 24. <http://www.competitionbureau.gc.ca/eic/site/cb-bc.nsf/eng/03798.html>; 25. [https://abpharmacy.ca/sites/default/files/StandardsOfPractice\\_May2014\\_v2.pdf](https://abpharmacy.ca/sites/default/files/StandardsOfPractice_May2014_v2.pdf); 26. [https://www.ab.bluecross.ca/dbl/pdfs/ahwdbl\\_sec1\\_critint.pdf](https://www.ab.bluecross.ca/dbl/pdfs/ahwdbl_sec1_critint.pdf); 27. [http://library.bcpharmacists.org/6\\_Resources/6-4\\_Drug\\_Distribution/5016-FYI-Drug\\_Interchangeability\\_Update.pdf](http://library.bcpharmacists.org/6_Resources/6-4_Drug_Distribution/5016-FYI-Drug_Interchangeability_Update.pdf); 28. College of Pharmacists of Manitoba, 2013; <http://www.cphm.ca/uploaded/web/Legislation/Pharmacy-Practice-Guide/Guide-to-Pharmacy-Practice-Final.pdf>; 29. [https://www.health.gov.nl.ca/health/prescription/idf\\_intro.html](https://www.health.gov.nl.ca/health/prescription/idf_intro.html); 30. <https://nbcpi.in1touch.org/document/2266/Drug%20Interchangeability%20document%20July%2031%202014.pdf>; 31. <https://novascotia.ca/dhw/pharmacare/interchangeable-products.asp>; 32. <https://www.nspharmacists.ca/wp-content/uploads/2016/05/PrescribingStandardsOfPractice.pdf>; 33. <https://www.ontario.ca/laws/statute/90p23>; 34. Drug Product Interchangeability and Pricing Act Chapter D-15, Prince Edward Island, 2014; 35. <http://legisquebec.gouv.qc.ca/en/pdf/cs/P-10.pdf>; 36. <http://formulary.drugplan.ehealthsask.ca/PDFs/TipsonPrescriptionWriting.pdf>; 37. [http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/liste\\_med/Liste\\_med\\_2018\\_09\\_27\\_en.pdf](http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/liste_med/Liste_med_2018_09_27_en.pdf); 38. Maier M, et al. *Can J Kidney Health Dis*. 2017;23;4:2054358116688227; 39. Butler JA, et al. *Transplantation*. 2004;77(5):769-89; 40. Williams AF, et al. *J Ren Care*. 2014 Jun;40(2):107-16; 41. Tong A, et al. *Nephrology Dialysis Transplantation*. 2011;26:344-54; 42. Doyle IC, et al. *Am J Health-Syst Pharm*. 2016;73:909-20; 43. Expert opinion of the Steering Committee.