Formulations, Compounding and Drug Safety – Under-Appreciated Issues

The Rosalind & Morris Goodman Family pediatric formulations centre of the CHU Sainte-Justine

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Medical and Scientific Director of the GPFC

CSPT-SPS Annual Meeting

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Disclosure Statement

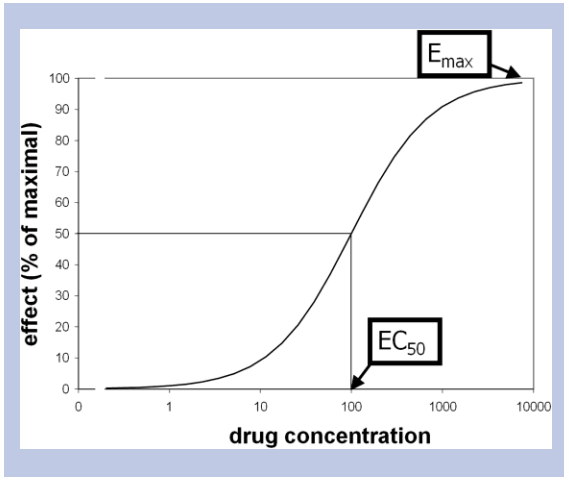
- GPFC :
  - Funded by the Morris and Rosalind Goodman Family Foundation and the CHU Sainte-Justine Foundation
  - Provided service contracts with Pharmascience, Leon Nanodrugs, Rare Disease Therapeutics, and Ethypharm (no longer providing services to industry for a fee)
  - No current service agreements ongoing

Determinants of Effective and Safe Therapy

Pharmace

Acceptable and palatable dosage form
Dose and dose volume/weight adjusted to the intended age group (dosing flexibility)
Convenient, reliable administration (accurate dose, suitable administration device)
Minimal manipulation by HCPs, parents or caregivers prior to use
Minimal administration frequency
Minimal impact on life style
Minimum nontoxic excipients
Transportable and low bulk/weight
Easily produced and stable in a variety of climates
Affordable
Commercially viable

HCP, health care professional.



Pharmacodynamics

Availability o gh-quality pediatric formulations can spell the difference between successful treatment or therapeutic failure and safe therapy or adverse events

Problem Statement

- Many drugs administered to children are used off-label and are **not available** as **commercial pediatric formulation**

- Need for manipulation of dosage forms designed for adults by health care professionals and parents ; *COMPOUNDING* is associated with many challenges
- An estimated 50% to 80% of all medications prescribed to children in Canada are given off label

Limited stability data
Taste issue with limited options available to mask bad-tasting APIs
Inaccurate dosing
Altered absorption
Lack of bioavailability data for compounded drugs
Lack of testing for purity, potency, content, or stability
Deficient environmental control with potential contamination of the compounded drugs
Exposure of HCPs and/or parents to toxic APIs
Lack of awareness of physicians
No or weak oversight by regulatory agencies

API, active pharmaceutical ingredient; HCP, health care professional.

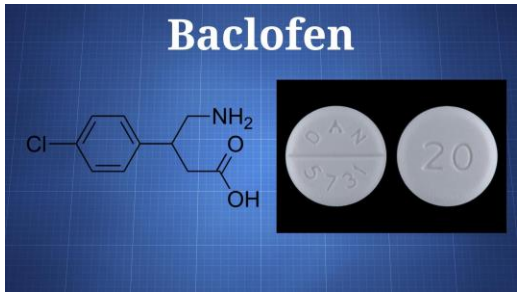
What is the Extent of Compounding?

- Studies looking at the percentage of prescribed drugs requiring compounding are scarce
- A Canadian study showed that 60% of new drugs approved for use by Health Canada in children less than 6 years of age between 2007-2016 did not come as a child-friendly formulation.
- A recent retrospective study (abstract) conducted at the Centre Hospitalier Universitaire Sainte-Justine on 2 separate days showed that:
  - Almost on quarter (23%) of all prescriptions for enteral administration in the hospital were for compounded preparations;
  - Nearly half (49%) of hospitalized children received at least one prescription for a compounded medication

Raja, P. et al, CMAJ Open, 2020. 8(3): p. E522-E529.
Landry E.K. et al. Pediatric Academic Society Annual Meeting 2021.

Parents find son's lifeless body after pharmacy switches sleep medication for toxic dose of another drug

news



Toxicity from a Clonidine Su

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[d]College of Pharmacy, University of New Mexico, Albuquerqu

ABSTRACT

Background: Clonidine is frequently prescribed to childre and deaths.

Case Report: A 3.5-year-old male with a history of a seizu excessive sleeping, agitation when awake, and possible seizure On presentation, he alternated between poor responsiveness an rate, 65 bpm; respiratory rate, 18 bpm; temperature 99.5°F; ar cology consult the next day noted a dry mouth, 2-mm pupils, with a diagnostic impression of clonidine overdose. The care clonidine suspension by a provided syringe. The pharmacy pro was a 30-day supply but the bottle was empty on day 19, lead tion in the bottle thus could not be confirmed. The child slowl drawn approximately 18 hours after his last dose later returne

Case Discussion: Compounding and liquid dosing errors ar an accelerated dosing error, but whether a compounding or sus

Conclusion: Particular care should be taken with medicatio pounded, and are prepared as liquids, where medication error

INTRODUCTION

Clonidine is frequently prescribed to children for a variety of in ical effects and death. We report a case of a massive overdose i

CASE REPORT

A 19-kilogram, 3.5-year-old male with a history of a seizure dis pected seizure activity. The primary caretaker reported that th

Keywords: clonidine, compounding, medication errors
Notes: There was no outside funding of any kind used for this
Corresponding author: Steven A. Seifert, MD, c/o New Mexico Po NM 87131–0001. *Email: SSeifert@salud.unm.edu*

Toxicology Obs

The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent national not-for-profit agency established for the collection and analysis of medication error reports and the development of recommendations for the enhancement of patient safety.

ISMP CANADA

Volume 11, Number 1 **ISMP Cana**

Oral Clo 1000-Fold Compoundi

ISMP Canada has received 3 reports of chi experiencing harm because of errors during preparati oral clonidine suspension from clonidine powder. bulletin provides information about the inci describes the dangers associated with clonidine over and suggests strategies to prevent recurrence of this of error.

Incident Reports

In each of the 3 incidents, a pharmacist working community pharmacy used clonidine powder (provid containers labelled by weight, in grams) to prep suspension for pediatric use. The prescribed dose clonidine ranged from 25 mcg (0.025 mg) to 125 (0.125 mg). In each case, there was a mix-up durin conversions among grams, milligrams, and microg and the concentration of the suspensions dispensed 1000 times greater than intended.

Each child required emergency treatment and admi to hospital. Two of the children were admitted t intensive care unit, and one of these required treatme severe hypotension.

Background

Clonidine is a centrally acting alpha$_2$-adrenergic ag approved for use in Canada for the treatmer hypertension (e.g., Catapres and generic agents; ava as 0.1 mg and 0.2 mg tablets).[1] In addition to its u treating hypertension, clonidine (Dixarit and ge agents; available as 0.025 mg tablet) has also approved for the relief of menopausal flushing in pa for whom hormone replacement therapy is unsuit With the availability of newer and better-studied hypertensives, however, the use of clonidine has w over the past couple of decades. With this less fre use of clonidine has come reduced familiarity wit drug and its dosing.

Clonidine is also used for off-label treatment of se conditions in the pediatric population.[3] In particular often used as a first-line treatment option for ped patients with tics.[4] The use of clonidine in combin with stimulant medications has been supported by va

Clonidine expos
a retrospective s

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ABSTRACT

Objective To describe trends in cl in children under 6. Clonidine has b popular for management of paedia disorders. Clonidine has a narrow t and toxicity can occur with inadver Clonidine is not recommended for 6 years.

Design and setting A retrospect exposures in children under 6 repor Wales Poisons Information Centre (largest poison centre), 2004–2017 with community clonidine utilisatio data from Australian Statistics on N 2015. Australian trends were comp exposure calls to US poison centres

Main outcome measures Trend dispensing; demographics, dose, ex source, symptoms, disposition.

Results There were 802 clonidine NSWPIC database, increasing 4.9% (95% CI 3.1% to 6.7%, p<0.001), increased dispensing, r=0.846 (95% 0.956, p<0.001). 78.6% were hosp toxicologists were consulted in 7.2% risk and/or morbidity. Clonidine wa the patient in at least 27.8%, provi prescribing outside of recommenda 19 056 clonidine exposures, with 3 2006–2016 (95% CI 2.2% to 5.3%

Conclusions Clonidine exposures are increasing, and this trend is not Exposures have a high hospital refe morbidity. Caution should be exerc clonidine, and parent/carer educati safe storage and increased vigilanc

To cite: Cairns R, Brown JA, Buckley NA. *Arch Dis Child* 2019;**104**:287–291.

INTRODUCTION

Clonidine is a centrally acting adrenergic agonist developed originally used as an antihype is seldom used for this indic long been superseded by safe tive options. Clonidine has re popularity in paediatrics for t behavioural disorders, includi hyperactivity disorder (ADHD) disturbances and post-traumatic

Clonidine has a narrow ther has the potential to cause c nervous system (CNS) toxicit dose for behavioural disturbance is 2–4 mcg/kg (immediate release), and toxicity may occur with little is known about Australian trends in clonidine therapeutic errors and poisoning. This study aims

Case Reports > J Emerg Med. 2020 Jul;59(1):53-55. doi: 10.1016/j.jemermed.2020.04.027.
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Clonidine Com Sedation in a P

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Affiliations + expand

PMID: 32389431 DOI: 10.1(

Abstract

Background: Clonidine is a attention-deficit/hyperactivit sedation, bradycardia, and h patients who are unable to t

Case report: A 12-year-old l presented to the emergency generalized sedation, bradyc 82/48 mm Hg). Resuscitation h, his vital signs and mental neurologic deficits. His parer compounding pharmacy; be formulation. Because his sig clonidine preparation was se concentration was approxim EMERGENCY PHYSICIAN BE toxicity, even if there is no k respiratory depression, brad patient and should prompt a

Keywords: clonidine; compounding; medication error; pediatric; toxicity.

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Pediatric clonidine poisoning as a result of pharmacy compounding error

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INTRODUCTION

Clonidine is an α_2-adrenergic and imidazoline receptor agonist used primarily as an antihypertensive agent. Other indications for clonidine include prophylaxis of migraine headaches, perimenopausal flushing, withdrawal from nicotine or opiates, Tourette's syndrome, and attention-deficit/hyperactivity disorder (1–3). Notably, the use of clonidine for its psychiatric indications among pediatric patients is increasing (4). Because adult antihypertensive preparations often contain more clonidine than indicated for pediatric use, some pharmacies compound clonidine specially for individual patients on site, a practice that produces additional opportunity for dosing error. We report two cases of pediatric clonidine toxicity caused by such pharmacy compounding errors.

CASE 1

A 9-year-old boy with attention-deficit/hyperactivity disorder was being treated chronically with methylphenidate and clonidine. On the morning of presentation to the emergency department (ED), the patient had complained of a severe headache, which was treated with acetaminophen and ibuprofen. The parents later noted the patient to be ataxic, dysarthric, and then lethargic, with an episode of urinary incontinence. No convulsive activity was observed, and the patient had no known access to his sister's seizure medications. The patient was brought to the ED, where his initial vital signs were temperature 96.9°F (36.1°C), pulse 56/min, respirations 16/min, and blood pressure 100/56 mm Hg. The patient arrived profoundly lethargic with pupils measuring 2 mm bilaterally. He was given naloxone 0.4 mg intravenously twice without notable effect. Pulmonary and abdominal examinations and the remainder of the cardiac and neurologic examinations were unremarkable. An electrocardiogram revealed sinus bradycardia at 47 beats/min with infrequent premature supraventricular complexes. Given the history of headache followed by lethargy, intracranial hemorrhage was suspected, and a pediatric neurologist was consulted. A head CT scan, complete blood count, and basic metabolic panel were within normal limits. Later in the ED, however, the patient's mental status waxed and waned: the patient sometimes was barely arousable and sometimes was alert, appropriately answering questions.

Further history revealed that the patient took his first dose of a new clonidine prescription the night before presentation. The patient's old prescription was a purple, grape-flavored syrup dosed at 0.05 mg (0.5 mL of 0.1 mg/mL solution) at bedtime. The new prescription, compounded at a local pharmacy, was a red, cranberry-flavored syrup labeled to indicate an equivalent nightly clonidine dose of 0.05 mg in 2-mL volume. The patient was admitted to the pediatric intensive care unit on the medical toxicology service. He required no further pharmacologic intervention and was discharged in stable condition the following day.

Comprehensive urine drug screening (using enzyme-multiplied immunoassay technique, thin-layer chromatography, and gas chromatography-mass spectroscopy [GC-MS]) from a specimen obtained in the ED showed the presence of acetaminophen and clonidine. The clonidine concentration of the new prescription was determined by GC-MS compared with a standard clonidine preparation of known concentration (Sigma Chemical, St. Louis, MO). The clonidine concentration was 2168.6 μg/mL, versus the drug label that indicated 25 μg/mL, an 87-fold dosing error. The pharmacy compounding this prescription was alerted to the error, and the parents discarded the remainder of the new bottle.

CASE 2

A 10-year-old boy with obsessive-compulsive disorder and Tourette's syndrome was being treated by his psychiatrist with clonidine (0.1 mg every a.m. and 0.05 mg every p.m.), risperidone, quetiapine, donepezil, and benztropine. He had complained of a headache and then presented with progressive somnolence over the next 1.5 days following a recent refill of his evening clonidine dose prescription. This prescription was compounded at a local pharmacy by combining immediate-release and sustained-release clonidine preparations and placing the mixture within gelatin capsules. The patient's mother suspected a potential dosing error since the new capsules were a different color from the patient's usual prescription. The powder contained within the capsules appeared the same. On arrival at the ED, the patient's vital signs were temperature 96.6°F (35.9°C), pulse 81/min, respirations 24/min, and blood pressure 86/45 mmHg. The patient initially appeared drowsy but was arousable and would intermittently scream and thrash about. Pupils were small (3 mm), and the face was slightly pale. The remainder of the cardiac, pulmonary, abdominal, and neurologic exams were normal insofar as the patient could cooperate. The patient was treated with a 350-cc intravenous bolus of 0.9% saline, following which his repeat blood pressure was 81/51 mmHg and his pulse dropped to 56/min. Intravenous atropine 0.5 mg was admin-

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Key Words: Clonidine toxicity, drug compounding, medication error

Compounding and Adverse Events

- Lack of data
  - Number of cases that occur in clinical practice are underestimated
    - No requirement to report AEs associated with compounded products
    - Problems go unnoticed as patients do not seek medical attention or doctors do not make the connection to the offending product.
    - Prescribers are often unaware whether the medication they are prescribing to a child is compounded contributes to the under reporting of problems associated with compounding.

Compounding and Adverse Events

- In a recent Canadian study looking at harmful pediatric errors in the community over a 5-year period, ISMP Canada found that calculation mistakes and errors related to the compounding process were the most frequently cited errors and compounding errors accounted for more than 35% of harmful incidents reported in children (data provided by ISMP Canada).
- A US systematic review of AEs from outpatient compounding by Watson et al. (2021) and a European published report (Isles, 2020) both conclude that errors in the preparation of a compounded medicine were more common in children.

ISMP Canada Safety Bulletin Volume 22 (5) • April 20, 2022
Watson CJ et al. J Med Toxicol. 2021 Apr;17(2):197-217.
Isles M. International Journal of Risk & Safety in Medicine 31 (2020) 133–144

Compounding and Therapeutic Failure

- 8 month old liver transplant recipient admitted for severe hepatic failure secondary to acute rejection
- Tacrolimus blood level found to be extremely low
- During hospitalization, his tacrolimus blood level returned within a therapeutic range
- Lack of adherence by the mother was suspected along with parental neglect

Tacrolimus concentration in the compounded suspension prepared by the local pharmacy = 0.04 mg/mL = **1/10 of expected concentration**

CHU Sainte-Justine

CHU Sainte-Justine

Département de pharmacie - secteur fabrication

Nom du produit : tacrolimus 0.5 mg/ml so fab (F)(G)
Format : 120 ml
Quantité : 3 bout

No produit : 360834
Stabilité 56 jour(s)
température pièce

Ingrédient, forme, dosage	Qté par unité	Qté totale
tacrolimus 5 mg caps	12 caps	36 caps
++véhicule pour suspension orale (ORA-PLUS)	60 ml	180 ml
++sirop simple so	60 ml	180 ml
++précautions NIOSH	0	0
++magistrale catégorie TROIS OPQ	3	9

Information étiquette:
Agiter bien.
Conserver à la température de la pièce.
Précautions NIOSH requises

Mode de préparation :

PRECAUTIONS NIOSH REQUISES
ATTENTION: STANDARDS DE MANIPULATIONS POUR IMMUNOSUPPRESSEURS SOIT GANTS,MASQUE, ETC.

1) Ouvrir et vider les capsules dans un mortier.
2) Mouiller la poudre avec une petite quantité d'Ora-Plus afin de former une pâte homogène.
3) Ajouter le reste de l'Ora-Plus ainsi que le sirop simple par dilution géométrique pour obtenir un mélange homogène.
4) Bien mélanger.

NOTES:
Poids de 140 mg de poudre au total par capsule (sans l'enveloppe) selon la compagnie.
On peut utiliser une bouteille de verre ou de plastique ambrée.
Stabilité en seringue orale ambrée estimée à 56 jours également à température de la pièce.

The GPFC Mission

- To facilitate market authorization of pediatric drug formulations in Canada by:
  - Identifying and communicating unmet pediatric formulations needs to key stakeholders
  - Contributing to a favorable clinical and regulatory environment
  - Contributing to uncovering incentives for manufacturers and life science organizations
  - Promoting cost effective treatment for children
- To promote safety of medicines administered to children

Improving Access to Commercialized Child-Friendly Medicines

How Did We Create Our Priority List?

1. Which drugs are currently compounded for oral administration in Canadian children and which ones are available in US and/or EU as commercial pediatric formulations ?
   - Study conducted at the Centre Hospitalier Universitaire Sainte-Justine
2. Which drugs should be prioritized first ?
   - Pan-Canadian survey
3. What is the pediatric market size ?
   - IMS data (now IQVIA) for all drugs on the list

Priority List

- 56 “old” drugs regularly compounded with a median of 35 years on the Canadian market
  - 27 (48%) have a suitable child-friendly commercial formulation outside of Canada
  - 18 (67%) have a Canadian pediatric indication
- 12 top drugs identified by Pan-Canadian survey
  - 9 have a suitable child-friendly commercial formulation outside of Canada
- Tacrolimus: pediatric market share (data from IQVIA)= 1,576,181 TRX units (7% of total Canadian tacrolimus market)[1]

Drugs	Number of hopitals that ranked drug as :	
	Most in need of a pediatric formulation, n (%) N=13	Most frequently compounded, n (%) N=13
~~Levetiracetam~~	8 (62)	10 (77)
Spironolactone	8 (62)	7 (54)
Tacrolimus	8 (62)	7 (54)
Clonidine	7 (54)	7 (54)
Hydro-chlorothiazide	6 (46)	6 (46)
PPI[1]	6 (46)	7 (54)
ACE inhibitors[3]	4 (31)	5 (38)
~~Amlodipine~~	4 (31)	2 (15)
Dexamethasone	4 (31)	10 (77)
Hydroxyurea	4 (31)	2 (15)
Sildenafil	4 (31)	4 (31)
Topiramate	4 (31)	4 (31)

Litalien C et al. Can J Hosp Pharm. 2020 Fall;73(4):247-256.
Gilpin A. et al. Paeditr Child Health 2018 Jun-Jul (Suppl 1):e53

Tacrolimus – Canadian Monograph

- Initial approval: 1996 (Fujuisawa Canada), 2006 (Astellas Canada)
- First-line immunosuppressive agent for the prophylaxis of rejection in both pediatric and adult solid organ transplantation (SOT)
  - Long-term treatment
  - Narrow therapeutic index (therapeutic drug monitoring)
- Available forms in Canada
  - Immediate-release capsules 0.5, 1 and 5mg (Prograf®, Sandoz®), extended-release capsules 0.5, 0.75, 1 ,3, 4 and 5 mg (Advagraf®, Envarsus PA®) and IV 5mg/mL (Prograf®)
  - Need to compound for young children unable to swallow
- Pediatric Indication ?
  - Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants
  - Treatment of refractory rejection in patients receiving allogeneic liver or kidney transplants
  - Pediatrics (< 18 years of age): Experience with Prograf in pediatric kidney and heart transplant patients is limited. Successful liver transplants have been performed in pediatric patients (ages 4 months up to 16 years) using Prograf, with the majority of these patients under 5 years of age

Tacrolimus – Issues with Compounded Formulation

- Errors in the preparation
- Limited stability data
- Under appreciation of the potential impact of compounding on the variability of tacrolimus PK profile

Hospital Pharmacy

Hosp Pharm. 2018 Jun; 53(3): 142–145.
Published online 2018 Apr 19. doi: 10.1177/0018578718769

Multifactorial Causes of Tacrolimus Errors: Look-Alike Names, Preparation Errors, and Compounding Please, no more teaspoon d

Michael R. Cohen[1] and Judy L. Smetzer[1]

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Abstract

A recent string of errors associated with tacrolim
prevent rejection in transplant recipients, prompt
related events reported to the US Food and Drug A
System (FAERS) and the ISMP National Medicatio
that tacrolimus has been involved in many report
caused by a wide variety of factors, the most com

Tacrolimus Availability

Tacrolimus is commercially available for oral use
capsules (immediate-release **PROGRAF** and gene
mg, 1 mg, and 4 mg tablets (extended-release **ENV**
mg/mL, 1 mL ampuls (Prograf) for intravenous (I

Tacrolimus Errors Occur

March 17, 2019
Michael J. Gaunt, PharmD
Pharmacy Times, March 2019 Respiratory, Volum

Avoiding Leading Decimal Point Doses and Educa

A string of errors associated with the high
rejection in transplantation recipients, pro
literature and analyze related events repo
Medication Errors Reporting Program.

The ISMP found that over the past decad
by a variety of factors.

COMMON TYPES AND CAUSES OF ERRO

Compounding errors. Errors during the co
10-fold errors when the incorrect capsule
substitution of a generic product for a bra
patients experienced problems with fluctu

Confused medication names. ISMP has re
blocker used to treat benign prostatic hyp
coordinator reported 2 incidences in whic
been prescribed tacrolimus 0.5 mg. Tragic
the transplanted liver.

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been prescribed tacrolimus 0.5 mg. Tragic
the transplanted liver.

Confusion when dispensing more than 1 s
patient's weight, type of organ transplant,
the available capsule or tablet strengths r

Institute for Safe Medication Practices Canada
REPORT MEDICATION INCIDENTS
Online: www.ismp-canada.org/err_index.htm
Phone: 1-866-544-7672

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ISMP Canada Safety Bulletin

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Anti-Rejection Medications: Analysis of Reported Errors

Patients who have undergone organ transplant require multiple medications to prevent organ rejection. Therapeutic management aims to suppress the immune response that can result in damage or loss of a transplanted organ while also ensuring there is a sufficient immune response to be able to fight infections.[1] In follow-up to several recent reports of incidents involving medications used to prevent organ rejection, a multi-incident analysis was conducted. The analysis identified system vulnerabilities, and selected system safeguards to improve medication safety.

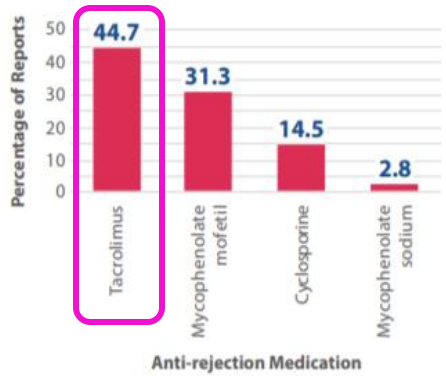
METHODOLOGY

Reports of incidents with anti-rejection medications were extracted from 3 ISMP Canada reporting databases (Individual Practitioner Reporting, National Incident Data Repository for Community Pharmacies, and Consumer Reporting) and the Canadian Institute for Health Information's (CIHI) National System for Incident Reporting (NSIR) database* for the period August 2016 to July 2021. The search terms used to extract the incidents included "transplant", "rejection", "graft", "host", "donor", "recipient", and "organ", as well as the generic and brand names of medications (immunosuppressants and corticosteroids for systemic use) prescribed to prevent rejection after a transplant. Incidents were excluded if it was not clear that the patient was taking these medications to prevent rejection of a grafted organ.

QUANTITATIVE FINDINGS

The 2446 incidents reported in the 5-year period were screened against the exclusion criteria, with a total of 179 incidents retained for the final analysis: 79 incidents from ISMP Canada databases and 100 incidents from the NSIR database.† Figure 1 shows the most common medications involved in

Figure 1. Top medications reported in incidents involving anti-rejection medications



* The databases are components of the Canadian Medication Incident Reporting and Prevention System (CMIRPS). More information about the databases is available from: http://www.cmirps-scdpim.ca/?p=12. NSIR data were provided by the Canadian Institute for Health Information (CIHI); however, the analyses, conclusion, opinions, and statements expressed herein are those of ISMP Canada.
† It is recognized that it is not possible to infer or project the probability of incidents on the basis of voluntary reporting systems.

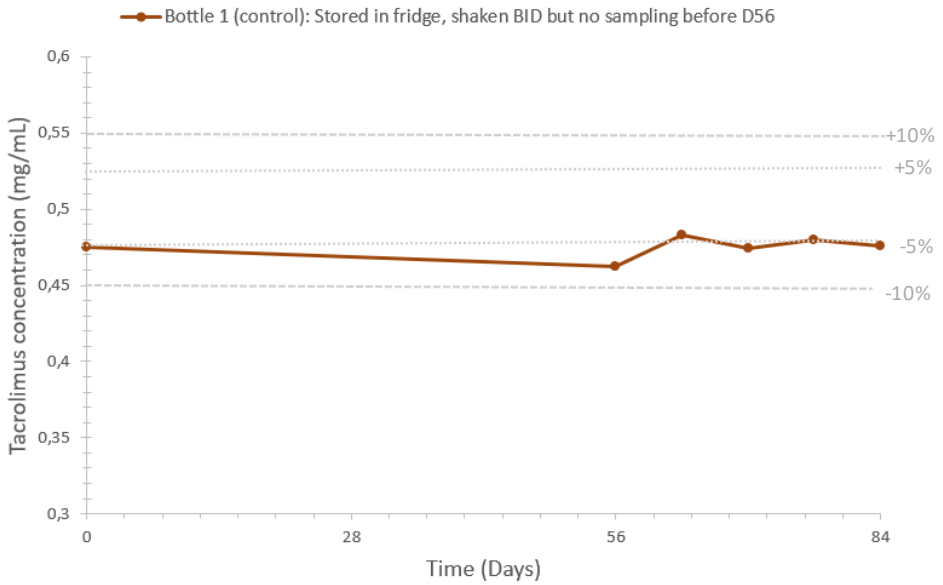
Stability of the Compounded Formulation

- Stability studies for storage conditions of tacrolimus compounded suspension conducted under controlled conditions;
  - Jacobson (1997): All the amber plastic bottles were stored at room temperature (24–26 °C). A 1-mL sample was withdrawn with a micropipette from each of the six bottles immediately after preparation and at 7, 15, 30, 45, and 56 days. **Result: Stable for 56 days at room temperature.**
  - Frisciu (2017): Each preparation was packaged in amber glass bottles and amber plastic syringes. Preparations were stored at 5°C or 25°C for up to 90 days an aliquot was removed from each bottle at each time point for analysis day 0,7,14,30,45,60, 75 and 90. **Results: Stable for 90 days at room temperature and in fridge.**

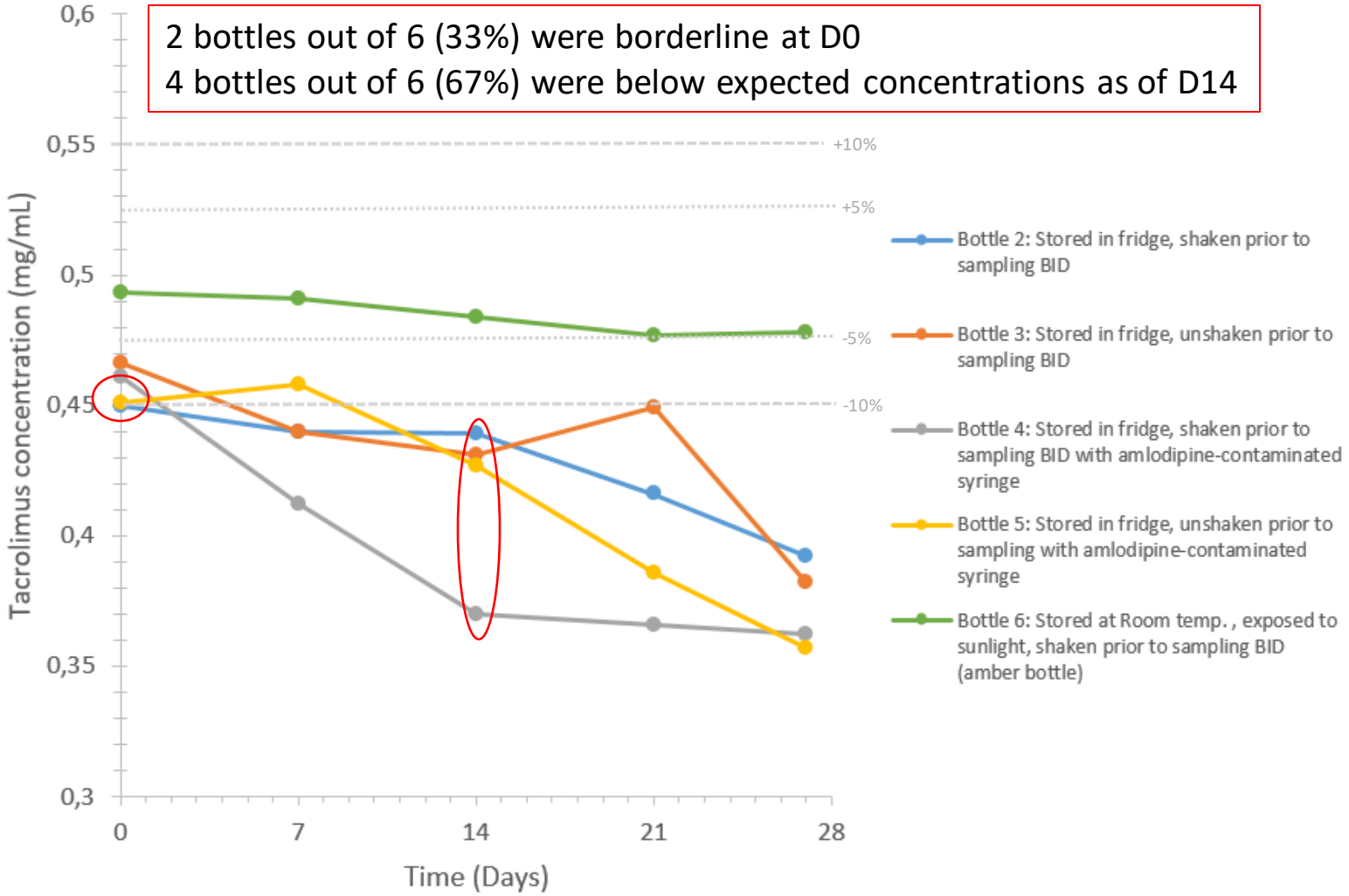
Stability of the Compounded Formulation

- A study mimicking real life use was conducted by the GPFC with participation from the Faculty of Pharmacy (UdeM)
  - Amber plastic bottles containing 150 mL tacrolimus 0,5mg/mL submitted to various conditions over 28 days and up du 84 days;
  - Twice daily sampling of 2 mL to reproduce BID dosing;
  - Scenarios looking at various parameters such as effect of time, temperature, sunlight exposition and agitation;
  - Concentrations of tacrolimus measured q 7 days from day 0 to day 28 (56 and 84 for control bottle)
  - Microbial contamination evaluated on day 0 and 28 (56 and 84 for control bottle).
  - Primary endpoints :
    - Tacrolimus concentrations measured in bottles compared to expected concentration (0.5 mg/mL +/- 5 and 10%) over time;
    - Presence or absence of microbial contamination on first and last day of sampling

Preliminary Results: Concentration of Tacrolimus Over Time



2 bottles out of 6 (33%) were borderline at D0
4 bottles out of 6 (67%) were below expected concentrations as of D14



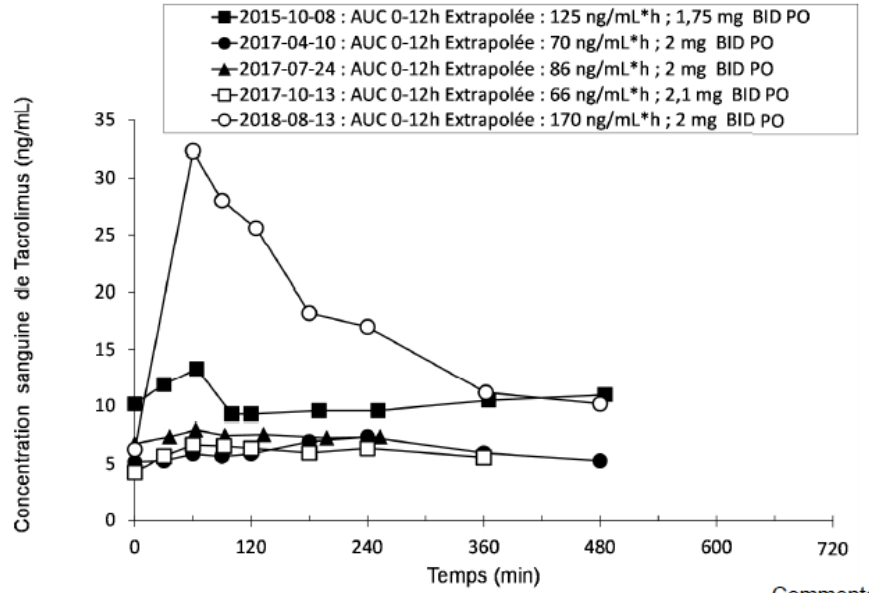
Commercial Capsules versus Compounded Suspension

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant
Université de Montréal

Unité de Pharmacologie Clinique
... la pharmacologie pédiatrique en temps réel

OPTIME
Optimisons la PharmacoThérapie Individualisée

RAPPORT ORIGINAL DU DOSSIER
COPIE DU MÉDECIN
COPIE DU PHARMACIEN



Commentaire :

Signature de l'infirmière de l'UPC :

F-2132 form. Informatisé (rév. 08-2018)

Rapport provenant du laboratoire de l'Unité de Pharmacologie clinique

Tacrolimus Granules for Oral Suspension

- 2001: First approved in Japan as Prograf® granules
- 2009: Approved in Europe (EMA) as Modigraf®
  - *Prophylaxis of transplant rejection in adult and paediatric, kidney, liver or heart allograft recipients. Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult and paediatric patients.*
- 2018: Approved in US (FDA) as Prograf® granules
  - *PROGRAF is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in adult and pediatric patients receiving allogeneic liver, kidney or heart transplants, in combination with other immunosuppressants.*
  - Submitted in response to a PMR for Astagraf XL
  - Received orphan designation
- Currently marketed in 32 countries (not in Canada)

Data Supporting Approval of Tacrolimus in Europe (EMA)

- 2001: Phase 1 Bioequivalence study
- Phase 2 Open-label non-comparative pilot study in pediatric liver transplant recipients (1996-1998)
- Phase 3 Open-label, prospective, randomized comparative study in pediatric liver transplant recipients (2000)
- Supportive studies from Japan
- Conclusion: The capsule and granules formulations were not bioequivalent, with the granules resulting in an 18% increase in AUC. In the context of the proposed 1:1 mg switch, the clinical relevance of this difference was thoroughly discussed. It was deemed acceptable as subjects are under close supervision with TDM.
- Follow-up measures:
  - Phase 4 OPTION study
  - Follow-up study to the OPTION study

Data Supporting Approval of Tacrolimus in the USA: FDA

- FDA did not request supplemental studies
- Accepted the bioequivalence study previously performed
- The difference in AUC between the capsule and the granules formulation was not considered clinically significant
- No need for a systematic review

Tacrolimus – Cost Comparison between formulations

	Oral Fomuation	Strength or Concentration	Cost per mg
UK[1]	Granules (Modigraf)	0.2mg/sachet	$11,12
		1 mg/sachet	$11,12
	Capsules (Prograf)	5 mg	$1,85
RAMQ[2]	Capsules (Prograf)	5 mg	$2,50
	Capsules (Sandoz)	5 mg	$1,89
CHU SJ	Compounded formulation[3]	0.5mg/mL	$4,33

1 Drug tarifs August 2022 : granules = 7,13 bp/mg caŝpsule= 1,19 bp/mg converted to CDN on 17Aug2022

2 Price from latest RAMQ listing date August 2022

Based on the section *Tarifs* of the *Manuel des pharmaciens* from the RAMQ, we estimate the cost of a compounded preparation of tacrolimus 0,5mg/mL to about **130$/60 mL(or 30 mg)** or **4,33 $/mg** which includes ;

- the active ingredient (6 x 12,50$ = 75$)
- the excipient (about 4$)
- the preparation under special conditions (43,63$) (Code de service Catégorie M3 on p. 216 of Manuel des pharmaciens)
- the packaging from the compounding pharmacy (6,05$) .

It is important to note that these are **NOT** high cost drugs

Tacrolimus Annual Cost Estimate

- Hypothetical case: 1 year-old child with hepatic transplant, weighing 10 kg and requiring 0,2 mg/kg/day in two doses = 2 mg/day

	Compounded	Commercial
Formulation	Oral suspension 0,5mg/mL	Granules for suspension 0,2 mg et 1 mg sachets
Preparation/ stability	• Prepared at the pharmacy • Requires special equipment (hood) • Stability = 56 days • Requires to be vigoursly shaken	• Prepared by caregiver • Diluted in water at the time of administration • Stability = 3 years
Cost/mg	4,33$	11,12$
Annual cost (2mg/d)	3 160$	8 117$

- High cost drugs such as Spinraza[mc] (intrathecal nusinersen) for spinal amyotrophy in children cost 708K$ for the first year and 354K$/year afterwards
- Risk of organ rejection or toxicity is higher with the compounded preparation
  - Estimated mean cost of hepatic transplantation in Ontario in 2002 was $120K (ranging from $30 à $690K)
  - In Québec-RAMQ : Interprovincial tarif for costly interventions (As of April 1st 2016): hepatic transplantation = $ 132K

https://www.cmaj.ca/content/168/2/206.1
https://www.ramq.gouv.qc.ca/SiteCollectionDocuments/professionnels/manuels/420-services-hospitaliers-internes/008_tari_interpro_serv_interne.pdf

New price tag put on liver transplants

The estimated average cost of a liver transplant in Ontario, including follow-up costs, is $121 732, but the range varies widely — from $30 505 to $690 431 — because of factors such as disease severity, post-transplant infection and biliary complications. The figure is based on 1998 data, with allowances for inflation.

The study, conducted by physicians from the universities of Manitoba and Toronto and published in the *Canadian Journal of Surgery* (2002;45[6]:425-34), noted that the affordability of organ transplantation has been questioned but few data on the cost of liver transplantation are available, even though 1 procedure a day — 350 annually — is performed at Canada's 5 liver transplant centres. The authors say that performing procedures earlier will reduce costs. As well, elimination or reduction of the incidence of cytomegalovirus infection will help cut costs by reducing drug costs and the length of stay in hospital.

The new price tag is 42% higher than a 1998 estimate by an Ontario working group, mainly because that group did not include some fees and estimated the length of hospital stay at only 16 days. The new study found that the mean length of stay for these patients is 43 days, including 9 days in the intensive care unit. — *Patrick Sullivan*, CMAJ

Why are tacrolimus granules not available in Canada ?

- Per discussion with manufacturer of Prograf (Astellas)
  - Market research concluded there was no interest from contacted health professionals ;
  - There was no complaint about the compounded suspension (GPFC's survey conducted in 2017 with pediatric hospital pharmacist showed the opposite)
  - Due to complexity of market access and lack of interest – no submission to Health Canada
  - Contrary to Europe (EMA) and the US (FDA), there is no obligation to submit pediatric formulations in Canada
- In 2020, the GPFC initiated a pilot project using an inverted model with tacrolimus to determine all the steps required and costs to bring the formulation to market

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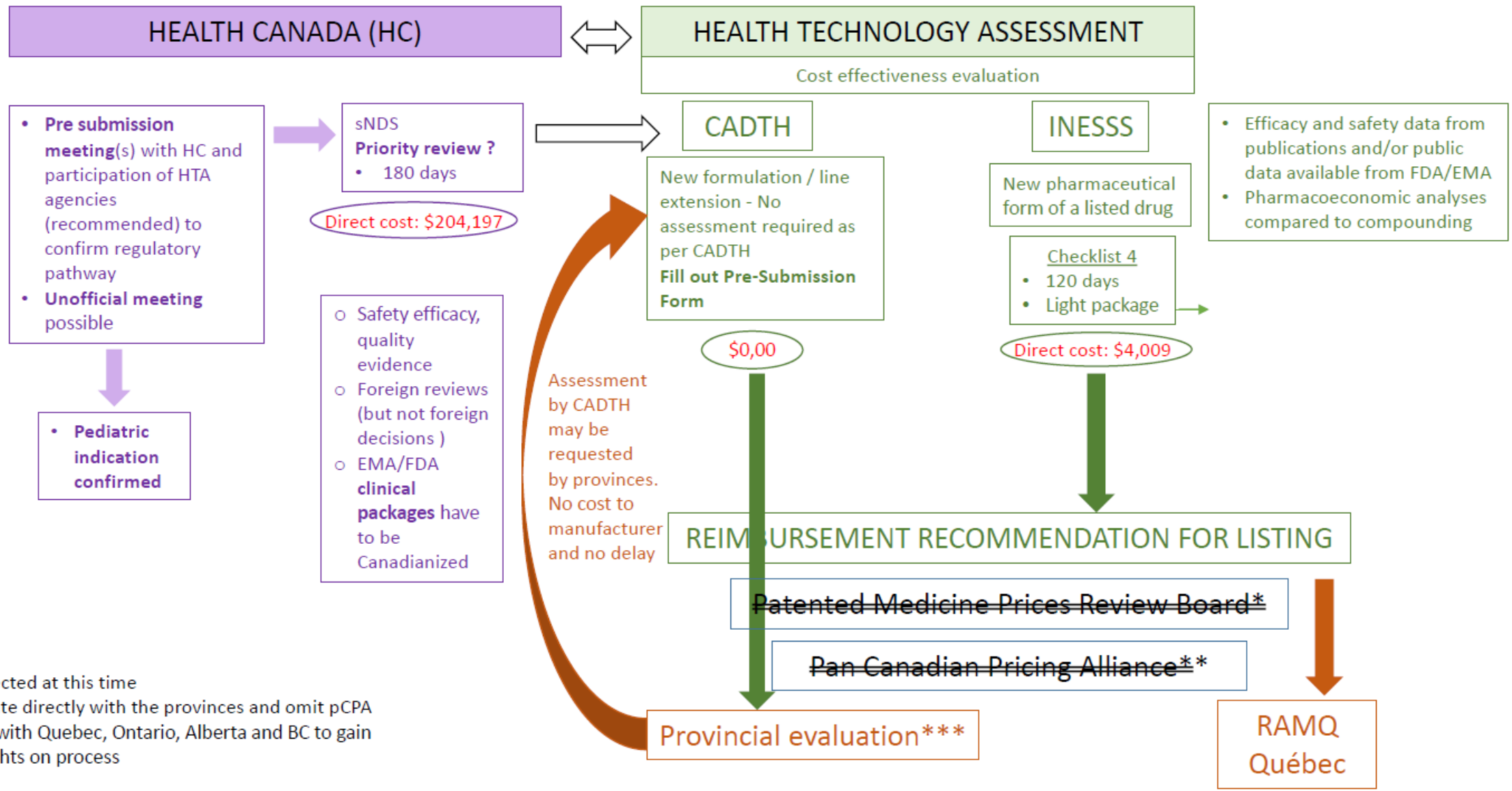
TACROLIMUS PILOT PROJECT

Aligned drug review process



* Not expected at this time
** Negotiate directly with the provinces and omit pCPA
*** Work with Quebec, Ontario, Alberta and BC to gain initial insights on process

Pricing: The Last Step to Access

- Need to show cost benefit compared to what is being reimbursed today
- Existing reimbursement in pediatric formulations may be compounded medications
- Provincial budget impact analysis is done using compounded medication as a comparator
  - Does not value the rigorous requirements for a commercial formulation

What's Next for Pediatric Formulations for Canadian Children ?

- Canada lags behind
  - 20 years after Japan, Canada is treating organ transplant in children with a sub-optimal preparation of tacrolimus
- Is this acceptable in the context of organ shortages ?
- What is the rationale to support a commercial preparation versus compounding?
  - Do we consider that there is an advantage to a GMP medication?
- How do we convince pharma to market age-appropriate formulations ?
  - Trusted foreign decision ?
  - Priority review ?
  - Financial incentives ?

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