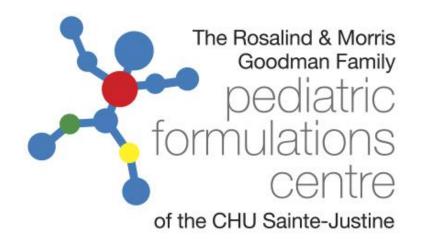
Advancing Pediatric Formulations



Dr. Catherine Litalien Andrea Gilpin Pediatric Chairs of Canada June 6 2019



Conflict of Interest Statement

The GPFC :

- Funded by the Morris and Rosalind Goodman Family Foundation
- Service contracts with Pharmascience, Leon Nanodrugs, Rare Disease Therapeutics, and Ethypharm

The Real Life...

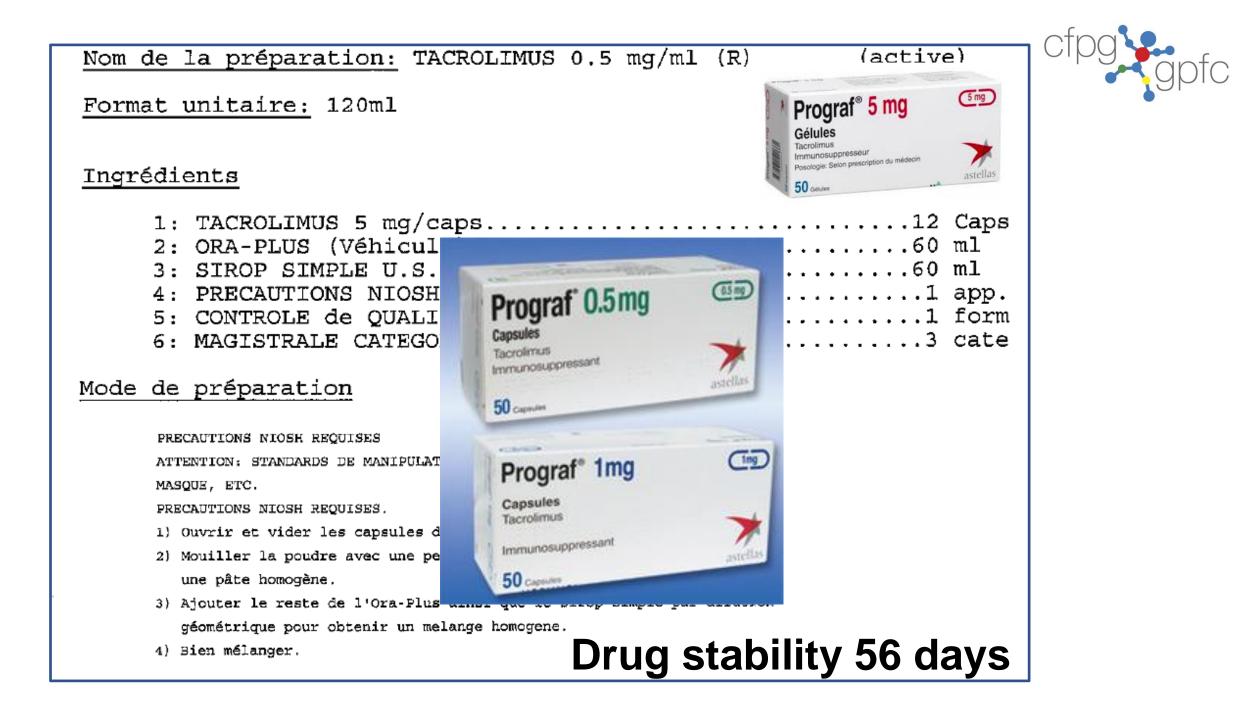


8 month old liver transplant recipient admitted for severe hepatic failure secondary to acute rejection

Tacrolimus blood level found to be extremely low

During hospitalization, his tacrolimus blood level returned within a therapeutic range

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





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







Problem statement



- Several drugs administered to children are not available as a commercial formulation adapted to their needs
- Health professionals and parents have to manipulate adult pharmaceutical forms



- Bad taste = Compliance issue
- Limited data on stability and few/no data on bioavailability
- Imprecise dosing
- Potential exposure of caregivers to toxic drugs at home
- Manufacturing standards and quality control ≠ Pharma industry
- Compounding is not standardized
- No system in place to evaluate efficacy and safety of compounded drugs
- Lack of knowledge/sensitivity by the prescribers



2007



European Paediatric Formulation Initiative

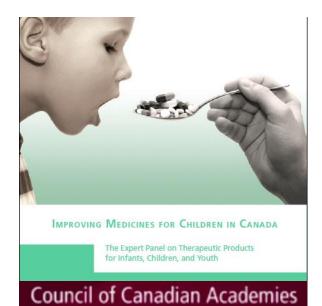


Workstreams

- Age-appropriate formulations
- Administrations devices
- Taste masking and testing
- Pharmaceutical excipients
- Biopharmaceutics



2014



Children respond to medications differently from adults; thus, **medicines must be studied** in children and **formulated for children**

The GPFC Mandate



- To accelerate the development and market authorization of pediatric drug formulations by:
 - Promoting a research-based approach
 - Contributing to a favorable clinical and regulatory environment
 - Contributing to uncovering incentives
 - Promoting cost effective treatment for children
- To promote safety of medicines administered to children

Improving Access to Child-Friendly Medicines

Scoping the Needs for Oral Pediatric Formulations in Canada

- Which drugs are currently compounded for oral administration in Canadian children ?
- Are they available in US and/or EU as commercial pediatric formulations ?
- Which ones should we prioritize first ?







- 57 drugs were identified
- 3 most frequent categories of drugs using AHFS Pharmacologic-Therapeutic classification:
 - Cardiovascular: 30 %
 - Central nervous system: 19 %
 - Anti-infectious: 11 %
- 98% are off-patent drugs
- On the Canadian market for a median of **35 years**
- (14 65 years)
- Canadian pediatric indication for 27 drugs (47%)





Ursodiol

20 mg/mL Dexamethasone 4 1 mg/mL Levetiracetam 50 mg/mL Domperidone 4 1 mg/mL Topiramate • 6mg/mL Hydroxyurea • 100 mg/mL Sildenafil

2.5 mg/mL Hydrocortisone • 1 mg/mL Amlodipine 1 mg/mL Gabapentin 100 mg/mL Tacrolimus • 0.5mg/mL Captopril 1 mg/mL Caffeine 10mg(base)/mlL Rifampicin 10 mg/mL Lamotrigine • 1mg/mL Metronidazole

50 mg/mL Sotalol 5 mg/mL Phytonadione 1 mg/mL Folic acid 1 mg/mL Baclofen

10 mg/mL Vancomycin 4 50 mg/mL Enalapril 1 mg/mL Amitriptylline 10 mg/mL Levothyroxine 25 mcg/mL Midazolam 5mg/mL Losartan

2.5 mg/mL Nitrofurantoin 10 mg/mL Sevelamer

50 mg/mL

ы.

Regulatory status Pediatric indication in Canada No pediatric indication in Canada

20

25

>30



Commercially Available Oral Pediatric Formulations in the US and/or Europe

n=28 (49 %)

Annual quantity of drugs compounded in Liters (L) at CHU Ste-Justine

15

10

Prioritize the Needs: Pan-Canadian Survey

- Thirteen centers among 16 contacted completed the telephone survey between April and June 2017 (81.3%)
- When sites were asked to list their 10 compounded medicines most in need of commercialized pediatric formulations:
 - 51 drugs were identified 12 are identified as top priorities

	Number of hopitals that ranked drug as :			
Drugs	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)		

9 with suitable pediatric formulations outside Canada



An Oral Solution of LEV is Approved for Use in Children in the US and Europe for Over 10 years...



- 1999 US: Tablets approved for adjunctive therapy for POS in adults
- 2000 EU: Tablets approved for adjunctive therapy for POS in adults
- 2002 EU: Oral Solution approved for adjunctive therapy for POS in adults
- 2003 CANADA: Tablets approved for adjunctive therapy for POS in adults
- 2003 US: Oral Solution approved for adjunctive therapy for POS in adults
- **2005 US & EU:** Tablets/Solution approved for adjunctive therapy for POS in adults and children ≥ 4 yrs
- 2006 US & EU: Tablets/Solution approved for adjunctive therapy for JME in adults and children \geq 12 yrs
- 2007 US: Tablets/Solution approved for adjunctive therapy for PGTC in adults and children \geq 6 yrs
- 2007 EU: Tablets/Solution approved for adjunctive therapy for PGTC in adults and children \geq 12 yrs
- 2009 EU: Tablets/Solution approved for adjunctive therapy for POS in adults and children \geq 1 mth
- 2011 US: Tablets/Solution approved for adjunctive therapy for POS in adults and children \geq 1 mth

2019 CANADA: NO PEDIATRIC INDICATION AND NO PEDIATRIC FORMULATION EXIST TODAY ...

POS = Partial onset seizure **JME** = Juvenile myoclonic epilepsy **PGTC** = Primarily generalized tonic-clonic seizure

And We Continue to Treat Children with ALL by Cutting Cytotoxic Tablets



- In Canada 6-mercaptopurine:
 - Approved for maintenance therapy
 - Included as long-term treatment (18-30 months) in all chemo protocols
 - Non-adherence to treatment is linked to treatment failure
 - Only 50 mg tablets are available therefore:
 - Tablet splitting
 - Compounding
 - Environmental toxicity
 - High risk of under/overdosing

Approved and marketed in Europe (2012), US and Australia (2014)





Advancing Two Medicines on Our Priority List



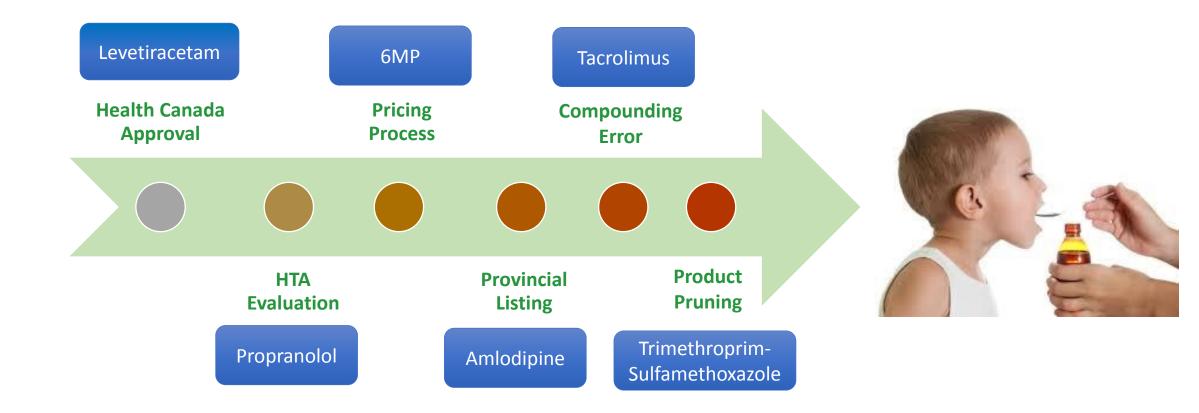
Two pediatric formulations have been submitted to Health Canada by one of our partners

- One has obtained marketing authorization in January 2019 (AMLODIPINE)
- One is under review by Health Canada (submission relying on third party data) (LEVETIRACETAM PO and IV)





Examples of Barriers Exist at Every Junction of the Drug Approval and Market Access Process





Why are Pediatric Formulations Unavailable in Canada ???

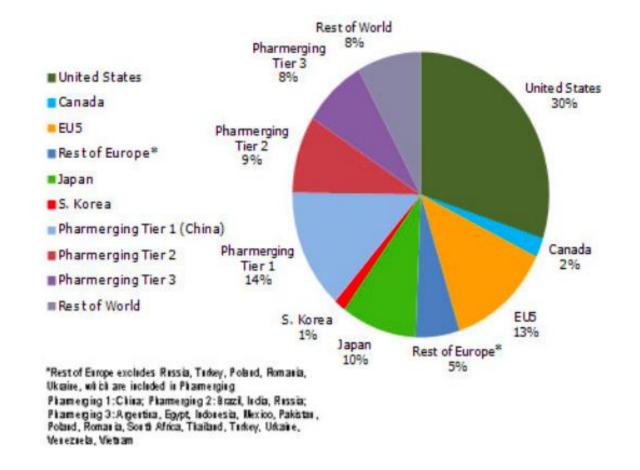
- Regulatory requirements are perceived as unclear and complex
- Reimbursement can be a challenge
- Small market size
- High costs related to pediatric formulation development
- No incentives





2016 – Market Share, US \$

- Pharmerging 1:
 - Chine
- Pharmerging 2:
 - Brésil, Inde, Russie
- Pharmerging 3:
 - Argentine, Égypte, Indonésie, Mexicque, Pakistan, Plogne, Roumanie,Afrique du Sud, Thaïlande, Turquie, Ukraine, Vénézuela, Vietnam



Pediatric market: < 10 % of Pharma market



Very Few Incentives for Pediatric Medications in Canada

Country/ Region	Incentives for Patented Products	Incentives for Off —Patent Products	
Canada	 + 6 months added to 8-year period of data protection 	• None	
US	 + 6 months of market protection to patents and/or exclusivity 505 (b)(2) : 3-5 years exclusivity Rare pediatric disease priority review voucher possible to keep or to sell 	 505 (b)(2):3-5 years exclusivity 	
EU	 + 6 months to Supplementary Protection Certificate (SPC) if compliance with agreed PIP + 1 year market protection if clinical studies required and MA granted Orphan- +2 years of market exclusivity if PIP is completed for orphan indication = 10 + 2 	 PUMA – 10 year marketing exclusivity 	

Six Consultation Letters Written to Advocate for Pediatric-Sensitive Standards

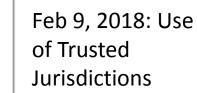


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KidsCAN

Jan 3 & Aug 30 2018: Proposed Health Canada Fees Structure

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September 11, 2018

Innuary Helio Sinector, Regulatory Reviews, Regulatory Affairs Sector Jenior Advisor & PHAC, Assistant Deputy Minister's Office Ireasury Board of Canada Haalth Products and Food Branch

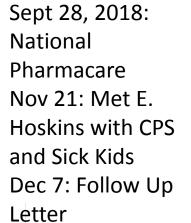
commentary to Regulatory Modernization Ini

The document herdeaux formulations control (BPC) would list as provide to paragetistic apparing patients includions within the payment Republicity Model and the process in tearing with one phase and they one measuring that adjustments of agenesis marked in the process in tearing this rule process in tearing the original structures of agenesis marked in the process in tearing the number paragetistic paragetistic generation and agenesis marked in the approxemation of the annual tear the structure of the approxement of agenesis marked in the approxemation of the approxement of the structures of the approxement of the averation applications process in Canada, Within the application of the application of the averation applications process in Canada. Within the application applications in the application of the averation applications process in the application of the application of the averation applications process in the application of the application of the averation applications and the interpretent of the application of the averation applications approxement of the applications. Canada the application applications applications applications of the applications form application applications applications applications applications applications of the applications. Canada the application applications applications applications applications applications of the applications. The application application applications aplications appl

The Goodman Pediatric Formulations Centre

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Sept 11, 2018: Regulatory Modernization





\$eptember 28, 201

Dr. Eric Hotkins, Chair Advisory Council on the Implementation of National Pharmacare Secretariat Brooke Clascon Building 20 Colongbing Driveway Ottawa, ON KIA OKS

Email: pharmacare-assurancemedicaments@canada.ca Commentary to Proposed Pharmacare with Regards to Pediatric Formula

entary to Proposed Pharmacare with Regard

Dr. Hoskins,

The Goodman Pediatric Formulations Centre (GPFC) would like to provide its perspective regarding pediatric formulations vis-i-vis the proposed implementation of a National Pharmacare Program. We are pleased to have the opportunity to comment on this anticipated change.

The Goodman Pediatric Formulations Centre

The GPFC has the goal of improving access to child-finendly medicines. We are the only Centre in Canada whose mandate is to assist in the development and commissibation of rate and effective age-appropriate formulations for children. The GPFC operates as a nor-for-profile organization, whose suchurie goal is to support the well-being of children by facilitating the availability of formulations adapted to their needs, for optimal tratement. Even though the GPFC works clearly with happital, health care providers and industry, our positions and actions are completely independent of these third parties.

The Problem: Canadian Children Do Not Have Access to Commerce

We need to have commercial pediatric formulations available for Canadin pedi commercialized pediatric formulations are available in other juridicitions, such as Europh, howver, these formulations <u>are gott, concentrations</u> and are an Canadian pediatric market is small and unlike the programs in the United States an commercial intentives, nor regulatory protection granted to bring commercialized Canada. Secondly, the pediatric regulatory sproved josthwy (<u>jogegode</u> as unlike the pediatric pediatric regulatory protection granted to bring commercialized Canada. Secondly, the pediatric regulatory sproved josthwy (j<u>ogegode</u> as unlike

elastica included is autoriting assume (on suggestions for your consideration, 1

The GWC believes the

sectage to the other important

mulations into Canada. Health Canada is a crucial first step in the drug area

referen that any changes that Health Canada can make to support pediatric

February 9, 2018

Proposed Use of Foreign Decisions C

The Goodman Pediatric Formulations Centre (GPFC) would like to contribute to the discussion regarding creating a regulatory pathway for the authorization of the sale of drugs already approved by trusted foreign regulators. This letter supplements the comments that we contributed to a telephone consultati that was held on February 9, 2018.

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The GPC has the module to improve access to child-financy medicines in C-ando. We are the only Centra in Cradek where solections is to ficialize the development of all and effective aper-paperprint formulations for children. The GPC operates as a non-for-profit organization, whose exclusive goal is to upport the well-based of children by factoring the vanishing for formulations adgred to their reads. Even though the GPC works collesy with heights), bath care providers and industry, our positions and actions are completed independent the garties.

Childre are not mini-adut. The relative late of invaliability of perfacting darge forms an level to transmer tailure a care avenut for children in Causal of analysis. Accessing published a report in 2014 estimation, "Improving Medicinator Children in Causal", which audites the childrenge in trading administrative for the darget of children in Causal", which audites the children and administrative the darget darget of the darget of the darget of the darget of the process by administrative the darget darget of the processing of the darget of the darget

There are several reasons why existing commercial pediatric formulations have the Canadian market. First, from a commercial perspective, the approximately si

Improving Medicines for Children in Canada, 2014, Council of Canadian Academie





Draft Guidance: Accelerated Review of Human Drug Submissions

This guidance document is being distributed for comment purposes only.



"Drugs with an indication targeting certain populations such as **pediatrics** (**especially formulations** where available adult formulations are unsuitable for pediatric use) or treatments for rare diseases may also qualify under this criterion. "

2.1.5 Product Eligibility Criterion #4: Evidence That the Drug Addresses a Health Care System Need by Delivering High Clinical Benefit for Public Health or Significantly High Clinical Benefit for Patients



Networking with Key Stakeholders







Global Accelerator for Paediatric Formulations (GAP-f)



CANADIAN CHILDHOOD CANNABINOID CLINICAL TRIALS







des adolescents et de leur famille par un leadership en formation, en recherche et en soins cliniques

KidsCAN

Two Policy Papers Joint with the Canadian Paediatric Society



-EMBARGO-

The material contained in the attached document is in draft form and has <u>not</u> been approved by the Canadian Paediatric Society and should not be made public, cited or circulated to anyone other than yourself without prior permission from the CPS office.

Therefore, this document is embargoed until it is published and/or released to the CPS members, the public and/or the press following its approval by the Board of Directors.

-EMBARGO-

1 Improving medications for children: A prescription for Canadian children and

2 youth

- Charlotte Moore-Hepburn, Andrea Gilpin; Canadian Paediatric Society, Task Force on Paediatric Drugs
 and Therapeutics
- 5

6 Introduction

- 7 Children have a right to the highest attainable standard of health, including the appropriate treatment
- 8 of disease¹. Yet children and youth continue to be under-represented in medication research^{2,3}, the

```
9 design of medication-related regulations and commercial medication development<sup>4</sup>.
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- 10
- 11 Policies governing the development, approval, and reimbursement of medicines are largely designed for
- 12 adult populations, neglecting the unique characteristics of children and youth. Research funding for
- 13 adult diseases is frequently prioritized over childhood illness as the current capacity for, feasibility of
- and expected commercial benefit from adult-focused research is presumed greater^{5,6,7}. New medicines
- 15 are often evaluated and brought to market based on principles of adult physiology and adult return-

Improving Paediatric Medications: A prescription for Canadian children and youth

Universal Canadian Pharmacare: The Paediatric Perspective

Universal Canadian Pharmacare: The Paediatric Perspective

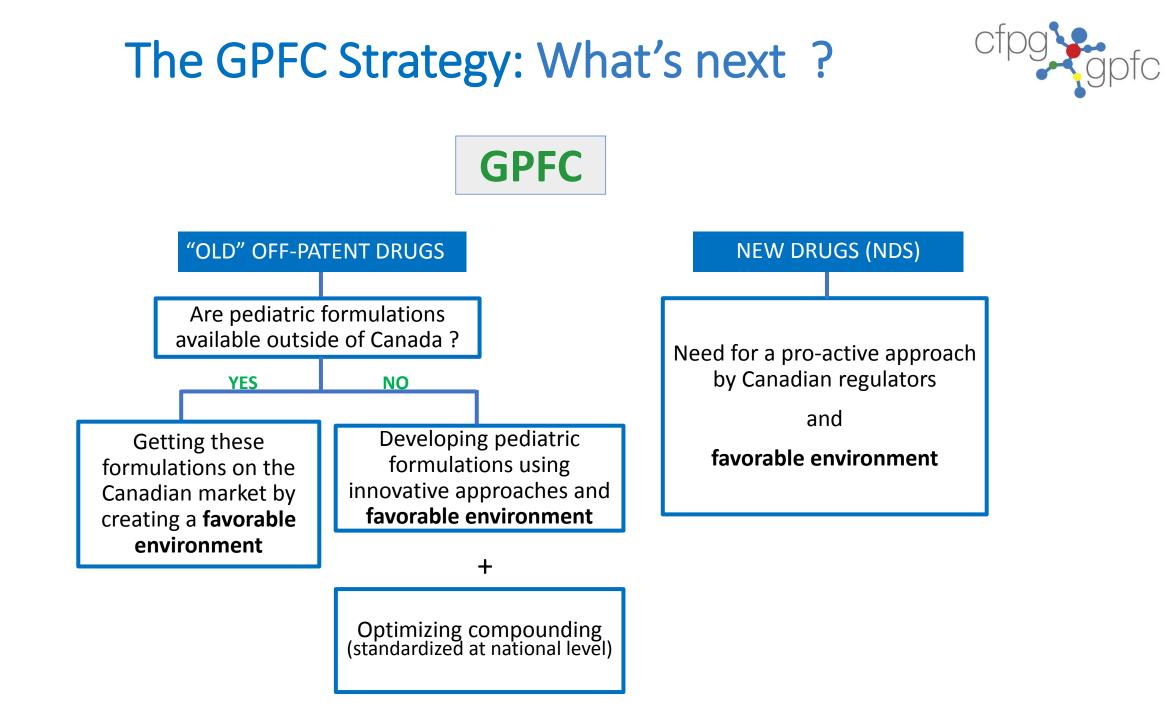
Authors: Tom McLaughlin, Geert 't Jong, Andrea Gilpin and Charlotte Moore-Hepburn

ABSTRACT

Children have unique challenges accessing affordable and effective prescription drugs in Canada. The current national Pharmacare debate provides an opportunity to prioritize and address these challenges after long-standing neglect. The pattern of drug use in Canadian children is much more heterogeneous than adults, and rare diseases are relatively concentrated in the paediatric population, meaning that children require comprehensive coverage for medically-necessary drugs. Canadian children currently rely heavily on compounded and offlabel prescription drugs, impacting palatability, safety, and efficacy. Currently, reimbursement decisions for paediatric drugs by Canadian health technology assessment bodies ignore return on investment outside of the healthcare system (e.g. when drug use reduces special education costs), and on providers and caregivers. Regardless of the specific Pharmacare model used, this paper recommends universal, comprehensive, and portable prescription drug coverage for children, a national, evidence-based drug formulary, and support for the development and approval of child-friendly drug formulations.

INTRODUCTION

Canada is currently the only high-income country with a universal public health insurance system that excludes prescription drug coverage (Morgan et al. 2015). Drug coverage is instead provided by a patchwork system of over 100 public and 100,000 private insurance plans (Kratzer et al. 2013). Public drug insurance is inconsistently available across provinces and territories and is limited to select populations, such as adults over 65, low-income Canadians, and individuals with mental or physical disabilities (Hoskins 2019). Nearly 1 in 5 Canadians report that they do not have prescription drug coverage, posing a significant barrier to their ability to access necessary medications. A similar number report that they, or someone in their household, has not taken a medicine as prescribed in the last year due to prohibitive cost, and almost one million Canadians reduce food or have to article medications for themedian



Canadian Sick Children Deserve the Best



Impactful Canadian Pediatric Formulation Initiative						
Advocacy	HCP & Associations Support	Pharma Industry Commitment	Knowledge, Expertise & Innovation			
Launching a major advocacy campaign at the provincial and federal levels to develop pediatric-specific regulations and policies to improve access to child-friendly formulations.	Bringing to action a network of health care pediatric organizations, professionals, and parent associations to improve access to pediatric formulations.	Getting pharmaceutical companies' commitment to develop and market the needed pediatric drug formulations, under the new proposed conditions.	Expanding knowledge by collecting patient- centric data to clearly outline the issues and to support actions from extended network. Consolidating expertise to support the cause and drive			

innovation

Conclusion

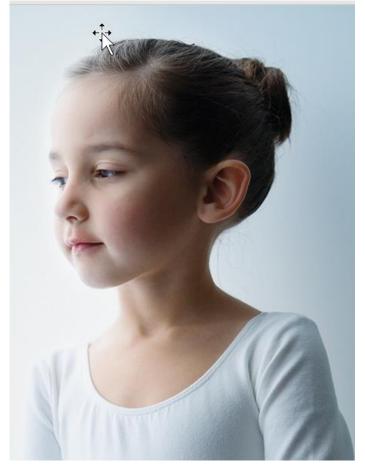


- Children deserve the same standards as adults i.e. high-quality GMP-grade pharmaceutical forms that are optimal to ensure efficacy and safety of drug treatment
- Canada is lagging behind when it comes to pediatric formulation, with several drugs currently compounded that are commercially available as child-friendly formulations outside of Canada
- There is a shared responsibility by all the players to create a favorable Canadian environment to improve access to commercialized formulations adapted to the needs of children
- Standardization of compounding at the national level would also optimize pharmacotherapy in children



The GFPC Needs You...

- As clinical expert to identify the needs and priorities
- As research experts to use innovative approaches in clinical trials to evaluate pediatric formulations
- As children advocates

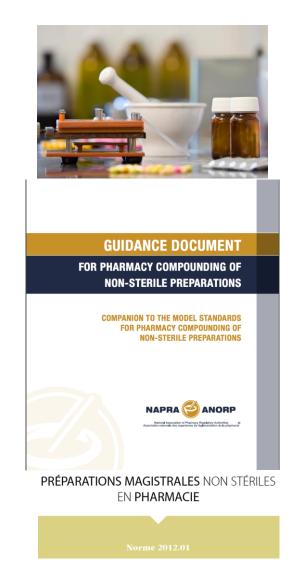


Short Video https://www.youtube.com/watch?v=4kDxlhabb7I&feature=youtu.be

Compounding

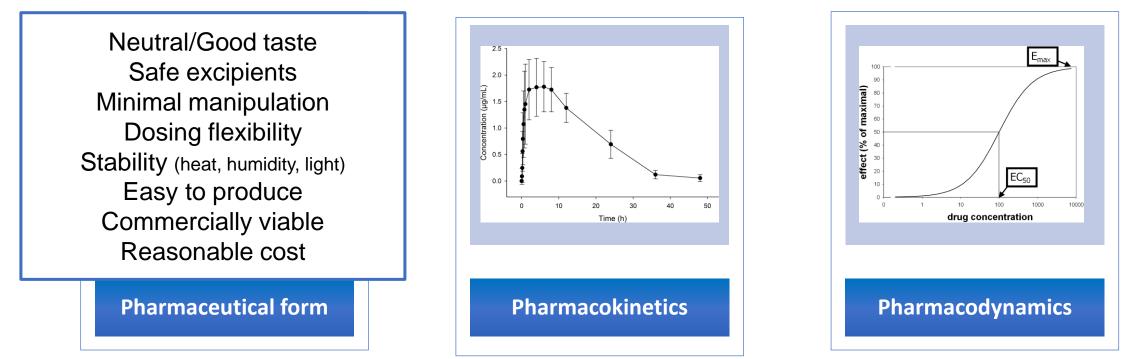


- Preparation of a drug for a particular patient due to the unavailability of a form adapted to its needs.
- Compounded drugs are prepared by a pharmacist or a trained pharmacy technician, based on a prescription and in accordance with standards such as those from NAPRA or ODQ (Quebec)



Determinants of Drug Efficacy and Safety

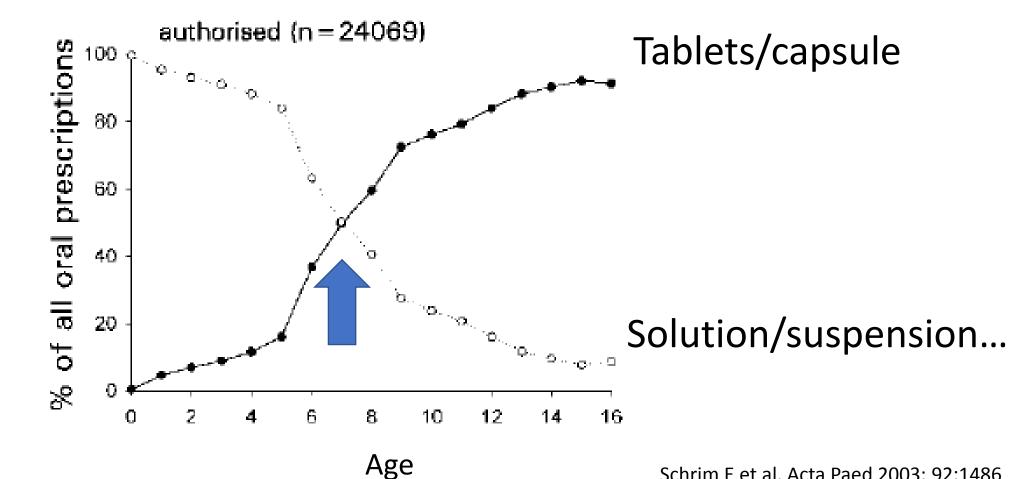




Access to pediatric formulations, that are easy to administer and are meeting high level pharmaceutical standards can make the difference between a therapeutic success and a failure, or between a safe treatment or the occurrence of adverse reactions



At What Age Is a Child Able to Take an Oral "Adult" Form ?



Which Pharmaceutical Forms Are Acceptable to Children ?



2006: EMA: Reflection paper, Formulation of choice for the paediatric population

Route Dosage Form	Preterm newborn infants	Term newborn infants (0d-28d)	Infants and Toddlers (1m-2y)	Children (pre school) (2-5y)	Children (school) (6-11y)	Adolescents (12-16/18y)
Peroral						
Solution/ Drops	2	4	5	5	4	4
Emulsion/Suspension	2	3	4	5	4	4
Effervescent DF*	2	4	5	5	4	4
Powders/	1	2	2	4	4	5
Multiparticulates						
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5.
Orodispersable DF	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5

Solid Pharmaceutical Forms: Beyond "Adult" Tablets



Powder containing fine granules



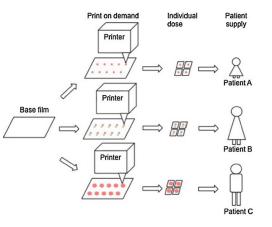


Mini-Tabs

Labelling of Enalapril from Neonates up to Adolescents



Orodispersible film





Formulations of Choice: "a Moving Target"



2008: WHO: Campaign "Make medicines child size"

• Recommendation: "Flexible solid dosage forms for all age groups"

2014: EMA: "Guidelines on pharmaceutical development of medicines for paediatric use"

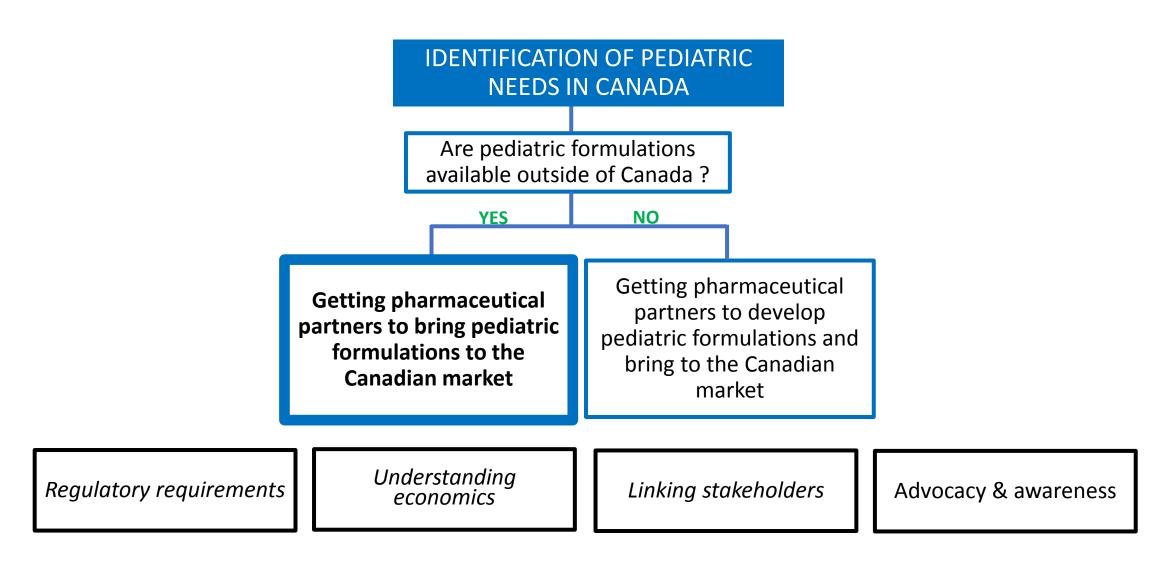
- Recommendation of oral solid forms based on age no longer apply
- Mini-tabs and pellets are considered as a potential option in younger children
- Need to demonstrate acceptability and safety of new oral pharmaceutical forms in the pediatric population





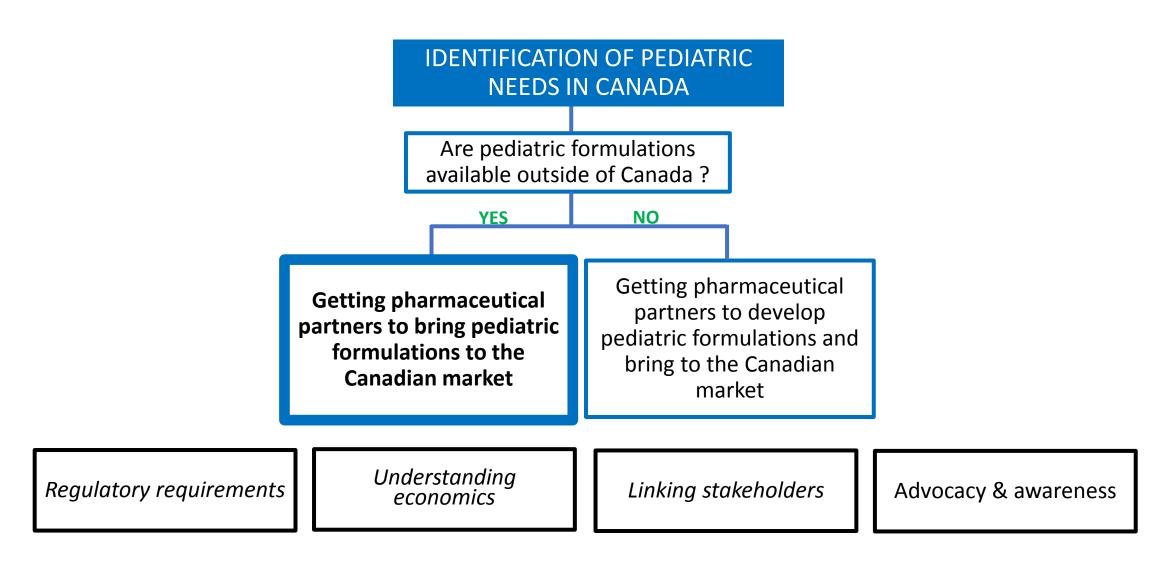
The GPFC Strategy 2016-2019





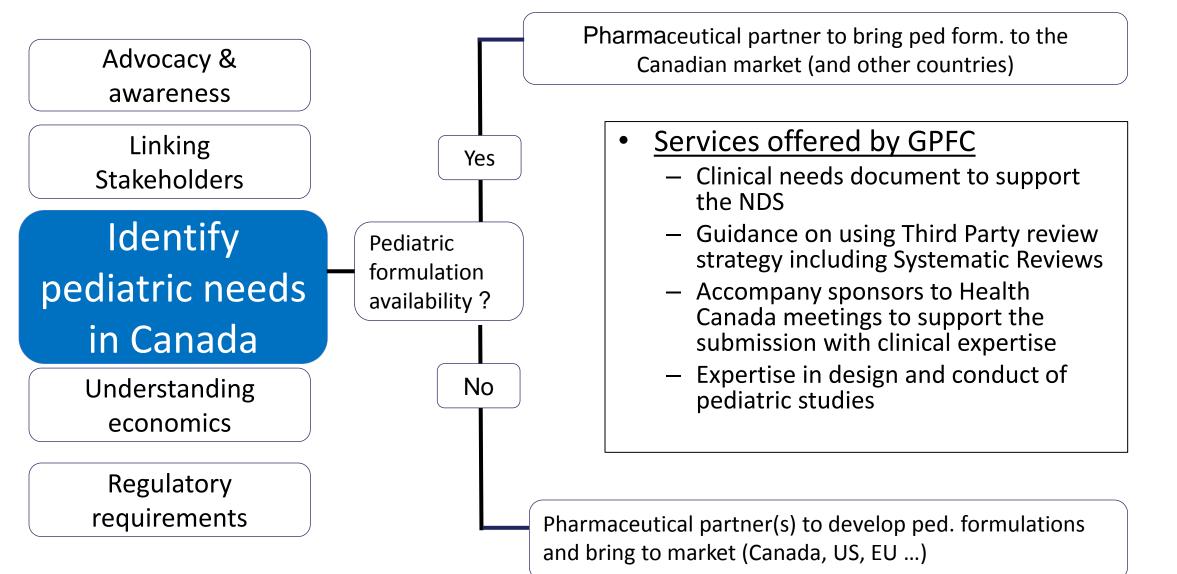
The GPFC Strategy 2016-2019





The GPFC Strategy 2016-2019







PPIs: Why are Canada and EU lagging behind ?

PPI unit dose packet	US	EU	Canada
Esomeprazole 2.5 mg	•		
Esomeprazole 5 mg	•		
Esomeprazole 10 mg	•	•	•
Esomeprazole 20 mg	•		
Esomeprazole 40 mg	•		
Omeprazole 2.5 mg	•		
Omeprazole 10 mg	•		
Pantoprazole 40 mg	•		

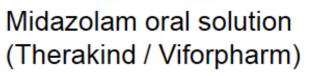




Drugs Approved through PUMA in 10 years

For children aged 19 years to less that 18 years BUCCOLAM* 10 mg Oromucosal Solution Midapolam	For children aged 5 years to less than 10 years BUCCOLAM ⁶ 7.5 mg Commutosal Solution	For children aged 1 year to less than 5 years BUCCOLAM* 5 mg	For children aged Smashin is loss than Typer BUCCCLAM" 2.3 mg Chamuchail Solution Militactium
For anomalised use only 4 pro-filled coal syringes of 2ml	Midazulam For eromacoud use only 4 pre-filled oral springes of 1.5ml	Oriomucosal Solution Midazolam For enemucosal use only 4 pre-filled and springes of trail	For promotion and only 4 pro-filled oral syringes of 0.3ml
Spann	BUCCOLAM T	0 mg	-





Propranolol oral solution (Pierre Fabre)





Glycopyrronium bromide oral solution (Proveca)

Hydrocortisone granules in capsules (Diurnal)

Cost of Pediatric Formulations



Wholesale Wh		Wholesale	Equivalent	the states		
Generic Name and C Solid Formulation					Cost per Tablet or Capsule	Liquid to Tablet Cost Ratio
	Lisin	onril			\$	
Lisinopril, 10-mg tablet		t = 20 mg = \$0.0	18		31.00	775
Enalapril, 5-mg tablet	Child weighing 20 kg= 2 mg = $$6.20$			8.95	21	
Indomethacin, 25-mg capsule		times more exp	-	.20	8.80	49
Glycopyrrolate, 2-mg tablet	//.5				9.90	14
Pyridostigmine, 60-mg tablet		(480-ml bottle)	International		10.50	11
Entecavir, 1-mg tablet	17.28	Baraclude solution, 0.05 mg per milliliter (210-ml bottle)	Bristol-Myers Squibb	4.06	81.20	5

Per patient cost is higher in pediatrics

Probst et al. N Engl J Med 2017; 376:795



Cost of Pediatric Formulations Development

- Costs affected by:
 - Complexity of the formulation

Cost of development: \$500,000-15 millions

Time needed: 2-6 years (2 yrs R&D)

- Number of pre-clinical and clinical trials required by the regulatory agencies
- Cost of the submission itself
- Market size
- Duration of market exclusivity, if applicable a high proportion of the drugs used in children are off-patent

Probst et al. N Engl J Med 2017; 376:795 C-P Milne, JB Bruss. Clin Ther 2008;30:2133-2145

How Can We Optimize Compounding ? Good Strain Composition of the Strain Compounding ? Good Strain Composition of the Strai

U.S. Project Going Global



https://www.ashp.org/Pharmacy-Practice/Standardize-4-Safety-Initiative

The birth of PaedForm

A pan-European Paediatric Formulary





The Story of Hemangiol in Canada



Published literature and input from Canadian clinical experts indicated that the <u>current preferred first-line treatment</u> for patients with IH in Canada is <u>compounded propranolol</u> tablets...

Although the HC review indicates there is a need for a safe, effective, consistent, and high quality treatment for IHs requiring therapy, CDR notes there is a <u>substantial incremental cost</u> for the submitted <u>propranolol oral</u> <u>solution.</u>

Hemangiol : \$273.70 per 120 mL bottle, 450 mg Oral propranolol tablets: \$1.2084, 450 mg Excipient and compounding fees: \$9.71 to ~\$30 per 450 mg

