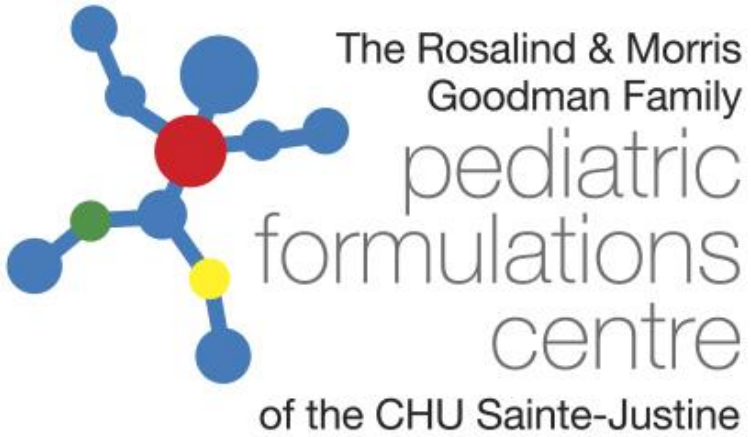
Advancing Pediatric Formulations



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**

Nom de la préparation: TACROLIMUS 0.5 mg/ml (R) (active)

Format unitaire: 120ml

Ingrédients

1: TACROLIMUS 5 mg/caps.....12 Caps
2: ORA-PLUS (Véhicul.....60 ml
3: SIROP SIMPLE U.S.....60 ml
4: PRECAUTIONS NIOSH.....1 app.
5: CONTROLE de QUALI.....1 form
6: MAGISTRALE CATEGO.....3 cate

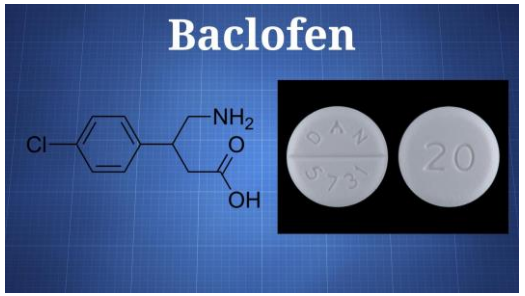
Mode de préparation

PRECAUTIONS NIOSH REQUISES
ATTENTION: STANDARDS DE MANIPULAT
MASQUE, ETC.
PRECAUTIONS NIOSH REQUISES.
1) Ouvrir et vider les capsules d
2) Mouiller la poudre avec une pe
une pâte homogène.
3) Ajouter le reste de l'Ora-Plus
géométrique pour obtenir un melange homogene.
4) Bien mélanger.

Drug stability 56 days

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

World Health Organization

make medicines Child Size

cfpg gpfc

2007

EuPFi

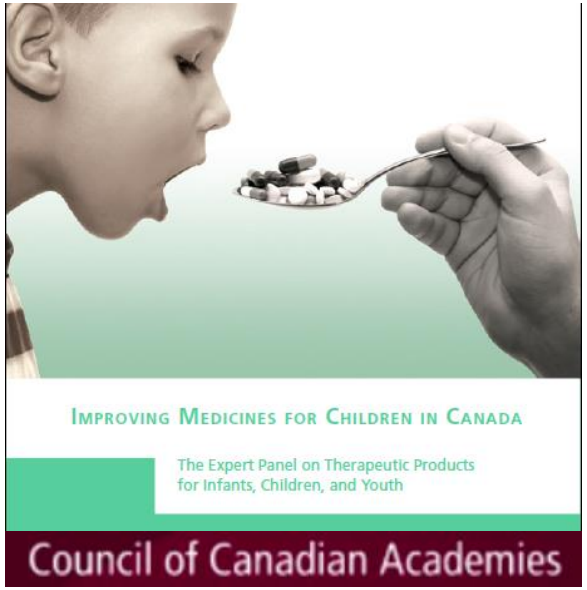
European Paediatric Formulation Initiative

uspfi United States Pediatric 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 ?

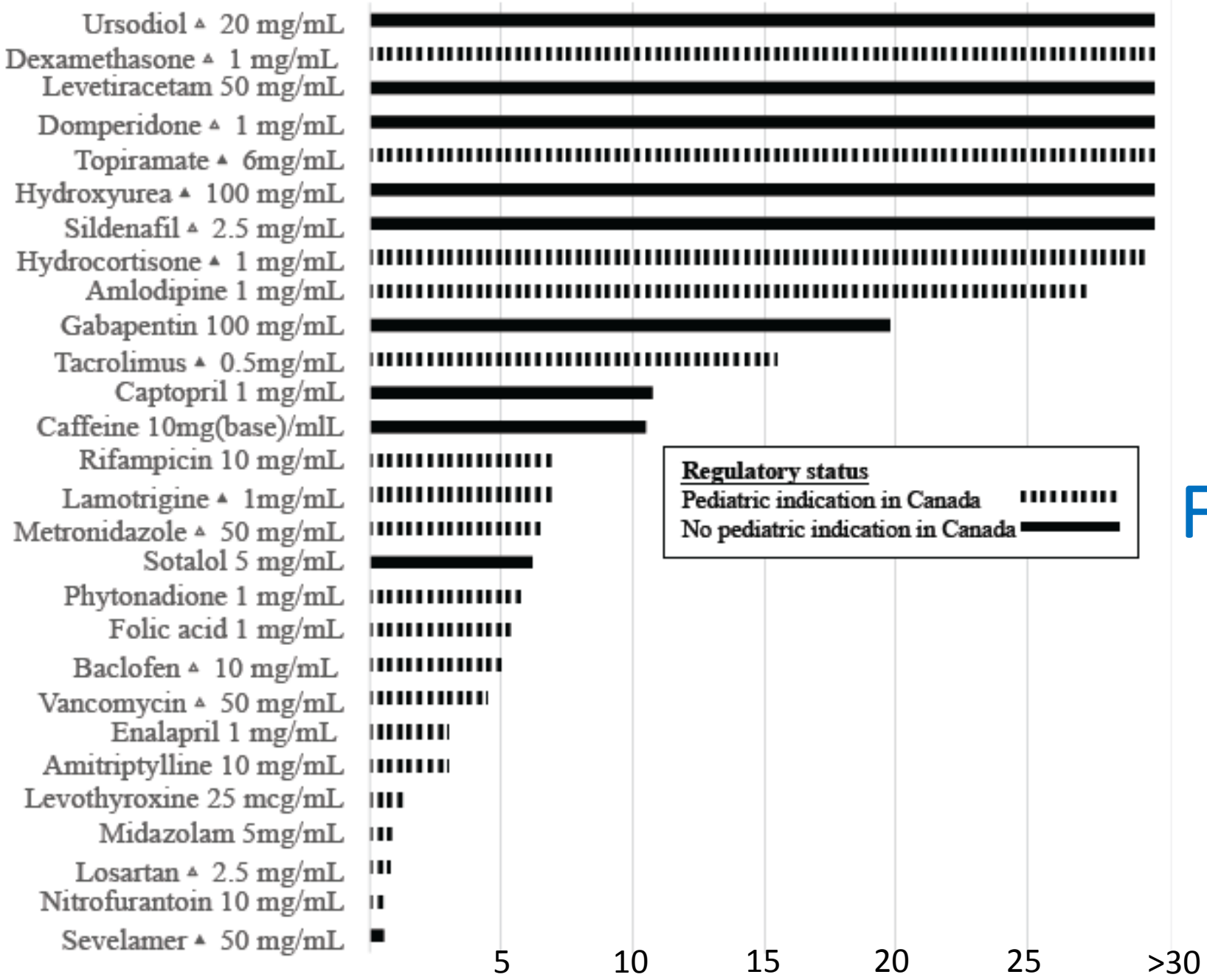
Drugs Frequently Compounded in a Canadian Pediatric Tertiary Hospital

- 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%)

*



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

n=28 (49 %)

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

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)

9 with suitable pediatric formulations outside Canada

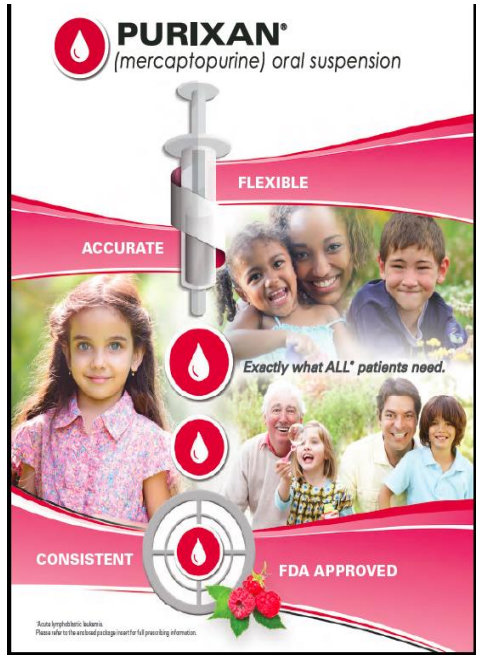
An Oral Solution of LEV is Approved for Use in Children in the US and Europe for Over 10 years…

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 ≥ 12 yrs
2007	US: Tablets/Solution approved for adjunctive therapy for PGTC in adults and children ≥ 6 yrs
2007	EU: Tablets/Solution approved for adjunctive therapy for PGTC in adults and children ≥ 12 yrs
2009	EU: Tablets/Solution approved for adjunctive therapy for POS in adults and children ≥ 1 mth
2011	US: Tablets/Solution approved for adjunctive therapy for POS in adults and children ≥ 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



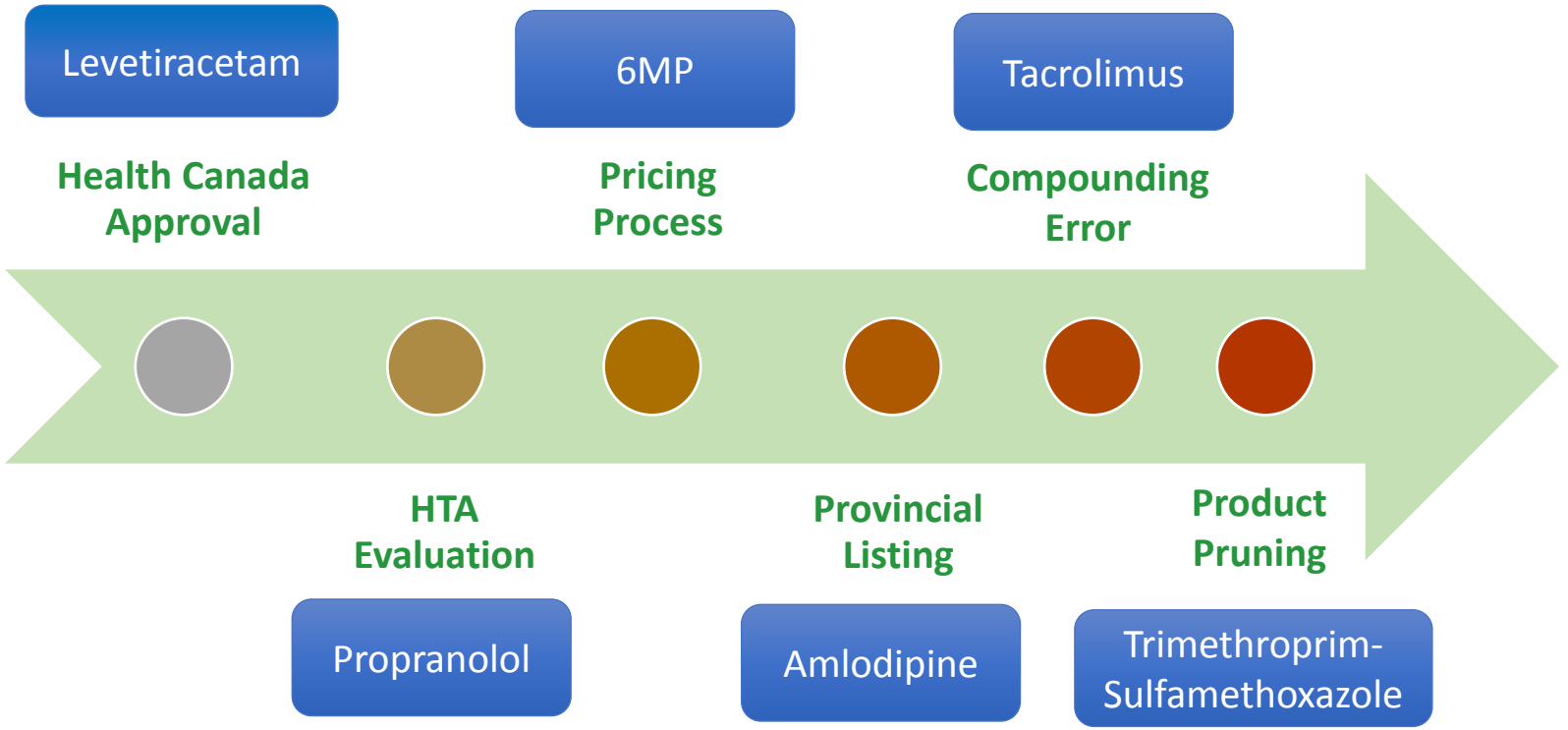
Approved and marketed in Europe (2012), US and Australia (2014)

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

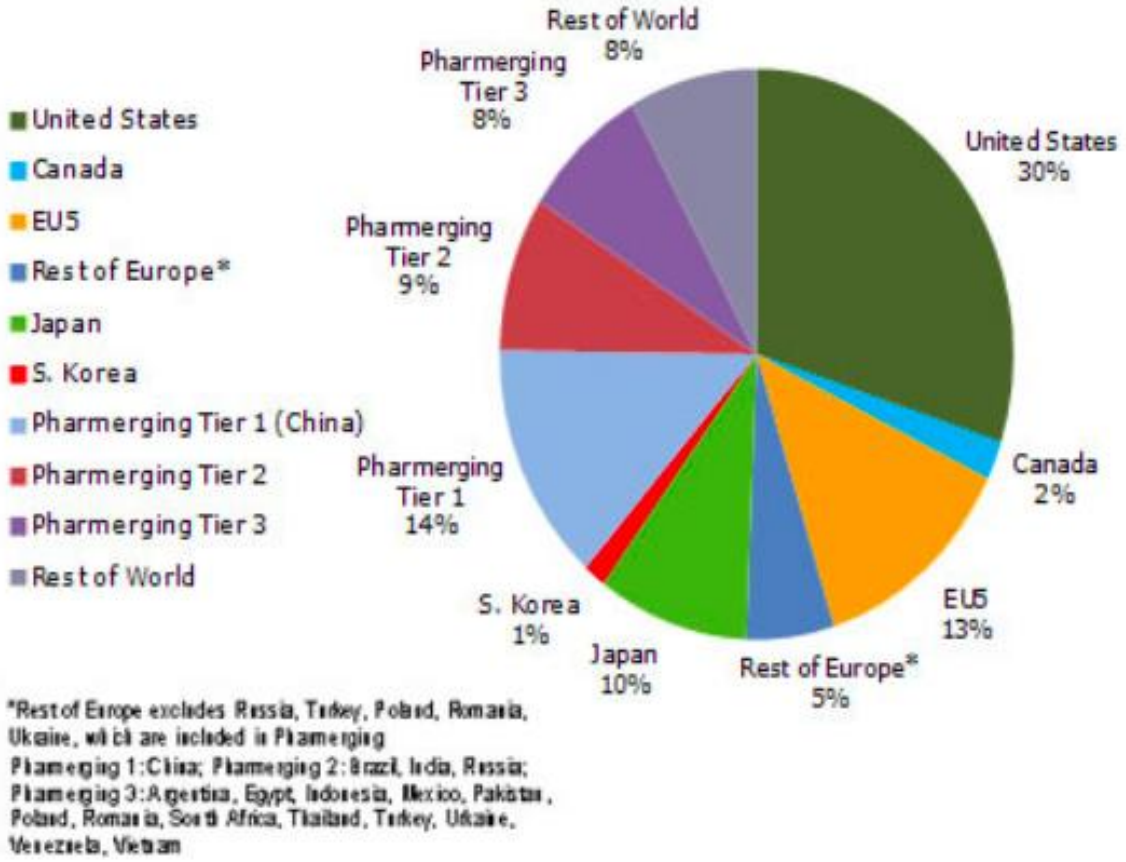


Why are Pediatric Formulations Unavailable in Canada ???

- 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

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

Feb 9, 2018: Use of Trusted Jurisdictions

Sept 11, 2018: Regulatory Modernization

Sept 28, 2018: National Pharmacare
Nov 21: Met E. Hoskins with CPS and Sick Kids
Dec 7: Follow Up Letter

Health Canada Santé Canada

cfpg gpfc

Draft Guidance: Accelerated Review of Human Drug Submissions

This guidance document is being distributed for comment purposes only.

Draft date

"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

Canadian Paediatric Society

MICYRN
better health for mothers and children

KidsCAN TRIALS

IAS Global Accelerator for Paediatric Formulations (GAP-f)

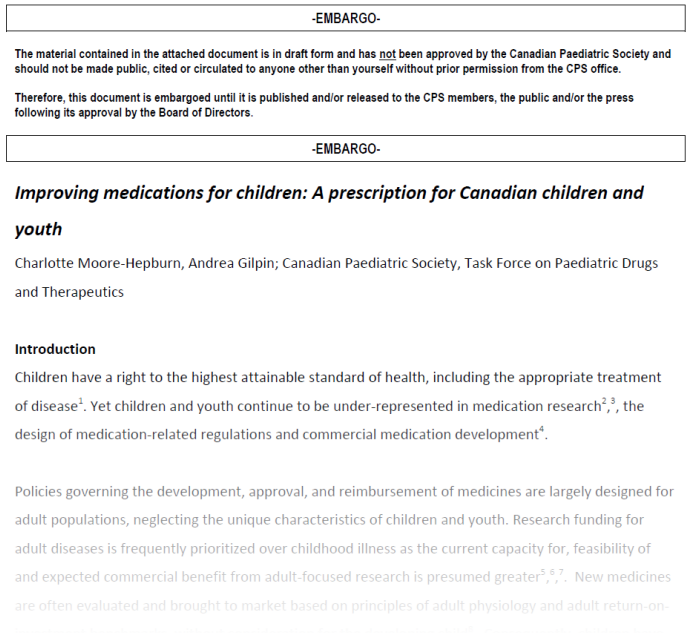
C4T CANADIAN CHILDHOOD CANNABINOID CLINICAL TRIALS

SickKids THE HOSPITAL FOR SICK CHILDREN

Children's Healthcare Canada | Santé des enfants Canada
Not a Member

Paediatric Chairs of Canada — Serving the Health Needs of Children, Youth and Their Families Through Leadership in Education, Research and Clinical Care
Directeurs de pédiatrie du Canada — Au service des besoins de sante des enfants, des adolescents et de leur famille par un leadership en formation, en recherche et en soins cliniques

Two Policy Papers Joint with the Canadian Paediatric Society



-EMBARGO-

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-EMBARGO-

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

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

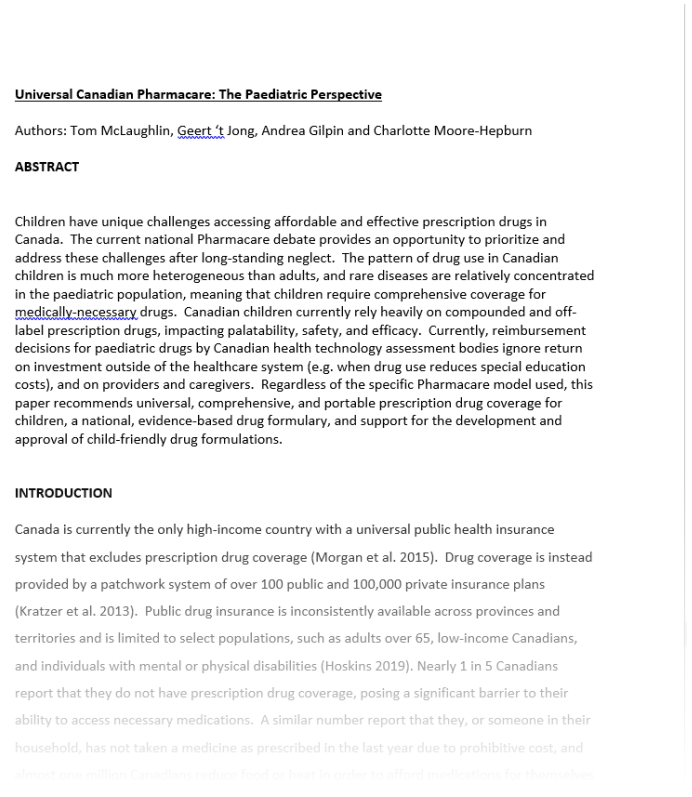
Introduction

Children have a right to the highest attainable standard of health, including the appropriate treatment of disease[1]. Yet children and youth continue to be under-represented in medication research[2,3], the design of medication-related regulations and commercial medication development[4].

Policies governing the development, approval, and reimbursement of medicines are largely designed for adult populations, neglecting the unique characteristics of children and youth. Research funding for 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 are often evaluated and brought to market based on principles of adult physiology and adult return-on-

- *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

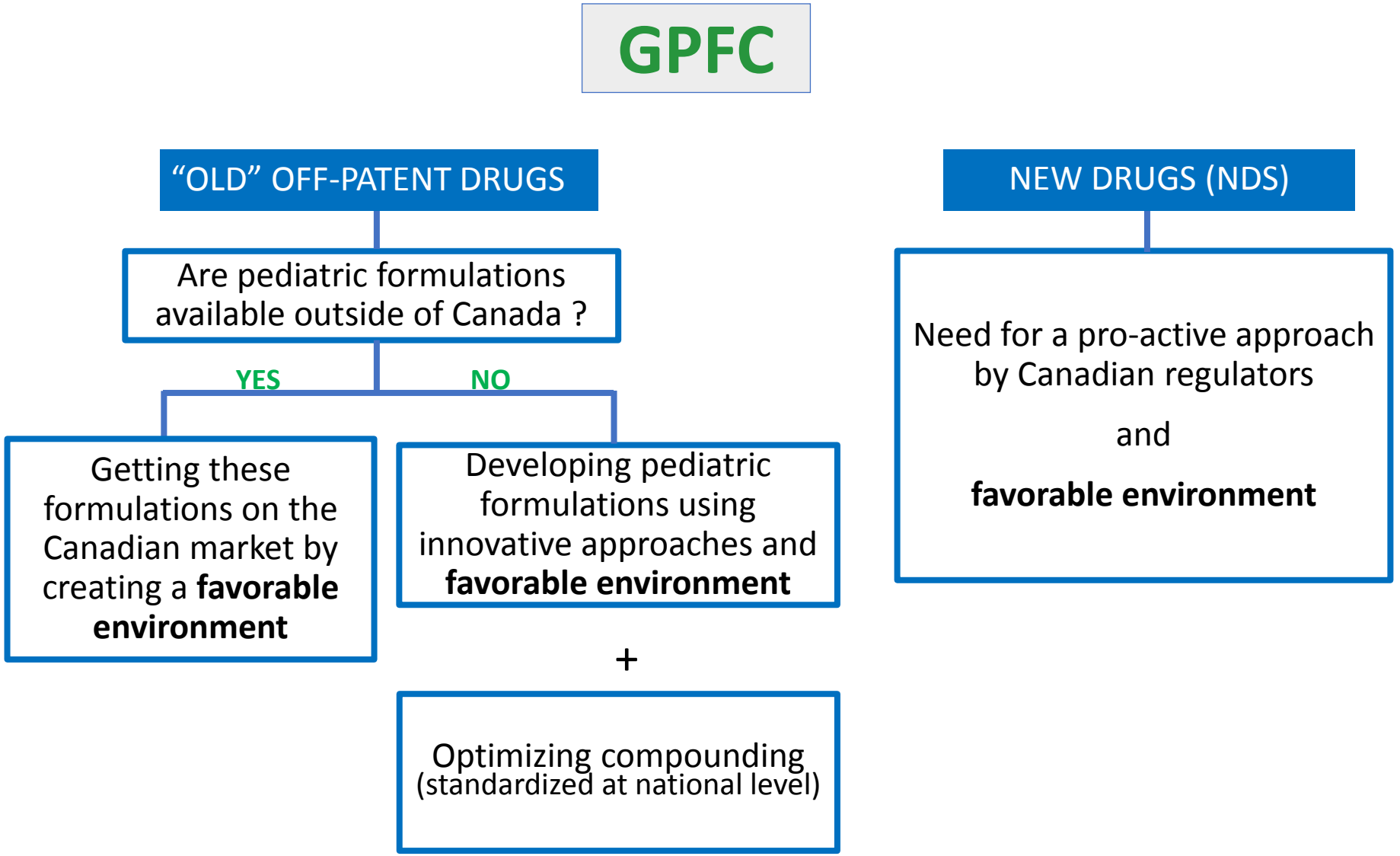
ABSTRACT

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 off-label 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.

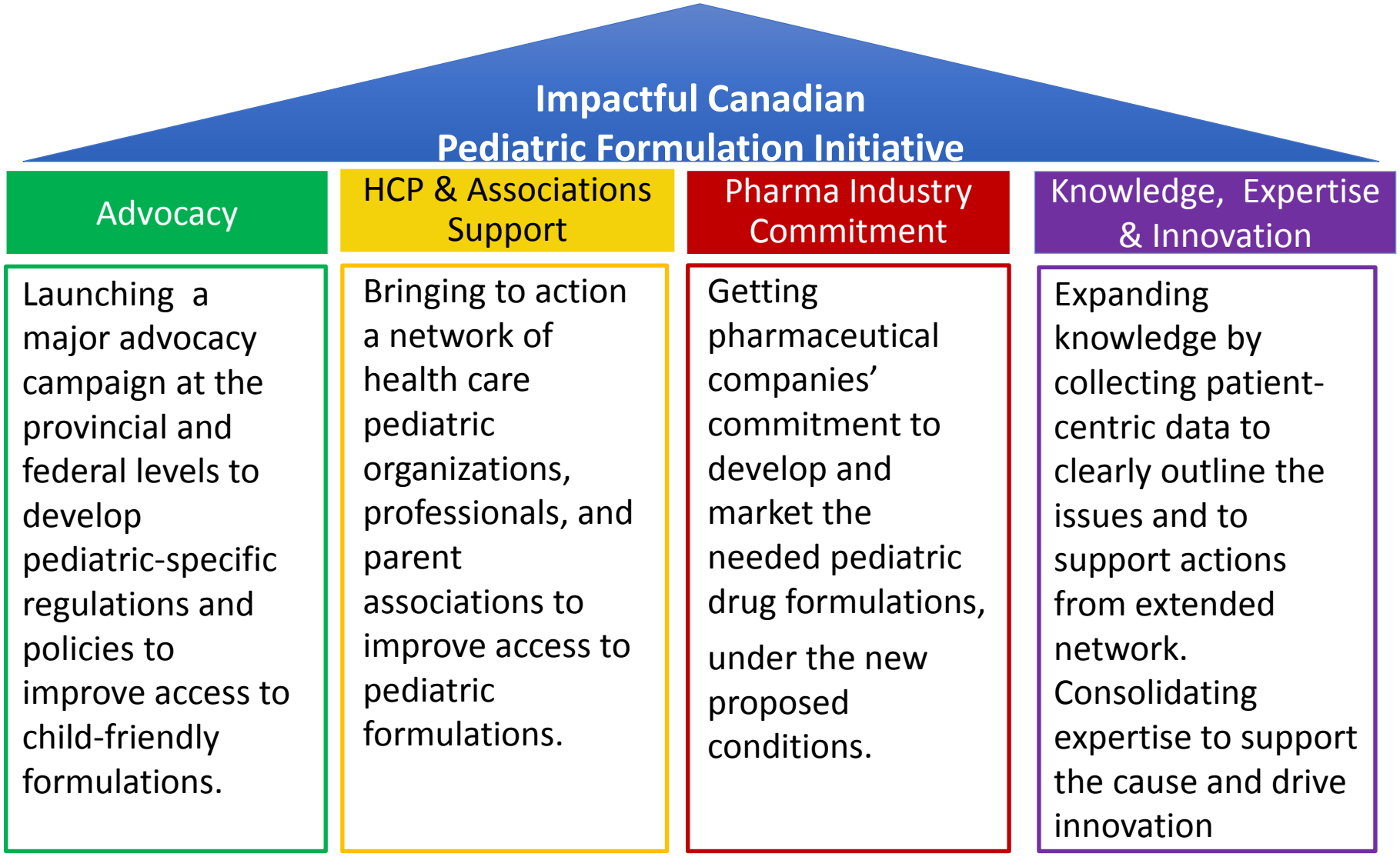
INTRODUCTION

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

The GPFC Strategy: What's next ?



Canadian Sick Children Deserve the Best



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

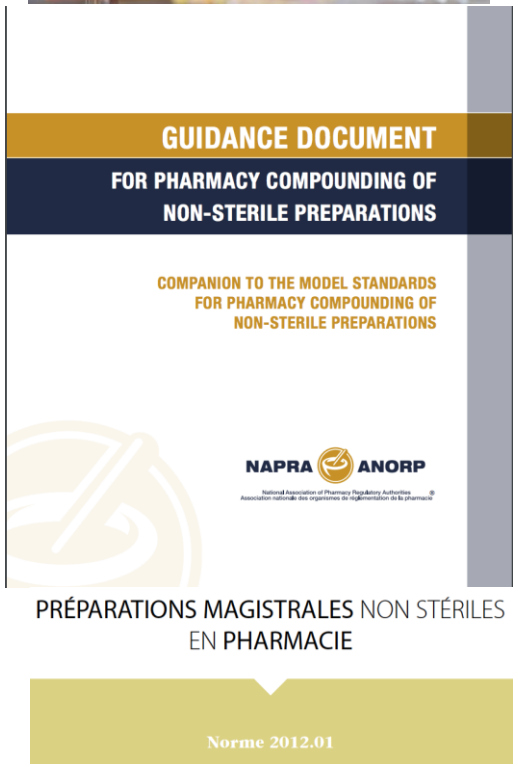
The GFPC Needs You…

- 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

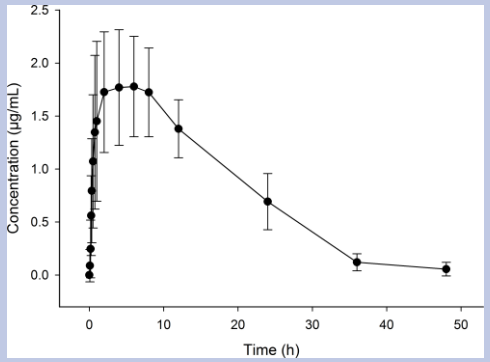
- Preparation of a drug for a particular patient due to the unavailability of a form adapted to its needs.
- Compounded drugs are prepared by a pharmacist or a trained pharmacy technician, based on a prescription and in accordance with standards such as those from NAPRA or ODQ (Quebec)



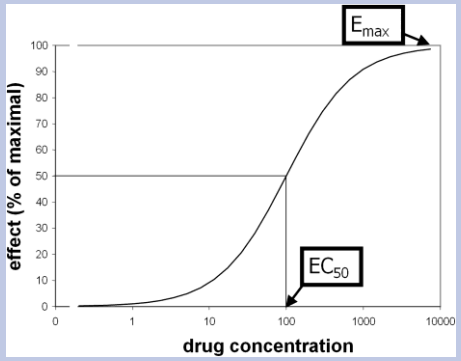
Determinants of Drug Efficacy and Safety

Neutral/Good taste
Safe excipients
Minimal manipulation
Dosing flexibility
Stability (heat, humidity, light)
Easy to produce
Commercially viable
Reasonable cost

Pharmaceutical form



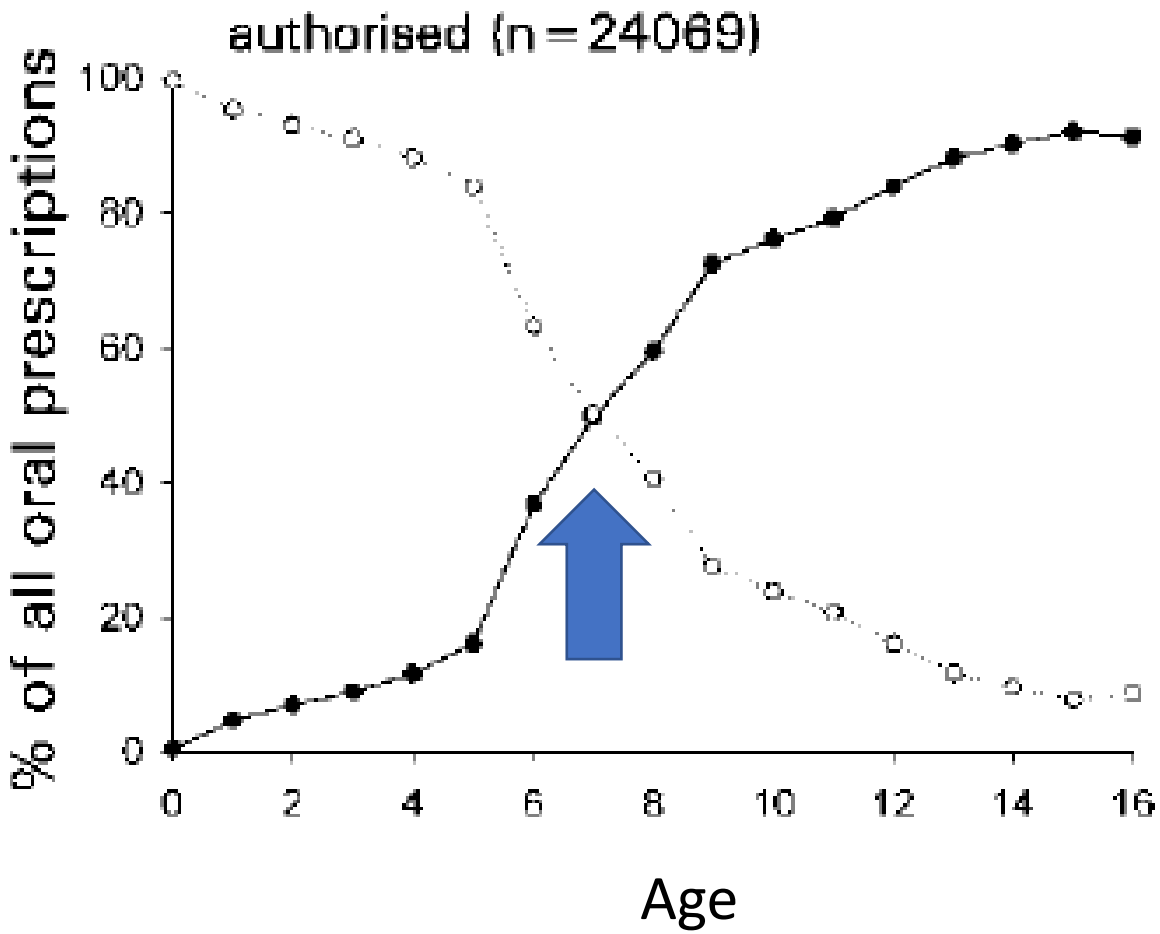
Pharmacokinetics



Pharmacodynamics

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 ?



Tablets/capsule

Solution/suspension…

Schrim E et al. Acta Paed 2003; 92:1486

Which Pharmaceutical Forms Are Acceptable to Children ?

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

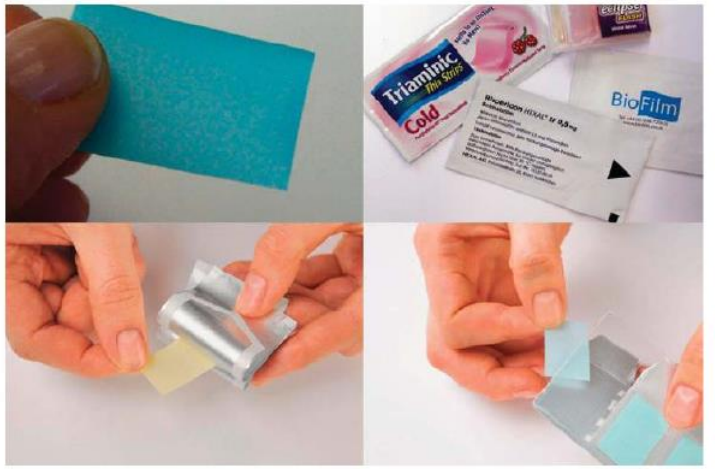
Route / Dosage Form	*Preterm newborn infants*	*Term newborn infants (0d-28d)*	*Infants and Toddlers (1m-2y)*	*Children (pre school) (2-5y)*	*Children (school) (6-11y)*	*Adolescents (12-16/18y)*
Peroral						
Solution/ Drops	2	4	5	5	4	4
Emulsion/ Suspension	2	3	4	5	4	4
Effervescent DF*	2	4	5	5	4	4
Powders/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

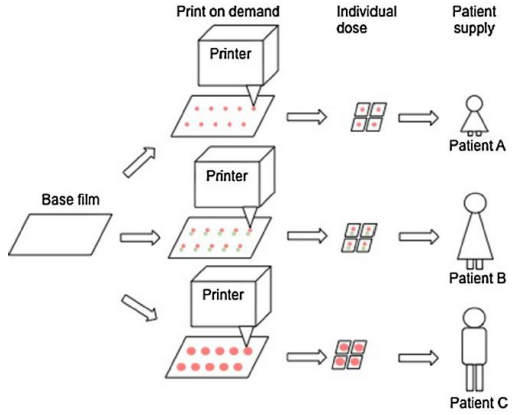
Powder containing fine granules

Mini-Tabs

Labelling of **E**nalapril from **N**eonates up to **A**dolescents



Orodispersible film



Formulations of Choice: "a Moving Target"

2008: WHO: Campaign "Make medicines child size"

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

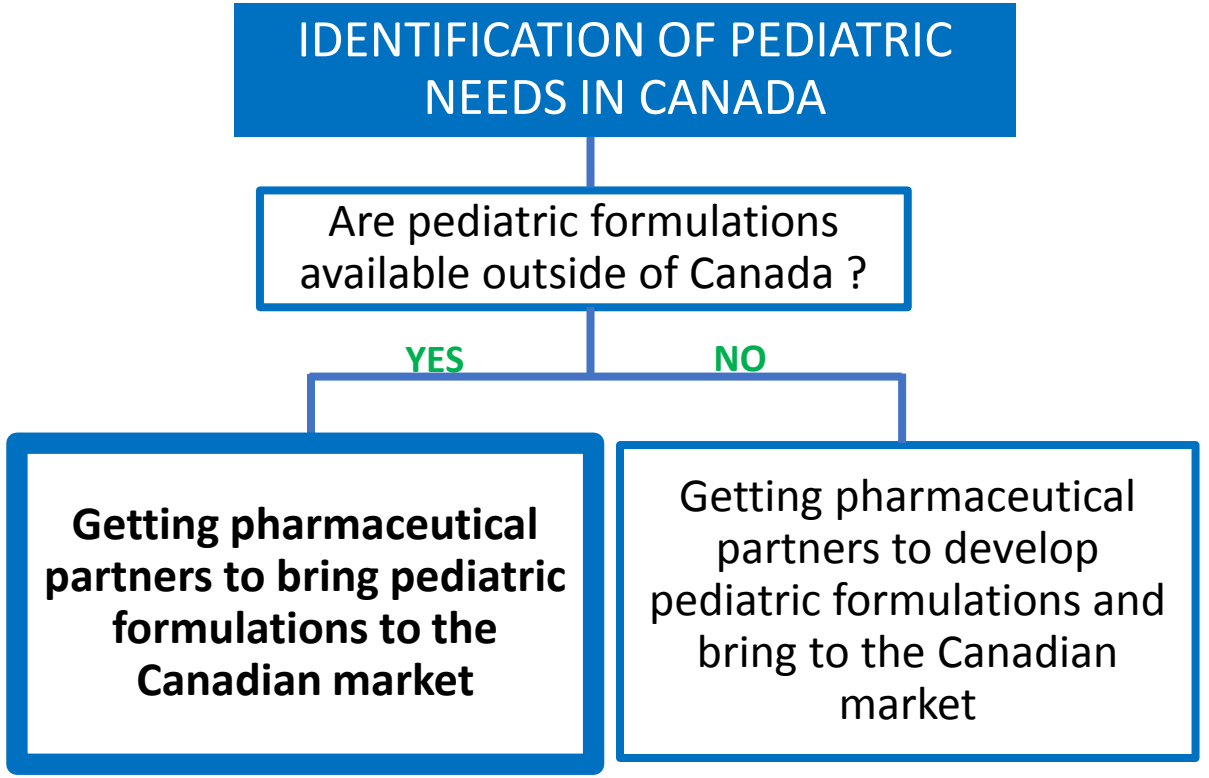
2014: EMA: "Guidelines on pharmaceutical development of medicines for paediatric use"

- 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

make medicines Child Size

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The GPFC Strategy 2016-2019



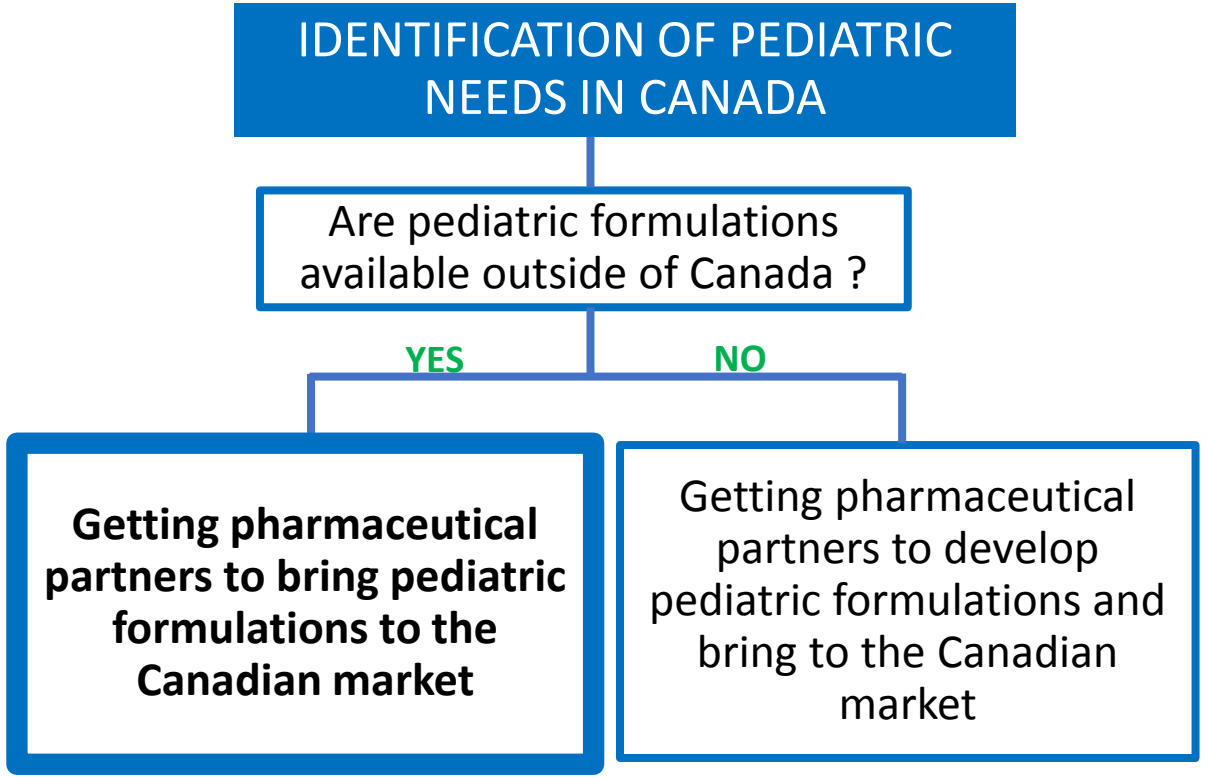
Regulatory requirements

Understanding economics

Linking stakeholders

Advocacy & awareness

The GPFC Strategy 2016-2019



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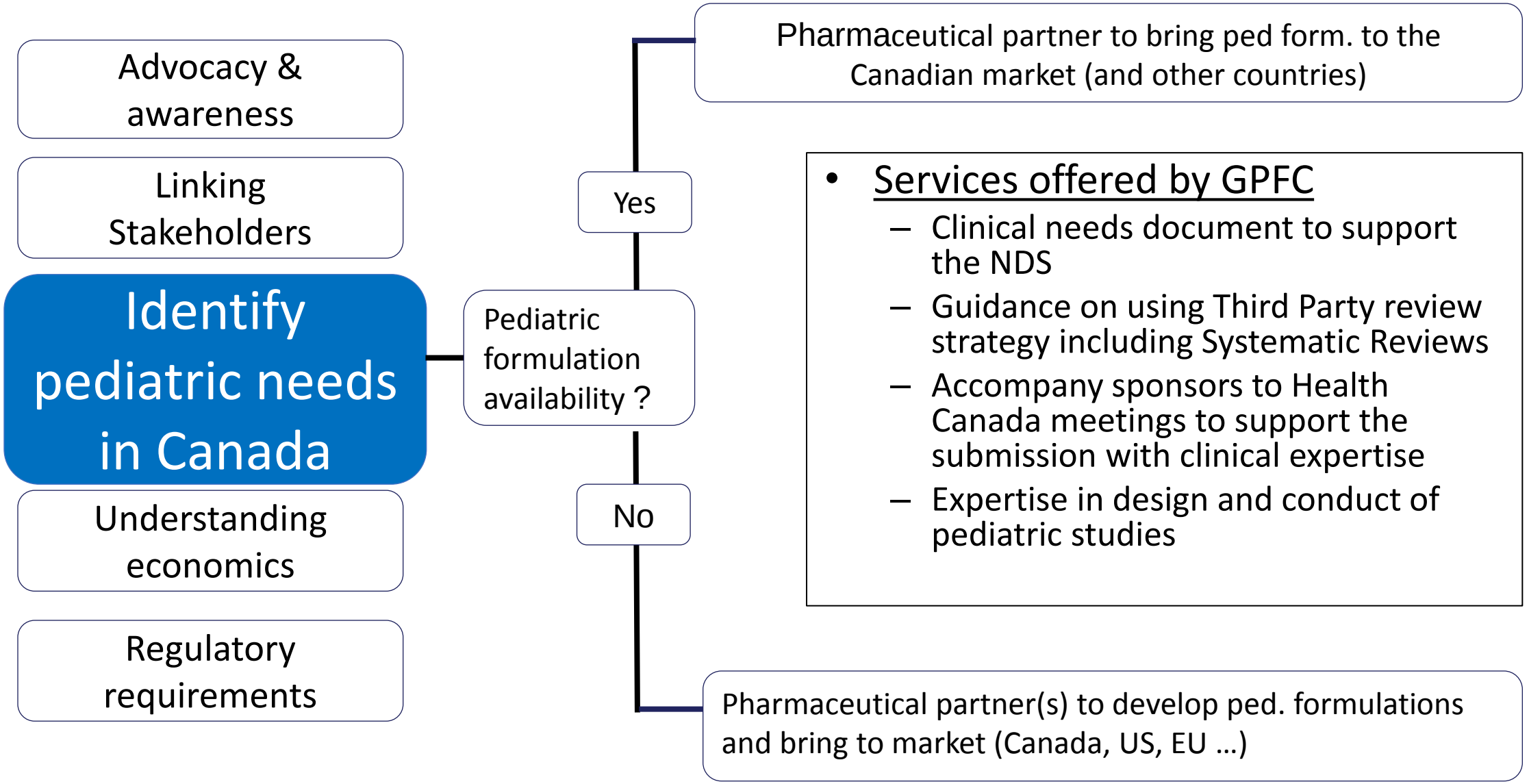


PPIs: Why are Canada and EU lagging behind ?

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

Midazolam oral solution (Therakind / Viforpharm)

Propranolol oral solution (Pierre Fabre)

Glycopyrronium bromide oral solution (Proveca)

Hydrocortisone granules in capsules (Diurnal)

Cost of Pediatric Formulations

Table 1. Wholesale Acquisition Cost of Select Generic Solid Medications for Oral Administration versus Branded Liquid Medications.

Generic Name and Solid Formulation	Wholesale Acquisition Cost per Tablet or Capsule	Liquid Formulation	Manufacturer	Wholesale Acquisition Cost per Milliliter	Equivalent Cost per Tablet or Capsule	Liquid to Tablet Cost Ratio
					$	
Lisinopril, 10-mg tablet					31.00	775
Enalapril, 5-mg tablet					8.95	21
Indomethacin, 25-mg capsule					8.80	49
Glycopyrrolate, 2-mg tablet					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

Lisinopril

Adult = 20 mg = $0.08

Child weighing 20 kg= 2 mg = $6.20

77.5 times more expensive

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
  - 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

Cost of development: $500,000-15 millions

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

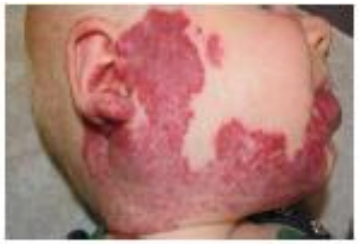
Probst et al. N Engl J Med 2017; 376:795
C-P Milne, JB Bruss. Clin Ther 2008;30:2133-2145

How Can We Optimize Compounding ?
How Can We Improve Safety?

U.S. Project Going Global

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

The Story of Hemangiol in Canada



Published literature and input from Canadian clinical experts indicated that the current preferred first-line treatment for patients with IH in Canada is compounded propranolol 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 substantial incremental cost for the submitted propranolol oral solution.

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

CADTH Common Drug Review
Pharmacoeconomic Review Report