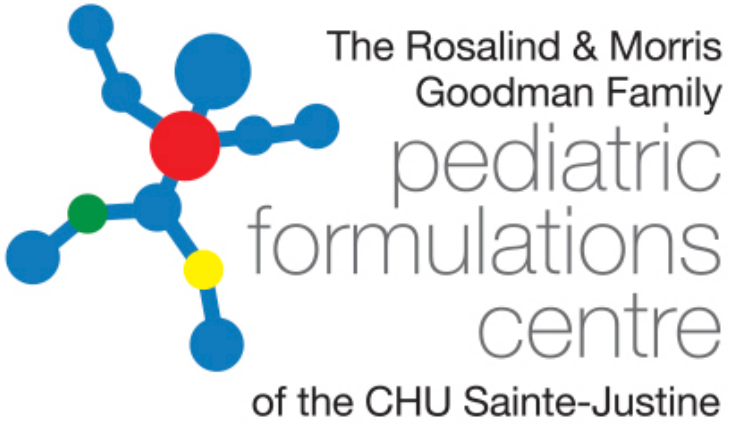
Building Expertise in Pediatric Formulations



Catherine Litalien, MD

ASCPT Annual Meeting

March 24, 2018

Disclosure Statement

- I have no financial relationships to disclose relating to this presentation

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

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**

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 (Vé.....60 ml
3: SIROP SIMPLE.....60 ml
4: PRECAUTIONS .....1 app.
5: CONTROLE de re.....1 form
6: MAGISTRALE C NS.....3 cate

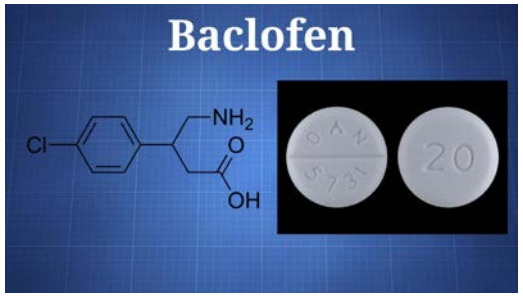
Mode de préparation

PRECAUTIONS NIOSH REQUIS
ATTENTION: STANDARDS DE IT GANTS,
MASQUE, ETC.
PRECAUTIONS NIOSH REQUIS
1) Ouvrir et vider les c
2) Mouiller la poudre av e former
une pâte homogène.
3) Ajouter le reste de l dilution
géométrique pour obtenir un melange homogene.
4) Bien mélanger.

Stability = 56 days

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

news



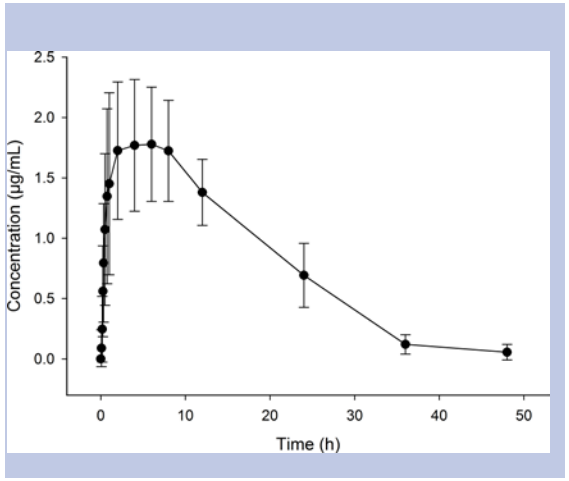
Problem Statement

- 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 is associated with many challenges
    - Bad taste = impaired adherence
    - Limited stability data with no bioavailability data
    - Inaccurate dosing
    - Environmental safety from home compounding
    - Different manufacturing practices and quality control compared to pharmaceutical company standards
    - Lack of compounding standardization
    - No system in place to evaluate efficacy and safety of the compounded drugs
    - Lack of awareness of prescribers

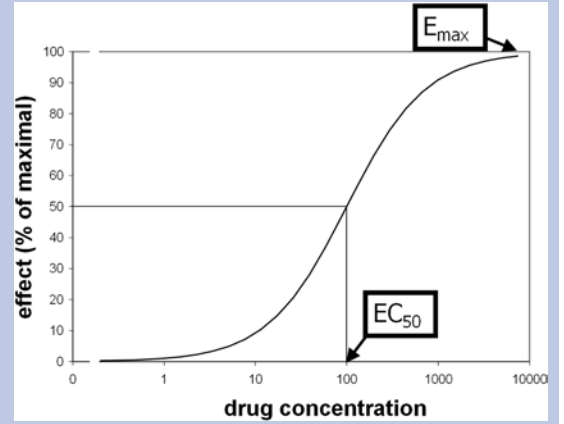
Determinants of Effective and Safe Therapy

Minimal/non-toxic excipients
Palatable
Minimal manipulation prior to use
Flexible dosing
Heat, humidity and light stable
Easily produced
Commercially viable
Affordable

Pharmaceutics



Pharmacokinetics



Pharmacodynamics

Availability of age-appropriate, innovative and high-quality pediatric formulations can spell the difference between successful treatment or therapeutic failure and safe therapy or adverse events

Acceptable Oral Dosage Form(s) in 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

Formulations of Choice: a Moving Target

2008: WHO: Campaign "Make medicines child size"

- Recommendation of solid dosage forms in all age groups

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

- No age range recommendation for solid oral dosage forms any more
- Mini tablets and pellet approaches are considered more favourably
- Requirement of evidence for the suitability of solid dosage forms

make medicines Child Size

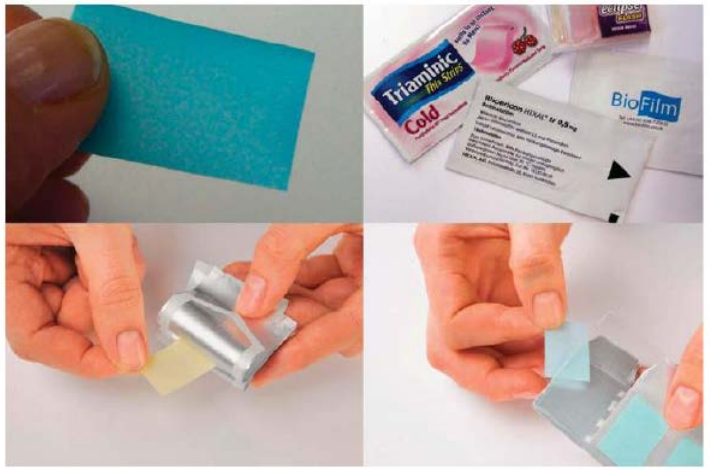
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Solid Oral Dosage Forms: Beyond the “Adult” Tablet

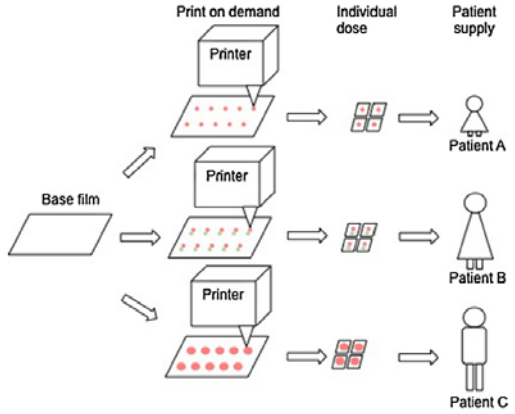
Dispersible tablet

Mini-tablet

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



Orodispersible film



The GPFC Mandate

- To facilitate 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

The GPFC Stragegy

Advocacy & awareness

Linking Stakeholders

Identify pediatric needs in Canada

Understanding economics

Regulatory requirements

Pediatric formulation availability ?

Yes

Pharmaceutical partner to bring ped form. to the Canadian market (and other countries)

No

Pharmaceutical partner(s) to develop ped. formulations and bring to market (Canada, US, EU …)

- <u>Services offered by GPFC</u>
  - Clinical needs document to support the NDS
  - Guidance on using Third Party review strategy including Systematic Reviews
  - Accompany sponsors to Health Canada meetings to support the submission with clinical expertise
  - Expertise in design and conduct of pediatric studies

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

- 60 drugs were identified
- 3 most frequent categories of drugs using AHFS Pharmacologic-Therapeutic classification:
  - Cardiovascular: 30 %
  - Central nervous system: 18 %
  - Anti-infectious: 10 %
- **98%** are **off-patent drugs**
- On the Canadian market for a median of **35 years**

(14 – 65 years)

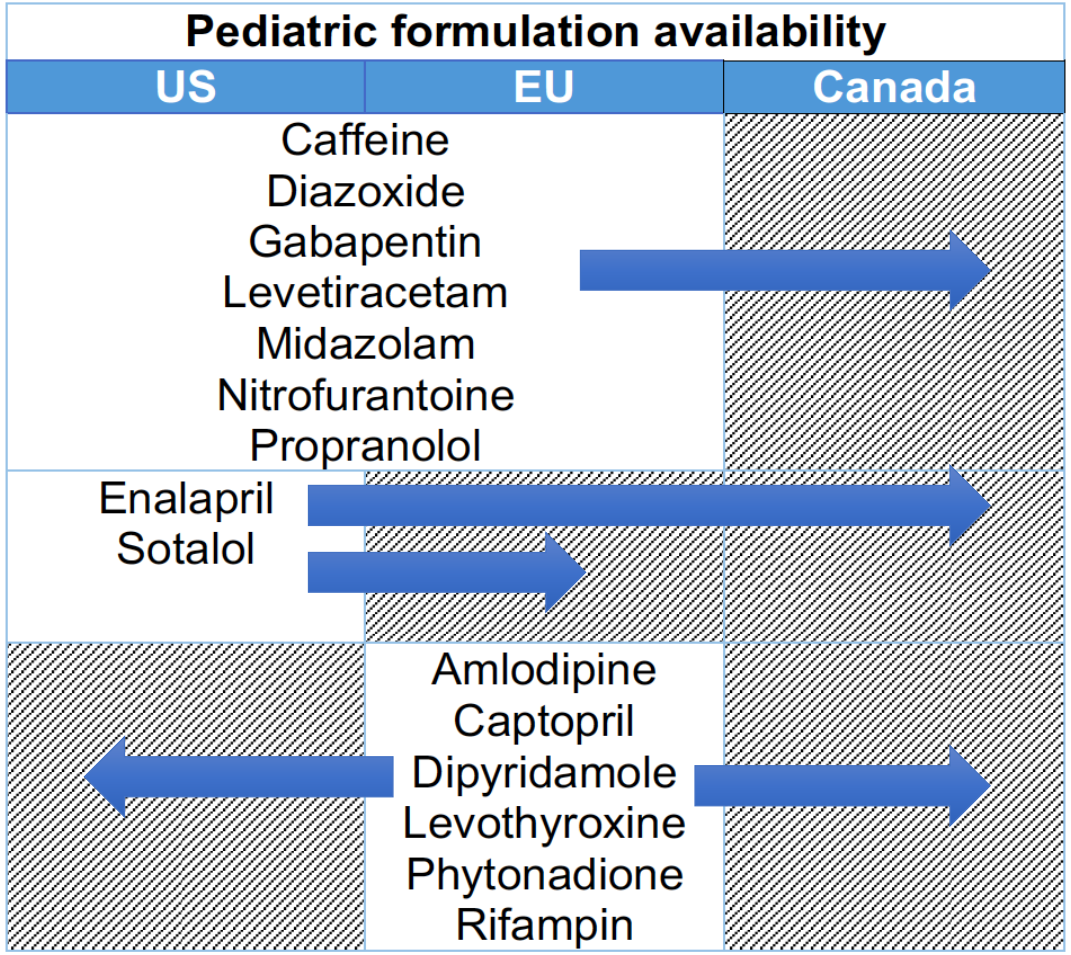
- Canadian pediatric indication for 23 drugs (38%)

*

Availability of Commercial Pediatric Oral Formulations in US and/or EU

Category	Definition	N=60, n(%)
1	▪ Liquid form with known safe ingredients	15 (25)
2	▪ Liquid form containing one or more ingredients with potential safety concerns in children (N= 14) ▪ Non-liquid oral form requiring manipulation by the parent before administration (e.g.,powder or granules for oral suspension) (N=3) ▪ Chewable tablets (N=1)	18 (30)
3	▪ No commercialized pediatric oral formulation in US or EU	27 (45)

Why Do We Have to Compound Medicines when Suitable Pediatric Formulations Exist ?



Category 1

Still Splitting Tablets to Treat Leukemia…

- In Canada, 6-mercaptopurine:
  - Approved for the treatment of ALL
  - Available only as 50 mg tablet resulting in:
    - Tablet splitting
    - Compounded liquid oral formulation
  - Consequences of underdosing or overdosing can be catastrophic
  - Environmental toxicity related to compounding
  - Prolonged treatment

Approved and marketed in EU (2012) and US (2014)

Pan-Canadian Survey: Prioritization of Needs

- 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:

A total of 51 drugs were identified

Drugs Most in Need of Commercialized Oral Pediatric Formulations in Canada

Drugs	Number of hopitals that ranked drug as :		Availability of pediatric oral formulations outside of Canada	
	Most in need of a pediatric formulation, n (%) N=13	Most frequently compounded, n (%) N=13	United States	Europe
Levetiracetam	8 (62)	10 (77)	Oral solution	
Spironolactone	8 (62)	7 (54)	No	
Tacrolimus	8 (62)	7 (54)	No	Sachets for oral suspension
Clonidine	7 (54)	7 (54)	No	
Hydro-chlorothiazide	6 (46)	6 (46)	No	
PPI[1]	6 (46)	7 (54)	Sachets for oral suspension[2]	
ACE inhibitors[3]	4 (31)	5 (38)	Oral solution	
Amlodipine	4 (31)	2 (15)	No	Oral solution
Dexamethasone	4 (31)	10 (77)	Oral solution[4]	
Hydroxyurea	4 (31)	2 (15)	No	
Sildenafil	4 (31)	4 (31)	Oral solution[5]	
Topiramate	4 (31)	4 (31)	Sprinkle hard capsules	

[1]Proton pump inhibitors; [2]for omeprazole and esomeprazole in the US and for esomeprazole in Europe; [3]Angiotensin converting enzyme inhibitors (captopril, enalapril); [4]contains propylene glycol and sorbitol; [5]contains sorbitol

Lev Oral Solution Has Been Approved for Children in US and EU for More than 10 yrs…

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
2017	**CANADA: NO PEDIATRIC INDICATION AND NO PEDIATRIC FORMULATION EXIST TODAY …**

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

Why Aren’t Pediatric Formulations Being Made Available in Canada?

- Regulatory pathway perceived as unclear or complex
- Market size too small
- Incentives are few
- Seeking reimbursement viewed as challenging

Regulatory Incentives for Pediatric Medicines

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

Approved PUMA Drugs over 10 Years

Midazolam oral solution
(Therakind / Viforpharm)

Propranolol oral solution
(Pierre Fabre)

Glycopyrronium bromide
oral solution (Proveca)

Pediatric Formulation: Pricing Considerations

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

Generic Name and Solid Formulation	Wholesale Cost per Tablet or Capsule	Liquid Formulation	Manufacturer	Wholesale 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

20 kg child = 2 mg = $6.20

77.5 times more costly

Higher per-patient costs

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

Costs to Develop and Manufacture a Pediatric Formulation

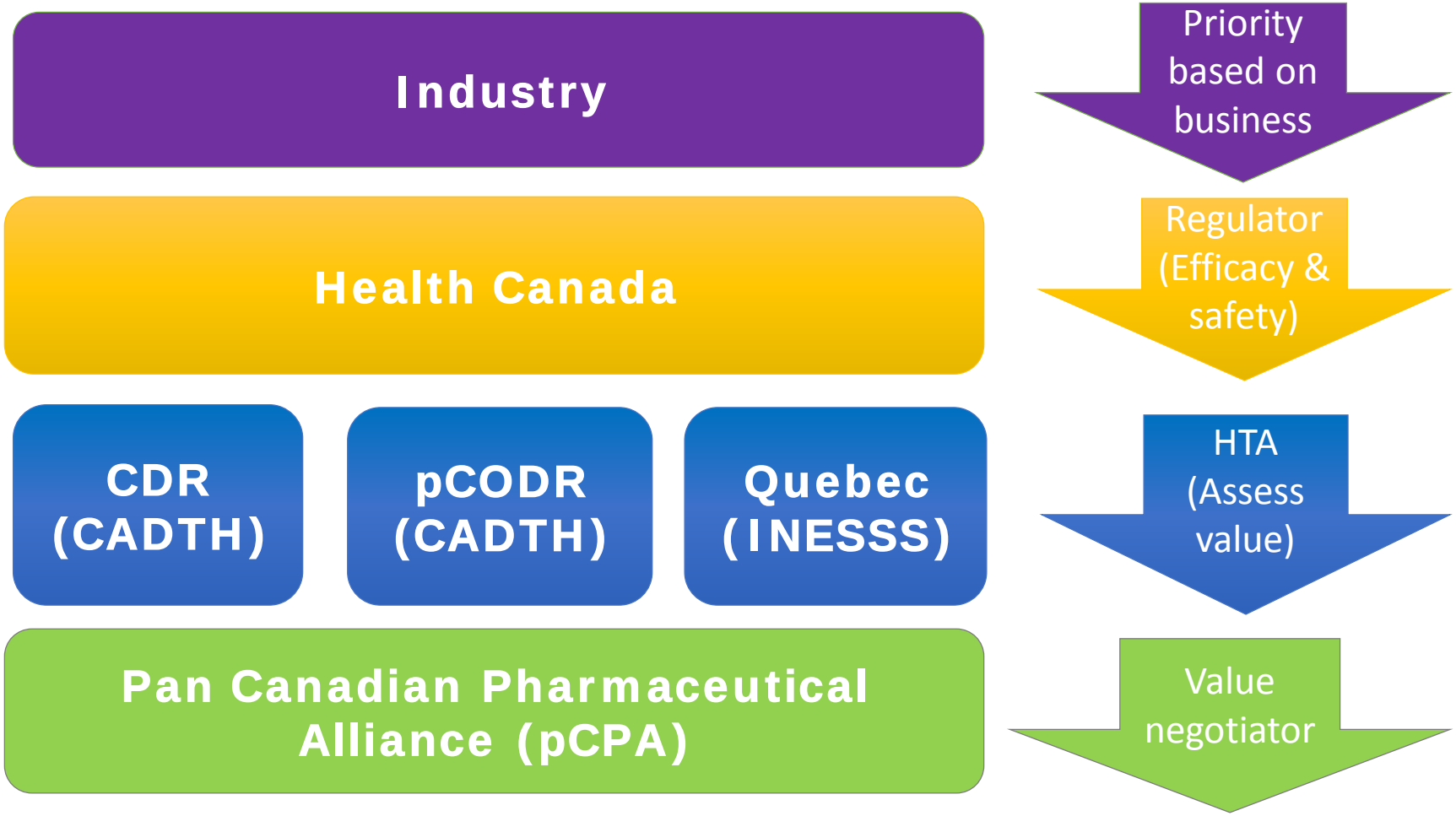
- Costs are affected by:
  - Complexity of the formulation
  - Extent of pre-clinical and clinical testing required by the regulatory authorities
  - Costs of regulatory filing
  - Size of the market
  - Length of market exclusivity, if any -> predominance of « off-patent » drug use in the pediatric setting

Cost of development: $500,000-15 million

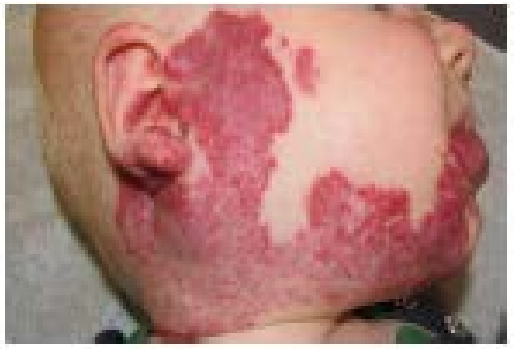
Time: 2-6 years (2 yrs R&D)

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

Current Pathway Leading to Drug Access in Canada



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

What About Trying a New Model for Pediatric Formulations for Off-Patent Drugs?

PATIENT-CENTRIC needs

STREAMLINING and
the regu
jur
Japan,
, etc...)

ONE MARKET AUTHORIZATION APPLICATION

INCENTIVES

Better global access of quality medicines for children

mar

Accelerated process

Commercially viable

pricing -> Affordable

"One stop shop"

Conclusion

- Children deserve high quality pediatric formulations meeting their needs to ensure safe and effective pharmacotherapy
- For new patented medicines, there are regulatory requirements as well as incentives in the US and EU to ensure the development of pediatric formulations
- For off-patent medicines, there is still a huge unmet need for the development and access of suitable dosage forms for children despite the availability of incentives -> need to define a new model

Working together we can make a difference…..

- GPFC is currently supporting a pharma company with two medicines, one of which is using a NDS relying on Third Party Review process
- We are looking for more partners
- We are speaking to major stakeholders
- We are willing to collaborate with international organizations
- Pharmaceutical companies that partner with us have a tremendous opportunity to be leaders

We leave you with a video:
https://www.youtube.com/watch?v=4kDxlhabb7I&feature=youtu.be

Dr. Catherine Litalien, Executive Director, GPFC
514-773-8212
catherine.litalien.hsj@ssss.gouv.qc.ca

Andrea Gilpin, General Manager, GPFC
514-465-2114
agilpin.cfpg@gmail.com

BACK-UP SLIDES

How Can We Move Forward with these Prioritized Drugs ?

From a regulatory perspective

Ped formulation available

Amlodipine, enalapril, lisinopril, 6-mercaptopurine, PPIs	→	Ped indication in Canada and US ± EU
Levetiracetam, sildenafil	→	**NO** ped indication in Canada but ped indication in US ± EU

"Suboptimal" Ped formulation or **NO** Ped formulation available

Dexamethasone, *tacrolimus, topiramate*	→	Ped indication in Canada and US ± EU
Spironolactone, clonidine, hydrochlorothiazide, hydroxyurea	→	**NO** Ped indication in Canada

Toward Better-Quality Compounded Drugs — An Update from the FDA

Janet Woodcock, M.D., and Julie Dohm, J.D., Ph.D.

Table 2. Examples of Adverse Events Associated with Drugs Prepared by Compounding Facilities over the Past 5 Years.

2014	Indiana	Several neonates experienced oversedation after receiving superpotent compounded midazolam.
2016	Indiana	Three infants had serious adverse events after receiving compounded morphine sulfate that was nearly 2500% as potent as it should have been.

Woodcock et al. N Engl J Med 2017;377:2509

U.S. Project Going Global

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

The birth of PaedForm

A pan-European Paediatric Formulary

Prof Dr Jörg Breitkreutz
Heinrich-Heine-Universität, Düsseldorf

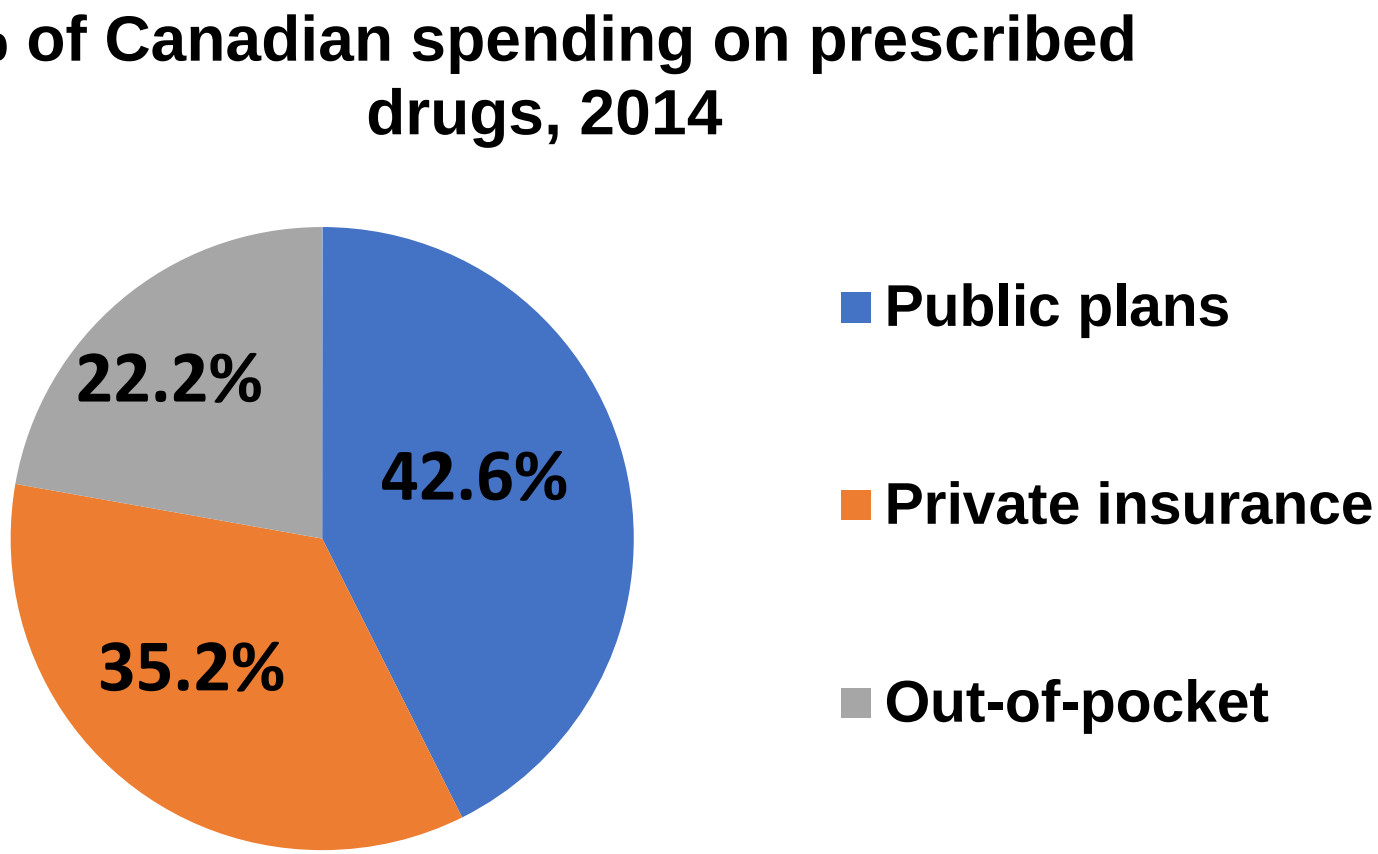
Dr Dirk Leutner
EDQM, Council of Europe

Pay

Public reimbursement status (WW)

Country	Public reimbursement
Austria	Individual reimbursement - No general reimbursement
Belgium	YES
CZ	YES
Canada	Ongoing process
Denmark	Individual reimbursement - No general reimbursement
Finland	YES
France	YES
Germany	YES
Italy	YES
Japan	YES
Korea	Ongoing process
Luxembourg	YES
Netherlands	YES
Norway	Individual reimbursement - No general reimbursement
Romania	Ongoing process
Spain	YES
Sweden	YES
Switzerland	YES
USA	No general reimbursement system, but covered by Medicaid
Croatia	YES
Greece	YES
Portugal	YES
Slovakia	YES
Slovenia	YES

Payment of drug costs



Source: Canadian Institute for Health Information (CIHI), *Prescribed Drug Spending in Canada, 2016: A Focus on Public Drug Programs*. 2015