Increasing Access to Safe and Effective Pediatric Formulations

Canadian Society of Pharmaceutical Sciences CSPS

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centre de formulations pédiatriques
de la famille Rosalind et Morris Goodman du CHU Sainte-Justine

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

Conflict of Interest Statement

- GPFC :
  - Funded by the Morris and Rosalind Goodman Family Foundation and Sainte-Justine University Hospital Foundation
  - Provided service contracts with industry in the past
  - No current service agreements ongoing

Three Fundamental Facts

1

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Children have a right to receive the **highest standards** of health care, including **optimal treatment** for disease

3

Every Canadian is at some point **a child** during his/her lifetime

UNITED NATIONS HUMAN RIGHTS OFFICE OF THE HIGH COMMISSIONER

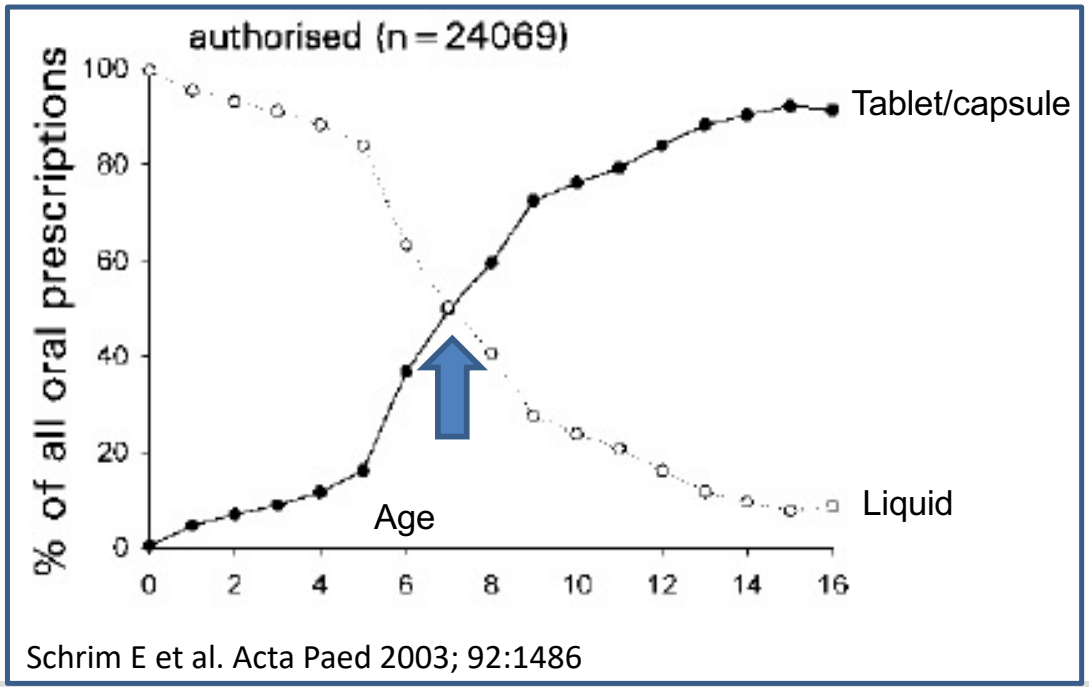
Convention on the Rights of the Child

November 1989

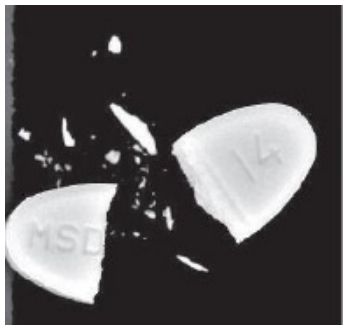
The problem with pediatric medications

- Most medications on the market are either tablets or capsules, unavailable as commercial formulations adapted to the needs of children
  - Kids are often unable to swallow
  - Pediatric dosage is based on weight so dosages are not fixed as those of adults

Age at which a child is able to take a solid oral form



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



Children are Not Mini Adults

- Metabolize drugs differently
- Developmental stages may mean variable drug responses
- Efficacy and safety may not be known or studied
- Administration is based on age group

One Size Does Not Fit All

Adult formulations may not serve children well:

- Taste acceptance/compliance
- Route of administration and dose flexibility
- Dosing concentration and volumes
- Drug excipients (e.g. alcohol or sugars)
- Ease of dosing
- Stability and bioavailability

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 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**

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

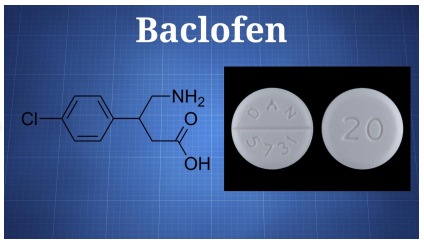
Mode de préparation

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

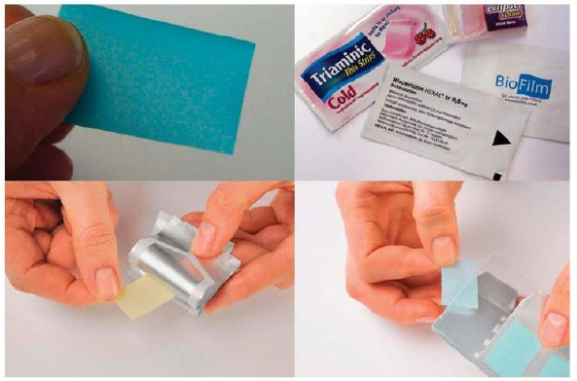
news



Solid Oral Dosage Forms: Beyond the “Adult Tablet”

Orodispersible tablet

Mini-tablet



Orodispersible film

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

Drugs Frequently Compounded in a Canadian Pediatric Tertiary Hospital

- 56 drugs were identified
- 3 most frequent categories of drugs using AHFS Pharmacologic-Therapeutic classification:
  - Cardiovascular: 30 %
  - Central nervous system: 20 %
  - Anti-infectious: 11 %
- 100% were off-patent drugs
- On the Canadian market for a median of 35 years

(14 – 65 years)

- Canadian pediatric indication for 27 drugs (48%)

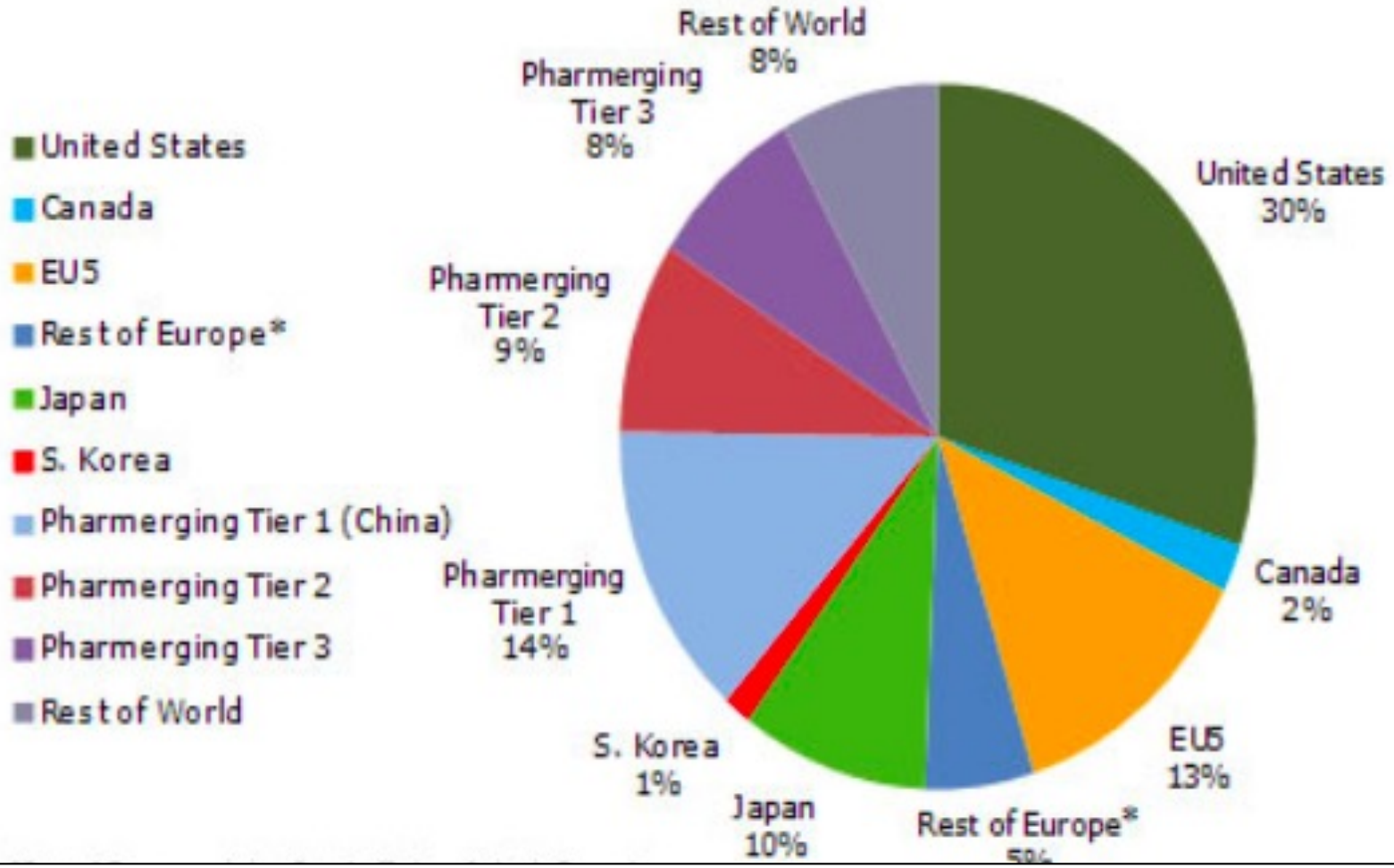
Litalien C. et al., Can J Hosp Pharm 2020

Why do These Formulations Not Exist in Canada?

- Mid to small market size
- Regulatory and reimbursement path (perceived to be) unclear
- Reimbursement landscape is complex and cumbersome
- Little incentive for investment
- Many drugs are off-patent

The GPFC is advocating in these areas to make change and to facilitate bringing these medicines to Canadian children.

2016 Global Drug Market Share



Pediatric market is < 10 % of the Canadian drug market which is 2% of the global pharmaceutical market

Recent successes: Levetiracetam

2016: GPFC identifies levetiracetam as a priority medication.

2016: PMS interested in marketing the liquid formulation in Canada: GPFC provides two reports to support regulatory submission

June 2018: Regulatory dossier submitted to Health Canada

July 2019: Heath Canada NOC

- **November 2019:** launch of IV form by Pendopharm
- **May 2020: l**aunch of oral solution by Pendopharm
- **As of today**: both formulations are under evaluation by INESSS and CADTH
- Reimbursement expected in 2021

Compounded LEV oral solution frequently used in epilepsy.
IV solution only available through SAP.

Recent successes: Amlodipine

2016 GPFC identifies the need for a pediatric formulation of amlodipine

2016: Pharmascience interested in marketing the liquid formulation in Canada: GPFC initiates supporting review

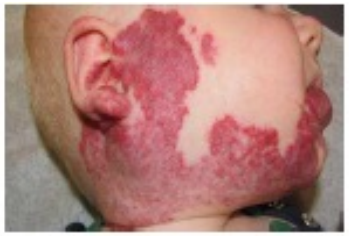
2018: Regulatory dossier submitted to Health Canada.

January 2019: Health Canada NOC

- **October 2019:** launched by Pendopharm
- **April 2020:** INESSS decision: Reimburse for patient who cannot take tablets
- **As of today:** Provincial listings pending

Compounded amlodipine oral solution is frequently used in neonatalogy, pediatric intensive care and grafted children

The case of propranolol



- Used in multiple indications in pediatrics (i.e. infantile hemangioma (IH), Fallot tetralogy, migraine, tachyarrhythmias)
- An oral solution prepared by the pharmacy with propranolol tablets has been used for years in concentrations of 1, 2 and 5 mg/mL
- A commercial oral solution of propranolol (Hemangiol) **3.75 mg/mL** indicated for the treatment of proliferating IH was approved in Canada in February 2016
- Initial recommendations by HTA agencies were made based on cost comparison with compounded preparations:
  - CADTH (03/2017) : Do not reimburse unless price significantly decreases.
  - INESSS (10/2017) : Do not reimburse
- Following negotiations with pCPA, Hemangiol was approved for reimbursement in October 2018 (RAMQ)
- In July 2020 Hemangiol was still not reimbursed by 2 of 12 Canadian provinces/territories as negociations were ongoing

Hemangiol Case – 3 Issues

Reimbursement is only for the approved indication

- Any other indication would not benefit from commercial form as it would not be reimbursed

Concentrations between commercial and compounded forms are different

- Potential to introduce dosing errors (3.75 mg/ml vs. 1mg/ml vs 5 mg/ml)
- Increased risk of error meant that some hospitals chose not to use the commercial form

Availability of commercial form may cost parents more out-of-pocket charges in co-pays if privately insured

- When commercially available public plans will pay 100%
- Private plans however could have an increase reimbursement costs

Regulatory Requirements & Incentives for Pediatric Medicines

cfpg gpfc

Country/Region	Population (millions)	Requirement	Incentive
US (FDA)	329	Yes PREA/FDASIA	Yes BPCA/FDASIA
Europe (EMA)	> 500	Yes	Yes
Switzerland	8.5	New law relating to pediatric development to be implemented	Yes (to be implemented)
Australia (TGA)	25	Information regarding EU or US development pediatric programs must be provided for new registration	No
Japan	126	No	Yes
Canada (HC)	37	No	Yes *(for NDS only)*

New Pediatric Medicines and Indications per Country/ from 2007 until 2015

Region	EU*	US	Japan	Canada
New pediatric medicines	80	76	12	38
New pediatric indications	141	173	38	107
Total	221	249	50	145

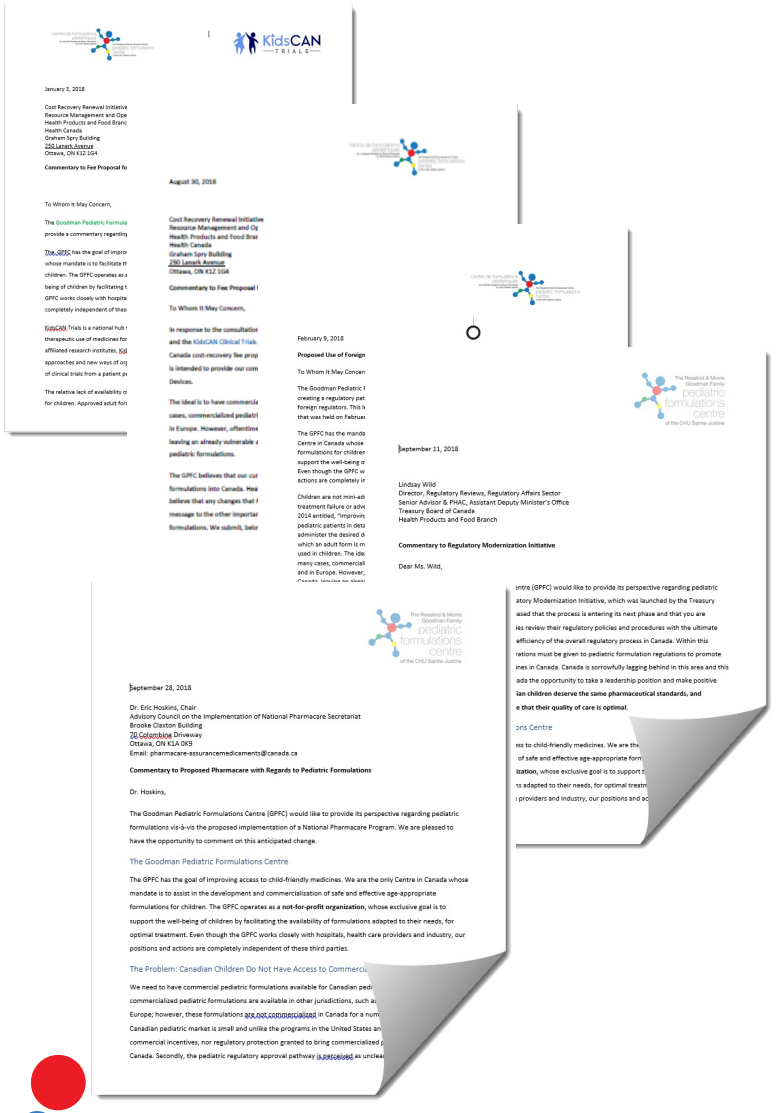
Note: the data provided by other regions included medicines that are not subjected to the obligations of the Paediatric Regulation. For the purposes of this analysis, these medicines were excluded (e.g. generics, hybrid medicines, biosimilars etc.). *EU data include products centrally authorized and national/decentralized and mutually recognized procedure products.

EMA database (SIAMED), NCA questionnaire

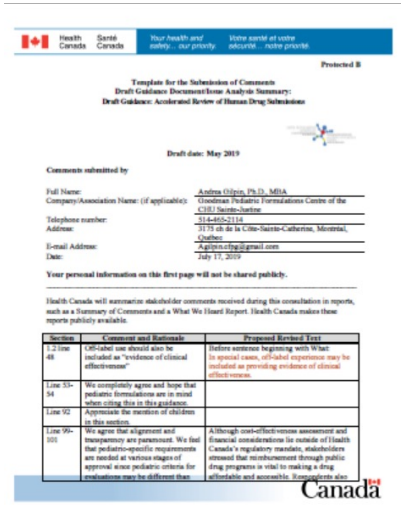
To Have Access to Pediatric Data and Child-Friendly Formulations Health Canada Needs to Institute a Pediatric Framework

- Both incentives and regulatory obligations are needed
- Pediatric community needs to align and propose solutions – Pediatric framework
- Advocacy is critical to ensure pediatrics is represented

The GPFC has written Advocacy Letters in Response to Consultations



6 Letters in Response to Consultations



17 July 2019 Response to Accelerated Review

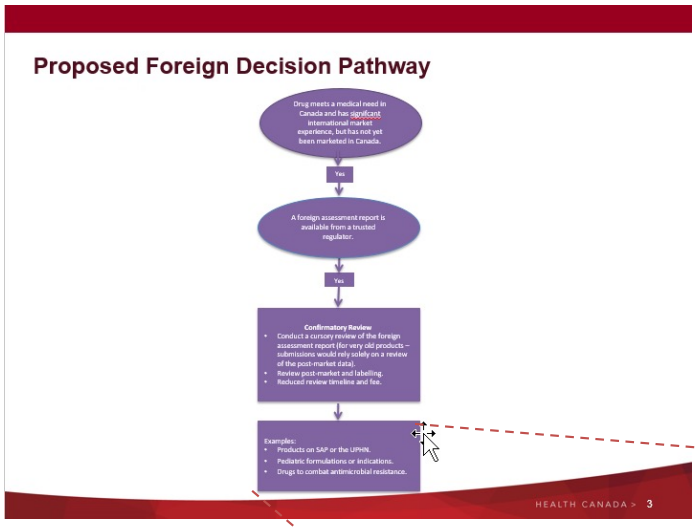
Advocacy Letters signed by 7 pediatric organizations

Pediatric Medications May Qualify for Accelerated Reviews

Health Canada Santé Canada

"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. "

Trusted Foreign Reviews



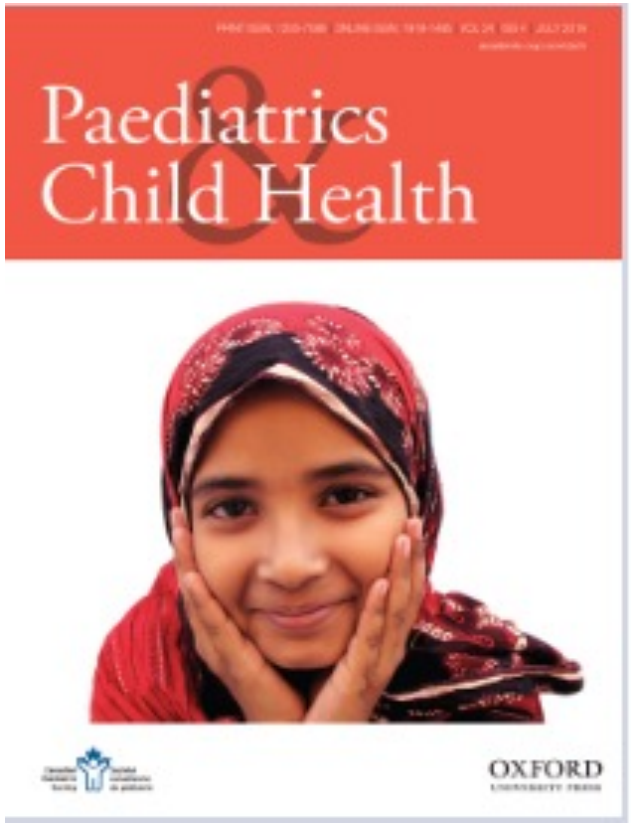
Draft Outline of Program:

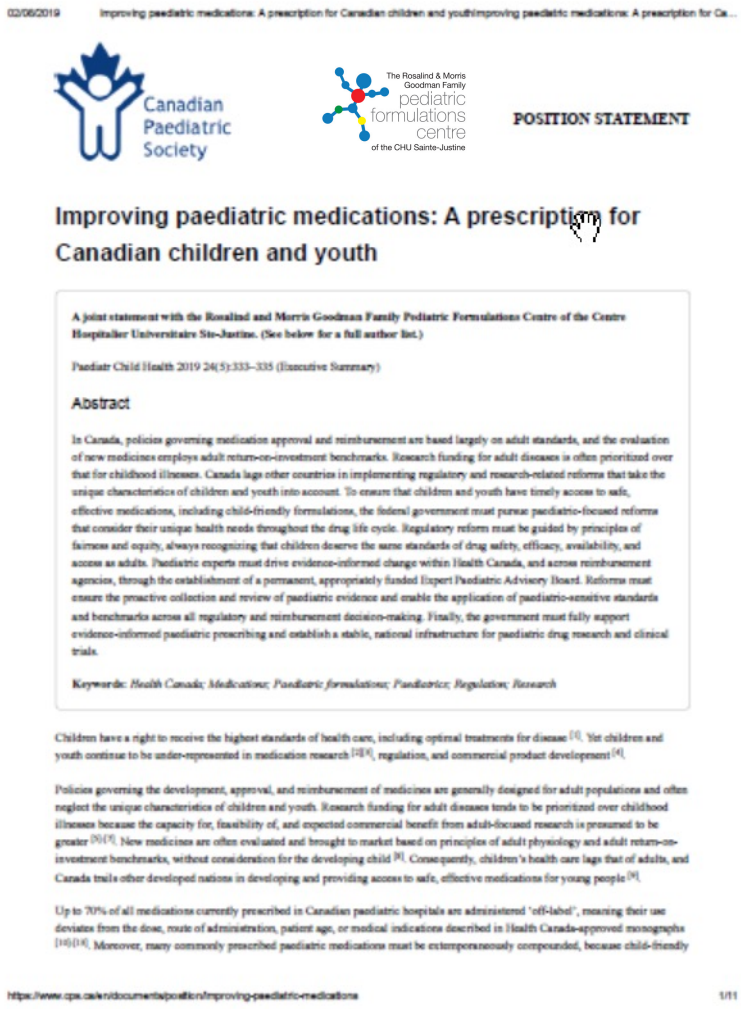
- Using approvals from trusted jurisdictions
- Cursory review at Health Canada
- Must be approved in 2 trusted jurisdictions
- Must be on the market for 15 years

Examples:

- Products on SAP or the UPHN.
- Pediatric formulations or indications.
- Drugs to combat antimicrobial resistance.

Position Paper Published with 17 Pediatric Organizations' Endorsement





02/06/2019 Improving paediatric medications: A prescription for Canadian children and youth

Canadian Paediatric Society

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

POSITION STATEMENT

Improving paediatric medications: A prescription for Canadian children and youth

A joint statement with the Rosalind and Morris Goodman Family Pediatric Formulations Centre of the Centre Hospitalier Universitaire Ste-Justine. (See below for a full author list.)

Paediatr Child Health 2019 24(5):333–335 (Executive Summary)

Abstract

In Canada, policies governing medication approval and reimbursement are based largely on adult standards, and the evaluation of new medicines employs adult return-on-investment benchmarks. Research funding for adult diseases is often prioritized over that for childhood illnesses. Canada lags other countries in implementing regulatory and research-related reforms that take the unique characteristics of children and youth into account. To ensure that children and youth have timely access to safe, effective medications, including child-friendly formulations, the federal government must pursue paediatric-focused reforms that consider their unique health needs throughout the drug life cycle. Regulatory reform must be guided by principles of fairness and equity, always recognizing that children deserve the same standards of drug safety, efficacy, availability, and access as adults. Paediatric experts must drive evidence-informed change within Health Canada, and across reimbursement agencies, through the establishment of a permanent, appropriately funded Expert Paediatric Advisory Board. Reforms must ensure the proactive collection and review of paediatric evidence and enable the application of paediatric-sensitive standards and benchmarks across all regulatory and reimbursement decision-making. Finally, the government must fully support evidence-informed paediatric prescribing and establish a stable, national infrastructure for paediatric drug research and clinical trials.

Keywords: *Health Canada; Medications; Paediatric formulations; Paediatrics; Regulation; Research*

Children have a right to receive the highest standards of health care, including optimal treatments for disease [1]. Yet children and youth continue to be under-represented in medication research [2][3], regulation, and commercial product development [4].

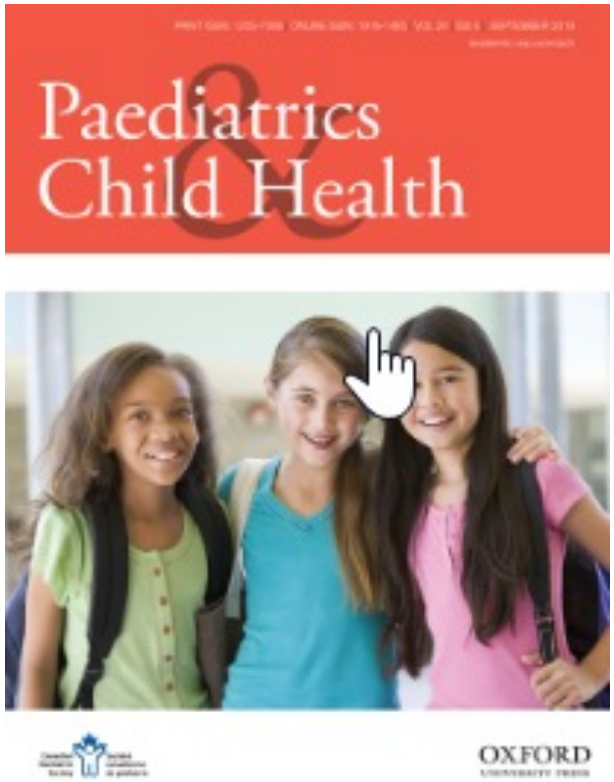
Policies governing the development, approval, and reimbursement of medicines are generally designed for adult populations and often neglect the unique characteristics of children and youth. Research funding for adult diseases tends to be prioritized over childhood illnesses because the capacity for, feasibility of, and expected commercial benefit from adult-focused research is presumed to be greater [5]-[7]. New medicines are often evaluated and brought to market based on principles of adult physiology and adult return-on-investment benchmarks, without consideration for the developing child [8]. Consequently, children's health care lags that of adults, and Canada trails other developed nations in developing and providing access to safe, effective medications for young people [9].

Up to 70% of all medications currently prescribed in Canadian paediatric hospitals are administered 'off-label', meaning their use deviates from the dose, route of administration, patient age, or medical indications described in Health Canada-approved monographs [10]-[14]. Moreover, many commonly prescribed paediatric medications must be extemporaneously compounded, because child-friendly

https://www.cps.ca/en/documents/position/improving-paediatric-medications 1/11

https://www.cps.ca/en/documents/position/improving-paediatric-medications

Policy Paper on Pediatrics and National Pharmacare



Canadian Paediatric Society

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

POSITION STATEMENT

Pharmacare in Canada: The Paediatric Perspective

A joint statement with the Rosalind and Morris Goodman Family Pediatric Formulations Centre of the Centre Hospitalier Universitaire Ste-Justine. See below for a full list of authors and their affiliations.

Principal author(s)

Tom McLaughlin, Geert 't Jong, Andrea Gilpin, Charlotte Moore Hepburn, Paediatric Drugs and Therapeutics Task Force

Abstract

Canada's drug insurance system is one of the most expensive in the world, yet millions of Canadians still struggle to access necessary medications. As a result, provincial, territorial and federal governments are considering public pharmacare policy proposals to ensure that all Canadians can access the medications they need. Pharmacare policies offer an opportunity to prioritize children and youth, whose unique drug needs have long been neglected. Prescription drug use is common in this population, with approximately half of Canadian children and youth requiring at least one prescription in any given year. Drug use remains concentrated, however, among those with complex, chronic, and serious diseases. Children and youth rely heavily on compounded and off-label prescription drugs, which impacts safety, efficacy, palatability, and cost. Reimbursement decision-making bodies do not appropriately value the unique benefits of paediatric drugs, including child-friendly formulations, improved quality of life for children and families, and cost-savings outside the healthcare system. Regardless of the pharmacare model ultimately implemented, ensuring universal, comprehensive, and portable prescription drug coverage for all children and youth is essential. To accomplish this, paediatric drug experts should develop a national, evidence-informed formulary of paediatric drugs. Health Canada should also improve processes to make commercial paediatric drugs and child-friendly formulations more available and accessible. The federal government must also support paediatric drug research and development to this end.

Keywords: *Pharmacare; Paediatric Pharmaceuticals; Drug Insurance; Pharmaceutical Economics; Drug Costs; Child Health Services*

Canada is currently the only high-income country in the world with a universal public health insurance system that does not include prescription drug coverage [1]. Drug coverage is instead provided by a patchwork system of over a hundred public, and an estimated 100,000 private, insurance plans [2]. Public drug insurance is inconsistently available across provinces and territories, and is limited to select populations, such as adults over age 65, low-income families, and individuals with mental or physical disabilities [3]. Nearly 1 in 5 Canadians report that they do not have prescription drug coverage, which limits their access to necessary medications. A similar number report that they, or other household members, have not taken a drug as prescribed within the last year due to prohibitive cost. Almost a million Canadians have reported sacrificing food or heat to afford medications for themselves and their children [4].

In addition to these fundamental problems of access and equity, Canada's patchwork system is costly, inefficient, and unsustainable. On average, drugs cost almost $1,100 per person per year, with over 20% of costs being "out-of-pocket" [5]. Canada pays the third highest per person costs for prescription drugs in the world: 62% higher than the United Kingdom, and more than twice that of

Health Canada's Annual Report 2019

"The health system is also evolving. For example, in 2019 we approved several new pediatric formulations for our youngest, and most vulnerable, Canadians. These formulations mean that healthcare professionals no longer have to rely on the longstanding practice of using medicines approved for adults."

Dr. Supriya Sharma

Chief Medical Advisor,

Health Canada

DRUG AND MEDICAL DEVICE HIGHLIGHTS 2019

MESSAGE FROM THE CHIEF MEDICAL ADVISOR

"The only thing that is constant is change". This was as true when Heraclitus, the ancient Greek philosopher, uttered it as it is now.

Science and technology continue to evolve, bringing change to the way we live and the world around us. New therapies such as telehealth devices, 3D printing, gene therapies and health products that use artificial intelligence are entering the global market at an advanced pace. These bring benefits to patients, but also challenges to regulatory organizations like Health Canada. These smart technologies continue to inspire our transformation efforts to ensure that we are ready for the future.

This past year brought forth many innovative products that will help Canadians maintain and improve their health. For example, Health Canada evaluated new medications that are unlike any other approved antibiotics, providing treatment options for hospitalized and critically ill patients with resistant infections. This past year also brought the approval of paradigm-changing cancer treatments that are based on the unique genetic makeup of an individual's tumour, regardless of where in the body it first started. Enabling the use of these treatments means that the health system, including the role of the regulator, must evolve as rapidly as the scientific advancements that give rise to them.

The health system is also evolving. For example, in 2019 we approved several new pediatric formulations for our youngest, and often most vulnerable, Canadians. These formulations mean that healthcare professionals no longer have to rely on the longstanding practice of using medicines approved for adults.

Some challenges to the health system, such as the opioid crisis, are being met with government-wide initiatives. In addition to our work on labelling and warnings for opioids, over the past year we focussed on restricting the marketing and advertising of these medications to ensure that they are used appropriately.

Health Canada recognizes that the challenges we face are not unique to our country. Our efforts such as the modernization of the way we oversee clinical trials and the creation of new pathways to assess novel innovative therapies for Canadians are enriched by the collaboration we have with international colleagues. Health Canada has built strong relationships with regulators worldwide to advance collaboration in our work on new safety standards, and to lead efforts in assessing new innovative products. Sharing work with other regulators maximizes our collective expertise and avoids duplication of effort. For example, collaboration with Australia resulted in the approval of two new anti-cancer drugs in 2019.

The pace of change will only get faster from here. Our efforts to respond to innovation in this interconnected world will prepare us well for the road that lies ahead.

Supriya Sharma
Chief Medical Advisor,
Health Canada

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HIGHLIGHTS
ind improve your health
2019

Canada

Summary of 2020 Objectives for the Pediatric Community

- Pediatric expertise is needed at every junction of the drug approval process
- Pediatric-specific criteria and alignment are needed at all steps in the drug approval and reimbursement process
- Health Canada must be proactive to request pediatric data and incentives must be developed
- Canadians should have access to pediatric data available elsewhere
- Research funding is needed in pediatrics
- Transparent, clear processes are needed

Canadian children deserve the same medication standards as adults

Next Steps fo

- Using an innovative patient-centric model, the GPFC has assembled a working group to tackle a medication on our priority list
  - Health Canada, INESSS, CADTH, industry, Children Healthcare Canada, Pediatric Chairs of Canada, Canadian Paediatric Society, major pediatric experts across the country
- Purpose is to uncover the challenges together
- Goal is to:
  - Test our inverted adaptive model
  - Identify where the process could be simplified and where pediatric alignment and expertise is needed.

6 ~~5~~ Rights of Medication Administration

- ✓Right Patient
- ✓Right Drug
- ✓Right Dose
- ✓Right Route
- ✓Right Time

✓ Right Formulation

Question

- How do you think we can better provide pediatric formulations to Canadian children?
- Are there barriers that you have identfied that are not discussed?

Contact Information

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