Considerations for the Pediatric Formulations of Cannabis Goodman Pediatric Formulations Centre (GPFC) of the CHU Sainte-Justine:



Andrea Gilpin, Ph.D, MBA General Manager February 2019



Why are we here?



- In Canada, we do not have access to the appropriate commercial formulations
- This can cause therapeutic ineffectiveness, adverse events or even treatment failure





True Cases

- 8-month-old liver transplant recipient with organ rejection
- 18-month old asthmatic infant refusing to take his prednisone
- Parents of a 3-year-old child with leukemia make a cytotoxic medicine at home
- 9-year-old boy died from a baclofen overdose thinking he was taking tryptophan, for his sleep disorder





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 Result is the Practice of Compounding to Adapt Adult Forms



 Many pediatric formulations exist in the United States and Europe but are not commercialized in Canada

Resulting in....

- Off-label use to adapt the adult form to an appropriate child-friendly form
- Compounding of the medication at the pharmacy

As many as 75% of all pediatric prescriptions may fall outside regulatory approval in Canada.

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
- No 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.







Mandate: Increase Child-Friendly Formulations in Canada

- To facilitate the development and market authorization of pediatric drug formulations by:
 - Leading the submission process of 25 medications on our priority list
 - Acting as a change agent to improve clinical, regulatory and access policies and procedures
 - Developing partnerships to provide access to much needed formulations on our priority list

Improving access to appropriate marketed formulations for children is our mandate.

The GPFC has written 6 Advocacy Letters in ¹⁹ **Response to Consultations**



Feb 9, 2018: Us of Trusted **Jurisdictions**



reating a regulatory pathway for the authorization of the sale of drugs already approved by trusted ments the comments that we contributed to a telep

he GPFC has the mandate to improve access to child-friendly medicines in Canada. We are the only Centre in Canada whose objective is to facilitate the development of safe and effective age-appropriate formulations for children. The DPC operates as a non-do-profit organization, whose exclusive goal is to support the well-being of children by facilitating the variability of formulations adapted to their needs. Then though the OPC works clearly with hospitali, heath care providers and industry, our goaldism and

resoment failure or adverse events for children. The Council of Canadian Academies published a repo 2014 entitled, "Improving Medicines for Children in Canada," which outlines the challenges in treating adjutric patients in detail". Approved adult forms often need to be modified in some manner to dminister the desired dose to children, and as such, are used off-label. Compounding is the process by risch an adult form is manipulated by a health care provider, or others, to adapt the adult form to be and in children. The ideal is to have commanial subtance formulations available for dusting

dicines for Children in Canada, 2014, Council of Can



Bagnaviter 13, 2018

othin the proposed Regulatory Modernization initiative, which was launched by the Treasury rocess is entering its next phase and that you are rved access to child-friendly medicines in Canada. Canada is sprrawfully lagging behind in this area and t lations. Canadian children deserve the same pharmar to ensure that their quality of care is optima

GPIC operates as a not-for-profit organization, whose esclusive post is to sup works closely with hospitals, health may providers and industry, our positions

Sept 11, 2018: Regulatory **Modernization**

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

September 28, 2018

Dr. Eric Hoskins, Chair Advisory Council on the Implementation of National Pharmacare Secretariat Brooke Clavron Building 20 Colombine Drivew Ottawa, ON K1A 0K9

Commentany to Drov and Dharmacare with Barards to Badiatric Loc

Dr. Haskins

The Goodman Pediatric Formulations Centre (GPFC) would like to provide its perspective regarding pediatric formulations vis-à-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-friendly medicines. We are the only Centre in Canada whos mandate is to assist in the development and commercialization of safe and effective age-appropriate formulations for children. The GPFC operates as a not-for-profit organization, whose exclusive goal is to support the well-being of children by facilitating the availability of formulations adapted to their needs, for potimal treatment. Even though the GPFC works closely with hospitals, health care providers and industry, ou ositions and actions are completely independent of these third partie

The Problem: Canadian Children Do Not Have Access to Comm

We need to have commercial pediatric formulations available for Canadian per commercialized pediatric formulations are available in other jurisdictions, such a Europe: however, these formulations are not commercialized in Canada for a nu Canadian pediatric market is small and unlike the programs in the United Stat incentives, nor regulatory protection granted to bring co

Collaborations









Global Accelerator for Paediatric Formulations (GAP-f)



Cannabis Pediatric Formulations Challenges

- Concentration of Dose of Oil
 - Larger patients (70-80kg) 20 ml two times per day
 - Concentration of liquid is currently ideal of smaller patients
- Spray
 - Low concentration of CBD
 - Multiple doses needed
- Taste & Smell
 - Can be variable depending on levels of terepines and flavonoids
 - Important for compliance
 - Carriers can change taste
- Excipients
 - Alcohol and polyethylene glycol levels
- Cost not a formulation concern but a challenge
 - Cash paying patients

Can amount to \$1500-\$2500 per month

Based on discussions with: Dr. Evan Lewis, MD, FRCPC Neurology Centre of Toronto (NCT) and Dr. Philippe Major, MD, FRCPC Dept of Pediatric Neurology, CHU Sainte-Justine





Current cannabinoid formulations



Name	Type of cannabinoid	Form/ Concentration	Potential issues in pediatrics	
Prescription cannabinoids (with approved indications)				
Nabilone (Cesamet)	THC analogue	Capsules 0.25, 0.5 and 1 mg	May be <u>difficult to swallow in younger c</u> hildren	
Nabiximols (Sativex)	Extracted CBD/THC	Buccal spray 2.5/2.7mg/spray	<u>Poor taste</u> , contains dehydrated <u>alcohol</u> and <u>propylene</u> <u>glycol</u> (concentrations unknown), ease of administration ?	
Cannabidiol (Epidiolex) ¹ US only	Extracted CBD	Solution 100 mg/mL	Contains dehydrated alcohol (concentration unknown)	
Dronabinol (Marinol/Synd ros) US only	Synthetic THC	Capsules 2.5, 5 and 10 mg/Oral solution 5 mg/mL	Capsules may be <u>difficult to swall</u> ow, liquid contains <u>dehydrated alcohol</u> (50% w/w) and propylene glycol (5.5% w/w)	
Medical cannabis (no official indications)				
Oral cannabis oils	TCH/CBD	Oils with variable concentrations of THC/CBD ²	Taste ? Especially in cases where the volume of administration is considerable ³	
Dried Cannabis	THC/CBD	To smoke/vape with variable concentrations	Not applicable in children	

1 Approved for pediatric use

2 At CHU Sainte Justine: 20:1 (CBD/TCH) / 20mg/mL of CBD is used at a maximum daily dose of 10mg/kg of CBD given BID. 3 As much as 20 mL/dose in older (heavier) children treated at the maximum daily dose

What is the ideal formulation of canabinnoids for children?

- Liquids, solids (tablets or capsules) or other innovative forms (i.e. films, minitabs, patch) taking into account:
 - Type of cannabinoid
 - CBD only
 - CBD/THC in what ratio in pediat-rics?
 - Dosing flexibility
 - First-pass effect/metabolism of drug
 - Ease of administration and taste
 - Safety of excipients avoid use of alcohol, propylene glycol, benzoic acid, sorbitol, phenylalanine above daily thresholds recommended by EMA

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EUROPEAN MEDICINES AGEN	CY TH
1 August 2013 EMACHMP/QMP/805880/2012 Rev. 2 Committee for Medicinal Products for Human Use (CHMP) Paediatric Committee (PDCO)	
Guideline on pharmaceutical development for paediatric use	t of medicines
for paeolatric use	





We Leave you with a Video that Provides the Challenges from a Parental Point of View





https://youtu.be/4kDxlhabb7l

Contact Information



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