

Considerations for the Pediatric Formulations of Cannabis

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



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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 Response to Consultations



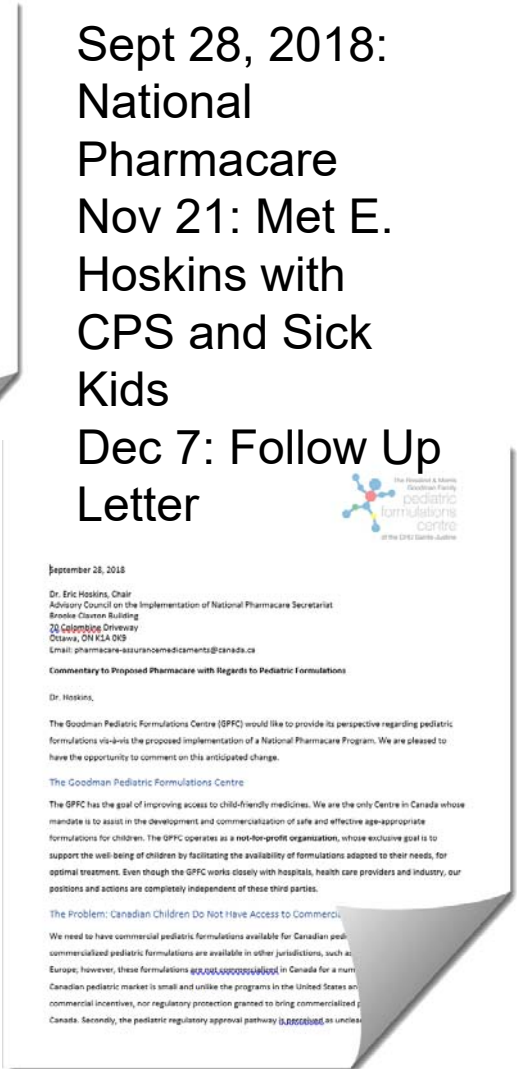
Feb 9, 2018: Use of Trusted Jurisdictions



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



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



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 terpenes 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</u> children
Nabiximols (Sativex)	Extracted CBD/THC	Buccal spray 2.5/2.7mg/spray	<u>Poor taste</u> , contains dehydrated <u>alcohol</u> and <u>propylene glycol</u> (concentrations unknown), ease of administration ?
Cannabidiol (Epidiolex) ¹ US only	Extracted CBD	Solution 100 mg/mL	Contains <u>dehydrated alcohol</u> (concentration unknown)
Dronabinol (Marinol/Syndros) US only	Synthetic THC	Capsules 2.5, 5 and 10 mg/Oral solution 5 mg/mL	Capsules may be <u>difficult to swallow</u> , 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 <u>volume</u> 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 cannabinoids 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



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



<https://youtu.be/4kDxlhabb7I>



