Annual Report 2020 | 2022

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

Message to our Readers

During the years 2020-2022, the Goodman Pediatric Formulations Centre (GPFC) has gone through important changes and challenges. In February 2022, Andrea Gilpin, who has been one of the pillars of the Centre, left us after 5 years as General Manager and Dr. Jean-Marie Leclerc, who succeeded me in 2019 as Executive Director, retired. Despite these departures, the Centre was able to maintain and expand its activities, thanks to the expertise and commitment of Sophie Bérubé, our scientific and clinical project lead since 2018. More recently, Denis Lebel was recently appointed as Executive Director and Dr. Raphael Kraus and Helene Roy have joined the crew.

During that period we were also hit by the pandemic which had a colossal impact on health care. Various drug shortages over the months have brought to the forefront the fragility of our supply system. This instability culminated in the shortages of acetaminophen, ibuprofen and antibiotics. With this crisis, thousands of Canadian parents have been confronted with the vital importance of access to age-appropriate formulations. The Centre and its members were asked at different tables and had many opportunities to speak about our cause.

In the last year, collaboration with Health Canada has been at the forefront. We have continued our discussions in connection with the Pediatric Drug Action Plan (PDAP). The GPFC has been invited to join the new Pediatric Expert Reference Group (PERG), which I co-chair, to put together the first national priority list of pediatric drugs (NPLPD) for Canada. During that time, we have also continued our contribution to advancing knowledge through various publications and position papers.

2023 is already turning out to be an exciting year for the Centre. The publication of the NPLDP and the prospect of incentives being put in place for the marketing of formulations on this list gives us optimism. The publication of the NPLDP is actually the first step in the inverted model that we have been promoting for the past few years. We will continue to advocate for incentives to make drugs on this list available and promote it to Canadian and foreign manufacturers. Canada's children and their parents seem closer than ever to improving their access to quality medicines.

We will also increase our efforts with Canada's Drug and Health Technology Agency (CADTH) and Institut national d'excellence en santé et services sociaux (INESSS) to ensure that the value of the formulations on the Canadian NPLPD list is recognized. The GPFC has also partnered with the University of Montreal and Médicament Québec to offer standardized compounded preparations that will improve safety while awaiting for approval and commercialization of child-friendly formulations.

Finally, all of this could not have been possible without the outstanding commitment of the Morris and Rosalind Goodman Family Foundation along with the CHU Sainte-Justine Foundation. Also, I would like to acknowledge the invaluable support of our external advisors, Jacques Dessureault and Yves Rosconi, throughout this journey.

I am very optimistic looking at the future ahead of us with our growing team. The Centre is healthy with an excellent reputation. The GPFC has become a key player in Canada when it comes to pediatric formulations needs, and a strong advocate for access to safe and efficacious drugs for Canadian children.

Dr. Catherine Litalien
Co-founder and Medical Director, GPFC

Arlo's Story

Before giving birth to Arlo, Candice, a mother and teacher in Winnipeg, Manitoba would never have imagined that providing an age-appropriate medication to her child would be so difficult in a developed country like Canada. She has since become a parent advocate sharing the undeniable need to make pediatric formulations a priority in Canada.

Arlo was officially diagnosed at 4 days old with salt wasting congenital adrenal hyperplasia, a rare form of adrenal insufficiency, which is a life or limb condition. Hydrocortisone is the preferred medication to treat this condition in growing individuals. It has to be administered multiple times a day to closely mimic the body's circadian rhythm which is vital for optimal growth, development, health and well-being.

In 2022 Arlo was hospitalized for three weeks. During that period, it was painfully clear the disadvantage that he and all other Canadian pediatric patients with adrenal insufficiency face. Despite the fact that hydrocortisone tablets have been on the Canadian market for over 60 years and approved for use in children, it is still difficult today to provide Arlo with a prescribed dose of 1.25 mg hydrocortisone since only 10 and 20 mg tablets, formulations designed for adults, are currently available in Canada. To get a lower strength of hydrocortisone (5 mg tablets are available in the US), Canadian physicians and pharmacists must go through the resource-intensive paperwork requested by Health Canada's Special Access Program. Substituting other medications for hydrocortisone is complex, may not work, and put children at risk of severe illness and adrenal crisis, which can be fatal. Parents/pharmacists must therefore resort to either cutting the tablets in multiple parts or crushing and suspending them in syrup. In other countries like the US, the United Kingdom and Australia, child-friendly hydrocortisone is available as granules, liquid form or lower strength tablets.

Arlo's situation is not unique. Many other medications used daily in the care of children with diverse acute and chronic conditions are exclusively available in adult forms in Canada, while successfully commercialized as child-friendly formulations in other countries.

Our Mission

To be the voice of Canadian children of all ages in order to improve access to formulations that meet their needs by creating a favorable environment. We want to:

> Facilitate the development and market authorization of safe and effective pediatric drug formulations by:

- Promoting a research-based approach to pediatric formulation development;
- Contributing to a clinical and regulatory environment that fosters pediatric formulation development and access;
- Contributing to uncovering incentives that could stimulate and attract the development of pediatric formulations and promote access;
- Identifying hurdles and challenges in the drug development process and access to pediatric formulations as well as in the regulatory landscape and act as a change agent;
- Promoting cost effective treatment for children.

> Promote safety of medicines administered to children by:

- Highlighting the shortcomings of compounded preparations to support the need for commercialized formulations;
- Standardizing compounding to improve safety while awaiting for commercial child- friendly formulations.

Our Team

The GPFC is committed to facilitating access to child-friendly formulations to ensure efficacy, safety and compliance of medicines for children. To achieve these important and ambitious goals, we have joined together to mobilize a collaboration of researchers, pediatricians and pharmacists with the requisite depth of expertise and breadth of influence. Created in 2016, the GPFC is a group within the CHU Sainte-Justine (CHUSJ) institution working in a non-for-profit manner towards the accomplishment of its mission.

The growing GPFC team continues to support the well-being of Canadian children by facilitating the availability of safe and effective formulations adapted to their needs.

FROM LEFT TO RIGHT:

Denis Lebel has been involved with the GPFC since its creation in 2016 as a hospital pharmacy lead. We are thrilled to announce that he is now assuming the role of Executive Director of the Centre, in addition to his new appointment as Head of the CHUSJ Pharmacy Department.

Sophie Bérubé, a pharmacist with over 20 years of experience in the pharmaceutical industry, is the scientific and clinical project lead at the GPFC since 2018.

Hélène Roy, a clinical pharmacist at CHUSJ for 20 years, is now the Associate Director of the Pharmacy Department and joins the team as the new hospital pharmacy lead of the GPFC.

Ginette Piteau, recently retired after 40 years acting as administrative assistant at the CHUSJ, is the administrative and finance assistant of the GPFC.

Dr. Catherine Litalien, a pediatric intensivist at CHUSJ for 15 years who now works in the Division of General Pediatrics co-founded the Centre. She is currently acting as Medical Director of the GPFC, after assuming the executive direction from 2016 to 2019.

Dr. Raphaël Kraus, a pediatric rheumatologist at CHUSJ, who also holds an M.Sc. in System Leadership and Innovation, has recently joined the GPFC team as Assistant Medical Director.

In order to achieve its mission, the GPFC works around the following pillars:

1. Advocacy efforts with key pediatric stakeholders at both the provincial and federal governments

2. Increasing awareness amongst healthcare providers and children's associations and developing collaborations

3. Collaborating with industry to support increased access to pediatric formulations in Canada

4. Increasing the body of knowledge regarding pediatric formulations

Main Achievements for 2020-2022

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Advocacy efforts with key pediatric stakeholders at both the federal and provincial governements

December 2, 2021

Dr. Stephen Lucas, Deputy Minister of Health Canada
Deputy Minister's Office, Health Canada
Brooke Claxton Building, Tunney's Pasture
Ottawa, Ontario K1A 0K9

Dear Dr. Lucas;

On behalf of our nine national child and youth health organizations, we are writing today to communicate our urgent and shared concerns related to the pediatric drug file at Health Canada. As we mark the first anniversary of the public release of the Pediatric Drug Action Plan (PDAP), we are alarmed by the lack of tangible progress made since its release, as well as the apparent absence of any modifications or updates to the initial PDAP after our organizations provided substantial feedback on the first iteration. We respectfully submit the following recommendations for action, and look forward to your timely attention to our serious concerns.

Over the last two years the GPFC has accelerated its advocacy activities with key pediatric stakeholders across the country. The focus has been the implementation of a pediatric regulatory framework along with alignement with Health Technology Assessment and reimbursement bodies.

Federal government

Following unveiling of the Health Canada Pediatric Drug Action Plan (PDAP) in November 2020 the GPFC has:

- Prepared and led a workshop to provide feedback on PDAP attended by over 60 stakeholders from the pediatric community;
- Held regular meetings with Health Canada on the PDAP;
- Co-signed a letter with Canadian Pediatric Society (CPS) on acceleration of PDAP endorsed by 9 pediatric organizations;
- Written a letter to Health Canada on the GPFC priority list of child-friendly formulations most in need in Canada endorsed by 9 pediatric organizations;

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- Led with several engaged members of the Canadian pediatric community the publication of a commentary in the Canadian Medical Association Journal on the importance of having a regulatory pediatric framework in Canada;
- Closely collaborated with Health Canada to prework on the National Priority List of Pediatric Drugs (NPLPD) with Catherine Litalien nominated to co-lead the Pediatric Expert Reference Group (PERG);
- Initiated discussions with politicians on the importance of the PDAP and access to pediatric formulations.

Commentary

Time for a regulatory framework for pediatric medications in Canada

Andrea Gilpin PhD MBA, Sophie Bérubé BPharm MSc, Charlotte Moore-Hepburn MD, Thierry Lacaze-Masmonteil MD PhD, Samira Samiee-Zafarghandy MD, Michael Rieder MD PhD, Emily Gruenwoldt MHA, Stuart MacLeod MD PhD, Catherine Litalien MD

■ Cite as: *CMAJ* 2022 May 16;194:E678-80. doi: 10.1503/cmaj.220044

Key points

- In Canada, numerous medications prescribed to children are used off label and do not have an age-appropriate formulation.
- In the United States and European Union, pediatric-focused policies have been in place for more than a decade to improve pediatric drug labelling and commercialization of child-friendly formulations.
- A pediatric framework is needed in Canada, with mandatory submission of pediatric data and formulations when use of a medication is anticipated in children, and suitable incentives for manufacturers for new and existing medications (both on and off patent).
- It would be opportune, given that Health Canada is currently undergoing reform, to add pediatric-specific requirements and incentives in the Canadian legislation to ensure children benefit from the same regulatory standards as adults.

Provincial governments

As part of the pilot project on tacrolimus (Adaptive Inverted Model) the GPFC:

- Initiated discussions on public listings with provincial governments of Alberta, Ontario and Quebec;
- Initiated discussions with the Québec Ministère de la santé et des services sociaux on the pilot project and conducted a budget impact analysis on the GPFC priority list for Quebec.

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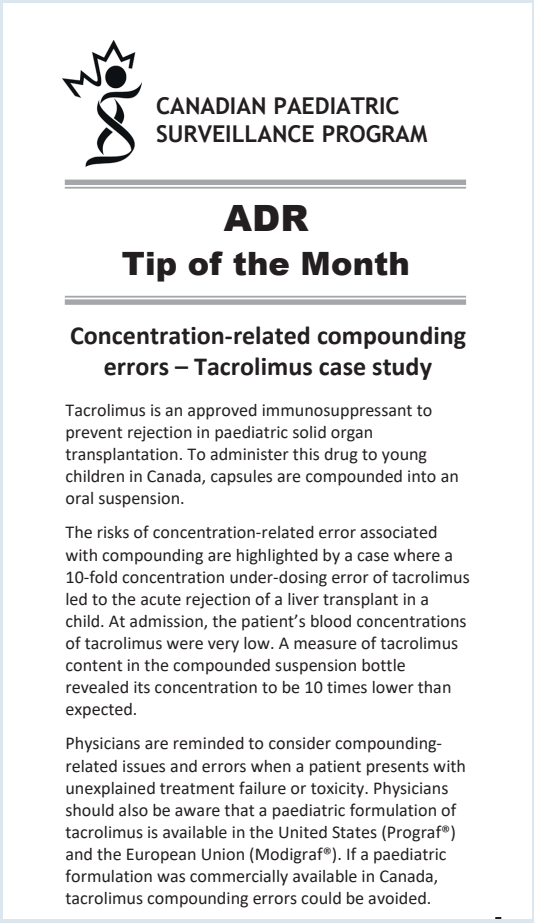
Increasing awareness amongst healthcare providers and children's associations and developing collaborations



CANADIAN PAEDIATRIC SURVEILLANCE PROGRAM

ADR
Tip of the Month

Concentration-related compounding errors – Tacrolimus case study

Tacrolimus is an approved immunosuppressant to prevent rejection in paediatric solid organ transplantation. To administer this drug to young children in Canada, capsules are compounded into an oral suspension.

The risks of concentration-related error associated with compounding are highlighted by a case where a 10-fold concentration under-dosing error of tacrolimus led to the acute rejection of a liver transplant in a child. At admission, the patient's blood concentrations of tacrolimus were very low. A measure of tacrolimus content in the compounded suspension bottle revealed its concentration to be 10 times lower than expected.

Physicians are reminded to consider compounding-related issues and errors when a patient presents with unexplained treatment failure or toxicity. Physicians should also be aware that a paediatric formulation of tacrolimus is available in the United States (Prograf®) and the European Union (Modigraf®). If a paediatric formulation was commercially available in Canada, tacrolimus compounding errors could be avoided.

The GPFC has maintained its previous collaborations and developed new ones with organizations in and outside of Canada.

Local collaborations

- Spoke at the Canadian Drug Information Association conference together with Health Canada on pediatric drugs;
- Led Med Safety Exchange webinar on pediatric formulations organized by ISMP (Institute of Safe Medication Practices) Canada;
- Collaborated to a Safety Bulletin on drug compounding published by ISMP Canada;
- Prepared 6 case studies on safety issues related to compounding that were published as ADR tips of the months on Canadian Pediatric Society website;
- Presented at the Canadian Society Pharmacology and Therapeutics annual meeting on safety issues related to compounding;
- Together with ISMP Canada, submitted a brief to the house of commons, on the importance of a regulatory framework for pediatric medications in Canada supported by Children Healthcare Canada (CHC) and CAH Advocates Canada;

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- Led a parent workshop endorsed by both CHC and ISMP Canada to discuss difficulties encountered with compounded pediatric formulations;
- Provided a letter of support to a parent advocate for access to a needed child-friendly formulation for Canadian kids suffering from CAH.
- Presented and regularly attended Global Accelerator for Paediatric Formulations Network meetings, an initiative of the World Health Organization;
- Participated to a survey on access to pediatric formulations in Canada by the Heidelberg Institute of Global Health.

International collaborations

- Led a publication reviewing paediatric formulations development and access with international experts in the pediatric community who are engaged to improve access to pediatric formulations adapted to the needs of children;
- Presented a case study on assessment of health technology issues encountered with pediatric formulations at the Boston Multi-regional Clinical Trials Centre of Brigham and Women's Hospital and Harvard in view of a conference on *"Access to Medicines for Children: Using Pediatric Extrapolation in Regulatory and HTA Decision-Making"*


BJCP British Journal of Clinical Pharmacology

INVITED REVIEW

From paediatric formulations development to access: Advances made and remaining challenges

Catherine Litalien, Sophie Bérubé, Catherine Tuleu, Andrea Gilpin, Émilie Kate Landry, Marie Valentin, Robert Strickley, Mark A. Turner

First published: 01 March 2022 | https://doi.org/10.1111/bcp.15293

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Collaborating with industry to support increased access to pediatric formulations in Canada

- Presented at the Canadian Society of Pharmaceutical Sciences on *Increasing Access to Safe and Effective Pediatric Formulations*;
- Established a revised priority list in 2021 focusing on 17 highly needed medications that was shared with Health Canada and made available for the public on its website;
- Had multiple corporate presentations during the last years with the intent to create partnerships at the national and international level;
- Continued to focus on existing formulations working with companies based in Europe to help build the business case to support commercialization efforts of several medications currently on the GPFC;
- Supported reimbursement efforts for levetiracetam and amlodipine at provincial and national levels;
- Provided support to a Canadian drug company who filed a pediatric formulation at Health Canada for an off-patent drug that is currently compounded and used off-label, by presenting at two Health Canada meetings.

6-mercaptopurine
Baclofen
Clobazam
Dexamethasone
Domperidone
Esomeprazole
Gabapentin
Hydrocortisone
Hydroxyurea
Levothyroxine
Metronidazole
Phytonadione
Rifampicin
Sildenafil
Sotalol
Tacrolimus
Topiramate

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Increasing the body of knowledge regarding pediatric formulations

During the reporting period we have conducted 2 studies to support our mission. Data collection, analysis and presentation of results were performed by students through grants for student work learning integration program from BioTalent who subsidized 75 % of the salary for 16-weeks.

- ***Determination of the Percentage of Active Prescriptions Requiring Compounding***

We are often asked about the impact of the lack of pediatric formulations for the care of children. In our recently published study, conducted at the CHU SJ, we were able to demonstrate that almost a quarter (23%) of prescriptions for drugs administered orally in hospitalized children required compounding, while almost half of children (49%) in the study had at least one prescription of a drug requiring compounding in their medical records. Since compounded preparations are a risky and last resort solution to treat children, their common use continues to astound. We invite you to consult the full article for a detailed status report.

- ***Real-World Variability of Tacrolimus Concentration in Compounded Suspension - a pilot study***

Because we suspect the quality of compounded drug formulations, to be sub-optimal and potentially affected by real-life use, we conducted a pilot study of tacrolimus compounded suspension (TCS). Nine bottles of TCS (150 mL – 0,5 mg/mL) were prepared by the hospital pharmacy and subjected to various conditions. TCS bottles were stored and handled according to various scenarios mimicking real-world use over time. We found that there was noticeable variability in preparation and stability of the bottles in controlled in-use conditions. Results of this pilot study were presented in 2023 at the annual meeting of the Canadian Hospital Pharmacy Association. In light of these results, we believe that a real-use study of TCS administered to pediatric patients is highly relevant. The GPFC is about to start this study.

- ***Partnership with Médicament Québec***

We also partnered with University of Montreal and Médicaments Québec to develop standardized compounding of drugs commonly used in pediatrics. Conducted by the pharmacy department of CHUSJ, this work will help the GPFC determine the shortcomings of such preparations to further support the need for commercial formulations and their reimbursement.

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Publications

Original papers/Posters:

- Landry É K, Autmizguine J, Bérubé S, Gilpin A, Lebel D, Leclerc J, Métras M-É, Litalien C: Drug prescriptions requiring compounding at a Canadian university affiliated pediatric hospital: A cross-sectional study. Pediatric Academic Societies, May 2021
- Litalien C, Bérubé S, Tuleu C, Gilpin A, Landry EK, Valentin M, Strickley R, Turner MA. From paediatric formulations development to access: Advances made and remaining challenges. British J of Clinical Pharmacol. (BJCP): March 2022 DOI: https://doi.org/10.1111/bcp.15293
- Gilpin A, Berube S, Moore-Hepburn C, Lacaze-Masmonteil T, Samiee-Zafarghandy S, Reider M, Gruenwoldt E, MacLeod, Litalien C. Time for a regulatory framework for pediatric medications in Canada. CMAJ, May 2022, 194(19):E678-E680. DOI: https://doi.org/10.1503/cmaj.220044
- Landry ÉK, Autmizguine J, Bérubé S, Kraus R, Métras MÉ, Lebel D, Litalien C. Drug prescriptions requiring compounding at a Canadian university affiliated pediatric hospital: A cross-sectional study. Children (Basel). 2023 Jan 11;10(1):147. https://www.mdpi.com/2227-9067/10/1/147

Collaborations:

- Sushko K, Litalien C, Ferruccio L, Gilpin A, Mazer-Amirshahi M, Chan AK, van den Ander J, Lacaze-Masmonteil T, Samiee-Zafarghandy S. Topical nitroglycerin ointment as salvage therapy for peripheral tissue ischemia in newborns: a systematic review. CMAJ. March 2021, 9(1):1-22 DOI: https://doi.org/10.9778/cmajo.20200129
- Huntsman RJ, Kelly E, Alcorn J, Appendino JP, Bélanger re, Crooks B, Finkelstein Y, Gilpin A, Lewis E, Litalien C, Jacobs J, Moore-Hepburn C, Oberlander T, Rod Rassekh S, Repetski AE, Reider MJ, Shackelford S, Siden H, Szafron M, 't Jong GW, Vaillancourt R. for the Cannabinoid Research Initiative of Saskatchewan and the Canadian Childhood Cannabinoid Clinical Trial 9C4T) Consortium. Improving the regulation of medical cannabis in Canada to better serve pediatric patients. CMAJ, October 2021, 193(41) E1596-E1599 DOI; https://doi.org/10.1503/cmaj.202169

Acknowledgments

The GPFC wishes to express particular thanks to the CHUSJ for its unwavering support contribution in kind which proved indispensable for the proper functioning of the Centre's activities. We wish to thank the Morris & Rosalind Goodman Family Foundation and the CHU Sainte-Justine Foundation for their support. We thank both Andrea Gilpin and Jean-Marie Leclerc for their dedication and accomplishments many of which are reflected in this document. We also thank Emilie Kate Landry (medical student) and Feriel Djebbar (pharmacy student) for their contributions to the research conducted by the GPFC. We are thankful for the support of our external advisors Yves Rosconi and Jacques Dessureault. We are fortunate to have many individuals who are moved by our mandate and who provide to the GPFC their advice, support and expertise, in kind. We could not be where we are today without all of these supporters who are passionate about kid's well-being.

Contact Person

DENIS LEBEL,
Executive Director of the GPFC
Denis.lebel.hsj@ssss.gouv.qc.ca