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ISMP CANADA
Institute for Safe Medication Practices Canada
Institut pour la sécurité des médicaments aux patients du Canada

Response to the Standing Committee on Health Study on Children's Health

The Institute of Safe Medication Practices Canada (ISMP Canada) and the Goodman Pediatric Formulations Centre (GPFC) of the CHU Sainte-Justine with support from CAH Advocates Canada and Children's Healthcare Canada, are pleased to jointly submit to the House of Commons Standing Committee on Health's study of children's health.

TIME FOR A REGULATORY FRAMEWORK FOR PEDIATRIC MEDICATIONS IN CANADA

Ten years after Health Canada's request for an in-depth, evidence-based assessment of therapeutic products in children and 7 years after publication of an expert panel report[1], Canada remains without a purposeful regulatory framework for pediatric medications and formulations approval, which is in sharp contrast with the United States (US) and European Union (EU). This failure to act engenders real-life consequences. The time for action is now.

Arlo's Story

Before giving birth to Arlo nine months ago, 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 (SW-CAH). With this condition Arlo's adrenal glands do not produce cortisol, a stress hormone that regulates other hormones in his body. He also has an aldosterone deficiency which means he has a hard time maintaining a healthy electrolyte balance. CAH is a rare form of adrenal insufficiency (AI), it is a life or limb condition. To live, Arlo needs to take hydrocortisone multiple times a day and extra doses may be required in times of stress, illness or injury.

Hydrocortisone is the preferred medication to treat AI in growing individuals.[2] It is the synthetic version of the body's natural cortisol with the least side effects. Hydrocortisone 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.

Recently Arlo was hospitalized for three weeks. During that period, it was painfully clear the disadvantage that he and all other Canadian pediatric patients with AI face. Despite the fact that hydrocortisone tablets have been on the Canadian market for over 60 years and approved for use in children, the Children's hospital could not 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 in child-friendly formulations in other countries. These include the 17 oral medications contained on the GPFC priority list such as 6-mercaptopurine (leukemia), dexamethasone (asthma and laryngitis), tacrolimus (prevention of graft rejection), gabapentin (epilepsy), metronidazole (infections) and hydroxyurea (sickle-cell anemia).

Impact of not having appropriate formulations for children

Every year, roughly half of Canada's 8 million children are given at least one prescription drug. The proportion is even higher among newborns and infants under the age of 1 year.[1] Despite their widespread use for children of all ages, from premature newborns to adolescents, many medications given to children have no commercially available, age-appropriate formulations. Pediatric care providers are faced with this challenge daily, forcing them to use these products off-label (outside their marketing authorisation). Pharmacists, nursing staff, parents or caregivers must therefore compound the drug (i.e., adapt the commercialised adult pharmaceutical forms by splitting or crushing adult tablets in liquid or food) to overcome this barrier in an attempt to appropriately treat sick children.

A recent retrospective study conducted at a tertiary pediatric hospital on two separate days showed that nearly half (49%) of hospitalized children received at least one prescription for a compounded medication.[3]

Safety issues related to compounding

Even though the practice of compounding is regulated by provincial pharmacy regulatory authorities and is essential to give young children access to medications, it cannot be considered an equivalent surrogate for a pediatric formulation approved by Health Canada. When compared to manufacturing standards (Good Manufacturing Practices) required by regulatory agencies for commercial products, compounding has multiple inherent limitations[4] (Table 1) with the potential for suboptimal adherence due to unpleasant taste, exposure to unsafe ingredients, underdosing resulting in therapeutic failure or overdosing with the potential for drug toxicity.

Table 1: Limitations of compounding

Limited stability data
Taste issue with limited options available to mask bad-tasting active pharmaceutical ingredients (APIs)
Potential for inaccurate dosing
Potential for altered absorption
Lack of bioavailability data for compounded drugs
Lack of testing for purity, potency, content, or stability
Limited environmental control with potential contamination of the compounded drugs
Exposure of healthcare professionals and/or parents to APIs
Lack of awareness of physicians of compounding practices and the variability in formulations used
Limited oversight by regulatory agencies

These risks reinforce the need for paediatric-specific formulations to ensure the safe and effective delivery of the intended medicine at the appropriate dose, essential to the health of this vulnerable population.

Although every available measure to ensure the safe delivery of compounded medicines, errors unfortunately do occur, leading to suboptimal efficacy and adverse events - even death. Andrew, an 8-year-old Canadian boy, died in 2016 after the compounding pharmacy dispensing his sleep medication (requiring tryptophan powder) accidentally substituted another medication (baclofen powder) in the compounded product.[5] Such tragedies are avoidable; it is our profound responsibility to prevent them.

When Canadian health care professionals have to resort to compounding, they have to work with a quality deficit, an information deficit and a risk excess compared to a commercialized child friendly formulation. This should be avoided whenever possible.

Access to pediatric formulations – Canada lags behind

A Canadian study at a tertiary pediatric hospital showed that almost half (48%) of frequently compounded medications were commercially available as child-friendly formulations in the US or EU. All of the 56 top compounded drugs in the study were old off-patent drugs that had been on the Canadian market for a median of 35 years.[6]

A study published in 2020 showed that 60% of newly approved drugs for use in children less than 6 years of age between 2007-2016 were unavailable as child-friendly formulations in Canada.[7] More recently, a study by a German group compared availability of pediatric formulations for drugs in the US and EU to those in 6 countries that do not have pediatric regulations in place (Australia, Brazil, Canada, Russia, South Africa and Kenya). Age-appropriate formulations were available for only 44% of newly approved pediatric drugs and 35% of generic equivalents in Canada. The authors concluded that countries without pediatric regulatory obligations have limited authorisation availability of novel medicines and that EU- or US-approved pediatric formulations often do not reach these countries.[8]

Recent children's ibuprofen/acetaminophen shortage highlights the importance of age-appropriate formulations

Shortages of liquid acetaminophen and ibuprofen have recently made headlines. With this crisis, millions of Canadian parents have been confronted with the vital importance of access to age-appropriate formulations.

Although this particular shortage will pass, many life-saving medications, such as Arlo's hydrocortisone, will remain unavailable in age-appropriate formulations without substantial regulatory action.

Recommendations: Canada needs a pediatric regulatory framework

In 2020, Health Canada established the Pediatric Drug Action Plan (PDAP) with the goal to improve children's access to safe and effective health products — a step in the right direction. However, Canada still does not have a purposeful regulatory framework for pediatric drug approval, which is essential for a coordinated and systematic approach to pediatric medications and formulations. With its ongoing modernization act, Health Canada's has an unprecedented opportunity to create a more agile system which has the potential to address this issue.

To ensure optimal access to on-label, high-quality manufactured pediatric medications and formulations, Health Canada's regulatory reform should include the following elements[9]:

1) A pediatric rule requiring manufacturers to submit for a pediatric indication and develop a pediatric formulation when use in pediatrics is anticipated. A similar system set up decades ago in the US and EU has proven successful.

2) A trusted foreign decisions pathway with pediatric-specific terms allowing Canadian pediatric submissions to rely on Trusted Foreign Decisions from select jurisdictions without requesting additional information or data. This mechanism would be an incentive for manufacturers as it would streamline and speed up the review and approval process when medications are approved in those jurisdictions.

3) A fee structure with reduced rates for pediatric medications would provide an incentive to manufacturers to submit pediatric information and formulations of older, off-patent medications. Other incentives for older drugs could include accelerated review, orphan drug designation, or certain forms of protection for medications identified as meeting a critical need.

We can and must do better. Canadian children, like Arlo, deserve the same access to pediatric medications available in suitable child-friendly formulations as children in other countries. Today, we look to you for political leadership to ensure children's health is seen as a national priority and to implement these achievable recommendations.

About Us:

About the Goodman Pediatric Formulations Centre of the CHU Sainte-Justine

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 safe and effective formulations adapted to their needs. Even though the GPFC works closely with hospitals, health care providers and industry, our positions and actions are completely independent of these third parties.

About the Institute for Safe Medication Practices Canada

The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent national not-for-profit organization committed to the advancement of medication safety in all healthcare settings. ISMP Canada works collaboratively with purposeful partners to promote safe medication practices.

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