Reforming Paediatric Drug Regulations in Canada: A Clinical and an Access Imperative

Réforme du règlement sur les médicaments pédiatriques au Canada : un impératif clinique et un impératif d'accès

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Abstract

Children deserve the same high standards for drug safety, efficacy and access as adults. Unfortunately, Canada lags behind leading international regulators in implementing reforms to ensure access to paediatric medications. Paediatric regulations, also known as paediatric rules in the US, include a mandate to submit paediatric data in all new drug applications

when paediatric use can be anticipated. Absent paediatric regulations, many medications with paediatric-specific indications in other countries remain "off-label" for Canadian children. In addition to concerns related to off-label drug safety, the absence of paediatric indications prohibits appropriate paediatric-specific health technology assessments and limits the evidence-based listing of paediatric medications on public and private formularies.

Résumé

Les enfants méritent les mêmes normes élevées d'innocuité, d'efficacité et d'accès aux médicaments que les adultes. Malheureusement, le Canada accuse un retard par rapport aux principaux organismes de réglementation internationaux dans la mise en œuvre de réformes visant à assurer l'accès aux médicaments pédiatriques. Le règlement sur les médicaments pédiatriques comprend le mandat de soumettre des données pédiatriques dans toutes les nouvelles demandes d'approbation de médicaments lorsqu'une utilisation pédiatrique est prévue. En l'absence de règlements pédiatriques, plusieurs médicaments qui ont des indications pédiatriques particulières dans d'autres pays demeurent « non conformes » pour les enfants canadiens. En plus des préoccupations liées à l'innocuité des médicaments non indiquée sur l'étiquette, l'absence d'indications pédiatriques empêche l'évaluation appropriée des technologies de la santé pédiatriques et limite l'inscription des médicaments pédiatriques sur les formulaires publics et privés.

Introduction

Following a series of tragic events in the early 20th century, foundational drug regulatory frameworks were developed with an eye to protect children from both the real and perceived dangers associated with drug discovery and novel therapeutics (Moore Hepburn and Rieder 2022). The elixir of sulfanilamide tragedy – so named after multiple children died from exposure to diethylene glycol used to dissolve antibiotic tablets too large for paediatric patients to swallow – is credited with stimulating the passage of the *Federal Food, Drug, and Cosmetic Act* (US Congress 1934) in 1938 (Weinshilboum 1987). The thalidomide tragedy – another child health tragedy associated with global public outcry – was central to the passage of the Kefauver-Harris amendments to the *Federal Food, Drug, and Cosmetic Act* in the 1960s (US FDA 2023). While these important legislative achievements aimed to protect citizens from unproven and unsafe pharmaceuticals through research and regulatory oversight, they had the unintended consequence of excluding children, both formally and informally, from both the research and regulatory enterprise. In the subsequent half-century, as research and regulatory systems evolved to optimize the safety and efficacy of marketed therapies for adults, high-quality data informing the safe and effective use of medications in infants, children and youth were rarely generated (Bourgeois et al. 2012) and were even more rarely submitted to regulators for review (Carmack et al. 2020; Raja et al. 2020). This dearth of data led Harry Shirkey in the late 1960s to label children as "therapeutic orphans" (Shirkey 1968: 119).

In the 1990s, leading international regulators recognized the unique physiological and pharmacological needs of paediatric patients and acknowledged that children deserve the same regulatory protections as adults. They identified major weaknesses in existing drug development and regulatory systems and implemented comprehensive paediatric-focused reforms (Bourgeois and Kesselheim 2019). Unfortunately, Canada did not. As a result, more than two decades after the US, European Union (EU) and leading mid-sized market regulators modernized their paediatric drug approval process, Canada remains without key paediatric provisions now considered best practice. These deficiencies result in critical clinical knowledge gaps for Canadian clinicians and significant access barriers for Canadian patients. This paper highlights one key element necessary for successful paediatric drug regulatory reform and, using four descriptive clinical case studies, articulates the challenges that result from the absence of child-friendly drug review policies in Canada.

What is Paediatric Regulation?

Paediatric regulation, referred to as the paediatric rule in the US, is one of the fundamental provisions in all model paediatric regulatory reform packages. The paediatric rule is a regulatory mandate that requires the generation and submission of paediatric safety and efficacy data in all new drug submissions wherein paediatric use can reasonably be expected (IOM Forum on Drug Discovery, Development and Translation 2008). Now implemented in leading jurisdictions around the world, the paediatric rule is widely accepted as international regulatory best practice (Moore Hepburn et al. 2019).

Paediatric regulations recognize that children are not "small adults." Drug absorption, distribution, metabolism and elimination vary by age and by molecule. Changes in body size, proportion and composition accompany the growth and development of paediatric patients, ranging from premature infants (undergoing postnatal adaptation) to adolescents (undergoing puberty) (van den Anker et al. 2018). Acknowledging this significant physiologic variation to ensure safe, effective and cost-effective use, manufacturers must specifically study medicines in neonates, children and youth, and submit the relevant data to regulators for review. Moreover, as weight-based constraints demand dose flexibility and as age-appropriate administration requires child-friendly drug formulations, palatable liquids, mini-tabs and chewable solids designed to accommodate paediatric needs must be developed (Batchelor and Marriott 2015; van den Anker et al. 2018). Once developed, these child-friendly products must be evaluated according to the same quality standards that are in place for adult patients.

Paediatric regulation first emerged following global calls to governments and industry to ensure that children were not excluded from the potential benefits of drug research, and after recognizing that legislative levers were necessary to ensure that manufacturers pursued paediatric-specific labelling. To address the first issue – the long-standing marginalization of paediatric patients from clinical research – both the US and EU invested in programs to develop and sustain robust paediatric clinical trial ecosystems. In parallel, to address the issue of regulatory neglect, both jurisdictions implemented regulatory frameworks that mandated

the submission of paediatric data with all new drug submissions (The Expert Panel on Therapeutic Products for Infants, Children, and Youth 2014). Specifically, in the US, the *Best Pharmaceuticals for Children Act* (US Congress 2002) and the *Pediatric Research Equity Act* (US Congress 2003) expanded funding for and the authorities of both the National Institutes of Health and the Food and Drug Administration (FDA) to facilitate the generation and mandate the submission of paediatric drug data to regulators. These two acts, together, are considered responsible for over 1,000 paediatric labelling changes in the US between 1998 and 2022 (Bourgeois and Kesselheim 2019; FDA 2022; US FDA 2023). Similarly, in the EU, Regulation (EC) 1902/2006 (EUR-Lex 2006) expanded the authority of the European Medicines Agency (EMA) to demand either paediatric data or a detailed plan to develop paediatric data in all new drug submissions, as well as in requests for new indications. From inception in 2007 to 2016, the EU authorized over 260 new medicines for children, most of them associated with the regulation's requirements (EMA 2017).

These reforms have resulted in robust paediatric research programs, higher-quality information for prescribers, enhanced regulatory support for paediatric-specific issues and more safe and effective "on label" medicines for children (EMA 2017). Based on the successes experienced by these leading regulators, many mid-sized market regulators have moved to implement similar regulatory frameworks.

Why is Off-Label Drug Use a Concern?

Health Canada–approved indications are specific to drug, condition and age and are designed to inform safe and effective use. In addition to guiding clinical care, these indications also serve as the basis for health technology assessments (HTAs) (evaluations of clinical and cost-effectiveness), thereby informing both listing and specific eligibility criteria on private and public formularies.

Off-label use occurs when a drug is given for a condition at a dose, by a route or to a population that has not been authorized by Health Canada (CADTH 2017), a practice that has long been associated with both efficacy and safety concerns (Guidi et al. 2022; Rawlence et al. 2018; Zito et al. 2008). The Adverse Drug Reactions In Children (ADRIC) study found that the odds ratio of an off-label and/or unlicensed drug being implicated in an adverse drug reaction compared with an authorized drug was 2.25 (Smyth et al. 2014). Moreover, given the relationship between population-specific indications and HTAs, off-label prescribing is not supported by formal cost-effectiveness review and is, therefore, often not eligible for public or private coverage. This creates critical access barriers for Canadian children, especially for those needing high-cost medications, and those medications listed on formularies with restrictions or covered only by limited use policies.

As therapeutic orphans and without modern regulatory protections, off-label prescribing in paediatrics in Canada is incredibly common. Up to 80% of all medications currently prescribed in Canadian paediatric hospitals are off-label (The Expert Panel on Therapeutic Products for Infants, Children, and Youth 2014), with neonates, children in intensive care

and children being treated for mental illness being most at risk (Czaja et al. 2015; T Jong et al. 2002; Zito et al. 2008). Importantly, rates of off-label prescribing are significantly lower and rates of paediatric-specific approvals are significantly higher in jurisdictions where paediatric regulations are in force, meaning that the same medications approved by the US, the EU and other mid-market regulators *with* paediatric indications are approved in Canada *without* equivalent paediatric information.

Why is Paediatric Regulation in Canada an Imperative?

Paediatric regulation in Canada is imperative because:

- Canada lags behind the US, EU and other leading regulators in the implementation of paediatric-sensitive drug regulations. Without a mandate for manufacturers to submit paediatric data, many new medications are brought to the Canadian market without a paediatric indication, even when paediatric use can be anticipated and despite paediatric indications having been secured in comparable jurisdictions (Gilpin et al. 2022). Paediatric regulation is necessary to ensure children benefit from the same regulatory standards as adults.
- Without evidence-based paediatric indications, drugs for paediatric patients must be prescribed off label. Off-label drug use is associated with an increased risk of adverse events, precludes age-specific HTAs and often prevents the listing of the medication for paediatric populations on both private and public formularies.

The Impact of Regulatory Neglect: Clinical Case Studies

While all paediatric therapeutic areas have experienced the negative impact of regulatory neglect, the medications necessary to treat paediatric rheumatologic disease provide uniquely constructive case studies that demonstrate the impact of Canada's regulatory deficiencies on patients and families and highlight the critical relationship between Health Canada–approved indications and access.

Over the past two decades, the treatment landscape of paediatric rheumatology has expanded dramatically, with new therapeutic options allowing many affected children and youth to experience disease remission, normal growth and pain-free physical functioning. However, while the early initiation of biologics and newer small molecule drugs have fundamentally changed outcomes, they have also introduced significantly higher outpatient medication costs as compared with prior therapies (Grazziotin et al. 2021). In recent years, several biologics approved with paediatric-specific rheumatology indications in the US and the EU have either not entered the Canadian market at all or have been approved by Health Canada without paediatric indications. In the case of paediatric rheumatologic disease, off-label prescribing is generally not feasible as private and public payers will not cover the annual costs associated with these drugs (up to $25,000/year) and out-of-pocket costs are prohibitive.

Case #1

Belimumab (Benlysta) is a biologic drug approved by Health Canada to treat systemic lupus erythematosus and active lupus nephritis in adults (GlaxoSmithKline 2011). In 2019, in both the US and the EU, belimumab became the first drug ever to be approved with a specific paediatric indication (GlaxoSmithKline 2019). The Pediatric Lupus Trial of Belimumab Plus Background Standard Therapy (PLUTO) (US National Library of Medicine 2022) study – the study providing the data necessary to secure a paediatric indication in those jurisdictions – involved several Canadian investigators and many Canadian paediatric patients (Brunner et al. 2020). However, despite the engagement with Canadian patients and academics and despite peer-reviewed, clinical trial results demonstrating efficacy and safety in paediatrics patients, paediatric data were not submitted by the manufacturer to Health Canada – and this medication remains without a paediatric indication in Canada. Without paediatric-specific drug regulations, Canadian children will continue to participate in clinical trials and contribute to the evidence base enabling paediatric indications in other countries but will remain without access to essential drugs.

Case #2

Tofacitinib (Xeljanz) is approved in the US and the EU for the treatment of polyarticular juvenile idiopathic arthritis (JIA) and, similar to belimumab, Canadian centres participated in the clinical trials required by foreign regulators to secure a paediatric indication (Ruperto et al. 2021). The paediatric rheumatology community anxiously awaited the approval of this medication as it represented a new class of drugs with efficacy similar to the biologics (Machado et al. 2018) but in pill formulation (as opposed to injection). Tofacitinib has been approved by Health Canada for moderate to severe rheumatoid arthritis in adults but not for JIA. At present, without a paediatric-specific indication, this medication may only be accessed through the manufacturer's Patient Assistance Program for qualifying paediatric patients. Accessing necessary drugs through a compassionate program is time-consuming for providers and poses significant risks to the patient (as compassionate programs may end or qualifying criteria may change at any time).

Case #3

Abatacept (Orencia) highlights the important issue of paediatric-friendly formulations. Many paediatric formulations available in the US and the EU are not available to Canadian children (Litalien et al. 2020; Moore Hepburn and Rieder 2022) meaning that dispensing the appropriate dose in a form suitable for a child requires specialized pharmacy compounding or in-hospital administration. Abatacept is a biologic in a unique drug class, available in intravenous (IV) and subcutaneous (SC) injectable forms for adults with rheumatoid arthritis and other conditions (Bristol-Myers Squibb Canada 2006). However, Health Canada has approved the medication for paediatric JIA only in the IV formulation (Ruperto et al. 2008). This is despite research supporting the approval of the SC formulation for JIA patients in

other jurisdictions (Brunner et al. 2018). An SC option would allow patients to administer this drug at home, reducing the cost and inconvenience associated with regular travel to an infusion site for medication administration. This highlights the fact that ensuring the availability of paediatric-friendly formulations in Canada is not only a quality, safety and equity issue, but also an issue with significant health system costs and impacts.

Case #4

Anakinra (Kineret) is an effective biologic for treating children with a rare but potentially life-threatening subtype of arthritis called systemic juvenile idiopathic arthritis (sJIA). Multiple small studies alongside years of global clinical experience have demonstrated its efficacy and safety in children (Giancane et al. 2022), and the EMA has formally approved anakinra for paediatric use. Unfortunately, anakinra does not have Health Canada's approval for sJIA, therefore, it remains off-formulary and out-of-reach for most Canadian children. In Ontario, successful physician advocacy led to public funding (via the Exceptional Access Program) for this medication. However, given the patchwork province-by-province approach to public formulary design, children outside Ontario remain without access (LeBlanc et al. 2012). Healthcare providers are instrumental in conducting clinical trials and are passionate advocates for patients, but they do not have the authority or mandate to petition for new indications. A paediatric regulation would ensure a systematic evidence-based approach to drug approval, including consideration of paediatric populations during both the new drug and new indications approval processes.

A Canadian Solution

The *Protecting Canadians from Unsafe Drugs Act (Vanessa's Law)* (2014) granted Health Canada additional authorities (including the authority to compel labelling changes in the face of serious drug safety signals), demonstrating that Canada's drug regulators may require additional powers to achieve their important mandate. Launched in 2018, the ongoing Regulatory Review of Drugs and Devices (R2D2) (Health Canada 2020) is a comprehensive plan to improve the efficiency and effectiveness of Health Canada's regulatory review process. Initiatives under R2D2 include generating novel priority review pathways for essential medications, renewing the Special Access Program and optimizing the use of real-world evidence to inform regulatory decision making. With Vanessa's Law demonstrating how expanding Health Canada's authorities can effectively address critical limitations in Canada's *Food and Drug Act* (1985), R2D2 provides a unique and time-sensitive opportunity to address the long-standing need for expanded Health Canada authorities to support safe, effective, on-label prescribing for paediatric patients.

At present, Health Canada does not have the authority to request paediatric-specific data if a manufacturer's submission does not include a specific paediatric indication. This is true even when paediatric use of the drug is expected, when paediatric data exist (including paediatric data generated by Canadian academics engaging Canadian patients in clinical

trials) and when a paediatric indication has been applied for and/or secured in a trusted foreign jurisdiction. To address the long-standing regulatory neglect, the *Food and Drugs Act* (1985) and its associated regulations must be amended to expand the authorities of Health Canada by introducing measures that mandate manufacturers to provide paediatric data with all new drug submissions and with all applications associated with a request for expanded (adult) indications. In alignment with best practices and international standards, studies should use age-appropriate formulations in their design and execution. With an eye to minimizing the burden on manufacturers, adopting the internationally recognized International Council for Harmonisation/European guidelines concerning paediatric data generation and modelling paediatric drug data submission requirements on US or EU formats will eliminate the undue administrative burden. This will also ensure Canada does not unnecessarily discourage manufacturers from bringing new and important products to our market.

To ensure the effective implementation of a paediatric regulation, the Canadian Paediatric Society recommends that the federal government create an Expert Paediatric Advisory Board (EPAB) "to review, guide, and co-ordinate activities related to paediatric medication approvals, associated clinical research, and reimbursement activities" (Moore Hepburn et al. 2019: 333). The creation of an EPAB would allow for the introduction of paediatric expertise to the review process and enable Health Canada to develop and further paediatric-focused goals and objectives.

Conclusion

Evidence-based paediatric indications are essential to ensure safe and effective care for infants, children and youth and to facilitate the listing of essential paediatric medications on public and private formularies. Paediatric regulations that mandate the submission of paediatric data with new drug submissions and with applications for new indications have been successful in other leading jurisdictions and are considered international best practice. Although this prospective system would not address those medications already on the market without appropriate paediatric labelling, paediatric regulation is an important first step forward, and one that has been tested and proven efficient and effective in other jurisdictions. By implementing a Canadian paediatric rule, Health Canada will begin to address the long-standing regulatory neglect experienced by our youngest citizens.

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