# Commentary: The Injustice of Paediatric Drug Labelling in Canada – A Call to Action

## Commentaire : L'injustice de l'étiquetage des médicaments pédiatriques au Canada – un appel à l'action

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### Abstract
Building upon the article by Moore Hepburn et al. (2023), this rejoinder acts to reinforce the inadequacy of current drug labelling laws and the urgency of the need for improved paediatric drug regulation in Canada. To facilitate a path forward, specific examples of success in other trusted foreign jurisdictions are provided. A call to educate parents and the public about the current lack of paediatric drug labelling and the ways that multi-stakeholder groups can work together to ensure safe and effective pharmacotherapy for Canadian children are highlighted.

### Résumé
Faisant fond sur l'article de Moore Hepburn et al. (2023), cette réplique insiste sur l'insuffisance des lois actuelles en matière d'étiquetage des médicaments et sur l'urgence d'améliorer la réglementation des médicaments pédiatriques au Canada. Pour faciliter la marche à suivre, des exemples précis de réussites dans d'autres pays de confiance sont fournis. L'auteure lance un appel à sensibiliser les parents et la population au manque d'étiquetage des médicaments pédiatriques et aux façons dont les groupes multipartites peuvent travailler ensemble pour assurer une pharmacothérapie sûre et efficace pour les enfants canadiens.

## Introduction

This author applauds the paediatric health advocacy efforts of providers Moore Hepburn, Chang and Levy: their paper entitled "Reforming Paediatric Drug Regulations in Canada: A Clinical and an Access Imperative" is a sweeping and comprehensive description of the state of drug regulation and labelling for children in Canada, with an important focus on current deficiencies (Moore Hepburn et al. 2023). This rejoinder serves to reinforce and amplify many of the topics discussed in their paper and also to give an example of how a trusted foreign jurisdiction (the US Food and Drug Administration [FDA]) has intentionally focused on paediatric regulatory science with great success.

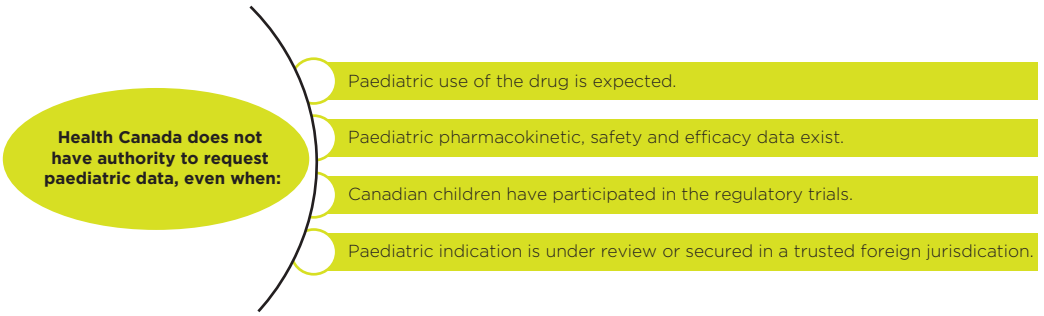
## Discussion

Children are a unique patient population that requires intentional drug regulatory attention. Children are an incredibly rapidly developing and changing patient population with times of extreme growth, ongoing maturation of organ function and, thus, an evolving drug toxicity and efficacy profile (van den Anker et al. 2018). Certain paediatric subpopulations (e.g., neonates) can be defined as orphans for drug development because drug labelling is so sparse and no new drugs have been developed to cater to these populations (Lewis et al. 2022). Because of varying body sizes and developmental stages, children have highly variable dosing needs requiring multiple different formulation types and dose strengths. Next, the diseases diagnosed in children may be similar to adult diseases or, in many cases, entirely distinct from adult diseases and require focused drug development efforts for paediatric indications. Given the unique paediatric issues described, regulatory attention and innovation are required for adequate drug labelling in children. The term "regulatory neglect" used by Moore Hepburn et al. (2023: 56) may seem like strong language but is, in fact, a very apt descriptor of the current state of paediatric drug regulation in Canada. Neglect is defined as leaving undone or unattended to especially through carelessness (Merriam-Webster 2023). While we cannot pinpoint the underlying source of current and ongoing regulatory neglect, we can work collectively to right this injustice.

There are many salient points made by Moore Hepburn et al. (2023) regarding paediatric drug labelling (see Figure 1). First, although other patient populations have benefited from regulatory reform, children have been functionally excluded from regulatory innovation in Canada. The enormity of this exclusion may not be known by many healthcare providers and parents. The current drug funding landscape of Canada, which includes variable provincial access and different formularies, makes federal guidance via comprehensive drug labelling uniquely important in this country. There is a clear injustice when Canadian children are enrolled and studied in international regulatory drug trials, yet do not benefit from eventual drug labelling and access. Finally, the examples of paediatric rheumatology therapies that were discussed showcasing different and overlapping barriers to drug access for children are current, ongoing and important. Inadequate or suboptimal treatment of paediatric rheumatic diseases (and many other paediatric onset diseases) has lifelong consequences including organ

and joint damage, mental health implications, increased healthcare spending and shortened life span (Luca and Feldman 2014). As paediatric providers and advocates for paediatric health in 2023, we cannot remain passive or complacent in the current state of paediatric drug regulation.

**FIGURE 1.** The lack of paediatric regulatory authority

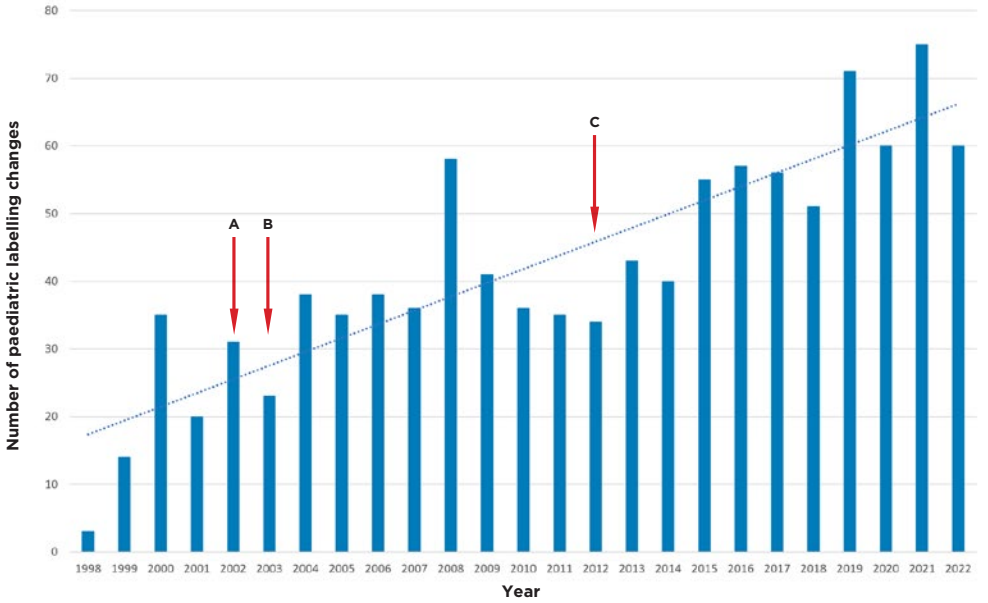



The lack of intentional focus on paediatric drug labelling and regulatory sciences causes great harm. Firstly, when a drug undergoes regulatory review in Canada, the potential paediatric populations that might use or benefit from this drug are not considered. This leaves many paediatric patient populations without adequate pharmacokinetic, safety or efficacy data and results in widespread off-label drug use. This off-label use leaves prescribers to surmise the best indications and dosing and leaves parents worried about the adequacy of prescribing premise and safety. Secondly, because children are not considered in the Canadian regulatory review, the importance of the availability of diverse and appropriate drug formulations is not considered. Without access to liquid, minitab or dissolvable formulations for the youngest children and children with developmental differences, Canadian providers and pharmacists are forced to compound drugs. The common use of compounded formulations leads to unanswered questions in the bioavailability and consistency of drug dosing. Finally, and very importantly, Canadian drug labels increasingly do not match the drug labels of our peer countries. This mismatch leaves Canadian children uniquely vulnerable to drug efficacy and toxicity issues that are being actively addressed in trusted jurisdictions.

There are some positive stories from peer countries regarding paediatric regulation. The US FDA has experienced great success in increasing the number of paediatric drug labels in the past 20 years based on innovative congressional lawmaking and intentional collaboration between regulators, funders, scientists and sponsors. As displayed in Figure 2, there have been steady increases in the number of drugs with paediatric labelling in the US since 2002. The FDA has a strong and thriving Office of Pediatric Therapeutics and increasingly has paediatric expertise on each of its many review committees. In recognition that many off-label drugs commonly used on children are older and off-patent, the Eunice Kennedy Shriver National Institute of Child Health and Human Development funds the Pediatric Trials Network (PTN; https://pediatrictrials.org/), which started in 2010. The regulatory-ready

clinical trials network uses the list of paediatric priority drugs identified through the *Best Pharmaceuticals for Children Act* (Ward 2023), and designs and executes clinical trials toward drug labelling. Since its inception, the PTN has submitted paediatric data for 26 products to the FDA and facilitated 18 paediatric label changes. The PTN uses key modern research approaches to facilitate paediatric drug research including advanced pharmacokinetic modelling methods, opportunistic sampling, real world data integration from electronic health records and pragmatic study designs.

**FIGURE 2.** Increasing paediatric drug labels by the FDA and the key regulatory landmarks that facilitated improved paediatric labelling




Arrow A: *Best Pharmaceuticals for Children Act (BPCA)* (2002) (NIH n.d.)
Arrow B: *Pediatric Research Equity Act (PREA)* (2003) (US FDA n.d.)
Arrow C: *The Food and Drug Administration Safety and Innovation Act (FDASIA)* (2012) (US FDA 2018) – permanently reauthorized BPCA and PREA

FDA = Food and Drug Administration.
*Source:* US FDA 2023.

Importantly, there are some deficiencies in current US paediatric regulations that are leading to the consideration of novel laws and approaches. For example, drugs that undergo FDA review in the category of orphan drug designation are exempt from the requirement of drug research plans in paediatric population. Specifically, the *Pediatric Research Equity Act* (Ward 2023) contains an exemption from paediatric research requirements for drugs for orphan diseases. This exemption was not problematic 10 years ago, but in the current drug approval landscape where approximately two-thirds of new drug approvals are through this orphan-drug-designation pathway, children are again increasingly left behind. In addition, although paediatric study plans are required at the time of new drug applications and new indication applications, there is no reliable consequence if sponsors do not actually complete the paediatric research plans as promised. Newer regulations that remove the paediatric

exemption for orphan drug development and give the FDA more authority to enforce paediatric research plans are required.

## Conclusion

Given the current landscape, what are the next steps to improve paediatric regulatory science in Canada? Public health officials and clinicians together can create social media campaigns to increase public awareness around the lack of paediatric drug labelling and its consequences. These social media and other media educational messages should be targeted toward Canadian parents, caregivers, patient advocacy groups and community-based organizations. Without adequate knowledge of the lack of current regulations in paediatric drug development, Canadian parents and caregivers are not empowered to advocate for change and to demand improved regulations to protect their children. A recent example of such an educational campaign is provided in the COVID-19 public health messaging. Funded through either the federal or provincial government, plain-language information can be co-developed by physicians, regulators and public health agencies and shared broadly across multiple platforms. With increased awareness, parent and community advocates can increase public dialogue around the importance of these issues during election cycles and other policy-making opportunities.

Next, the Canadian government can make investments in developing a robustly staffed and dedicated "Office of Paediatric Therapeutics" at Health Canada and develop partnerships with paediatricians across the country to provide expertise and guidance to this office. A key to success in advancing paediatric drug labelling will be the ability of this new office to identify key knowledge gaps and partner with research funders and the academic community to fill those gaps to facilitate paediatric drug labelling. For example, if there are certain paediatric populations where the trial methodology needs to be improved or if specific safety and efficacy data that are key to drug labelling are lacking, this office can partner with the Canadian Institutes of Health Research to create specific calls for research funding opportunities to address these gaps. Health Canada can develop or strengthen ongoing relationships with funders and academic scientists to intently focus on advancing regulatory science and innovative clinical trial design in paediatric drug development. The success of this office could be measured in multiple ways including its facilitation of new regulatory pathways for paediatric drug labelling, a quantifiable increase in drugs labelled for children in Canada and an increase in scientific grant funding earmarked for clinical trial innovation and regulatory-rigour paediatric drug trials.

Finally, Health Canada can continue international partnerships including participation in the "Paediatric Cluster," which includes regular international paediatric coordination calls, allowing drug regulators from the US, Europe, Japan and Canada to streamline and coordinate paediatric drug development plans (US FDA 2022). In this forum, regulators from the newly created Office of Paediatric Therapeutics will have up-to-date knowledge of international paediatric drug development programs that are under design or ongoing, and can

understand what Canadian-specific issues will hinder or facilitate labelling of new products for children. Based on this knowledge of potential barriers for new drug classes or entities, regulators can partner with lawmakers to ensure adequate innovation in drug labelling pathways to keep Canadian paediatric drug labelling current with international peers.

It is possible to overcome injustice. Naming the problem and quantifying the impact is an important early step, and Health Canada has started doing so with ongoing efforts, such as creating a "National Priority List of Pediatric Drugs" (Government of Canada 2023). Parents, healthcare providers, child health advocates, medical societies, patient advocacy groups, regulators, funders and sponsors, all have an important role to play in improving the state of paediatric drug labelling regulations in Canada.

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