

Time for a regulatory framework for pediatric medications in Canada

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Children are currently underserved by drug approval regulations in Canada. They need medications that they can easily swallow, are adequately studied in their age group, are safe and effective, allow dosing flexibility and contain safe nonmedicinal ingredients. At present, these requirements are not fully met. We discuss how Health Canada's regulatory reform should include pediatric-focused prescribing considerations.

An estimated 50% to 80% of all medications prescribed to children in Canada are given off label, as their use deviates from the dose, age, route of administration, formulation or indication described in the product monograph.¹⁻³ For young children, the commercial preparation (often a tablet for adults) has to be modified for administration, a practice called compounding. Compounded formulations prepared at the pharmacy or the patient's home are not in keeping with pharmaceutical manufacturing standards, and have the potential to cause patient harm.^{4,5} A recent study showed that only 47% and 28% of product monographs of newly approved medications in Canada have pediatric-specific information and indications, respectively.⁶ Another Canadian study at a tertiary pediatric hospital showed that 48% of frequently compounded medications were commercially available as child-friendly formulations in the United States or European Union.⁷

Both the US and EU have implemented pediatric-targeted policies over the past 2 decades to promote clinical drug research involving children to ensure safe, evidence-based pediatric drug labelling and to encourage the development of pediatric formulations. When pediatric use of a product is anticipated, the US Food and Drug Administration (FDA) requires a pediatric study plan as a prerequisite to a new drug application. Similarly, the European Medicines Agency (EMA) mandates that sponsors complete a pediatric investigation plan before their application for market authorization. Both the FDA and EMA also have incentives to promote the development of pediatric medications and formulations.^{8,9} Between 2007 and 2015, both the EU and US had twice as many new pediatric medications approved, and 32% and 62% more new pediatric indications, respectively, than Canada.¹⁰ Incentives and legal obligations have strongly affected the submission of pediatric data for appropriate labelling.^{8,10} For

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.

instance, between 1998 and December 2021, the labels of 967 medications in the US were updated to include pediatric information, mainly to comply with legal requirements.¹¹

In contrast to the US and EU, Canada does not have a purposeful regulatory framework for pediatric drug approval. For existing medications (both off- and on-patent), the current framework does not authorize Health Canada to request manufacturers to update product monographs when pediatric efficacy or safety data are available, and does not provide incentives to encourage manufacturers to market pediatric formulations that exist in other trusted foreign jurisdictions. For new drug submissions, manufacturers are not obligated to seek pediatric indications, nor to develop pediatric formulations when pediatric usage is anticipated. Incentives are few and limited to new medications, with a potential additional 6-month extension of data protection for manufacturers conducting pediatric clinical trials.¹² As a result, many medications submitted for approval in Canada are for adult use only, even when the same medications are approved for pediatric use or provided in child-friendly formulations in other jurisdictions.

Numerous cases illustrate substantial differences in the availability of pediatric information and formulations in Canada compared with the US and EU. Levetiracetam, an antiepileptic drug that is commonly prescribed for children, was approved for pediatric use in Canada only in 2019, along with a child-friendly formulation, whereas a pediatric indication was granted in the US and EU 14 years earlier, with a marketed oral solution suitable for children. Intravenous injection of abatacept was approved to treat adult and juvenile rheumatoid arthritis in Canada in 2006 and 2008, respectively; the subcutaneous formulation was approved for use in adults only in 2013. In the US and EU, the subcutaneous injection was approved for children in 2017 and 2019, respectively, but the Canadian label still states that subcutaneous injection of abatacept has not been studied in children. As a consequence, many children in Canada endure monthly intravenous infusions of abatacept, as the lack of pediatric approval prevents public reimbursement of the subcutaneous route. Similarly, sofosbuvir tablets for treatment of hepatitis C are still indicated only for adult use in Canada, lagging the US and EU, where sofosbuvir was approved for use in children 12 years of age and older in 2017, and for children as young as 3 years in 2020, based on studies in these populations. A pediatric formulation of oral pellets for younger children is also available in both jurisdictions. Despite this, the pediatric section of the Canadian label states that sofosbuvir's safety and effectiveness have not been established in pediatric patients.

Health Canada is currently developing a regulatory innovation for health products, the agile licensing for drugs,¹³ which has the potential to address some of these problems. In general, these new regulations aim to better support the oversight of drugs, both before and after sale, and to improve safety by better communicating the risks and benefits of drugs, introducing more enforcement powers for Health Canada and developing tools to manage risks and uncertainties. These regulations will increase harmonization of data requirements across various jurisdictions and, in certain situations, allow marketing in Canada once approval is obtained by a trusted regulator, with only a limited review by Health Canada. The use of trusted foreign reviews and decisions to streamline Health Canada's approval of pediatric indications and formulations would be a tangible and welcome solution. The new agile regulations are wide in scope and the details of how and to what extent they will benefit pediatric pharmacotherapy for existing and new medications remain to be seen. Key success factors must include unique considerations (e.g., pathways, fee structures) for pediatric submissions, including pediatric formulations and indications.

Ideally, Health Canada's regulatory reform will include 3 elements to ensure optimal access to on-label, high-quality manufactured pediatric medications and to improve care for children. First, for new drug submissions with anticipated pediatric use, a manufacturer should either be required to submit pediatric data, along with child-friendly formulations (if available), or a pediatric study plan. Pediatric files submitted to regulators in other countries should be included, as these data are readily available to manufacturers. For approved and on-market medications, the new framework should allow Health Canada to request label changes to address actual (or potential) safety or efficacy concerns associated with incomplete labelling or to address the lack of pediatric formulations. An expert pediatric advisory board could support Health Canada with these

pediatric-specific processes. Second, incentives to prompt manufacturers to submit new pediatric indications and formulations should be offered, in addition to the existing 6-month extension for data protection, which falls short for off-patent medications. Third, 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 some form of protection for medications identified as meeting a critical need.

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,² it is time for action. Health Canada's ongoing reform to create a more agile system is an unprecedented opportunity to ensure that children in Canada have the same access to new medications and pediatric formulations as those in other countries, and to guarantee that the most up-to-date pediatric information is included in Canadian drug labels. Children deserve the same regulatory standards as adults.

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