Title:
Where are we with pediatric drug data in Canadian drug monographs? A descriptive analysis

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Acknowledgements:
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Funding statement and declaration of authors' competing interests:
The authors received no financial support for the research, authorship, and/or publication of this article, and report no conflicts of interest in this work.

Abstract

BACKGROUND: Optimal drug therapy in children relies on the availability of pediatric-specific information. European and American legislative initiatives have resulted in the increase in evidence-based pediatric pharmacotherapy data. In Canada, there is no comparable initiatives in place and hence we aimed to describe the quality and quantity of pediatric information in monographs of new drugs approved by Health Canada.

METHODS: The most updated Canadian drug monographs of all new drugs approved by Health Canada from January 2007 until December 2016 were systematically reviewed. We excluded drugs that were withdrawn from the Canadian market.

RESULTS: During this study period, Health Canada approved 281 drugs, 275 of which met our inclusion criteria. Pediatric-specific information and indication were present in 128 (47%) and 76 (28%) of the drug monographs respectively. Only 15 (10%) of all oral drugs were available in child-friendly, age-appropriate dosage forms. The majority of the monographs (228, 83%) were revised in the most recent three years (2016-2018). Of all pediatric age groups, neonates had the lowest number of indications listed in the product monographs (11, 4%).

INTERPRETATION: The majority of new drugs approved by Health Canada do not contain pediatric or neonatal information in their product monographs and therefore are used “off-label”. Canadian children are in need of regulatory mechanisms to promote neonatal and pediatric drug development, and also enhance the submission of pediatric data, by manufacturers, from other jurisdictions. All of which will contribute to safe and effective neonatal and pediatric pharmacotherapy for Canadian children.

Introduction

Optimizing pharmacotherapy in children has been the goal of many American and European governmental legislative initiatives. These initiatives have been introduced to mandate or provide incentives for pharmaceutical companies to conduct studies to assess the safety and efficacy of drugs in the pediatric population, and provide equally rigorous therapeutic information for children as their adult counterparts.[1-3] In the US, the Best Pharmaceuticals for Children Act (BPCA) (2002) and the Pediatric Research Equity Act (PREA) (2003) are some of the legislations that have established incentives and requirements to encourage pediatric drug development. The Food and Drug Administration Safety and Innovation Act (FDASIA) (2012) made the BPCA and PREA into law, with amendments such as a requirement for submission of pediatric study plans by pharmaceutical companies. More recently, in 2017, the Food and Drug Administration Reauthorization Act (FDARA) was signed into law, to facilitate the development and approval of drugs and devices for pediatric populations.[4] In the European Union, the Pediatric Regulation came into force in 2007, and aimed to stimulate the development of pediatric medicines.[5-6] These regulatory initiatives have resulted in pediatric drug trials, with subsequent labeling changes for new and expanded pediatric indications and other safety and efficacy pediatric data.[7]

An increasing gap exists between Canada and other global leaders concerning the advancement in pediatric drug development.[8-9] In Canada, the only legislative initiative to include children in drug development, the Pediatric Extension, was implemented in 2006.[10] This regulation applies for innovative drugs only, and grants a six-month extension to the eight-year period of data protection to manufacturers upon

the provision of pediatric pharmacotherapy evidence within the first five years of drug approval.[10] Considering the lack of regulatory initiatives which potentially impede the availability of evidence-based drug therapy for Canadian children,[7,11] we aim to characterize the current availability of pediatric-specific data and dosing information in Canadian monographs of new drugs approved between 2007 and 2016.

Methods

This study was an analysis of publicly available information in Canadian drug monographs. We identified new active substances (NASs) approved by Health Canada between January 1, 2007 and December 31, 2016 using the Annual Drug Submission Performance reports. NASs represent new chemicals or biological substances that have not previously been approved for sale as a drug in Canada. We excluded NASs that were withdrawn from the Canadian market. Next, we obtained the most recent versions of drug monographs from Health Canada's Drug Product Database (https://health-products.canada.ca/dpd-bdpp/). We reviewed each monograph for the availability and quality of pediatric-specific clinical and dosing information, specifically the presence of pediatric indications, dosing, safety, and pharmacokinetic data, and the availability of pediatric-friendly oral dosage forms (Supplement 1).

We defined a pediatric indication as an approved use in populations younger than 18 years of age. We defined pediatric information as the presence of any data pertaining to the use of a particular medication in children (such as information from studies performed in children) and defined safety information as pediatric-specific warnings, contraindications or adverse effects. We considered oral liquids, granules, or dispersible or chewable tablets formulated specifically for pediatric use to be pediatric-

friendly oral dosage forms. We used the Anatomical Therapeutic Chemical (ATC) classification system to categorize each NAS based on the drug's primary indication and mechanism of action. For monographs that included pediatric data, we recorded the type of study from source of the data with regard to the study design and population.

Four independent reviewers extracted the data and entered it into a REDCap database. To ensure accuracy of the collected data, one investigator checked the first ten drugs reviewed by each abstractor and a random sample (10%) of all remaining drugs. We reported data as counts and percentages and means and standard deviations in all NASs and subgroups of non-biologic and biologic drugs.

Results

Health Canada approved a total of 281 new drugs between 2007 and 2016. We included 275 of these drugs, excluding two with the same medicinal ingredient (nitisinone), and four that were withdrawn from the Canadian market (ezogabine, sitaxsentan, daclizumab, and idebenone). The years with the lowest and highest number of approvals were 2008 and 2013, with 16 and 40 drug approvals, respectively.

Of all monographs, 271 (98%) listed an adult indication. The four with only pediatric indications were three biological products (two vaccines [pneumococcal polysaccharide conjugate vaccine 10-valent adsorbed and human rotavirus live attenuated oral vaccine] and one allogenic stem cell therapy [remestemcel-L]) and one drug for treatment of attention deficit hyperactivity disorder (guanfacine).

NASs belonged to 18 different therapeutic classes (Table 1). The classes with the greatest number of drugs were oncology, infectious disease, and hematology (Table 1). The routes of administration were oral (144, 52%), intravenous (108, 39%), and

topical (23, 8%). At the time of data abstraction, 253 (92%) NAS monographs had been revised since original drug approval, with the large majority (228, 90%) being revised between 2016 and 2018.

Pediatric information, including pediatric-specific indications, dosing, or safety information, was available in 128 (47%) of all drug monographs. Pediatric indications were listed in 76 (28%) of all monographs. The four therapeutic classes with the highest proportion of drugs with pediatric indications were infectious disease (47%), allergy/immunology (43%), endocrine/metabolic (40%), and hematology (39%). None of the drugs in anesthesia/analgesia, dermatology, or urology had pediatric indications (Table 1). Furthermore, no pediatric indication was included in the monographs of drugs approved for critical conditions such as pulmonary arterial hypertension, diabetes, hepatitis C, and invasive systemic infections (Table 2). All monographs with pediatric indications provided pediatric dosing recommendations; however, the majority of the pediatric indications and dosing information pertained to the 12 to 17 years of age (68, 24%) and decreased by age with only 10 (4%) and 1 (<1%) of monographs providing indication and dosing recommendations for term and preterm infants (Figure 1). Only 15 (10%) of the 144 drugs with oral dosage forms were available in a child-appropriate oral formulation.

Pediatric-specific safety information was included in 98 (36%) of all drug monographs**.** Specifically, pediatric-specific adverse effects, warnings and contraindications were present in 76 (28%), 64 (23%), and 14 (5%) monographs, respectively. The source of pediatric information was from studies in exclusively pediatric populations (73, 57%), mixed pediatric and adult populations (35, 27%),

animals (13,10%) and studies on different drugs in the same class (7, 5%). Additionally, in one drug monograph, pediatric information was based on studies exclusively in adults.

Of all NASs, 203 (74%) were non-biologics. In this subgroup of non-biologic drugs, 84 (41%) and 41 (20%) monographs contained pediatric information and indication(s), respectively. The safety information and pediatric-friendly oral formulation were similar to the total NASs (32% and 7% respectively). Availability of dosing information for different pediatric age groups also followed the same pattern as the total NASs (Figure 1). Of the 72 biologic medicinal products, 35 (49%) included a pediatric indication in their most recent labeling, out of which 9 (26%) were vaccines. The non-vaccines biologic medicinal products with pediatric indications belonged to hematology (n= 9), infectious diseases (n=6), endocrine/metabolic (n=5) and oncology (n=3).

The annual percentage of drugs with pediatric indications listed in the most recent drug monographs, did not show any clear pattern of improvement over the 10-year period of the study (Figure 2).

Interpretation

Our findings demonstrate that only one in four drugs approved by Health Canada over a recent 10-year period contain a pediatric indication in their most recent monographs and less than 50% include any pediatric information. Furthermore, when a drug was found to have a pediatric indication along with dosing information, it was most often for the adolescent age group (12-17 years), leaving behind children, infants, and neonates.

Our study reviewed the available data in the most updated monographs of the included drugs with the vast majority of the monographs being updated within the past three years. We did not observe any clear pattern of improvement for the presence of pediatric indications in the newly approved drugs, reflecting either the lack of pediatric efficacy and safety data or failure from manufacturers to submit to Health Canada existing pediatric information available in other jurisdictions. Both underline the importance of a Canadian regulatory framework that requires and incentivizes manufacturers to provide pediatric evidence for any drug with potential use in children, and also the need for a Canadian research environment that supports pediatric drug trials.

Our study included new drugs approved after the implementation of Health Canada's market-exclusivity regulation, with the majority of included drugs having between three to a full five years for provision of pediatric information. The observed consistent lack of pediatric data emphasizes that this market exclusivity incentive is insufficient by itself in Canada's small pediatric market to promote availability of pediatrics data.

Since the first pediatric drug development regulatory initiative by the US FDA in 1997, over 1200 pediatric studies have been submitted to the FDA and 700 drug labels have been revised.[2] We observed only 76 of drug monographs, with a pediatric indication, in Health Canada approved drugs over a recent 10-year period. For almost all drugs with pediatric indications, there was an overlapping adult indication, reinforcing the available evidence that new drug approvals are mainly driven by the adult commercial opportunity[12], leaving Canadian children as therapeutic orphans. We

avoided excluding any drug based on presumption of adult only indication. We chose this approach as evidence has shown many pediatric conditions are treated with medications developed for adults with completely different indications and that in conditions like adult malignancies, considering a drug's molecular mechanism of action, rather than indication, may accelerate drug development in pediatrics.[13] The RACE for Children Act by the FDA, which will come into force in 2020, was signed into law with the aim to promote the development of new anticancer drugs for children.[14] The RACE Act mandates that molecular entities need to be reviewed for the pediatric applicability through their molecular target and the biology of pediatric malignancies rather than the pediatric relevance of their adult indication.[13-14]

Our findings show despite clear advancement in therapeutic options for critical conditions like invasive systemic fungal infections, hepatitis C, methicillin-resistant *S. aureus* infections, pulmonary hypertension, or psychotic disorders for adults, only a few of these newly approved therapeutics contained pediatric indications and none had any neonatal information. This finding is concerning as such health conditions are associated with major morbidity and death and also financial burden on neonatal and pediatric health care.[15]

There is evidence for a systematic delay in submission of new drugs to Health Canada, up to two years, as compared to regulatory authorities in United States and Europe.[11] The delay in submission by large pharmaceutical companies would mean the available pediatric data is not readily accessible in Canada. Furthermore, given the observed paucity of pediatric indications in our studied drugs, it is unclear to what degree the available pediatric information ultimately reaches the Canadian drug

monographs. This delay in the new drug submission is primarily due to Canada being a small market and the regulatory and reimbursement processes being complex without any pediatric specific pathways or fee structures. Health Canada does not have any mandate to solicit pediatric data proactively from a manufacturer and therefore this creates a gap in the number of pediatric indications included in the product monographs, as supported by this study. The ability of Health Canada to proactively require the submission of pediatric data from manufacturers combined with appropriate incentives would be a significant step to rectifying this situation.

Critically ill infants hospitalized in neonatal intensive care units, are exposed to a large number of medications, the majority of which do not have safety, efficacy and dosing information and the few available options are known to be impacted by a serious risk of drug shortage.[16-17] Our results demonstrate that neonates remain pharmaceutical orphans with less than 5% of all newly approved drugs providing any neonatal indications, and only one drug providing indications for premature infants. This finding calls for action as premature infants have the highest number of reported adverse events among children and almost every pediatric drug development advocacy document uses the vulnerability of this population as a non-deductive argument in support of critical need for pediatric drug studies.[18]

We have found that 90% of the drugs with oral dosage forms had unmet pediatric formulation needs. This unmet formulation needs in pediatric patients results in manipulation of adult pharmaceutical forms for use in children which can cause medication errors as well as safety and toxicity issues, especially in premature neonates.[19] Additionally, many adult formulations are not palatable to children. Child-

friendly, age-appropriate drug formulation is an essential part of pediatric pharmacotherapy and the new pediatric regulatory environment in the US and Europe has resulted in a global collaboration to strengthen its development.

The past 20 years have shown the clear advancement of pediatric drug development worldwide. The United States and Europe's regulatory authorities and the pharmaceutical industry collaborate closely to ensure appropriate assessment of drug safety and efficacy in children across all age groups. Furthermore, the significant advancement in the science of extrapolation and the availability of real-world data have enhanced the efficiency and feasibility of pediatric drug trials.[20] Canada is currently not part of this global alignment which, and based on our results, there is a great need for Canadian children to be at par with children in other developed countries.

The American and European governmental initiatives which mandate and monitor pediatric medicine research, provide a useful framework for Canadian legislators. As the drug approval process in Canada is primarily industry-driven, regulatory mandates for pediatric drug development should come into force in order to increase the data contained in regulatory submissions when use in children is expected. In addition to a sustained investment for advancement of pediatric medicine research, a mandate should be given to the Canadian federal research funding agencies to provide dedicated specific funding, such as what is currently done in the United States and Europe.

This study has some limitations. We were not able to analyze the inclusion of pediatric data when the product was first submitted to Health Canada as only the most recent product monographs were available. This however, provided us with the most

current available information for Canadian children. A comparison of availability of pediatric information or indication of the studied drugs in their FDA and EMA labeling was also not available for the current study. Strengths of this study include broad inclusion criteria, over a 10-year period which can provide a complete description of new drug approval in Canada.

Conclusion

Newly approved drugs in Canada lack important pediatric drug information and rarely offer pediatric-friendly dosage formulations, perpetuating “off-Label” drug use in this vulnerable population. In order to provide Canadian children with safe and effective drug therapy, Canadian regulatory mechanisms are needed to ensure submission of pediatric data and formulations by manufacturers when use in children is anticipated. Such regulations will promote the neonatal and pediatric drug studies and enhance the inclusion of existing pediatric information in the Canadian drug monographs. All of which contribute to optimal neonatal and pediatric pharmacotherapy in Canadian children.

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Table 1: Pediatric-specific indication, and child-friendly, age-appropriate oral dosage forms for new drugs by therapeutic drug class.

	Number of NAS				
Therapeutic class	**NAS approved**	**Pediatric indication (all)***	**Non-biologics approved**	**Pediatric indication (non-biologic)****	**Pediatric-friendly oral dosage form(s)*****
Oncology	54 (20%)	4 (7%)	36 (18%)	1 (3%)	**0**
Infectious Disease	38 (14%)	18 (47%)	32 (16%)	12 (38%)	3 (14%)
Hematology	28 (10%)	11 (39%)	14 (7%)	2 (14%)	1 (10%)
Endocrine/ Metabolic	25 (9%)	10 (40%)	18 (9%)	5 (28%)	3 (21%)
Allergy/ Immunology	23 (8%)	10 (43%)	9 (4%)	1 (11%)	1 (20%)
Cardiology	18 (6%)	2 (11%)	15 (20%)	1 (7%)	1 (7%)
Neurology	17 (6%)	5 (29%)	16 (8%)	5 (31%)	3 (23%)
Pulmonology	15 (5%)	5 (33%)	13 (6%)	5 (38%)	1 (17%)
Gastrointestinal	11 (4%)	3 (27%)	10 (5%)	2 (20%)	1 (13%)
Ophthalmology	10 (4%)	2 (20%)	8 (4%)	2 (25%)	**0**
Psychiatry	10 (4%)	2 (20%)	10 (5%)	2 (20%)	**0**
Rheumatology	8 (3%)	1 (13%)	4 (2%)	**0**	**0**
Obstetrics/ Gynecology	5 (2%)	1 (20%)	5 (2%)	1 (20%)	**0**
Anaesthesia/ Analgesia	3 (1%)	**0**	3 (1%)	**0**	**0**
Dermatology	3 (1%)	**0**	3 (1%)	**0**	**0**
Diagnostic imaging	3 (1%)	1 (33%)	3 (1%)	1 (33%)	**0**
Nephrology	2 (1%)	1 (50%)	2 (1%)	1 (50%)	1 (50%)
Urology	2 (1%)	**0**	2 (1%)	**0**	**0**
Total	**275**	**76**	**203**	**41**	**15**

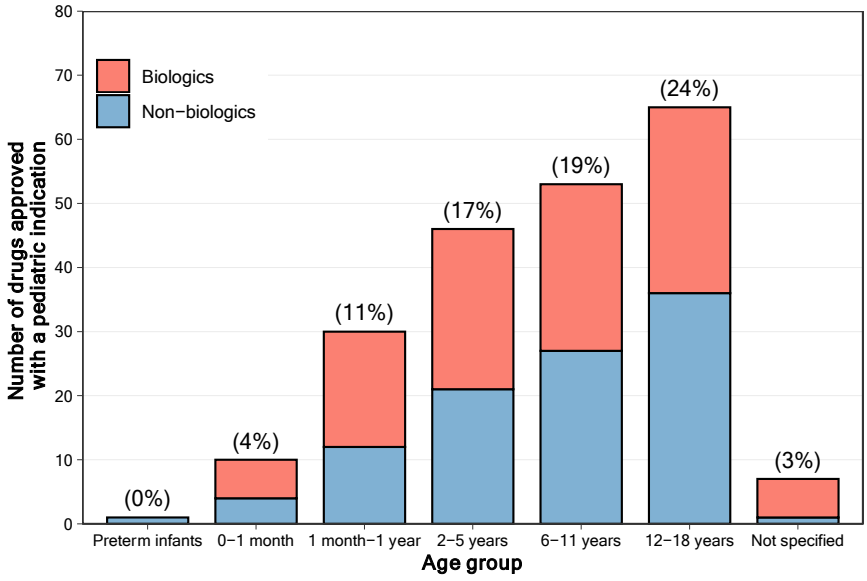
*Percentage expressed of all NAS in therapeutic class
**Percentage expressed of all non-biologic NAS in therapeutic class
*** Percentage expressed of all drugs which were available in oral dosage forms
NAS: New active substances

Table 2: Pediatric drug approval by therapeutic class and age group

Therapeutic class	Age group						Total	Examples of indications of approved drugs with no pediatric data
	12 – 18 y	6 – 11 y	2 – 5 y	1 mo – 1 y	Neo-nates	Age not specified		
Allergy/ Immunology	9	8	8	4	0	1	10	Crohn's disease, plaque psoriasis, seasonal allergic rhinitis, systemic lupus erythematosus, ulcerative colitis,
Anesthesia/ analgesia	0	0	0	0	0	0	0	Intensive care unit sedation, severe pain, topical analgesia
Cardiology	2	1	0	0	0	0	2	Arrhythmia, dyslipidemia, hypertension, pulmonary arterial hypertension
Dermatology	0	0	0	0	0	0	0	Actinic keratosis, basal cell carcinoma, eczema, rosacea
Diagnostic Imaging	1	1	1	1	1	0	1	Hepatic or cardiac vascular imaging
Endocrine/ Metabolic	10	10	10	9	4	0	10	Cushing's syndrome, diabetes
Gastro-intestinal	2	2	2	1	0	0	3	Chronic idiopathic constipation, opioid-induced constipation, nausea/vomiting,
Hematology	8	7	7	5	3	3	11	Anemia, embolism treatment and prevention, hemostasis, stroke prevention, thrombocytopenic purpura, polycythemia vera
Infectious Disease	17	13	10	8	2	0	18	Hepatitis C, human immunodeficiency virus, invasive systemic fungal infections, methicillin-resistant *Staphylococcus aureus* infections
Nephrology	1	1	0	0	0	0	1	Hyponatremia
Neurology	3	3	2	0	0	1	5	Parkinson's disease, dementia, partial-onset seizures, restless leg syndrome, relapsing remitting multiple sclerosis, reversal of neuromuscular blockade
Obstetrics/ Gynecology	1	0	0	0	0	0	1	Uterine fibroids, vasomotor symptoms associated with menopause
Oncology	4	4	3	2	1	0	4	Acute lymphoblastic leukemia, breast cancer, chronic lymphocytic

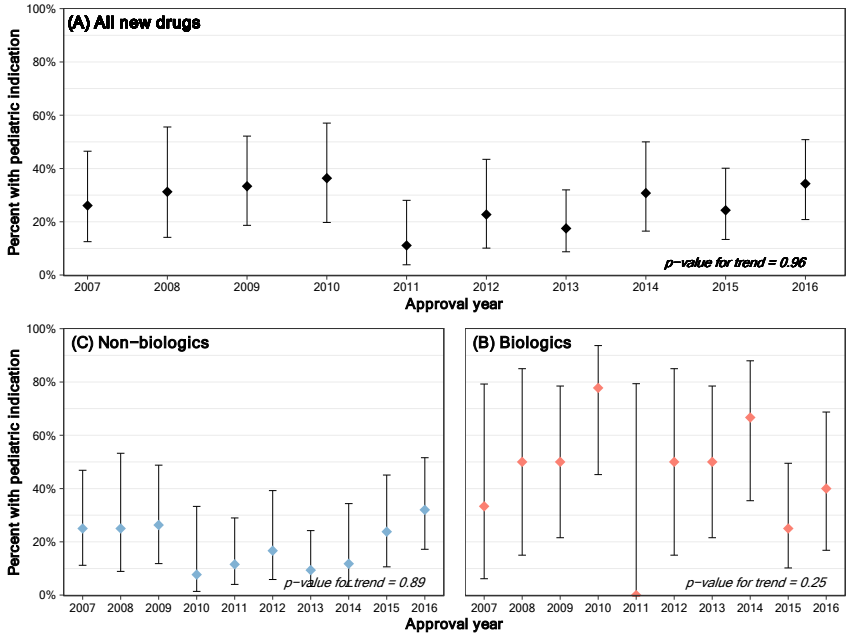
								leukemia, chronic myelogenous leukemia, colorectal cancer, gastric cancer, hepatocellular carcinoma, leukemia, lymphoma, melanoma, multiple myeloma, non-small-cell lung carcinoma, ovarian cancer, renal cell carcinoma, soft tissue sarcoma, prostate cancer
Ophthal-mology	2	2	2	1	1	0	2	Actinic keratosis, age-related macular degeneration, ocular pain, open angle glaucoma, postoperative inflammation
Psychiatry	2	0	0	0	0	0	2	Anxiety, maintenance of alcohol abstinence, antipsychotics, major depressive disorder
Pulmonology	5	3	2	0	0	0	5	Chronic obstructive pulmonary disease, chronic bronchitis, emphysema, asthma, idiopathic pulmonary fibrosis
Rheuma-tology	1	1	1	0	0	0	1	Gout, psoriatic arthritis, rheumatoid arthritis
Urology	0	0	0	0	0	0	0	Benign prostatic hyperplasia, overactive bladder

Figure 1: Age-specific pediatric indications for 275 new drugs approved by Health Canada (2007-2016).



The number in parenthesis shows the percentage of all drugs with a pediatric indication in each age category. Cochran–Armitage test for trend $p < 0.001$.

Figure 2: Percentage of 275 new drugs approved by Health Canada with a pediatric indication (2007-2016).



Error bars show the 95% confidence interval for the percentage. P-values from Cochran–Armitage tests for linear trend.