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Position Statement

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Improving paediatric medications: A prescription for Canadian children and youth

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A joint statement of the Canadian Paediatric Society and the Rosalind and Morris Goodman Family Pediatric Formulations Centre of the Centre Hospitalier Universitaire Sainte-Justine. **The complete statement is available at www.cps.ca.**

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EXECUTIVE SUMMARY

Children have a right to the highest attainable standard of health, including the appropriate treatment of disease (1). Yet children and youth continue to be under-represented in medication research (2,3), the design of medication-related regulations, and commercial product development (4).

Policies governing the development, approval, and reimbursement of medicines are largely designed for adult populations, neglecting the unique characteristics of paediatric patients. Research funding for adult diseases is frequently prioritized over childhood illness as the current capacity for, feasibility of, and expected commercial benefit from adult-focused research is presumed greater (5–7). New medicines are often evaluated and brought to market based on principles of adult physiology and adult return-on-investment benchmarks, without consideration for the developing child (8). Consequently, children have fallen behind adults, and Canada has fallen behind other nations, with respect to safe and effective medications (9).

Up to 80% of all medications currently prescribed in Canadian paediatric hospital settings are administered 'off-label', meaning that use deviates from the dose, route of administration, patient age, and/or indication in the Health Canada-approved monograph (10–12). Moreover, many commonly prescribed paediatric medications must be extemporaneously compounded, as child-friendly formulations (e.g., oral liquids) are not commercially available. Both off-label prescribing and compounding are associated with significant risk, including adverse reactions and efficacy concerns (13,14).

In 2016, the Canadian government announced a significant review of federal regulatory policy (15). This commitment provides a unique opportunity to rectify long-term system shortcomings, as well as strengthen and streamline the safety and availability of paediatric medications for the future.

Governance: The need for expert paediatric leadership

The federal government should establish a permanent, dedicated, appropriately funded Expert Paediatric Advisory Board (EPAB) to review, guide, co-ordinate, and align activities related to paediatric medication approvals, associated clinical research, and reimbursement activities.

The EPAB should be situated at the portfolio level and report directly to both the Minister and Deputy Minister of Health. EPAB should include leadership from paediatric clinical, academic and administrative domains. Parent and patient engagement should be deliberate and inform both priority setting and decision making.

Regulatory and reimbursement systems: The need for process redesign

Currently, Health Canada may request, but does not require, manufacturers to submit paediatric data or apply for a paediatric indication, when a submission is filed. In accordance

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with international best practices, Health Canada should proactively solicit paediatric-specific data for all submissions where paediatric use is expected or anticipated.

Health Canada should also explore financial incentives to encourage submissions for paediatric medications, including off-patent medications. By their nature, off-patent medications do not benefit from market exclusivity provisions or intellectual property protections, eliminating powerful market motivators. A regulatory approach that incentivizes manufacturers to expand access to effective off-patent paediatric products is required.

Where additional clinical data are required to support a paediatric submission, Health Canada should work with research funding partners to ensure paediatric drug research, including clinical trials, drug registries, and/or postmarket studies, are adequately supported. In parallel, Health Canada is encouraged to develop, apply, and evaluate novel methods and evidence standards that are sensitive to children and youth (16,17). Aligning health policy with health research funding is essential to address clinical gaps and optimize impact across all systems.

Clear and transparent paediatric-specific guidance on regulatory and reimbursement processes must be developed. Health Canada should engage in regular dialogue with manufacturers when questions arise regarding regulatory processes, and with reimbursement agencies when establishing paediatric-specific benchmarks. Clarity of process, and appropriate Health Technology Assessment (HTA), will lower barriers, costs and uncertainty, attracting paediatric submissions to Canada.

Lastly, regulatory modernization efforts will be met with limited success if HTA agencies do not undergo simultaneous reforms. To that end, paediatric experts must advise ongoing activities at CADTH and INESSS, as well as federal pricing bodies. This should be a responsibility of EPAB, and the Board should be empowered to align regulatory, HTA and reimbursement policy standards.

Child-friendly formulations: The need to expand commercial access

Ideally, child-friendly formulations should be commercially available for all medications necessary to care for Canadian paediatric patients. Achieving this goal requires the commercialization of paediatric formulations available in trusted foreign jurisdictions, as well as investments in new commercial formulations. Moreover, manufacturers should be encouraged to develop novel paediatric drug delivery systems (i.e., minitabs) (18). These innovations have the potential to translate into safer, more accurate, and acceptable drug administration in children.

Evidence-informed prescribing: The need for safe and accessible prescribing guidance

Ideally, product monographs should contain complete prescribing information for all relevant patient groups, including children and youth, and should be updated as evidence becomes available. Unfortunately, many monographs are outdated, and industry is neither compelled nor incentivized to update them (19).

At present, there is no single, comprehensive, evidence-informed, continuously updated accessible resource on which prescribers and dispensers can base decisions for paediatric patients. A national reference for paediatric medicines, including compounding standards, is necessary to optimize best practice prescribing for common paediatric conditions, reduce variation in treatment, and ensure effective knowledge sharing for emerging therapies in paediatric rare disease (20). This online resource should enable real-time reporting of adverse events associated with both commercially available and compounded medications. Once reported, postmarket trends should be examined for both recognized and off-label uses, facilitating the collection of real-world evidence (21) for the evaluation of medicines throughout their lifecycle.

Paediatric research: The need for dedicated focus, funding, and innovative research design

Federal research budgets should include dedicated portfolios for paediatric drug research proportionate to the population size and reflecting the anticipated return on investment from child-focused inquiry (22).

To enhance research efficiency, barriers to conducting paediatric clinical trials should be removed, including efforts to reduce unnecessary duplication in multijurisdictional Research Ethics Board reviews, enhance research sharing platforms, and establish standards for the pooling and comparability of data. Health Canada should remove impediments associated with studies utilizing off-label yet evidence-based medications, actively relabeling these off-label drugs that are foundational to paediatric clinical trials. Importantly, with organized and sustained investment in national paediatric clinical trials infrastructure, such as that built by the Maternal Infant Child Youth Research Network (MICYRN), Canada will be positioned to serve as an international leader in paediatric research, attracting both commercial-led clinical investigation and large-scale private–public partnerships.

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Potential Conflicts of Interest: AG reports receiving payments from IQVIA, Pharmascience, Leon Nano Drugs and Rare Disease Therapeutics. JA reports that she is part of a Data Safety Monitoring Board and an Adjudication Committee for a clinical trial in children, for which Astellas is the sponsor. For this activity, she has received financial compensation. AD reports that he is a pCODR expert member for the Canadian Agency for Drugs and Technologies in Health. YF reports participating in a ZoLi clinical trial. EG is CEO of Children's Healthcare Canada and Executive Director of Paediatric Chairs Canada. SI received fees from AbbVie in 2017 and is receiving a grant from UCB Pharma. DL is on the Board of Directors of the Ontario Rheumatology Association and the Canadian Rheumatology Association and receives honoraria. She also receives Advisory Board honoraria from Amgen. She is also an investigator for clinical trials with UCB, GSK and Janssen. SM reports receiving payments from Ontario Genomics, Genome Canada; Reformulary Group; Innovative Medicines Initiative and Apopharma. SPM reports receiving payments from various legal firms unrelated to the manuscript for providing expert opinion in regards to causation of neonatal brain injury. He also reports research grants unrelated to drug development from CIHR, OBI, Kids Brain Health Network, CP Alliance. MP has received payments from the Canadian Association of Pediatric Nephrology, Royal College of Physicians and Surgeons of Canada and the International Pediatric Nephrology Association. BP reports that he is Member of Clinical Advisory Board, Shoppers Drug Mart. MR is a Scientific Advisor for Adept Diagnostics. CL states that contracts between Goodman Pediatric Formulations Centre and Pharmascience Inc, Leon-Nanodrugs GmbH, Rare Disease Therapeutics Inc support pediatric formulation submissions to Health Canada (Systematic review, Pediatric Formulation Development Plan (PERFORM), Pediatric Market and Clinical Assessment (PMCA)). She reports that the GPFC has received financial payments for the work done according to contracts but that she has not received any personal honoraria or salary from the GPFC. GJ, TL-M, LLD, MO and CMH have no conflicts to declare.

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