August 23, 2023

Centre for Policy, Pediatrics and International Collaboration
Biologic and Radiopharmaceutical Drugs Directorate
Health Products and Food Branch
Health Canada

VIA EMAIL

To Whom It May Concern:

On behalf of our seven national child and youth health organizations, we are writing to thank you for the opportunity to provide feedback on the *Draft guidance document on submitting pediatric studies and pediatric development plans* to Health Canada. This draft guidance has been eagerly awaited by the entire paediatric community and we commend Health Canada, and its dedicated staff, for its continued commitment to implementing a comprehensive paediatric regulatory framework. This guidance document represents a significant step forward in the agency's efforts to address the longstanding regulatory deficiencies in the paediatric drug space, and we believe that it will serve as a valuable tool to improve both access to and the safety of paediatric medications for all children and youth in Canada. As leaders in the paediatric community, we congratulate you on achieving this milestone.

With respect to the current draft guidance, we specifically commend Health Canada for electing to support an option to accept either the U.S. Food and Drug Administration (FDA) initial Pediatric Study Plan (iPSP) or the European Medicines Agency (EMA) Pediatric Investigation Plan (EU-PIP) as a Pediatric Development Plan (PDP). This aligns with the work of comparable, small-market regulators, and enables important, ongoing global harmonization initiatives in this space. Accepting plans approved in trusted foreign jurisdictions will significantly reduce the potential for friction from current or future sponsors that may arise in response to this data request but will not impair Health Canada's ability to assess critical paediatric information. Importantly, accepting plans without a separate review is an approach that has been implemented in Switzerland with success. Overall, the risks of not having iPSPs and/or EU-PIPs submitted due to the burdens associated with additional review appears to significantly outweigh the potential risks of accepting these plans as submitted. With the aim of guidance focused on increasing the number of evidence-based, on-label paediatric medications in Canada, we are heartened by and fully support this approach.

We do, however, have some significant concerns related to the current version of the draft guidance. With an eye to optimizing the ultimate positive impact of this initiative, we respectfully offer the following recommendations:

Recommendation 1: Expedite the regulatory changes necessary to mandate the submission of PDPs and paediatric data in all drug submissions when paediatric use of a medication can be expected or anticipated.

There is unanimous agreement in the Canadian paediatric community that reducing our dependence on off-label prescribing is an urgent priority. The current draft guidance offers a voluntary pathway for sponsors to submit paediatric studies and study plans with a new drug submission (NDS) or a supplement to a new drug submission (SNDS). While this policy clearly demonstrates an interest on the part of Health Canada to increase the number of drug submissions that include paediatric-specific data, in the absence of a mandate, we fear that the voluntary policy will not measurably increase the number of submissions that include this critical paediatric information.

Definitive evidence from leading jurisdictions has demonstrated that voluntary submission systems are ineffective[1], and they have therefore implemented mandatory paediatric data submission policies to ensure sponsors submit safety and efficacy information for drugs expected to the used in the paediatric population in a timely manner. Learning from decades of international experience, to meaningfully "move the needle" on off-label prescribing, the submission of paediatric data must be a requirement in Canada.

While we recognize the importance of a policy pilot, we feel strongly that this voluntary model must transition to a mandatory system within a set timeframe. To that end, we ask for your commitment to implement regulations that require paediatric data submission within a maximum of 24 months from the launch of the pilot. Appreciating the time-intensive nature of regulatory reform, we also ask that the voluntary system remain in place until the mandatory submission requirements are in place.

Canada's current regulatory framework remains more than two decades out-of-step with international best practices with respect to ensuring access to safe and effective paediatric medications. We urge Health Canada to prioritize this critical component of the Pediatric Drug Action Plan (PDAP) and mandate the submission of paediatric data in all drug submissions when paediatric use of a medication can be expected or anticipated.

Recommendation 2 - Develop a comprehensive plan to communicate the details of the policy pilot to sponsors, including explicit references to: (1) the PDAP (in the overview section of the guidance document), and (2) existing incentives that can accompany participation in the pilot program.

Given that participation in the policy pilot is voluntary, and is not accompanied by any new, paediatric-specific, industry-focused incentives, we are concerned that engagement with the guidance document will be low. In light of these significant limitations, and in order to optimize uptake of this policy pilot, it will be essential for Health Canada to generate a robust communication plan that outlines: (1) the objectives and importance of this initiative, (2) Health Canada's broader paediatric drug strategy (including, but not limited to, the intention to transition to a regulation framework that requires

[1] Gilpin A et al. Time for a Regulatory Framework for Pediatric Medications in Canada. CMAJ 2022 May 16; 194:E678-80. Doi: 10.1503/cmaj.220044

mandatory paediatric data submission), and (3) any available incentives that may accompany participation in the pilot program.

Over the last several years, Health Canada has invested significant time and resources in the development of a comprehensive PDAP. The PDAP reflects the shared aims of Health Canada and the paediatric community, and the policy pilot supported by the draft guidance is one of the key initiatives of this ambitious plan. We feel it is a missed opportunity to not highlight to sponsors that this policy pilot is a part of a broader program of work designed to ensure that children and youth in Canada have access to the medications that they need in age-appropriate formulations. The overview of the guidance document should include a link to the PDAP, as well as information outlining the planned transition of this voluntary guidance to a mandatory paediatric data submission requirement. By promoting the PDAP, and by clearly embedding this work in the larger set of initiatives underway, Health Canada will better communicate the importance of the policy objectives and, by extension, signal to sponsors the importance of complying with the guidance.

Major concerns remain that the absence of paediatric-focused industry incentives will significantly diminish engagement with the pilot program. Ideally, this pilot policy should include specific incentives for sponsors to generate and submit paediatric data. At present, the only paediatric-specific incentive available to industry is a six-month paediatric data extension, an incentive which has fallen short of desired expectations. In parallel with the launch of this policy pilot, we strongly encourage Health Canada to develop and implement additional paediatric incentives to remove all barriers to the submission of robust paediatric data, including opportunities to align regulatory review with health technology assessment and to streamline reimbursement considerations for essential paediatric medications.

Recommendation 3 – Revise the direction in the "when to submit studies and plans" section of the guidance to ensure consistency and clarity in the language and to more clearly outline the circumstances that should prompt the submission of a PDP to Health Canada.

To optimize the uptake of this guidance, we feel it is essential to more clearly outline the various contexts that should prompt the submission of paediatric data to Health Canada. More specifically, we recommend the language explicitly state that PDPs should be submitted both (1) when a new drug is submitted, and (2) when a new adult indication is requested. Removing the "may" language will more clearly communicate the importance of submitting paediatric data in all cases when paediatric use can be expected or anticipated and will better align with expectations in leading jurisdictions.

Moreover, in alignment with the U.S. Research to Accelerate Cures and Equity (RACE) for Children Act, we recommend that Health Canada more clearly request the submission of paediatric data for novel therapeutics directed at molecular targets when such data is submitted to other jurisdiction(s). An increasing number of life-saving mediations coming to the market focus on a molecular target, and as such, are not optimally regulated under disease-specific indications. Children and youth should be positioned to take advantage of the latest molecular breakthroughs, agnostic to diagnosis. As Canada moves to correct a longstanding regulatory deficiency, we should endeavor to ensure our policy guidance is as modern as clinical science demands.

Recommendation 4 – Remove the exclusion for biosimilar drugs.

We understand that, under section 505B91 of the U.S. Food, Drug and Cosmetic Act, a biosimilar product that is interchangeable with a reference product and is not considered to have a "new active ingredient" is exempt from the Pediatric Research Equity Act (PREA). That is, however, not the case for biosimilar drugs that have not been determined to be interchangeable. That distinction is important and must be recognized before biosimilars are systematically excluded from this guidance document.

In addition, recognizing that many reference biologics in Canada were approved in the absence of a paediatric data requirement, the majority of biologic products with a paediatric indication in the United States and the European Union lack a similar paediatric indication in Canada. While we recognize that the National Priority List for Paediatric Drugs (NPLPD) project is attempting to redress these critical indication gaps, we feel that any and all pathways to expand evidence-based indications for the paediatric population should be utilized. There is no benefit to Canadian children and youth to exclude biosimilar drugs from this pilot project.

Recommendation 5 – Remove the exclusion of third-party data submission pathways.

We understand that abbreviated new drug applications submitted under section 505(j) of the U.S. Food, Drug and Cosmetic Act are granted special exemptions under PREA. However, given our notable differences in paediatric regulatory practice and market size, the need for and specific use of third-party data submission pathways in Canada, as compared to the United States, is fundamentally different.

Again, we see no benefit to Canadian children and youth to categorically exclude submissions through the third-party data submission pathway from this pilot project. At every opportunity, high quality data to support the safe and effective use of paediatric drugs should be solicited and reviewed.

Recommendation 6 – Establish and fund a permanent Expert Paediatric Advisory Board (EPAB) to advise on the clinical, regulatory, reimbursement and research activities deriving from the implementation of mandatory paediatric data submission.

For the guidance document to achieve its ambitious objectives, it will be essential to engage with paediatric experts as specialized external stakeholders and to embed paediatric experts within both the Ministry of Health and Health Canada institutional infrastructures.

Paediatric clinical and pharmacy expertise will be essential to appropriately evaluate iPSPs or EU-PIPs not yet approved by the FDA or EMA, or Canadian PDPs under the pilot project. To ensure that the submissions are both feasible and suitable, and to assess the clinical relevance and appropriateness of study designs and nominated end points, experts in paediatric medicine and clinical trial design must be formally engaged. All leading jurisdictions that have successfully implemented mandatory paediatric data submission policies have done so having formalized relationships with paediatric clinical leaders. It would be out-of-step with international best practice to implement this policy without similar disease and discipline-specific expertise.

In addition, a higher-level EPAB is essential to review, guide and co-ordinate activities across the Health Portfolio as Canada works to right the longstanding, complex and unique issues facing the paediatric population (including, but not limited to, the significant misalignment between the new drug submission process, the Special Access Program, health technology assessment review and reimbursement system as well as national post-market surveillance activities). Paediatric leaders are required to address the complete life cycle of safe, effective and accessible medications for children and youth.

Recommendation 7 – Conduct a robust evaluation of the guidance document pilot.

We highly recommend defining a priori metrics that are specific and measurable, to determine the success of the policy pilot project. Possible metrics include:

(1) Total number of submissions to pilot (acknowledging that low engagement may not speak to a lack of willingness to submit data in the future, but rather a lack of incentives to participate in a voluntary policy pilot)
(2) Total number of iPSPs submitted / Total number of EU-PIPs submitted / Total number of PDPs submitted
(3) (A) Drug classes, (B) Indications, (C) Molecular Targets, (D) Age Bands for all drugs submitted to pilot
(4) Total number of "First in Class" submissions

In addition to these quantitative measures, we also highly recommend a structured qualitative evaluation, specifically seeking to understand the motivations and experiences of those sponsors who elected to participate in the pilot, as well as the barriers to participation that prevented other sponsors (who submitted an NDS during the pilot period but did not submit a PDP, or equivalent) from electing to participate.

Again, we celebrate and congratulate Health Canada on this incredibly important work. We strongly support the direction of this work and maintain an authentic desire for this policy pilot to be a success. As always, we look forward to working with you in partnership as this, and the other critical initiatives under the PDAP, are developed and implemented.

Sincerely,

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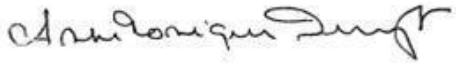

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About the Canadian Paediatric Society

The Canadian Paediatric Society is the national association of paediatricians, committed to working together to advance the health of children and youth by nurturing excellence in health care, advocacy, education, research and support of its members. Founded in 1922, the CPS represents more than 3,600 paediatricians, paediatric subspecialists, paediatric residents and others who work with and care for children and youth.

About the Goodman Pediatric Formulations Centre of the CHU Sainte-Justine

The GPFC has the mandate to improve access to child-friendly medicines in Canada. We are the only Centre in Canada whose objective is to facilitate the development of, safe and effective age-appropriate formulations for children. The GPFC operates as a not-for-profit organization, whose exclusive goal is to support the well-being of children by facilitating the availability of formulations adapted to their needs. Even though the GPFC works closely with hospitals, health care providers and industry, our positions and actions are completely independent of these third parties.

About MICYRN

MICYRN is a federal not-for-profit, charitable organization founded in 2006 to build capacity for high-quality applied health research. It now links 20 maternal and child health research organizations based at academic health centres in Canada; is affiliated with more than 20 practice-based research networks; provides support to new and emerging teams; and has established strong national and international partnerships.

About Children's Healthcare Canada

For Canadian leaders in children's healthcare, we are the only national association that enables local improvements and contributes to system-wide change by building communities across the full continuum of care. Our members deliver health services to children and youth, and include regional

health authorities, children's tertiary/quaternary and rehabilitation hospitals, community hospitals, children's treatment centres and home/respite care providers.

About the Pediatric Chairs of Canada

We are the national network of academic leaders in paediatric medicine strengthening the future of paediatrics and improving the health outcomes of all children, by working together to advance evidence-based care, education and research.

About the Canadian Society of Pharmacology and Therapeutics

The Canadian Society of Pharmacology and Therapeutics (CSPT) is a national not-for-profit charitable organization that aims to foster the application of educational and research excellence to drug discovery and therapeutic choice. CSPT is recognized for its involvement with the Royal College of Physicians and Surgeons of Canada fellowship training program in Clinical Pharmacology and Toxicology, as well its support of graduate/postdoctoral trainees and academic researchers across the country.

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About the Canadian Childhood Cannabinoid Clinical Trials

C4T is an academic-led team of parents, doctors, pharmacists, nurses and scientists who are studying medical cannabis used by children. Our goal is to move cannabinoid use from the era of anecdote to evidence to treat health concerns in children.