April 9, 2021

Dear Ms. Crocker,

On behalf of our nine national child and youth health organizations, we are pleased to submit a formal response to Health Canada's proposed Pediatric Drug Action Plan (PDAP). This summary reflects the content shared and discussed during our stakeholder webinar on February 3, 2021.

First and foremost, the pediatric community is heartened by the recent release of the proposed PDAP. We remain committed to working with you and your colleagues at Health Canada to ensure that this plan is complete and implemented with optimal impact. However, after our collective review of this most recent proposal, we firmly believe there are several critical omissions in the plan, and we are grateful for your attention to our concerns.

We believe that Health Canada understands many of the pediatric-specific challenges currently facing Canadian children, families and health care professionals, and the current PDAP highlights four major areas of concern for the pediatric community. Specifically, we agree that the (1) inadequate receipt of pediatric data for regulatory review, (2) unnecessary, time-intensive and costly barriers to pediatric clinical trials, (3) economic challenges associated with developing, marketing and maintaining a stable and up-to-date pediatric drug supply and (4) current widespread use of off-label medications in this population are four of the most pressing issues in the pediatric drug space.

However, in addition to these four priorities highlighted in the current PDAP, several crucial issues were not addressed. In this letter, we have outlined six actions that are necessary to include in the objectives of the Office of Pediatrics and Patient Involvement (OPPI), and important to emphasize in the next iteration of the PDAP.

Recommendation 1: Implement immediate regulatory change that mandates the submission of pediatric data in all drug submissions when pediatric use of a medication can be expected or anticipated

There is unanimous agreement that the mandatory submission of pediatric data to Health Canada, when pediatric use can reasonably be expected or anticipated, is an urgent priority. With regards to ensuring access to safe and effective pediatric medications, Canada's regulatory framework remains two decades out-of-step with international best practice. Therefore, regulatory change confirming the obligatory submission of pediatric data to Health Canada must be a priority for the Office of Pediatrics and Patient Involvement.

Importantly, the pediatric community is sensitive to the commercial challenges associated with our small market, as well as the regulatory burden associated with a new requirement to review pediatric data with all new drug submissions. To that end, we believe that Health Canada should accept the submission of pediatric data in the same form as required by leading international jurisdictions (including, for example, the PSP as required by the United States and/or the PIP as required by the European Union).

Recommendation 2: Accelerate and expand the use of Trusted Foreign Decision Pathways

As part of a comprehensive pediatric drug strategy, we urge Health Canada to implement the use of Trusted Foreign Decisions. The recent experience of the COVID-19 Interim Orders (IOs) demonstrates that Trusted Foreign Decision pathways can be both accelerated and streamlined. The requirement in the Trusted Foreign Decisions draft guideline for 15- years of post-market experience in the trusted jurisdiction reflects almost the entire "lifespan" of a pediatric patient, eliminating the opportunity for individual children and youth to access life-sustaining medications throughout this critical developmental window. Moreover, this requirement does not align with what is known regarding the detection of serious safety events, and neglects Canada's responsibility to the global community in terms of participating in appropriate pediatric post-market surveillance. The pediatric community would be keen to explore alternative, pediatric-specific market experience requirements, and would be eager to explore the possibility of flexible Trusted Foreign Decision rules based on risk, disease prevalence, and therapeutic area.

We similarly urge Health Canada to generate flexible, agile and innovative pathways to ensure rapid access to life-saving pediatric medications for critical pediatric illness. Developing these novel pathways in collaboration with pediatric clinical experts, researchers, patients and their families will ensure they address the current barriers to timely care, and meet the needs of this hugely vulnerable population when facing critical illnesses that have treatment options available elsewhere.

Recommendation 3: Develop a dedicated pediatric "Off-Label Drug Use" strategy, focused on high-cost drugs

There is agreement amongst the pediatric community that older and off-patent medications, a mainstay of pediatric practice, require urgent regulatory attention and will demand a unique, specific and ambitious plan. Recognizing the absence of commercial incentives to submit new indications or formulations, there is a genuine risk that product monographs for essential pediatric medications will continue to omit critical pediatric data, even when specific safety risks exist or when robust evidence exists to supports safe and effective use. The effort to reverse the Canadian reliance on off-label prescribing should be commensurate to the degree of regulatory neglect that generated the status quo.

We are pleased that Health Canada is exploring how best to enable a more flexible, risk-based set of regulations, including a risk-based oversight and management strategy, for clinical trials. This will provide incentives to independent investigators for conducting category B (OECD classification) clinical trials, where information on the efficacy and safety of the medicinal product (although for a different disease, indication or population) is available. However, the need for this type of flexible regulation underscores the persistent and pervasive disconnect between evidence and product labelling.

Recognizing that the comprehensive revision of all monographs for products used in clinical practice is neither practical nor feasible, we strongly urge Health Canada to focus this strategy on medications approved for use in the last 15 years, medications with approved paediatric indications in trusted foreign jurisdictions, medications with pediatric-specific safety risks and medications considered "high cost" (including, but not limited to, biologic drugs). This work should be guided by pediatric experts who can prioritize those monographs most in need of revision.

We would also welcome future conversations exploring the development of a robust, dynamic public access database for pediatric prescribers that would contain up-to-date clinical evidence and expert recommendations. Several leading international jurisdictions, including New Zealand, the United Kingdom and the Netherlands, have already developed similar databases, with much success. This potential resource could serve as a bridge between the product monograph and the patient given the urgent current need and the inauspicious current state.

Recommendation 4: Address our continued reliance on compounding medications

Health Canada must appreciate the full scope of the impact of our continued reliance on compounded medications for the pediatric population. While essential in select cases, compounding perpetuates a "second-tier" medication safety system for patients unable to tolerate the dose, or dosage forms, of commercially available products. There are currently no regulatory pathways to streamline, nor programs to incentivize, the commercialization of pediatric-friendly formulations available in comparable jurisdictions. Simultaneously, there are no national standards to govern the practice of compounding for medications without suitable dosage forms for children. The full cost –

including both direct and indirect costs – associated with our continued reliance on compounding must be considered when prioritizing and pricing medications for children. Health Canada -together with Health Technology Assessment (HTA) partners- must work to ensure access to appropriate formulations at a fair and affordable price.

Recommendation 5: Invest in pediatric-focused post-market surveillance activities, including the establishment and expansion of stable, permanent pediatric post-market safety and efficacy surveillance infrastructure

As novel products enter the market, as prescribing patterns for children and youth evolve, and as the importance of Real World Evidence (RWE) in regulatory decision-making increases, special attention to the unique needs of children in the post-market space is required. Recognizing that "children are not little adults", that medications prescribed to children and youth must attend to their developing bodies and brains and that many serious and impactful adverse events have been recognized only after regulatory approval and entry of the drug into the market, short and long-term post-market surveillance systems must be comprehensive and robust. Any Pediatric Drug Action Plan must include specific resources dedicated to safety and effectiveness in the Real World space.

Recommendation 6: Establish an Expert Pediatric Advisory Board (EPAB)

In order for the PDAP to achieve its ambitious aims, it will be essential to both partner with pediatric experts as specialized external stakeholders as well as to embed pediatric experts in the Ministry of Health and Health Canada institutional infrastructure. The optimal approach to advance pediatric drugs in Canada will involve a "complete life cycle" perspective. To address the significant misalignment between the new drug submission process, the Special Access Program, the HTA and reimbursement system as well as national post-market surveillance activities, the pediatric community continues to see a need for an Expert Pediatric Advisory Board (EPAB). Canada has the distinct advantage of having a robust community of experts in pediatric drug therapy who are keen to work with government partners in pursuit of our common goal of optimal drug therapy for Canada's children. A permanent and appropriately resourced EPAB, at the Health Portfolio level and accountable to the Deputy Minister of Health, should actively advise government on regulatory, reimbursement, and research activities related to pediatric medications and therapeutics. This high-level advisory body 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 pediatric population.

More specifically, the EPAB would play a critical role in the development of a national priority drug list for both medicines development and reimbursement, as well as a national formulary. The insight of the EPAB would also be critical to informing the development of essential, effective and impactful incentive models to encourage pediatric drug and formulation development and address economic barriers.

In summary, we wish to emphasize how pleased we are to see this preliminary Pediatric Drug Action Plan. It is clear that Health Canada is listening to the Pediatric Community's

concerns and is willing to explore meaningful solutions to longstanding problems related to pediatric medications in Canada's regulatory infrastructure. We all believe now is the time to take action, and the Canadian pediatric community is willing and able to maintain our close and valued collaboration with Health Canada, and its Office of Pediatrics and Patient Involvement, to establish specific deliverables, targets and timelines. Canadian children cannot wait any longer.

Best regards,

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About MICYRN and KidsCAN Trials

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 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 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 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 CIHR-GSK Chair in Paediatric Clinical Pharmacology

The CIHR-GSK Chair in Paediatric Clinical Pharmacology is the only endowed Chair in Paediatric Clinical Pharmacology in Canada and is dedicated to the goal of conducting clinically impactful research with the goal of ensuring effective and safe drug therapy for children in Canada and beyond.

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.

About the C17 Council-Children' Cancer & Blood Disorders

The C17 Council is an organization composed of the institutionally appointed heads of the sixteen pediatric hematology, oncology, and stem cell transplant programs across Canada. We represent the interests of children and adolescents with cancer and blood disorders and act as an authoritative Canadian voice.

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.