June 14, 2021

Dear Mr. Saulnier,

Thank you for the opportunity to inform Canada's National Strategy on High-Cost Drugs for Rare Diseases (the "Strategy"). By hosting two pediatric-focused consultations, the government has demonstrated a sincere interest in understanding the impact of rare diseases on child health and the delivery of pediatric health care and has exhibited a willingness to develop a plan that will meet the needs of Canadians of all ages. We are heartened by your attention. We look forward to working together towards our shared goals of improved access, evidence-based funding decisions, and sustainable prescribing and de-prescribing practices.

The summary below reflects the comments offered during our two consultation sessions on April 12, 2021. The participants included delegates from eight national child and youth health organizations and leading experts in pediatric rare disease and pediatric health technology assessment. Please know that we all remain willing to engage with government through the strategic development and implementation process and are happy to discuss any of these issues at greater length, should that be of help.

Issue #1: Rare disease is not "rare" in children

While a rare disease, by any definition, is uncommon, when considered together, rare diseases are relatively frequent. Notably, the burden associated with rare disease is concentrated in the pediatric population. It is currently estimated that 1 in 15 children is born with a rare disease. Moreover, over 70% of all rare diseases manifest in childhood and 1 in 4 pediatric hospital beds is currently occupied by a child with a rare disease. Recognizing this epidemiology, the current clinical presentation patterns and ongoing health system impacts, children and youth must be at the center of any rare disease strategy.

> **Recommendation #1: The National Strategy on High-Cost Drugs for Rare Disease (the "Strategy") should be child-centered and should include dedicated funds to improve access to pediatric medications, dedicated investments to establish pediatric-focused registries, pediatric clinical trials infrastructure and pediatric health technology assessment (HTA) standards as well as dedicated support for critical pediatric**

regulatory reform. The investment should be proportional to the rare disease burden experienced by the pediatric population.

Issue #2: Pediatric patients in Canada have experienced longstanding regulatory neglect

While regulatory decisions remain independent from matters of price, cost and access, reimbursement processes and judgements are inextricably linked to regulatory decisions, including which drugs may be reviewed and ultimately covered for which Health Canada-approved indications. Unlike comparable regulators, including the United States Food and Drug Administration and the European Medicines Agency, manufacturers are not obliged to submit pediatric data to Health Canada as part of the New Drug Submission (NDS) process, even when pediatric use can be expected or anticipated (the "pediatric rule"). Moreover, manufacturers are not obliged to submit pediatric data to Health Canada when that same manufacturer has submitted pediatric data or has applied for a specific pediatric indication for that same drug in other jurisdictions. Sadly, this passive omission holds even when Canadian children and youth have participated in the clinical trials that have informed specific pediatric indications submitted for review by other international regulators. This omission is particularly striking for those paediatric patients living with rare disease, and for those in urgent need of novel or innovative therapies.

Demonstrable benefits have been afforded to paediatric patients in jurisdictions that require the submission of paediatric data with all new drug submissions. Due, in part, to the lack of a similar requirement in Canada, it is estimated that 80% of pediatric prescriptions in Canada are "off label". Consequently, any funding decisions limited to Health Canada-labelled indications risk significantly reducing or eliminating access to vital medications for Canadian children and youth. In addition, the scope of the reviews undertaken by national Health Technology Assessment bodies, namely the Canadian Association for Drugs and Technology in Health (CADTH), are dictated by Health Canada-approved indications. With many new market entrants excluding pediatric data from their submissions, national HTA recommendations often reflect only adult conditions and outcomes.

Regulatory reform is an essential step necessary to ensure that Canadian children enjoy the same high standard of drug safety, efficacy, availability and access as do adults. After more than two decades without a "pediatric rule" (or equivalent) in Canada, Health Canada must immediately implement regulatory change to compel the mandatory submission of pediatric data to support pediatric indications and safe pediatric use when use in children and youth can be expected or anticipated. Recognizing that this regulatory change will be associated with an increased regulatory review volume (associated with increased costs for Health Canada), this Strategy provides a meaningful opportunity to finally resolve Canada's longstanding regulatory deficiencies negatively affecting the pediatric population. Ultimately, children deserve the same protections from the drug regulatory system as adults, and our regulatory system must be funded to achieve this aim.

Recommendation #2: Given the longstanding regulatory neglect experienced by the pediatric community, decisions related to funding and access under the Strategy must be informed by pediatric experts using the best available evidence and must be purposely decoupled from Health Canada's approved indications.

Recommendation #3: The Strategy must support, and fund (if necessary), the modernization of the drug approval process for pediatric medications. Specifically, this Strategy must ensure that Health Canada will proactively request manufacturers include pediatric-specific data in all new drug submissions when pediatric use can be expected or anticipated (i.e. a Canadian "pediatric rule").

Issue #3: Children and youth in Canada are often victims of a "postal code lottery"

Among the patchwork of existing public and private drug insurance programs across Canada, coverage for life-saving and life-sustaining medications for children is highly variable. This variability includes not only the decision to list (or not list) a medication on a public formulary but also specific drug/disease eligibility criteria, including age-based coverage distinctions (where drugs may be funded for adults or adult conditions and not similarly funded for infants, children and youth).

This variability is fuelled by a lack of consistently applied expert consensus and clinical evidence. Children are especially vulnerable to this "postal code lottery" as the available evidence is often limited in the pediatric age group, and when evidence does exist, there is often a significant gap between the product monograph and the data. Given the small and close-knit nature of rare disease communities, the variations in access across jurisdictions can be acute, and particularly devastating given the often degenerative, or possibly fatal, nature of rare diseases and the lack of effective alternative therapies.

The federal government has a vital role in ensuring equity and advancing evidence-informed prescribing and de-prescribing. Best practice should not vary by province or territory, and access to optimal therapy should not be based on a child's socioeconomic status or residence. A national reference for pediatric medications is urgently needed to ensure both optimal use and optimal outcomes. This prescribing database will expand access to available scientific evidence and facilitate the translation of pharmacovigilance data to front-line providers. This resource could be linked to more comprehensive disease-focused clinical guidelines (see below) and should enable real-time reporting of adverse events.

Recommendation #4: The federal government must play a leadership role in ensuring equitable access to high-cost medications to ensure optimal outcomes for all children regardless of child's socioeconomic status, insurance status and jurisdiction

Recommendation #5: The Strategy should dedicate stable funds to support the development of an online, open-access formulary to ensure that all pediatric providers have access to the best possible information.

Issue #4: Drugs are only one element of rare disease care

While high-cost therapeutics are often a critical component of care for patients with rare disease, it is important to remember that ensuring optimal outcomes demands more than enabling access to one single, expensive drug. For high-cost drugs to yield the best possible patient results, medications must be prescribed by highly experienced professionals, working in interdisciplinary teams (when appropriate), with access to the ancillary medicines (both high cost and low cost), other evidence-based therapies, including physical, respiratory and occupational therapy (as indicated) as well as proper nutrition. Ideally, therapy is also done in the context of a research program, focused on understanding the impact of current interventions and long-term, well defined, real world outcomes relevant to patients and families. To focus exclusively on access to high-cost medications, excluding other necessary treatments and services, will under-realize the anticipated impact of the drug.

> **Recommendation #6: To ensure that the optimal disease outcomes expected following the administration of high-cost medications are achieved, the Strategy should invest in the development of rigorous, peer-reviewed clinical guidelines outlining total disease care. Prescribing high-cost medications should require compliance with comprehensive disease care guidance.**

Issue #5: Robust Health Technology Assessments (HTAs) are essential both to protect the sustainability of our health care system and to ensure appropriate access to high-value medications that serve the needs of children and families

It is important to acknowledge that not all rare disease medications are high-cost and that not all high-cost drugs represent high value to patients, families or health care systems. Over the last two decades, the paediatric community has been disproportionally affected by predatory and other egregious pricing strategies pursued by drug companies. To that end, the paediatric community feels strongly that robust, open and transparent HTA processes, informed by practicing paediatric experts and tightly aligned with regulatory approval pathways, are vital to protect children and families and ensure the long-term sustainability of our treasured public institutions.

At the same time, recent advances in small molecules, immunotherapies and gene-based medicine have substantially improved outcomes for paediatric patients with life-limiting and life-threatening conditions. And many of these transformative therapies are associated with significant costs. Acknowledging the enormous potential associated with these advances, the paediatric community again recognizes the central importance of HTA to improving child health.

At present, no public HTA or reimbursement entity, at any level of government or in any jurisdiction, is required to consider the unique attributes of the pediatric population. At

present, HTAs and reimbursement bodies rely on calculations, principles, benchmarks and price-to-volume rations based exclusively on adult norms.

Unfortunately, the clinical and economic data necessary to complete traditional HTAs is often lacking for pediatrics, making it difficult to perform Quality Adjusted Life Year (QALY) and other standard HTA measures. In addition, the indirect cost-benefit profile for pediatric therapies, specifically precision therapies, differs substantially from those of adults. Moreover, valid and reliable instruments for assessing the quality of life at different ages and stages of development often do not exist, and the lack of data on the developmental and late effects of rare disease drugs complicates efforts to accurately assign long-term benefits and costs associated with their use in children. Without pediatric-sensitive HTA methods and policies that require pediatric-specific HTA analyses, HTA bodies may continue to recommend excluding pediatric drugs from drug formularies. A national strategy on high-cost medications for rare diseases must recognize the unique returns on investment provided by pediatric drugs.

Recognizing that societal values attached to children are different than those attached to adults, unique pediatric standards should be informed by epidemiological, physiological, pharmacological and ethical considerations specific to this population. In parallel, pending resolution of the longstanding regulatory deficiencies relating to paediatric data in the regulatory approval process, HTA bodies must be allowed to consider evidence-based pediatric indications not included in the Health Canada label. Moreover, opening the "black box" that is the regulatory and HTA process to include paediatric rare disease stakeholders in a meaningful way would be a positive acknowledgement of the importance, vitality and exclusive expertise held by these communities.

Recommendation #7: The Strategy should dedicate funds to support the development, application and evaluation of pediatric-sensitive standards of clinical and economic evidence to inform the HTA and pricing process.

Recommendation #8: Health Canada should work collaboratively with national and provincial HTA bodies (including CADTH, INESS, and relevant provincial listing decision-making bodies) to ensure the uniform application of pediatric-sensitive standards as mandatory core elements of HTA review (for all medications, including and especially high-cost medications).

Issue #6: Children often require specialized formulations to ensure appropriate dosing, safe administration and tolerability

Children, especially small children, require flexible dosing based on weight or body surface area. Children often also require medications in a liquid or a quick-dissolving form, as many cannot swallow tablets or capsules. When a medication needed by a child is not available in an appropriate form or dose, compounding (either by a pharmacy or at home) is required. Compounded medications not only often have an unpleasant taste and/or texture, which may

compromise adherence, but compounding may also be associated with an increased risk of dosing error, reduced drug uniformity and may impact bioavailability, stability and potency.

Commercially available child-friendly formulations are associated with higher costs. However, this additional expense must be weighed against the known safety, quality and palatability benefits of medications produced under commercial manufacturing standards. Children and youth deserve access to medicines produced under the same safety and tolerability standards as adults.

> **Recommendation #9: When evaluating the costs associated with commercially-prepared pediatric-friendly formulations, HTA and pricing bodies must account for the interval safety and adherence benefits associated with medications that do not require pharmacy or family compounding.**

Issue #7: Rare disease registries are an important and feasible tool to generate Real World Evidence

National rare disease registries enable the generation of timely, cost-effective Real World data. The collection of pre-defined outcome variables, informed by expert consensus, clinical evidence and patient input, facilitate the regular evaluation and re-evaluation of medication efficacy and safety and allow for effective decisions regarding the continuation or de-prescribing of high-cost drugs. Such registries may also accelerate conditional drug approvals and the entry of novel therapies into the Canadian market by providing active post-market surveillance and intensive pharmacovigilance to advance our shared understanding of effect and risk outside of clinical trial settings.

In order to realize the potential of RWE rare disease registries, permanent and stable infrastructure funding is required. This funding is necessary to ensure that RWE registries are robust and built to answer the critical outstanding RWE questions. They should be developed according to a set of rigorous national rare disease registry standards and, where possible, align with similar international RWE efforts. Careful thought is required to ensure that appropriate people and entities have access to RWE data (including academics and funders), with elements available to the general public to support transparency and public confidence. Recruitment, retention, public education and data protection will be critical to the long-term success of a registry-based strategy.

Importantly, ongoing RWE strategies supported by CADTH, CIHR and other funding bodies should be integrated to eliminate unnecessary and costly redundancies and optimize the Strategy's key objectives.

> **Recommendation #10: The Strategy should invest in the development of high-quality, high-impact rare disease RWE registries that include the measuring of systematically selected, pediatric-sensitive patient preferences.**

Recommendation #11: The Strategy should explore how to encourage, and possibly mandate, participation in registries for recipients of publicly funded high-cost medications.

Issue #8: Stable investment in pediatric clinical trials infrastructure (including distributed multi-site infrastructure) is necessary to generate necessary pediatric data and to attract clinical trials to Canada

Canada is a recognized international leader in pediatric clinical pharmacology, pediatric clinical drug trial design and child health services research. Under the leadership of established and effective, and highly collaborative pediatric clinical research networks, efforts are currently underway to streamline the launch of multi-center clinical trials, including a CIHR-supported initiative (CHEER; www.cheerchildhealth.ca) to introduce a single pediatric REB review system. In parallel, an increasing number of Canadian pediatric academic centers are focused on forwarding enterprise-wide precision medicine strategies. Together, these attributes prime Canada to be positioned as a "destination of choice" for drug development for rare diseases.

An investment in Pan-Canadian paediatric clinical trial infrastructure would ensure efficient trial implementation through effective site coordination, rapid study feasibility assessments and effective national and international standards. This investment would also promote innovation, collaboration and enable Canada's participation in important global studies, all of which will facilitate early access to new and potentially life-saving therapies for Canadian children and youth.

To realize this opportunity, coordinated national efforts are necessary to sustain existing research programs, translate innovative methods across research domains, and ensure that advances in trial design and network development are understood and applied by regulatory and HTA bodies. To that end, the Strategy should invest in the establishment of permanent, stable infrastructure to support pediatric clinical trials (i.e. MICYRN, KidsCAN) with a focus on drug trials, as well as pediatric-focused cost-effectiveness and patient engagement research. Research budgets should include dedicated funding for pediatrics that is proportional to population size and rare disease burden and should account for the economic and social returns on investment derived from child and youth health research.

Importantly, the Strategy provides a unique platform to forge new and important relationships between Health Canada and Canadian scientists pioneering and perfecting novel methods and innovative trial design. This expertise, including specialized knowledge in platform trials and Bayesian methods, is a unique strength of the Canadian pediatric academic clinical environment. When paired with infrastructure support, these will draw additional investment from Pharma, having identified Canada as a model R & D destination.

Recommendation #12: Canada should take advantage of its unique position as a highly advanced health care system, with a small, well-networked and highly

collaborative pediatric community to attract international innovative clinical trials for rare diseases.

Recommendation #13: The Strategy should invest in stable pediatric clinical research infrastructure. Investment should be proportional to population size and rare disease burden.

Issue #9: Pediatric expertise is essential to forward a child-centred national rare disease strategy

Health Canada recently affirmed its commitment to child and youth health by opening the Office of Pediatrics and Patient Involvement (OPPI) in the Centre for Regulatory Excellence, Statistics and Trials. Establishing an office dedicated to pediatric issues in the Health Products and Food Branch is an important signal that this population requires and deserves special regulatory attention.

Acknowledging the importance of this population, Health Canada must formally collaborate with pediatric experts to help review, guide and coordinate the activities related to pediatric medication approvals, including the design and implementation of rare disease best practice clinical guidelines, the development of rigorously designed and monitored rare disease registries, and the development, application and evaluation of pediatric-sensitive standards for clinical evidence in the regulatory space and HTA analysis.

Recommendation #14: The Strategy should support (and fund, if necessary) a permanent, dedicated Expert Pediatric Advisory Board (EPAB) to direct pediatric-focused activities across the Health Portfolio.

In conclusion, as pediatric experts, we have proudly witnessed the positive outcomes associated with recent advances in clinical medicine, including the introduction of novel small molecules and advances in gene-based therapy. These advances have had profound effects on children and youth living with rare diseases. However, it is important to note that not all rare disease is associated with catastrophic illness, not all orphan drugs are high cost, and high cost does not necessarily mean high value. Many medications for rare diseases are not novel, and several crucial rare disease therapies are not are associated with significant capital, research or development costs. Our health system and this important Strategy should support access not only to high-cost medications but to equitable, comprehensive care, ensuring optimal outcomes for all children and youth with rare diseases. Canada can achieve this by developing a sound, child-centred national rare disease strategy that is designed and implemented in partnership with paediatric experts from across the country.

To protect patients, families and the sustainability of the health care system, the pediatric community is willing to stand with the federal government in opposition to inappropriate and exploitive drug pricing and to support necessary actions to counter problematic and otherwise unexplainable price hikes.

Sincerely,

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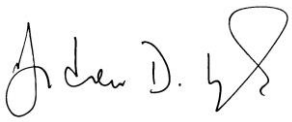

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About MICYRN and KidsCAN Trials

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.