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Dear Mr. Young and the Regulatory Modernization Committee,

Collectively, The Goodman Pediatric Formulations Centre of the CHU Sainte-Justine (GPFC), the Maternal Infant Child and Youth Research Network (MICYRN), Children's Healthcare Canada, the Pediatric Chairs of Canada, CIHR-GSK Chair in Paediatric Clinical Pharmacology, and the Canadian Paediatric Society, would like to provide our perspective regarding pediatric medications and formulations within the proposed Regulatory Modernization Initiative. We are pleased that you are requesting that departments and agencies review their regulatory policies and procedures with the ultimate goal of improving the transparency and efficiency of the overall regulatory process in Canada. It is our pleasure to provide our comments on the four regulatory modernization initiatives as indicated in the Canada Gazette Part I, Volume 153, Number 26 (June 29, 2019).

In general, we believe that special considerations must be given to regulations to promote improved access to safe, efficacious and child-friendly medicines in Canada. Although some progress has been made, Canada continues to lag behind in this area, and this modernization effort affords Health Canada the opportunity to take a leadership position in the way that pediatric submissions are managed. **Canadian children deserve the same pharmaceutical standards and treatment options as adults**.

Although Regulatory Modernization addresses a much larger mandate, this letter will focus on the needs of pediatrics within these modernization efforts. Children are not mini-adults, and as such, need practices and policies supported by legislation to ensure that their needs are appropriately met, as acknowledged by many authorities including the Canadian Council of Academies. In July 2019, Minister Petitpas Taylor acknowledged the importance of having improved access to pediatric treatments and indicated that this is currently underway in Health Canada's modernization efforts. We applaud the Minister's recognition of this unmet need. The conduct of clinical trials, as well as the submission of, and data requirements for, pediatric medicines also need to be carefully revised to ensure that there are no unnecessary barriers to either study, access, or use of these pediatric medications when proven safe and effective in Canada.

Recently, key partners in the Canadian pediatric community published a policy paper entitled Improving Paediatric Medications: A prescription for Canadian children and youth (herein referred to as the Policy Paper). In this paper, we provide five recommendations to the Minister of Health to improve access to safe, efficacious and child-friendly medications to Canadian Children. We summarize these recommendations below; as we feel that certain aspects of the recommendations offered provide support for the four areas of modernization in which the Treasury Board is seeking consultation.

1. Establish and fund a permanent Expert Pediatric Advisory Board (EPAB) at the Health Portfolio level. Accountable to the Deputy Minister of Health, this Board should advise on regulatory, reimbursement, and research activities related to pediatric medications and therapeutics.
2. Direct Health Canada to: (1) Proactively solicit and review pediatric-specific drug data when pediatric use is expected or anticipated; (2) Develop policy pathways to increase submissions for pediatric medications, indications, and formulations; and (3) Work collaboratively with Health Technology Assessment agencies to develop and evaluate pediatric-specific standards and benchmarks for use in both regulatory and reimbursement contexts.
3. Direct Health Canada to: (1) Promote the use of foreign reviews and decisions to support the efficient commercialization of priority pediatric medications and child-friendly formulations; and (2) Review the Special Access Program to support timely access to essential medications for children and to identify priority targets for commercialization in Canada.
4. Fund the development of a national, comprehensive, continuously updated online resource to support consistent, evidence-informed prescribing in all centres and jurisdictions across Canada.
5. Invest in pediatric drug research and clinical trial infrastructure, ensuring alignment between priority regulatory, reimbursement, and research activities.

Below we will address the four regulatory modernization initiatives sought in the consultation request and further elaborate where the recommendations above could specifically support these efforts.

1. Targeted Regulatory Reviews (Round 2)

Inflexible and complex processes that are not tailored to pediatrics will, unfortunately, preclude that research, innovation and child-friendly medicines available elsewhere in the world will become available to Canadian children. It is therefore of utmost importance when revising any regulatory policies and procedures that there are specific considerations given to the needs of Canadian children. We recommend working with experts in the pediatric community (where the EPAB could play an important role) throughout the process to ensure that pediatric needs are met, and that no inadvertent constraints are created.

Although the second round of this initiative has other areas of interest, we will focus our comments on "International Standards" where the Targeted Reviews Committee is examining strategic opportunities to better incorporate international standards in regulation. In this regard, there are three areas where alignment internationally could facilitate access to pediatric medications:

1.1. Use of Trusted Foreign Reviews & Decisions

We understand that Health Canada has established a committee whose mandate is to evaluate a new regulatory pathway for the sale of medicines already approved by trusted regulators. The objective is to facilitate Canadian access to drugs that meet a health care system need/medical need. **We believe that pediatric medicines and formulations could greatly benefit from this initiative**, which is supported in our third recommendation of the Policy Paper.

Although we have not yet seen a draft guideline for Trusted Foreign Review, we have had the opportunity to review a presentation entitled, "Use of Foreign Reviews & Decisions: Current Thinking" in May of 2018. From this documentation, we understand that the spirit of this program is for Health Canada to have an abbreviated review once a product is already approved in a trusted foreign jurisdiction and that this process would waive the requirement to submit a clinical data package, assessment reports and post-market information for very old products, in addition to having lower fees for submission. To be eligible for this program, medicines would have to be approved by two trusted foreign regulators and have 15 years of post-market experience. Although we are highly supportive of this program, **we strongly believe that in pediatrics there is no need to have 15 years of market experience in other jurisdictions**. In contrast to adults, many of these medications are currently being used in Canadian children off-label, and therefore market experience does exist and should be included in part of the evaluation. **Of all initiatives proposed, we believe this could have the largest impact on the health of our Canadian children, and we urge the Treasury Board to make it <u>one of its priority policies</u> in early 2020**.

1.2. Aligned Reviews Between Health Canada and Health Technology Assessment Agencies (HTAs)

Aligned reviews between Health Canada and the Canadian Agency for Drugs and Technologies in Health (CADTH) and l'Institut national d'excellence en santé et en services sociaux (INESSS) (hereinafter referred to as Health Technology Assessment agencies (HTAs)) should accelerate reviews and allow issues to surface earlier in the process. Pediatric-specific criteria are required in the entire review process, an area where the EPAB (as recommended above) could provide pediatric expertise and recommendations for these aligned reviews. This alignment should shorten the time to market for industry and provide clarity in the process up-front in the submission process, both of which will contribute to encouraging more pediatric submissions in Canada. Finally, this process could be shortened

or simplified by allowing data from other trusted jurisdictions (such as Australia or the United Kingdom) to be used for both regulatory and HTA steps which would be beneficial.

1.3. International Work Sharing Programs

ACSS Program

The Australia Canada Singapore Switzerland (ACSS) Consortium was established as a means to foster regulatory collaboration and synergy between regulators and to address emerging scientific and regulatory issues regarding health products, which is supported in our second recommendation in the Policy Paper. Not only does this reduce the regulatory burden and cost, but also the approval can result in access to millions of children in four middle-sized countries in an expedited fashion. We understand this program is underway and we would encourage this avenue as a potential pathway to encourage pediatric medications and formulations to be commercialized in Canada, especially when the commercial market opportunity is limited. **Transparency on how this program functions, the costs and timelines involved would be important for industry to use this new pathway**. Operating on a case-by-case basis is not an option, as it does not provide enough information for industry when they are establishing their business case.

Clinical Trials International Working Group

Supporting the fifth recommendation in the Policy Paper, an international pediatric research initiative is already underway and could be strengthened. Canada's MICYRN, whose mandate is to remove barriers to high quality pediatric research by facilitating the development of streamlined best practices, standardization, and process improvement, is currently chairing a working group on **international collaborations, made of regulators and pediatric network representatives** from Japan, the United States, Australia, Europe and Canada. This new group is actively performing an environmental scan of the regulatory submission process and review for pediatric clinical trials in each jurisdiction to compare and explore efficiencies for the streamlining of the regulatory pathways in an international capacity. It would be our recommendation that the workstream that is responsible for the international work-sharing programs at Health Canada build upon the work that has already been done by MICYRN to attract more innovative pediatric clinical research in Canada.

Access to pediatric data available internationally

In Europe and the United States, pediatric data are required to be part of the regulatory submission unless a waiver is requested and granted. Given this requirement, pediatric data are often available in these jurisdictions, yet Canada does not have easy access to these data hence the second recommendation in the Policy Paper for Health Canada to have a proactive approach to require the submission of pediatric data to support pediatric indications along with child-friendly formulations. The inaccessibility to pediatric data is primarily due to the fact that Health Canada cannot demand that a manufacturer submit

pediatric data. It would be highly beneficial to the pediatric community to have access to the pediatric data that are generated internationally. **We request that the international work-sharing program cited above explore ways that pediatric research and formulations available elsewhere can be made available in Canada, with regulatory backing and incentives, to help inform healthcare providers in treatment decisions.**

2. The Red Tape Reduction Act

We understand that the Red Tape Reduction Act aims at reducing the administrative burden on business when developing regulations using the "One-for-one" Rule. In our experience, the lack of clarity in the requirements for pediatric submissions at every junction of the drug approval and market access process may create unnecessary back and forth communication as processes are clarified or more information is required on each dossier submitted. Not only is the process unclear, but the GPFC has an example where the lack of alignment between Health Canada and HTA caused Health Canada to approve a medication, and the downstream HTA process did not recommend the medication for listing (Policy Paper Recommendation 2). **Clarity, alignment, and transparency in all new policies and procedures to include the appropriate pathway for pediatric medicines and formulations** would be an essential improvement and would contribute to decreasing the barriers to entry for pediatric medicines and formulations.

3. Exploring options to legislate changes to regulator mandates

The approaches that the Treasury Board should consider to ensure regulatory efficiency and economic growth during this modernization process is to provide the opportunity of all stakeholders for their input on draft documents. Despite a lengthier process, this allows a variety of views to be presented, in reaction to any drafts, and a better understanding of any unintended consequences that could arise. For pediatrics specifically, this should take form by inviting the pediatric community in any consultations or discussions (the EPAB could play a role to support this).

The impact of the new regulations in pediatrics could be measured by the number of new pediatric indications and/or data included in product monographs as well as by the number of new pediatric formulations on the Canadian market. In a study recently presented at the European Society for Developmental Perinatal and Paediatric Pharmacology Patel et al. (Arch Dis Child, 2019) looked at all product monographs of new active substances approved in Canada from 2007 to 2016. One of their main findings was that more than 80% of all new active substances were only approved in adults. A decrease in this rate following implementation of the new regulations could be used to benchmark improvements.

We would be amiss to recommend these initiatives without highlighting that the addition of pediatric-specific processes or requirements will **create a need to have the newly formed "Office of Pediatrics and Patient Engagement" at Health Canada to be fully funded and dedicated to this overall mandate, and operationally, have the ability and capacity to manage**

pediatric submissions. This would be in addition to the EPAB recommended above. The newly formed, Office of Pediatrics and Patient Involvement now falls within the Centre for Regulatory Excellence, Statistics and Trials within the Biologics and Genetics Therapies Directorate (BGTD). In addition to the Office of Pediatrics and Patient Involvement, there are four other Offices that comprise BGTD. Given this complex structure, we are not convinced that our recommendations of pediatric specific reviews along with mandating pediatric submissions could be supported by this existing structure. Dedicated funding and human resources are needed to ensure that pediatric files would be managed expeditiously while keeping pediatric needs in mind.

4. Suggestion for the next annual Regulatory Modernization Bill

We highlight two areas where inflexibility in the system currently prevent pediatric research or commercialization of pediatric medicines.

4.1.1. Simplification of the Regulatory Process for Pediatric Formulations along with Regulatory Incentives for Off-Patent Medications

There are pediatric formulations that exist in other jurisdictions that are not commercialized in Canada, partially due to the perceived complex regulatory and reimbursement processes as well as the small market opportunity that exists in Canada. We have identified a certain number of medications that should be commercialized to ensure optimal treatment. However, many of these medications are generic with no patent protection and there are no incentives for manufacturers to market these medications in Canada. Canada lags behind other G7 countries in having access to many pediatric formulations. Two solutions are provided that, together, we believe would be impactful for improving access to pediatric formulations:

1. **Simplification of the regulatory process for these off-patent medications, such as the use of trusted foreign reviews and decisions, with lower fee structures**
2. **The provision of incentives, such as reimbursement exclusivity**

4.1.2. Risk-Based Approach for Regulating Clinical Trails

With the current legislation, the Clinical Trial Application approval process results in a number of additional requirements including compliance assurance, reporting, training, investigational product accountability, and labelling; all of these tasks pose barriers to conducting high quality pediatric clinical trials in Canada.

Health Canada is considering a risk-based approach for the modernization of the Food and Drug Act that would certainly improve the number of clinical trials that are conducted in pediatrics in Canada. Existing regulatory policies at Health Canada have been designed primarily to ensure oversight of industry-initiated studies with new therapeutic agents. In pediatrics, this is not the most frequent type of research undertaken by academic researchers, who conduct investigator-initiated trials with marketed therapeutic agents for off-label uses yet are subject to the same application and reporting requirements.

The ability to stratify clinical trials by risk category would reduce the administrative burden and provide a strong incentive for investigators to conduct more trials with off-labeled pharmaceutical products in children, thus generating the needed evidence for the use of these medications. As clinical trial evolution moves forward an important consideration will be the evaluation of novel and innovative clinical trial approaches to special populations such as children.

Pediatric Incentives and Drug Research is Essential to Improving Pharmacotherapy in Children

Collaboration between Health Canada and CIHR to fund pediatric drug research in Canada is essential to improve access to pediatric data. The Food and Drug Administration Modernization Act (1997) and Best Pharmaceuticals for Children Act (BPCA) (2002, amended in 2007 and renewed in 2012) offer financial incentives in the form of patent extensions for companies that voluntarily test their drugs in pediatric patients. BPCA also provides a mechanism by which off-patent therapeutics might be studied through a collaboration between the FDA and National Institutes of Health. The National Institute of Child Health and Human Development (NICHD) is responsible for funding these studies from its annual budget and has been sponsoring the Pediatric Trials Network (PTN) with more than $95 million (USD) since its creation. This an alliance of clinical research sites cooperating in the design and conduct of pediatric clinical trials. PTN research provides evidence for optimal dosing of commonly used medications in infants and children, improving healthcare for these patients. In Canada, MICYRN has similar goals of developing a consortium to assist in providing a streamlined approach to conducting clinical trials, but its funding is quite limited. A similar funding strategy needs to be adopted between Health Canada and CIHR to fill the gap that exists in Canada in pediatric research for off-patent drugs as well as creating an environment that fosters increasing the number of pediatric clinical trials, gathering real-world data and real-world evidence to monitor post-market safety and adverse events.

Summary

Many of the initiatives already underway will go a certain distance to make a difference to improve access to pediatric medicines in Canada. We have seven million children in Canada, and at one time, we have all been children. **The lack of pediatric-specific policies and practices supported by regulations and incentives is unacceptable and results in Canadian children having access to a lower standard of medication evidence and access than in adults. The establishment and funding of an EPAB is of utmost importance, along with a fully funded and appropriately, resourced Office of Pediatrics and Patient Involvement at Health Canada,** should be carefully considered for the reasons cited above. A second key initiative, also supported by the EPAB, is the **ability for Health Canada to request pediatric data, to support pediatric indications and pediatric formulations, to sponsors when it is known that use in**

pediatrics will occur. Finally, these must be coupled with an incentive program. As pediatric specific practices, policies and regulatory requirements/legislations and incentives exist in other jurisdictions, we have the opportunity to evaluate and learn from these programs to build a Canadian one that meets our needs and is tailored to our health care system.

Thank you for your kind consideration in this matter. We are a group of national pediatric experts who are willing to support Health Canada in its modernization efforts. We encourage the Treasury Board to contact any of the undersigned, at any time, to discuss our proposed recommendations. It would be our pleasure to work with both the Treasury Board and Health Canada to find solutions that take into consideration the needs of Canadian children.

Best regards,

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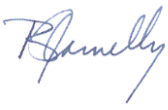

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About the Goodman Pediatric Formulations Centre of the CHU Sainte-Justine

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 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 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.