August 26, 2019

Dear Agile Regulations Project Team,

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 Paediatrics Society, are submitting this response to the request for feedback regarding the "Agile regulations for advanced therapeutic products and clinical trials" Discussion Paper dated July 2019. We are pleased to contribute to this consultation effort as representatives of a number of important stakeholders in the national pediatric community.

Although the "Agile Regulations Discussion Paper" is larger in scope, this letter will focus on the needs of pediatrics when addressing "new and increasingly complex health products". Children are not mini-adults, and as such, need special accommodations in health policies to ensure that their needs are appropriately met. 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, pediatrics medicines also need to be carefully revised to ensure that there are no unnecessary barriers to either study, access, or utilize these medications – when proven safe and effective in Canada. Inflexible and complex processes that are not tailored to pediatrics will, unfortunately, preclude that research, innovation and medicines available elsewhere in the world will be unavailable to Canadian children. It is therefore of utmost importance when revising any regulatory policies and procedures that there is specific consideration given to the needs of Canadian children. We recommend working with experts in the pediatric community throughout the process to ensure that that pediatric needs are met, and that no inadvertent constraints are created.

Risk-Based Approach for Regulating Clinical Trials

It is acknowledged in the Discussion Document, that under-represented, small or geographically dispersed patient populations may discourage the conduct of clinical trials in Canada. Moreover, Canada's competitiveness in the pediatric clinical trial space is significantly impacted as a result of the administrative requirements in the current *Food and Drug Act* for therapeutic agents. 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.

We are therefore delighted that Health Canada is considering a risk-based approach for the modernization of the Food and Drug Act. Existing regulatory policies at Health Canada have been designed primarily to ensure oversight of industry-initiated studies with new therapeutic

agents. In paediatrics, 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 Organisation for Economic Co-operation and Development (OECD) supports a risk-based initiative and has proposed a new framework for the oversight of clinical trials that involves a determination of risk using a stratified approach based on the marketing status of a product. Many investigator-initiated Phase 2 or 3 trials in children meet the Category B definition of OECD, i.e. "tested according to treatment regimens outside the marketing authorization and supported by published evidence and/or guidance and/or established medical practice".

In Europe, the Draft EU Regulation 2012, outlined in the OECD paper, follows a *low-intervention* risk assessment model. A clinical trial that is determined to be *low-intervention risk* is subject to less stringent rules related to monitoring, regulatory content in trial master files, and traceability of investigational products. To qualify as a *low-intervention risk* clinical trial, it must meet requirements outlined by the regulators, documenting that the investigational medicinal product is already approved. Reference to the OECD council of Governance of Clinical Trials classification is made in the "Regulation (EU) No 536/2014 of the European Parliament and of the Council of April 16th, 2014 on clinical trials on medicinal product". The Preamble of the Regulation states the following: "*The risk to subject safety in a clinical trial mainly stems from two sources: the investigational medicinal product and the intervention. Many clinical trials, however, pose only a minimal additional risk to subject safety compared to normal clinical practice. This is particularly the case where the investigational medicinal product is covered by a marketing authorization, that is the quality, safety and efficacy has already been assessed in the course of the marketing authorization procedure or, if that product is not used in accordance with the terms of the marketing authorization, that use is evidence- based and supported by published scientific evidence on the safety and efficacy of that product, and the intervention poses only very limited additional risk to the subject compared to normal clinical practice*." In the Canadian pediatric research community, a large proportion of the clinical trials on medicinal products in Canadian children meet the aforementioned criteria and therefore, a risk-based stratified approach would encourage the number of pediatric clinical trials conducted in Canada. Both academia and industry would see benefit: less stringent regulatory requirements would be advantageous for Investigator-Initiated research and the reduction of some administrative barriers would be enticing for more industry sponsors. Eventually, Canadian children – like children in Europe - would get an opportunity to benefit from progress in pharmaceutic developments.

Canada's MICYRN, whose mandate is to remove barriers to high quality research by facilitating the development of streamlined best practices, standardization, and process improvement is currently chairing an **international working group with 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.

An example of a risk related adaptation to regulatory requirements at Health Canada exists and may be used to support the need for streamlining, while also acting as a template with which to build a pediatric focused process. On January 4, 2013, regulatory amendments to Part C, Division 3 of the Food and Drug Regulations pertaining to Positron-Emitting Radiopharmaceuticals (PERs) came into force. Prior to this, researchers performing basic research with PERs in humans were required to submit clinical trial applications (CTAs). Health Canada determined that the use of PERs in basic research in humans typically poses minimal health risks, provided certain criteria are met. In collaboration with members of the research community, they developed what they felt to be a more appropriate regulatory oversight that reduces and simplifies regulatory requirements while mitigating the risks to humans by ensuring that the products used are safe and of high quality. A simplified application process, known as a BRAP, was developed that includes provisions pertaining to the submission of an application, good clinical practices, good manufacturing practices, labelling, record-keeping and adverse reaction reporting. The responsibility of research ethics boards remains the same, ensuring oversight of clinical trials under the clinical trial regulations.

One of the unsolved problems in daily pediatric care is to get a drug in a form that is feasible and acceptable to take by a young child. Regarding formulations that are routinely adapted for pediatric administration but that are not yet indicated on the product monograph, there is an urgent need to conduct studies on the efficacy and safety of these medications in various age groups. As many of these medications have been in use for decades, considerable market experience already exists; this should be considered when evaluating the level of risk of proposed clinical trials comparing pediatric formulations. Here, offering a flexible regulatory framework while maintaining Health Canada's important role of ensuring safe and effective medications for Canadians, is possible.

The ability to stratify clinical trials by risk category would 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. Canada is fortunate in having a good number of child health research experts with expertise and experience in the design, conduct and evaluation of novel clinical trials in children.

We agree that food and special dietary products should be evaluated with a level of rigorousness and scrutiny similar to medicinal products. Requiring food products manufacturers to conduct clinical trials in Canada will translate in evidence for their use and safety that is often lacking, particularly in neonates and infants. However, many comparative effectiveness studies or randomized clinical trials with food products have been traditionally conducted by academic researchers worldwide and in Canada. To prevent hampering those efforts, we also recommend the use of a risk-based strategy with different levels of scrutiny and less stringent regulatory requirements, where applicable. The development of an *Expert Paediatric Advisory Board* at Health Canada that could serve as a cross-branch resource for Health Canada would be an important enabler of these strategies. Canada's academic community is well positioned to

provide expertise to Health Canada to move towards our common goal of safe and effective drug treatment for Canada's children.

Creating a flexible approach for authorizing Advanced Therapeutic Products (ATPs)

We appreciate the tremendous work that has already been done to build the Health Canada Concierge Service and understand that this pathway is designed for the marketing authorization of Advanced Therapeutic Products (e.g. gene therapy medicinal products, somatic-cell therapy medicinal products and tissue engineered products). Many of these unique products are developed for conditions affecting both children AND adults. Most often children are the primary beneficiaries. As the revolution in cellular, genetic and biologic therapy moves forward we anticipate that many of these novel therapies should be regulated via an ATP pathway.

> Examples include cellular therapies. While CAR-T therapy was approved under existing regulations, it is a therapy that would have benefited from ATP marketing authorization. As genetic therapies and engineered tissues enter into therapeutic evaluation approaches such as ATP authorization will be more and more important.

Given that many products which are likely to be evaluated via the ATP route are likely to be produced by small or mid-size biotechnology enterprises without the long regulatory experience of large multi-national drug companies, the concept of a concierge to help direct submissions is appealing notably in encouraging Canadian innovators to develop and test their innovative treatments in Canada rather than going to the United States or Europe.

While there is agreement on the risk-based approach and that the concierge service is helpful we would like to also acknowledge that the following gaps need to be addressed:

1. A strategic rare disease policy
2. Evidence review that is more contextual and flexible for high risk trails of novel therapeutics
3. Recognition and investment in the value and contributions of real-world evidence using patient registries and the disease community to support conditional approvals and post-marketing commitments.

In conclusion, we strongly recommend that an *Expert Paediatric Advisory Board* (EPAB) be established and appropriately funded, as outlined in the Improving Paediatric Medications: A prescription for Canadian children and youth Policy Paper. The EPAB should sit at the Portfolio level, should be accountable to the Deputy Minister of Health, and should advise on regulatory, reimbursement and research activities related to paediatric medications. We also believe that the EPAB could provide invaluable advice and support to a variety of initiatives within the healthcare system. For example, the EPAB could support the new regulatory pathway for ATPs

that involve pediatric indications. We also envision the EPAB being useful to assist in selecting priority medications for any pediatric investigation plans, determining areas where clinical data are needed and identifying medication gaps where attention should be focused to improve pediatric care. Moreover, the new proposed National Pharmacare program suggests that it should "respond to the specific and unique needs of children and youth" (Recommendation 29). In this effort, the EPAB could be an important contributor to elucidating an essential pediatric medications list that would be included in the first phase of implementation of the national drug formulary (January 2022). Canada's academic community is well positioned to provide expertise to Health Canada to move towards our common goal of safe and effective drug treatment for Canada's children, and we believe that the EPAB is one method of contributing to this goal.

Should you have any further questions or wish to set up a meeting with the undersigned, in Ottawa or Toronto, it would be our pleasure to discuss this further with you.

Best regards,

Thierry Lacaze, MD, PhD
Scientific Director, MICYRN
KidSCAN Trials Lead

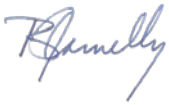
Michael Rieder MD, PhD
CIHR-GSK Chair in Paediatric
Clinical Pharmacology
Western University

Andrea Gilpin, Ph.D, MBA
General Manager
GPFC of the CHU Sainte Justine

Catherine Litalien, MD, FRCPC
Medical and Scientific Director
GPFC of the CHU Sainte-Justine

Geert 't Jong, MD, PhD
Chair, Drugs and Hazardous Substances
Committee
Canadian Paediatric Society

Emily Gruenwoldt
President and CEO
Children's Healthcare Canada



Robert Connelly, MD
President
Pediatric Chairs of Canada

Charlotte Moore Hepburn, MD
Director of Medical Affairs
Canadian Paediatric Society

Cc: **Megan Bettle**, Director, Regulatory Review of Drugs and Devices, BGTD
Liz Anne Gillham-Eisen, Director, Office of Policy and International Collaboration, Biologics and Genetic Therapies Directorate, Health Canada
Jean-Marie Leclerc, Executive Director, GPFC of the CHU Sainte-Justine
David K. Lee, Chief Regulatory Officer, Health Products and Food Branch
Celia Lorenco, Director, BGTD Health Canada
Pierre Sabourin, Assistant Deputy Minister - Health Products and Food Branch at Health Canada
Supriya Sharma, Senior Medical Advisor to the Deputy Minister and Senior Medical Advisor, Health Products and Food Branch
John Patrick Stewart, Director General, Therapeutic Products Directorate

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.