The Rosalind & Morris Goodman Family pediatric formulations centre of the CHU Sainte-Justine

September 28, 2018

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Commentary to Proposed Pharmacare with Regards to Pediatric Formulations

Dr. Hoskins,

The Goodman Pediatric Formulations Centre (GPFC) would like to provide its perspective regarding pediatric formulations vis-à-vis the proposed implementation of a National Pharmacare Program. We are pleased to have the opportunity to comment on this anticipated change.

The Goodman Pediatric Formulations Centre

The GPFC has the goal of improving access to child-friendly medicines. We are the only Centre in Canada whose mandate is to assist in the development and commercialization 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, for optimal treatment. Even though the GPFC works closely with hospitals, health care providers and industry, our positions and actions are completely independent of these third parties.

The Problem: Canadian Children Do Not Have Access to Commercialized Pediatric Formulations

We need to have commercial pediatric formulations available for Canadian pediatric patients. In many cases, commercialized pediatric formulations are available in other jurisdictions, such as in the United States and in Europe; however, these formulations are not commercialized in Canada for a number of reasons. Firstly, the Canadian pediatric market is small and unlike the programs in the United States and Europe, there are neither commercial incentives, nor regulatory protection granted to bring commercialized pediatric formulations to Canada. Secondly, the pediatric regulatory approval pathway is perceived as unclear. Thirdly, once marketing

approval is received, reimbursement groups may, or may not, recommend these medications to the provinces for public listing. All of these processes contribute to the complexity of the Canadian system and discourage commercialized formulations to be marketed in Canada.

When Commercialized Formulations are Not Available

When commercialized pediatric formulations are not available to Canadian children, adult forms need to be modified (i.e. crushing a tablet, dissolving it in water and diluting it in an oral vehicle) to suit the dosing needs of children. Although the exact percentage of compounding used in children is unknown, a common understanding is that many medications given to Canadian children have no commercially available, age-appropriate formulations resulting in the manipulation of adult dosage forms. As such these manipulated medications, fall outside of regulatory approval, with the efficacy and safety risk this presents[1]. Using a safe and effective commercialized formulation is strongly preferred by healthcare providers, pharmacists, parents and patients.

The Proposed Pharmacare Program Would Provide Equal Access to Pediatric Formulations Across Canada

Currently in Quebec, l'Institut national d'excellence en santé et en services sociaux (INESSS) makes formulary decisions for the Quebec government while the Canadian Agency for Drugs and Technologies in Health (CADTH) makes listing recommendations for the rest of Canada. However, provincial, federal and territorial governments decide whether they follow the recommendations of CADTH and INESSS, leading to variations in drug listings decisions across the country. The unintended result is that patients may or may not have access to pediatric formulations depending on where the medicine is listed. The inequality of access to these pediatric medications across the country is unacceptable. In a country such as Canada, it is inconceivable that pediatric drugs would not be equally accessible to this vulnerable population.

A National Pharmacare Program Would Simplify the Health Care System and Increase Transparency in Decision-Making

The Federal Government needs to promote a regulatory and reimbursement system that is able to evolve and fit an economy where innovation and change are the norm, and where the pediatric drug market is small. The GPFC believes that it is imperative to provide special considerations for the Canadian pediatric population with respect to making pediatric formulations readily available in Canada. Increasing the number of commercialized

[1] Improving Medicines for Children in Canada, 2014, Council of Canadian Academies.

formulations in Canada would address a clear unmet medical need. The proposed National Pharmacare Program would simplify the reimbursement and access of medicines, and decrease the time of review, by having one agency, CADTH, lead both.

A Centralized Pharmacare Program Could Provide National Reimbursement Exclusivity for Pediatric Formulations

The lack of pediatric incentives for manufacturers to submit their applications in Canada, along with the complex reimbursement and pricing processes, are barriers that discourage manufacturers from bring pediatric formulations to Canada. Moreover, many of these pediatric formulations are generic medicines where there are no incentives available for commercialization in Canada. As stated above, a National Pharmacare System would simplify the process and would also make possible the development of incentives, such as providing reimbursement exclusivity. The ability to develop incentives specific to pediatric formulations would be a significant step forward to improving access to child-friendly medicines in Canada.

Improved Quality Health Care Between Hospital and Community Pharmacies

Discrepancies between in-hospital and out-of-hospital formularies may exist and could introduce errors for a pediatric patient. In situations where commercialized formulations may be listed on certain formularies, while the compounded drug are listed on others, may cause differences in concentrations between the two formulations which could potentially lead to medication errors if the dose conversion is not properly done. A National Pharmacare program would provide consistency between hospital and public drug plan sectors, reduce possible dosing errors and would ensure continued high quality patient care throughout the patient journey.

Better Tracking of Utilization Rates of Pediatric Medicines at a National Level

Currently there is very limited information available on drug use in pediatrics patients. Market Research data from companies such as Iqvia (formerly IMS Brogen Quintiles) can provide some insight on number of prescriptions and units of medications dispensed at the community pharmacy level but this information does not cover in-hospital use and does not provide any information on the indications, dosages used or safety. A National Pharmacare program would allow for a national utilization rate and therefore better understanding of the needs of the pediatric population across Canada.

The GPFC Supports a National Pharmacare Program

The GPFC urges all stakeholders, Health Canada, Reimbursement Agencies, Pricing Bodies and the Provinces and Territories, to coordinate and align as much as possible to improve access to pediatric formulations. Success is unattainable until this occurs.

The GFPC supports an expanded mandate of CADTH to maintain the common National Prescription Drug Formulary (including Québec) to ensure harmonization among the drug formularies. Guidelines and decision-making processes should be as transparent as possible. A significant step towards simplifying the reimbursement and listing processes would be achieved by having CADTH manage the National Prescription Drug Formulary, which should encourage more pediatric formulations to be commercialized in Canada.

Finally, and most importantly, a common voluntary National Prescription Drug Formulary would ensure equal access to pediatric formulations for all Canadian children.

Best regards,

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The Rosalind & Morris Goodman Family pediatric formulations centre of the CHU Sainte-Justine

September 11, 2018

Lindsay Wild
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Commentary to Regulatory Modernization Initiative

Dear Ms. Wild,

The Goodman Pediatric Formulations Centre (GPFC) would like to provide its perspective regarding pediatric formulations within the proposed Regulatory Modernization Initiative, which was launched by the Treasury Board of Canada Secretariat. We are pleased that the process is entering its next phase and 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. Within this context, the GPFC believes that considerations must be given to pediatric formulation regulations to promote improved access to child-friendly medicines in Canada. Canada is sorrowfully lagging behind in this area and this modernization effort affords Health Canada the opportunity to take a leadership position and make positive change in pediatric formulations. **Canadian children deserve the same pharmaceutical standards, and treatment options than adults to ensure that their quality of care is optimal**.

The Goodman Pediatric Formulations Centre

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The Problem: Canadian Children Do Not Have Access to Pediatric Formulations

Canadian Pediatric Medicines are Often Compounded

The lack of availability of pediatric dosage forms can lead to treatment failure or toxicity in children. Approved adult forms often need to be modified in some manner to administer the desired accurate dose to children, and as such, are used off-label. Compounding is the process by which an adult formulation is manipulated by a health care provider, family members, or others, to adapt the adult formulation to be used in children. Compounding is regulated by provincial pharmacy standards, based on Guidelines published by the National Pharmacy Regulatory Authorities (NAPRA) on behalf of pharmacy colleges. NAPRA guidelines admittedly fall short of Health Canada's Good Manufacturing Practices (GMPs) in multiple ways and, even though compounding may be acceptable in some circumstances, it should not be considered an equivalent surrogate for a Health Canada approved formulation that has been assessed for use in children. Given that compounded medicines are not overseen by Health Canada for full compliance with the current known rigorous requirements, the compounded medication's characteristics and specifications are not always known, well established or controlled, before their use in children. This is particularly true with reference to: stability, potency, content uniformity, purity (chemical and microbial) or bioavailability, amongst others. Most importantly, the administration of the appropriate dose cannot be guaranteed because of the variables outlined above. Moreover, most of the compounded medicines have an unpleasant taste, which leads to compliance challenges with the children to whom these medications need to be administered. Although every measure is taken to ensure that compounded medications provide the most accurate dosing and are safe, errors do occur. In 2017, an immunosuppressive drug called tacrolimus (a medicine that is pivotal to prevent rejection in pediatric organ transplant recipients), was shown to have compounding errors at several junctures as outlined in this ISMP article. As a concrete example, an eight-month old liver transplant child was admitted to the CHU Sainte-Justine with acute liver rejection as a consequence of a compounding error by the community pharmacy, resulting in the boy receiving one tenth of the prescribed dose. We strongly believe that this very vulnerable patient population should have access to the most appropriate formulations to optimize success of these transplants.

Although the exact percentage of compounding used in children is unknown, a common understanding is that many medications given to children have no commercially available, age-appropriate formulations resulting in manipulation of adult dosage forms. As such these manipulated mediations, fall outside of regulatory approval,

with the efficacy and safety risk this presents[1]. Some compounding is needed in oncology products with the concerns and obvious health risks it brings to the individuals preparing the needed pediatric formulations[2]. In the NIOSH Alert cited below, some health care workers who had to manipulate toxic substances, using the appropriate safety-operating procedures, were found to have measurable concentrations of the hazardous drugs in their urine. To provide another example, 6-mercaptopurine (which is used to treat children with leukemia) needs to be compounded daily by the family, at home, for a period of two to three years. This has the potential to expose the entire family to this toxic chemical, which is unacceptable given a commercialized pediatric formulation has been available since 2012 in Europe and 2014 in the United States. A video is linked to illustrate the challenges from a patient and caregiver perspective. This video also demonstrates the potential exposure and danger to family members when compounding at home.

Compounding can have a deleterious effect on the efficacy of a medication. As a third example, omeprazole and lansoprazole are two commonly used proton pump inhibitors (PPIs) in pediatrics, including children as young as a few weeks of age. There is no pediatric formulation in Canada for these PPIs[3]. In both product monographs, it clearly states that the capsules or tablets must not be chewed, broken or crushed (due to an enteric coating), yet Canadian pediatric hospitals manipulate these adult forms daily and in so doing, they crush or break the adult formulation which may destroy the enteric coating. The purpose of the enteric coating is to prevent its dissolution in the stomach for absorption further in the digestive tract. The crushing of the tablet or capsule is expected to significantly reduce the efficacy of the drug, as much of it will not survive the acidity of the stomach. This is a striking, yet powerful example of why compounding is simply not appropriate and significantly compromises successful treatment for our children.

The Solution: Streamline Regulatory Process so that Industry Submits their Pediatric Formulations in Canada

The ideal is to have commercial pediatric formulations available for Canadian pediatric patients. In many cases, commercialized pediatric formulations are available in other jurisdictions, such as in the United States and in Europe. However, these commercial pediatric formulations are often not marketed in Canada, leaving an already vulnerable patient population without access to commercially available pediatric formulations. This

[1] Improving Medicines for Children in Canada, 2014, Council of Canadian Academies.
[2] NIOSH Publication September 2004-165. "Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in a Health Care Setting" https://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf
[3] Of note, esomeprazole is the only PPI for which a pediatric formulation is available in Canada (10 mg delayed release granules for oral suspension) which requires manipulation and does not meet the dosing flexibility for those younger than 1 year of age.

represents a clear unaddressed medical need that could be partially solved through improved regulatory processes.

Challenges that Prevent Industry from Submitting Pediatric Formulations in Canada

There are several reasons why existing commercial pediatric formulations have not been introduced into the Canadian market.

- Firstly, the Canadian pediatric market is extremely small and unlike the programs in the United States and Europe, there are neither commercial incentives, nor regulatory protection granted, to bring commercialized pediatric formulations to Canada. Due to these factors, it is impossible to build a viable business case to bring commercialized child-friendly medicines in Canada. This results in American and European children having access to pediatric formulations whereas our Canadian children can only have the compounded equivalent, with the significant limitations and associated risks.

- Secondly, the pediatric regulatory approval pathway is perceived as unclear and there is significant concern that it will include costly additional clinical studies targeting very restricted patient populations. In the case where there is no need for further clinical studies, the costs for the preparation of a Canadian New Drug Submission can involve considerable investment (>$100,000 to $250,000). This investment does not include the Health Canada fees to submit the dossier for review. Given that Health Canada is preparing to increase the fees in its Revised Fee Proposal for Drugs and Medical Devices, we believe that this significant augmentation in submission fees will only heighten the already significant barrier precluding pediatric formulations from being submitted for market approval in Canada.

- Thirdly, the Health Canada framework was conceived with the adult population in mind, which does a disservice to our children. Despite, the creation of the Office of Pediatric Initiative, in 2005, and the Pediatric External Advisory Committee, in 2009, (currently inactive) children are orphaned within the Health Canada system. In 2012, the Minister of Health, on behalf of Health Canada, asked the Council of Canadian Academies to provide an evidence-based and authoritative assessment of the state of research and regulation leading to the approval of therapeutic products for children, in Canada and abroad. This report clearly stated that, “children respond to medications differently from adults, and medicines must be studied in children and formulated for children”. Despite the conclusions in this report, in 2018, we see very little progress to improve access to child-friendly medicines and we find this truly disappointing.

- Fourthly, the mandate of Health Canada is to ensure the efficacy and safety of the drugs that are submitted to the agency. Given that in the case of pediatrics, very few applications are submitted, and given the nature of Health Canada to only respond to submissions, Health Canada's responsibility is very limited. However, one needs to realize that the lack of pediatric incentives, pediatric expertise and clear pediatric regulatory pathway within Health Canada, all contribute to the lack of child-friendly medicines. Health Canada therefore plays a role in the extensive practice of compounding for Canadian children.

- Finally, if and when approved by Health Canada, reimbursement groups may not list these medications, as the health technology assessment (HTA) are based on criteria applicable to adult forms, which may not apply, or be possible, in children. Therefore, reimbursement for a pediatric formulation may be rejected. A recent example of this unfortunate situation occurred with propranolol (Hemangiol®) where the company received a Notice of Compliance but both reimbursement agencies (Canadian Agency for Drugs and Technologies in Health (CADTH) and Institut national d'excellence en santé et en services sociaux (INESSS)) did not support its use. INESSS did not recommend propranolol reimbursement based on comparison with the compounded medication, while CADTH recommended reimbursement only with a significant price reduction. Both these agencies used the price of the compounded formulations as the basis of their cost assessment. It is impossible for a medication manufactured in a highly controlled, GMP quality environment be compared to that of medicine compounded in a pharmacy. The good news about propranolol is that it recently completed negotiations at Pan-Canadian Pricing Alliance and it will become accessible to Canadian children soon. This example does underscore the uncertainty experienced by industry and further highlights the importance of having an aligned transparent system. In this regard, Health Canada and the HTA agencies have taken some steps towards coordination with the use of Aligned Reviews (Section 3.2); however, this has been limited in use, and without congruency between these agencies there is potential for significant inefficiencies for all stakeholders involved. This aspect will not be discussed further but does add to the complexity behind the business decision of whether to bring a pediatric formulation in Canada.

Working Together to Find Potential Solutions

The GPFC is a not-for-profit organization that is working as a facilitator between industry, regulatory and reimbursement agencies to bring commercialized pediatric formulations into Canada. It is already a difficult and challenging situation for the reasons cited above. Given the mandate of Health Canada's modernization efforts is to promote a regulatory system that is able to evolve and fit an economy where innovation and change are the

norm, we believe that it is imperative to provide special considerations for the Canadian pediatric population with respect to facilitating the process behind making pediatric formulations readily available in Canada. Increasing the number of commercialized formulations in Canada, would address a clear unmet medical need.

The GPFC believes that our current healthcare system does not serve well bringing pediatric formulations into Canada. Health Canada is a crucial first step in the drug approval process and we believe that any changes that Health Canada can make to support pediatric formulations registrations would send a message to the other important organizations involved in authorizing access to these pediatric formulations. We highlight six issues accompanied with six solutions that would be agile and adaptive and which would reduce barriers to innovation and competitiveness in the area of pediatric formulations.

1. *Priority Review Designation for Pediatric Formulations*

We conducted a survey with hospital pharmacists from 13 pediatric Canadian institutions in 2017. A total of 40 compounded drugs were identified as a priority by at least one institution. Among these, 12 drugs were identified as a priority by at least one third of the centers, and are now on our priority list of much needed pediatric formulations. *For 75% of the drugs on the priority list, pediatric formulations have been approved in other jurisdictions and are not being brought into Canada for the reasons cited above*. Moreover, almost all of these are old generic drugs for which there are no incentives or any intellectual property protection, making these drugs less interesting to invest time and money in for their Canadian registration.

The clinical effectiveness of the drug products approved in other jurisdictions have been established, and although not all medicines on the list are approved to treat serious or life-threatening conditions, the risk of any error in compounding remains, and can have deleterious consequences in a population that is already vulnerable. To provide another unfortunate example, in 2016 an eight-year-old boy who had been receiving tryptophan for a sleep disorder, sadly died due to an unfortunate human error. Tryptophan had to be compounded to a suspension by a community pharmacy, which had filled the prescription/performed the compounding in the past. That evening, the child was given his usual dose of the medication and was found deceased in bed the next day. It became known that there had been a selection error at the pharmacy whereby baclofen, an antispasticity agent, had been erroneously used instead of tryptophan to prepare the suspension. Although cautious measures are taken at the pharmacy-level to ensure such errors do not occur, there are risks inherent to the compounding/reformulation and the standard cannot meet quality found in a commercial preparation. CBC Article. ISMP Article.

Recommendation:

Together with Health Canada, a priority list for pediatric formulations is identified and it is highly recommended that any submission for these formulations would be assigned a priority review designation. This shortened review of 180 days would provide an incentive for industry to invest in these medications. There should also be consideration for those pediatric formulations that may not be considered a priority where, nonetheless a need exists.

2. *Fee Reduction for Pediatric Formulation Submissions*

Health Canada has recently provided the public with a Revised Fee Proposal for Drugs and Medical Devices (dated May 24, 2018). Within this new proposal, there are revised and reduced fee structures for small businesses. In addition, we observed that there was specific mitigation for waiving fees based on individual product sales. Within this context, there is a fee waiver for a first pre-market drug submission for any medicine contained on the *List of Drugs for an Urgent Public Health Need.* Furthermore, a new mitigation was proposed, where all fees would be waived for publicly funded health care institutions or unique organizational structures.

Moreover, when a pediatric formulation is approved either in the United States or in Europe, we believe that the Health Canada Review should be based on foreign reviews and approvals, therefore, less onerous and thereby justify a reduced review fee. We understand that Health Canada is working towards a policy for the use of Trusted Foreign Reviews and we comment on this further in Section 3.1.

Recommendation:

We recommend that the pediatric formulations priority list, jointly developed by Health Canada and GPFC should be added to the *List of Drugs for an Urgent Public Health Need*. Specifically for pediatric formulations, we would request that the fee waiver/significant reduction not only be on the first submission but on all submissions for drugs on the *List of Drugs for an Urgent Public Health Need*.

We would like Health Canada to consider the GPFC a unique organizational structure that could benefit from such a waiver, should it wish to submit a drug for marketing authorization on its own.

Should adding pediatric formulations to the *List of Drugs for an Urgent Public Health Need* not be an option, we would request that Health Canada consider pediatric formulations a unique type of product, to which a fee waiver/significant review fee reduction, be applicable in order to facilitate bringing to the Canadian market pediatric formulations to better serve an already very vulnerable patient population with unique medical needs.

For pediatric formulations already approved in US and/or EU, we recommend reduced fees/fee waiver such as outlined in Section 3.1, below.

3. *Streamline Data Submission Requirements for Pediatric Formulations*

3.1. Using Trusted Foreign Regulatory Decisions

The GPFC understands 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. The GPFC asserts that pediatric formulations could greatly benefit from this initiative and we have provided our feedback both in writing and by teleconference to the consultations earlier this year. We feel this initiative would have a significant positive impact on the health of our Canadian children.

Recommendation:
We recommend that once a trusted foreign regulator approves a pediatric formulation, it becomes eligible for the Canadian market. We do not believe that the pediatric formulation should be marketed for a prescribed period of time in the trusted foreign regulator country(ies) before it is admissible for this program in Canada. One needs to remember that failure to have such formulations result in the practice of compounding with its inherent risks. As outlined in Section 2, we believe that significant reduced fees or a fee waiver for pediatric formulations for this type of submission is warranted.

3.2. Use of Aligned Reviews between Health Canada and Health Technology Assessment Organizations

On June 22, 2018, Health Canada published a Notice to Industry regarding Aligned Reviews Between Health Canada and health technology assessment organizations. This Notice provides the option for industry to have their applications reviewed by Health Canada and health technology organizations in parallel, instead of in sequence, which could save considerable time in the review process.

Recommendation:
We believe this is a valuable approach to be used for pediatric formulations. Our recommendation is that the specific considerations for pediatric populations are taken into consideration when these applications are being reviewed. To do so, we request that a pediatric expert be included as part of both the Health Canada and health technology assessment organizations evaluation committee. In addition, we recommend that an expert from the GPFC also be part of this committee to contribute to the evaluation of such submissions.

3.3. Continuation of Drug Submissions Relying on Third Party Data & Published Data Only Category

With one of our pharmaceutical partners, we have successfully used the Drug Submissions Relying on Third Party Data. This mechanism has been productive in the GPFC attracting a partner to submit one pediatric formulation in Canada. However, in one case, the sponsor used a Published Data Only filing category, for a generic drug submission, which was anticipated to have a fee of approximately $20,000. Recently, Health Canada has re-classified this into a Clinical or Non-Clinical Data and Chemistry & Manufacturing submission, which has increased the fees to $176,000. Not only was this unexpected, but the significant increase in fees may deter this industry partner from submitting any pediatric formulations in the future.

We understand that the Published Data Only category of filing is proposed to be abolished as outlined in the May 2018 Revised Fee Proposal for Drugs and Medicinal Devices. The reasons cited are that the workload and level of effort required, depending on the Published Data used, could more easily be merged into another submission category. In pediatrics, we are challenged in attracting industry partners to Canada under the existing fee structure, and should this plan come to fruition as it is indicated, we will only further reduce the currently low interest in bringing these much-needed pediatric formulations to our Canadian market.

Recommendation:
When using Drug Submissions Relying on Third Party Data provide a reduced fee structure or fee waiver for companies that submit pediatric formulations in Canada. It is envisioned that the Drug Submissions Relying on Third Party Data could be replaced by the Trusted Foreign Regulatory Decisions depending on how that program is developed. We recommend a concomitant reduced fee as it would be expected that Health Canada resources required for revision would be decreased compared to a regular submission.

3.4. Review Canadian Specific Labelling Requirements and Sample Testing

Health Canada requires Canadian specific labels for products sold in Canada, without regard for the low sales volume of products sold for pediatric indications. This can be prohibitive as manufacturing and packaging lots are large and the requirement for Canadian-specific labels results in Canadian companies/affiliates purchasing a large quantity from its manufacturing plant, resulting in most of it being destroyed and written off because most of the inventory will expire before it can be used.

In another example, if the product is manufactured in a non-Mutual Recognition Agreement (MRA) country, Health Canada requires samples to be retained and tested in Canada, which adds significant costs thereby making it unattractive to bring small volume products into Canada.

Recommendation:
Adapt the Canadian specific labelling requirements such that Canadian specific lots do not need to be manufactured. In addition, Health Canada should explore alternative approaches to meeting the GMP requirements for small volume products, such as reliance on Certificates of Analysis from non-MRA could be considered in these exceptional circumstances. As an aside, one should question what is safest for children's medicines: a drug produced by a non-MRA manufacturer or one compounded at the pharmacy or by caregivers.

4. Provide Incentives for Pediatric Formulations

Health Canada has the authority to request but cannot require innovative companies to submit pediatric data, or apply for a pediatric indication, where a new drug submission is filed for approval in Canada. Both the EMA and the FDA require pediatric data from manufacturers for approval of new drugs, and therefore the data exist, yet Health Canada do not have access to this data unless filed by the innovator company. The sole incentive in Canada is found under the Canadian Data Protection framework, which can reward innovator companies who file a new drug submission for a new chemical entity that contains pediatric data by providing an additional six months of exclusivity during which time Health Canada will not accept the filing of a generic competitor. In both the US and the EMA, a two-pronged approach has improved the development of pediatric formulations and indications: the first is providing some market exclusivity or benefit to any potential new drug filer, the second is requiring pediatric studies as part of the new drug application. Health Canada does not require that the new drug submission include the pediatric data and consequently, the number of pediatric submissions is low.

In Canada, many of the medicines have been marketed for years by the innovator without a suitable pediatric formulation, and are now subject to generic competition. Generic products, by their definition, do

not benefit from market exclusivity provisions or intellectual property protection and therefore there is no incentive to bring pediatric formulations that are available and approved for pediatric use in other jurisdictions, to the Canadian market. This is not viable and therefore a *different regulatory approach is urgently needed*.

In the case where there is no commercialized pediatric formulation of an off-patent medicine (in any of the trusted foreign jurisdictions) and a manufacturer chooses to develop a pediatric formulation and obtain a pediatric indication, again, there is also no incentive for this investment.

Furthermore, the generic manufacturers are often challenged at the pricing and provincial reimbursement part of the approval process where the provinces demand the lowest price possible without taking into consideration the consequence of not having pediatric formulations be brought into Canada.

Although the EMA and FDA pediatric approval programs do have certain challenges, they have resulted in a greater number of pediatric indications and formulations. The availability of safe and effective medicines for Canadian children would be significantly improved if industry submitted, and Health Canada used, these existing pediatric data.

Recommendation:

For patented products, Health Canada considers developing a similar system, to what has been developed at the EMA and FDA, containing both an incentive, in the form of market protection, and a requirement to submit pediatric data for innovative companies.

For off-patent medicines for which a pediatric formulation exists elsewhere with available pediatric data, we recommend that Health Canada consider providing a 4-6 year data protection.

For off-patent medicines where no pediatric formulations are available, there is a desperate need to develop incentives such as the Pediatric Use Market Authorization (PUMA) program. The PUMA offers 8 plus 2 years of data and market protection. Considering that pediatric studies will be required, there should be alignment between Health Canada and CIHR to fund this research. This is similar to the NIH supporting pediatric trials to provide data to the FDA.

A leadership position from Health Canada and the Minister of Health to entice pediatric formulation submissions and to ensure alignment throughout the process is essential and cannot be understated. It is possible to use elements of the EMA and FDA programs, however, such a program would need to be tailored to accommodate the needs of our health care system.

5. *Building on the Rare Disease Framework*

In August 2018, Health Canada disclosed an updated Rare Disease/Orphan Drug Approach. In this framework, Health Canada encourages sponsors to request regulatory advice on submissions regarding rare diseases before filling their applications, including a website link to request for such meeting. Within this framework, the guidance provides early access to promising new drugs for patients suffering from a serious, life-threatening, or severely debilitating, disease for which there is no drug presently marketed in Canada, or, where there is a significant increase in efficacy and/or significant decrease in risk is achieved. Although

pediatric formulations are not considered new drugs, many pediatric medicines are compounded, and this may increase the risk of unsuccessful and unsafe treatment in a very vulnerable small population, as largely explained above.

> **Recommendation:**
> Allow pediatric formulation applications to use the Rare Disease Framework. Consider providing the same six-month pediatric extension to the 8-year term of market exclusivity for those drugs that are on patent. It is important to note that this data exclusivity would not apply to the majority of pediatric formulations, as most are generic (see Section 4).

6. *Australia Canada Singapore Switzerland Consortium: One Submission – Approval in More Than One Jurisdiction*

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. Not only does this reduce the regulatory burden and cost but the effort for approval can result in access to million of children in four middle-sized countries, in an expedited fashion.

> **Recommendation:**
> We believe that such an initiative will have a positive impact in pediatric formulations and are interested in applying to use this new program with a pediatric formulation. We sincerely hope that this is a viable option for helping to contribute to a viable business model as well as attract industry to bring their commercial formulations into Canada.

Innovation: New Pediatric Forms

We understand that the Government of Canada is seeking views on areas that could be impacted by new or disruptive technologies. The GPFC would like to explore using new types of forms that could be better adapted for use in children. For a long time, liquid forms have been viewed by health care professionals as the most appropriate forms for the younger children unable to swallow capsules or tablets. This has been challenged over the past decade, with flexible solid oral dosage forms (e.g. minitabs, pellets etc.) now considered as viable options for all pediatric age groups. The GPFC is working with potential partners to develop new and innovative pharmaceutical forms that are more adaptable, can be taste-masked and are simpler to administer to children. Given these are new pediatric forms, industry will need guidance on, not only the clinical studies required to

support the submission, but also the best and simplest regulatory path for these generic medicines. This will support bringing innovation in Canada.

Together, Let's Make a Difference for Canadian Children

The challenges that the medical environment faces in treating children in Canada is real and unique, and the GPFC respectfully submits all of the above recommendations for consideration. Compared to adults, the pediatric population is small, and consequently, a positive business case is difficult to build with the current uncertainty in both the regulatory, reimbursement and provincial listing decisions. Reducing or eliminating any of these barriers could make a significant difference for our Canadian children. Where possible, the GPFC has provided solutions using already existing frameworks or guidelines. We are also willing to consider other options.

We urge all stakeholders, Health Canada, Reimbursement Agencies, Pricing Bodies and the Provinces and Territories, to coordinate and align as much as possible to improve access to pediatric formulations. Success is unattainable until this occurs. We understand that due to the complexity of the structure of the health care system that aligning the various agencies and partners is a tremendous task but we would be amiss without specifically mentioning that this is critical to improve access to commercially available pediatric formulations. Children cannot be the victims of this complexity.

Of the recommendations offered in this letter, we believe the biggest two significant regulatory changes that could positively impact pediatric formulations in Canada, is to **Use Trusted Foreign Regulatory Decisions** (Section 3.1) and to provide **Incentives for Pediatric Formulations for Off-Patent Medicines** (Section 4). Specific to the Trusted Foreign Regulatory Decision proposed framework, we feel that the reward of developing pediatric programs in these areas, even if they are launched ahead of those equivalent programs in adults, would be essential. The GPFC would be pleased to offer its expertise to help develop specific pediatric formulation guidelines to assist Health Canada in any capacity needed. In conclusion, we believe that treatment of the pediatric population with appropriately adapted medicines will be welcomed and applauded by health care providers, parents and, most importantly, children.

Thank you for your kind consideration in this matter. We encourage you to contact Andrea Gilpin, General Manager, GPFC, at any time to discuss this multifaceted issue. It would be our pleasure to work with Health Canada to find an innovative and agile solution that takes into consideration the needs of Canadian children.

Best regards,

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August 30, 2018

Cost Recovery Renewal Initiative
Resource Management and Operations Directorate
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Commentary to Fee Proposal for Drugs and Medical Devices

To Whom It May Concern,

In response to the consultation request, in January, the Goodman Pediatric Formulations Centre (GPFC), and the KidsCAN Clinical Trials partnered to provide a commentary regarding the proposed Health Canada cost-recovery fee proposal. We have attached a copy of this letter for your reference. This letter is intended to provide our comments to the May 24, 2018 Revised Fee Proposal for Drugs and Medical Devices.

The ideal is to have commercial pediatric formulations available for Canadian pediatric patients. In many cases, commercialized pediatric formulations exist in other jurisdictions, such as in the United States and in Europe. However, oftentimes, these commercial pediatric formulations are not marketed in Canada, leaving an already vulnerable and unaddressed population without access to commercially available pediatric formulations.

The GPFC believes that our current healthcare system does not serve well bringing pediatric formulations into Canada. Health Canada is a crucial first step in the drug approval process and we believe that any changes that Health Canada can make to support pediatric formulations would send a message to the other important organizations involved in authorizing access to these pediatric formulations. We submit, below, some suggestions for your consideration.

Fee Reduction for Pediatric Formulation Submissions

As outlined in the revised proposal dated May of this year, we noted that there is:

- Revised/reduced fee structures for small businesses.
- Specific mitigation for waiving fees based on individual product sales, regardless of the size of the company, including a fee waiver for a first pre-market drug submission for any medicine contained on the *List of Drugs for an Urgent Public Health Need*.
- New mitigation where all fees would be waived for publicly-funded health care institutions or unique organizational structures.

Recommendation:

- We recommend, with Health Canada to develop a joint pediatric formulations priority list, and that this list should be added to the *List of Drugs for an Urgent Public Health Need*.
- In absence of adding pediatric formulations to the *List of Drugs for an Urgent Public Health Need*, we would request a unique and reduced fee structure for pediatric formulation submissions.
- Many pediatric medicines are generic and therefore have no incentive or intellectual property. Given this, we recommend that all pediatric formulation submissions have their fees waived or have their submissions at a very reduced fee.

We would like to confirm that the GPFC will be considered as unique organizational structure that benefits from such a waiver, should it wish to submit a drug for marketing authorization on its own.

Published Data Only Fee Category of Submission

We understand that the Published Data Only Fee Category of filing is proposed to be abolished as outlined in the May 2018 Revised Fee Proposal for Drugs and Medicinal Devices. The reasons cited are that the workload and level of effort required could more easily be merged into another submission category. In pediatrics, we are challenged in attracting industry partners to Canada under the existing fee structure, and should this plan come to fruition as it is indicated, we will not be able to improve access to these much needed pediatric formulations resulting in continued compounding which bears its own risks. We believe that Canadian children deserve the same pharmaceutical standards that is required in adults.

To provide a concrete example, working with one of the GPFC's pharmaceutical partners, the sponsor has used the Drug Submissions Relying on Third Party Data. This mechanism has been productive in the GPFC attracting a partner to submit a pediatric formulation in Canada. We appreciate this pathway and support its current use for pediatric formulations.

In this case, the sponsor submitted a drug using a Drug Submissions Relying on Third Party Data with an assumed Published Data Only Fee category (submission fee $19,530). The assumption for using the Published Only Fee category was that the dossier only used published data and that it was not a new active substance. Furthermore, although the clinical review was needed, there was no analysis or raw data to analyze as these data came from published sources or foreign review data. It is important to note that this is a generic drug, with a small market, where no incentives or protection is available.

Health Canada has recently responded to the sponsor that all Drug Submissions Relying on Third Party Data are always classified as a Clinical/CMC submission, which has fees of $176,000.

However, this is not stated in the Health Canada Guidance Document entitled Drug Submissions Relying on Third Party Data. The categorization of using Drug Submissions Relying on Third Party Data is also not outlined in the Human Drug Application Review Table. Not only was this unexpected, but the significant increase in fees may deter this industry partner from submitting any further pediatric formulations. We provide this example as it is incongruent with the guiding principles of the Revised Fee Proposal of being reasonable, minimizing impact and more importantly, ensuring fees are predictable.

Recommendation:

Continue the Drug Submissions Relying on Third Party Data and provide a reduced fee structure, or fee waiver, for companies that submit pediatric formulations in Canada. The fees involved cannot be the same as for a full clinical submission with a known active ingredient ($180,000) as this would be prohibitive, from a business perspective, for these mature generic drugs. We also believe that it is critical to transparently outline the fees for pediatric submissions so the investment required is clear from the start of the project.

Using Trusted Foreign Regulator Decisions

The GPFC understands 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 access for Canadians to drugs that meet a health care system need whereby Health Canada would do a cursory review of the submission. The GPFC asserts that pediatric formulations could greatly benefit from this initiative and we have provided our positive feedback both in writing and by teleconference to the consultations earlier this year.

Recommendation:

We have not yet seen the proposed fee structure for such a program as it is currently in development. We recommend that for pediatric formulations that a fee waiver be granted, or be minimal, as the review effort would be cursory. We also advocate for the Trusted Foreign Regulator Decision be permitted to be submitted to Health Canada without any delay after the trusted foreign regulation decision.

The GPFC is a non-profit organization that is working as a facilitator between industry, regulatory and reimbursement agencies to bring commercialized pediatric formulations into Canada. It is already a difficult and challenging situation for the reasons cited. KidsCAN is also a non-profit organization whose aim is to facilitate pediatric clinical trials and research by centralizing these activities in Canada. The recommendations suggested herein would not be expected to impact Health Canada's cost recovery needs significantly, as we would not expect a large number of pediatric formulation submissions per year. Adopting some of these measures, would also stand as an acknowledgement by Health Canada of the need for more pediatric formulations and better drugs for children. We need support to bring these much needed pediatric formulations into Canada, and to do so we need some flexibility from all the stakeholders in the approval process, including Health Canada, to achieve this goal.

We are encouraged by the modifications to the program that have been made in this second drafting process. We support the notion of having fees specific to individual products (regardless of company size) and we support the proposal of having fees completely waived for unique organizational structures, such as academia and/or health institutions. We sincerely thank the task force for providing these considerations in the revised proposal.

The pediatric population is small and a positive business case is difficult to build with the current uncertainty in both the regulatory, reimbursement and provincial listing decisions. Moreover, organizing clinical trials in Canada can be challenging. KidsCAN Trials is a national organization whose mandate is to facilitate and coordinate research, training and knowledge transfer in the safe therapeutic use of medicines for children. The establishment of a central hub, such as KidsCAN Trials, increases the efficiency of doing clinical trials in Canada. The streamlining of the approval, reimbursement, pricing and listing process will also make a difference for our Canadian children. The GPFC could offer its expertise to assist Health Canada in further revising the proposed cost structure to develop specific pediatric fee structures that would approach being acceptable to industry while understanding the constraints imposed on Health Canada.

Thank you for your consideration in this matter. We encourage you to contact Andrea Gilpin, General Manager, GPFC, at any time to discuss this further. It would be our pleasure to work with Health Canada to find a reasonable, fair and predictable pediatric fee structure that takes into consideration the small market sizes involved in Canada.

Best regards,

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About the GPFC

The GPFC has the goal of improving access to child-friendly medicines. We are the only Centre in Canada whose mandate 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 KidsCAN

KidsCAN Trials is a national hub to coordinate research, training and knowledge transfer in the safe therapeutic use of medicines for children. By federating all academic child health centres and their affiliated research institutes, KidsCAN Trials will encourage new processes and practices, new policy approaches and new ways of organizing care for children. A video is provided to outline the importance of clinical trials from a patient perspective.

February 9, 2018

Proposed Use of Foreign Decisions Consultation

To Whom It May Concern,

The Goodman Pediatric Formulations Centre (GPFC) would like to contribute to the discussion regarding creating a regulatory pathway for the authorization of the sale of drugs already approved by trusted foreign regulators. This letter supplements the comments that we contributed to a telephone consultation that was held on February 9, 2018.

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.

Children are not mini-adults. The relative lack of availability of pediatric dosage forms can lead to treatment failure or adverse events for children. The Council of Canadian Academies published a report in 2014 entitled, "Improving Medicines for Children in Canada," which outlines the challenges in treating pediatric patients in detail[1]. Approved adult forms often need to be modified in some manner to administer the desired dose to children, and as such, are used off-label. Compounding is the process by which an adult form is manipulated by a health care provider, or others, to adapt the adult form to be used in children. The ideal is to have commercial pediatric formulations available for Canadian patients. In many cases, commercialized pediatric formulations exist in other jurisdictions, such as in the United States and in Europe. However, oftentimes, these commercial pediatric formulations are not marketed in Canada, leaving an already vulnerable and unaddressed population without access to the commercially available pediatric formulations.

There are several reasons why existing commercial pediatric formulations have not been introduced into the Canadian market. First, from a commercial perspective, the approximately six million children in

[1] Improving Medicines for Children in Canada, 2014, Council of Canadian Academies.

Canada (of which only a small percentage are ill) results in a market size that is too small to build a sustainable business case.

Second, the regulatory approval pathway is perceived as unclear, resulting in significant concern on the part of drug companies that it will include costly additional clinical studies targeting very restricted patient populations.

Third, once approved by Health Canada, reimbursement groups may not list these medications, as the health technology assessments (HTA) are based on criteria applicable to adult forms, which may not apply, or be possible, in children. Therefore, reimbursement for a pediatric formulation may be rejected.

Fourth, unlike in the United States and Europe, there are no commercial incentives or regulatory protection granted to bring commercialized pediatric formulations to Canada. This has the effect of allowing American and European children access to pediatric formulations whereas our Canadian children can only have the compounded equivalent, with the significant limitations and risks that this may bear.

Finally, the Orphan Drug Framework, which was an area under which some pediatric medicines might have gained approval, has now been pulled, leaving no options for special accommodations for pediatric medicines.

The proposed Health Canada initiative to consider creating a regulatory pathway using already approved authorization by trusted foreign regulators would contribute to the solution to improve access to child-friendly formulations in Canada. In particular, the challenges related to the formulations of pediatric populations was specifically mentioned in the Health Canada Consultation Document. The GPFC would strongly support this initiative and would be willing to participate to contribute its expertise in this endeavour. Our goals are aligned with Health Canada: we would like this new pathway to ensure the efficacy and safety of the medicines brought into Canada while at the same time providing improved access to important pediatric formulations for Canadian children in a timely manner.

Proposed Criteria

- We agree with using one complete set of unredacted review reports from a *de novo* assessment from a trusted foreign regulator. In instances where the product is very well established and has been on the market for many years but where data packages and review reports may not be available, it would be acceptable to rely on supplementary post-market and labelling information only. This last point is particularly important in pediatrics where many medications are off-patent (generic) and have been in use for many decades.
- We agree the language should be in English or French (translated, if needed, with the translation certified to its accuracy via a letter from the translator), and any additional correspondence between the foreign regulator and the sponsor should be provided in the submission, as well as the approved foreign labels (with translations) from any of the trusted regulators.
- We agree that *publically available or published* post-market data from foreign jurisdictions would need to be included in the application, as well as the Risk Management Plan (if applicable). In the potential situation where only a limited amount of publically available or published post-market

data are available, we believe that this the proposed framework should remain an avenue to be used to bring pediatric formulations to Canada. As mentioned previously, ensuring the safety of those pediatric formulations that use this pathway are of utmost importance; however, many of the pediatric medicines that are currently used are presently compounded and therefore health care providers already have experience with these medications. We feel this distinguishes pediatric formulations from adult medications and should be specifically considered when limited published or post-market data are available.

- We agree that the sponsor would need to attest to any differences between the foreign and Canadian application. Guidelines of how to present data from multiple jurisdictions would need to be defined.
- Although we are not experts in the CMC process, it appears to us that minor differences in chemistry, manufacturing and formulation should be acceptable with sponsors providing a summary of any differences. Guidelines on how to present data from multiple jurisdictions would need to be defined.
- We agree that the Drug Master File (DMF) information and Canadian Good Manufacturing Practice (GMP) information must be submitted in the Canadian dossier. Using information used on other jurisdictions to make the process as simple as possible would be important. Guidelines on how to present data from multiple jurisdictions would need to be defined.
- Regarding Canadian-specific labelling it is our opinion that keeping this process as simple as possible would be very important. Guidelines on how to present data from multiple jurisdictions would need to be defined. Moreover, since in pediatrics often it is smaller companies that commercialize these medicines in Canada, the process should keep in mind the smaller infrastructure of these organizations and keep the process as similar as possible to other trusted jurisdictions.

Questions Posed by Health Canada to Stakeholders Regarding the Proposal

1. What are your views on the development of a use of foreign decisions pathway?

The GPFC feels that this is an mandatory step in increasing child-friendly formulations to Canadian children. In a study performed in 2017, the GPFC determined the most commonly oral pediatric medicines that were compounded at the CHU Sainte-Justine. The goal of this study was to determine what compounds were already available in a pediatric formulation in the US and/or Europe and to identify a prioritized list. These data were later confirmed in a Pan-Canadian study. We identified sixty medicines that are in need of a commercialized formulation in Canada. Ninety-eight percent of these medications are off-patent and have been on the Canadian market for a median of 35 years. Of these, only 23% had a pediatric indication in Canada.

The list of 60 compounds were then further classified into three categories: those liquid forms with known safe ingredients (25%), those that could be improved (30%) and those where there were no commercialized pediatric oral formulations in the EU or US (45%). Focussing on the first

category, where there is an approval of a pediatric formulation in another jurisdiction, a regulatory pathway such as the one outlined by Health Canada, in this Consultation, would tremendously advance the access of these medications to Canadian children.

We wanted to provide a concrete example (and video) of how this framework could positively impact the lives of Canadian children. In Canada, 6-mercaptopurine is approved for the treatment of acute lymphoblastic leukemia (ALL). It is only available in an adult dose of 50 mg which results in health care providers and caregivers splitting the tablets to make a compounded liquid oral formulation. This medication is cytotoxic and great care must be taken for a caregiver not to expose themselves or other family members to this medication. Mercaptopurine has a narrow therapeutic window which means that a slight dosing error may cause serious complications. In many cases, mercaptopurine is used as maintenance therapy for two years and is dosed twice a day by a parent or caregiver; therefore, the potential for exposure to family members does exist. A liquid formulation has been approved and marketed in the EU since in 2012 and in the US since 2014. Yet, in Canada, we continue to crush tablets of a cytotoxic drug when a pediatric oral formulation is available. If the framework proposed existed, we believe that we would not be crushing tablets as we are today.

2. Do you have any comments on who should be considered a trusted partner?

We believe that the US FDA, the EMA, and MRHA are reasonable trusted agencies but would defer to those who have experience with foreign regulatory agencies. Specific to pediatrics, both the FDA and the EMA have legislation that requires sponsors to provide pediatric data if it is determined that there is a possibility for use in children. We believe a similar process should be instituted in Canada to follow their lead.

3. What are your views on adding the Therapeutic Goods Administration (TGA) from Australia, SwissMedic, the MHRA to the list of trusted regulators?

Given that the Canada, Australia, Switzerland, Singapore harmonization already exists and one medication has successfully been through the approval process, we believe that these countries have already been vetted as trusted regulatory partners. The GPFC supports using these jurisdictions as trusted partners.

4. How should we define an “adequate period of time” (years of marketing in the foreign jurisdiction)?

Concerning pediatric formulation approvals in Canada, we do not believe that any period time is needed for a product that is already in use off-label and is compounded. If a trusted foreign jurisdiction has approved a medication, then it should be eligible for submission in Canada as it has already been evaluated and approved for commercialization in the trusted jurisdiction.

5. Should there be additional criteria for this proposed pathway?

   Within this framework a special consideration should be attributed to pediatrics.

6. Health Canada will conduct a cursory clinical review of the submission package. Are there any thoughts on this process?

   In order to comment on this cursory review, we would need to know what Health Canada refers to when performing a cursory review process.

Additional Questions for Consideration from the GPFC

- In the event there is more than one foreign regulator that has approved a medicine, would the sponsor have to combine all approvals for submission to Health Canada or could the sponsor choose one reference country? If they can choose the reference country, the criteria for the choice of the reference country would have to be outlined.
- What would make this proposed regulatory framework different from the Guidance Relying on Third Party Data? Clarity on the purpose and use of each guideline would be important.

Fees

In pediatrics, the fees that would be charged for such a submission is a critical point. The barriers are already perceived as being high to introducing pediatric formulations into Canada. We would request that special consideration to the fee structure be given to pediatric applications, given the small market size and the other challenges identified above. In addition, given it is a cursory review of an existing dossier we would expect the fees to be in line with an abbreviated review.

Patent and data protection

Given that many of the medicines used in pediatrics are off-patent (generic), and no protection is offered to those generic companies who commercialize already existing pediatric formulations in other jurisdictions, any initiative or data protection that could be offered to incentivize these companies would be a major step in the right direction to providing safe and commercially available formulations to Canadian children.

Review by Panel with Pediatric Expertise

Given that development and administration of pediatric medicine brings its own challenges that are quite different from what is experienced in adult populations, we would recommend having at least one pediatric expert on any committee reviewing applications using data submitted by trusted foreign regulators for pediatric indications or formulations.

On the teleconsultation that occurred on February 9, 2018, it was asked of participants to consider what a "conservative approach" would entail. In pediatrics, we would like to emphasize that many of these products are already in use, off-label, for many years and are being compounded. Any such conservative approaches that Health Canada would apply should consider that the situation is very different in pediatrics and therefore may require a modified pathway that may be less conservative than what may be applied in adults.

The GPFC is a non-profit organization that is working as a facilitator between industry, regulators and reimbursement agencies to bring commercialized pediatric formulations into Canada. Its mandate is already difficult and challenging for the reasons cited above. We fully support this initiative and would respectfully request that the Committee consider special considerations for pediatrics.

Thank you for consideration in this matter. We encourage you to contact the Goodman Pediatric Formulations Centre at any time to discuss this further. It would be our pleasure to work with Health Canada to contribute and provide our expertise in pediatrics to support this important initiative.

Best regards,

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Commentary to Fee Proposal for Drugs and Medical Devices

To Whom It May Concern,

The Goodman Pediatric Formulations Centre (GPFC) and the KidsCAN Clinical Trials have partnered to provide a commentary regarding the proposed Health Canada cost-recovery fee proposal.

The GPFC has the goal of improving access to child-friendly medicines. We are the only Centre in Canada whose mandate 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.

KidsCAN Trials is a national hub to coordinate research, training and knowledge transfer in the safe therapeutic use of medicines for children. By federating all academic child health centres and their affiliated research institutes, KidsCAN Trials will encourage new processes and practices, new policy approaches and new ways of organizing care for children. A video is provided to outline the importance of clinical trials from a patient perspective.

The relative lack of availability of pediatric dosage forms can lead to treatment failure or adverse events for children. Approved adult forms often need to be modified in some manner to administer the desired

dose to children, and as such, are used off-label. Compounding is the process by which an adult form is manipulated by a health care provider, or others, to adapt the adult form to be used in children. Compounding is regulated by provincial pharmacy standards, based on Guidelines published by the National Pharmacy Regulatory Authorities (NAPRA) on behalf of pharmacy colleges. NAPRA guidelines admittedly falls short of Health Canada's Good Manufacturing Practices (GMPs) in multiple ways and, even though compounding may be acceptable in some circumstances, it should not be considered an equivalent surrogate for a Health Canada approved formulation that has been assessed for use in children. Given that compounded medicines are not approved in full compliance with Health Canada's rigorous requirements, the medication's characteristics and specifications are not always known, well established or controlled: such as the stability, potency, content uniformity, purity (chemical and microbial) or the bioavailability of the compounded product in children. More importantly, that the appropriate dose is being administered is not always known. Moreover, if the compounded medicine has an unpleasant taste, then compliance with the child can be challenging. Although the exact percentage of compounding used in children is unknown, a common understanding is that 75% of all compounded prescription medications may fall outside of regulatory approval[1]. Research and clinical trials can elucidate and increase the understanding in these areas and are a vital part of improving child-friendly formulations to Canadian children. A video is linked to illustrate the challenges from a patient and caregiver perspective.

The ideal is to have commercial pediatric formulations available for Canadian patients. In many cases, commercialized pediatric formulations exist in other jurisdictions, such as in the United States and in Europe. However, oftentimes, these commercial pediatric formulations are not marketed in Canada, leaving an already vulnerable and unaddressed population without access to the commercially available pediatric formulations.

There are several reasons why existing commercial pediatric formulations have not been introduced into the Canadian market. Firstly, from a commercial perspective, the approximately six million children in Canada (of which only a small percentage are ill) results in a market size that is too small to build a sustainable business case.

Second, the regulatory approval pathway is perceived as unclear and there is significant concern that it will include costly additional clinical studies targeting very restricted patient populations. In the case where there is no need for further clinical studies, the regulatory costs for the preparation of a Canadian

[1] Improving Medicines for Children in Canada, 2014, Council of Canadian Academies, pg 22.

New Drug Submission utilizing an NDA or an MAA can involve considerable costs (>$100,000 to $250,000), not including the fees related to that review.

Third, once approved by Health Canada, reimbursement groups may not list these medications, as the health technology assessments (HTA) is based on criteria applicable to adult forms, which may not apply, or be possible, in children. Therefore, reimbursement for a pediatric formulation may be rejected.

Fourth, unlike in the United States and Europe, there are no commercial incentives or regulatory protection granted to bring commercialized pediatric formulations to Canada, resulting in American and European children having access to pediatric formulations whereas our Canadian children can only have the compounded equivalent, with the significant limitations and risks that this may bear.

Finally, the Orphan Drug Framework, which was an area in which some pediatric medicines could have worked, has now been stopped, leaving no options for special accommodations for pediatric medicines.

The GPFC and KidsCAN have read Health Canada's "Fee Proposal for Drugs and Medical Devices" and is responding to this proposal by submitting this letter. The GPFC and KidsCAN understand that other regulatory jurisdictions have a full cost recovery fee structures for the various services offered to review, or allow the sale of medications. Given the inaccessibility of commercialized pediatric formulations in Canada that already exists, we can only expect that this new proposed fee structure would further exacerbate the significant existing problems for pediatric formulations. As cited in the Fee Proposal, costs associated with a New Drug Submission will change from $173,106 to $312,562, or an 80% increase. In pediatrics, this will augment the barrier to provide Canadian children access to commercially available pediatric formulations that are available elsewhere.

The GPFC is a non-profit organization that is working as a facilitator between industry, regulatory and reimbursement agencies to bring commercialized pediatric formulations into Canada. It is already a difficult and challenging situation for the reasons cited above. KidsCAN is also a non-profit organization whose aim is to facilitate pediatric clinical trials and research by centralizing these activities in Canada. Building on an existing mitigation strategy, we would like to submit for your consideration that fees associated with the submission of pediatric formulations could be granted a waiver when the fee exceeds a certain percentage of the anticipated Canadian pediatric market. Alternatively, perhaps the

pediatric formulations approvals could use the already proposed medical urgent need framework outlined in the Proposal. Such a waiver would not be expected to impact significantly on Health Canada's cost recovery needs, while providing drug developers with an incentive to consider introducing a pediatric formulation where a need exists. This measure would also stand as an acknowledgement by Health Canada of the need for more pediatric formulations and better drugs for children.

The challenge facing pediatrics in Canada is real and unique, and the GPFC and KidsCAN would therefore respectfully recommend using a waiver or specialized fee remission schedule specific for pediatric medications (both for new indications and new formulations). The GPFC could offer its expertise to help design a fee structure that would approach being acceptable to industry while trying to meet the cost recovery needs of Health Canada.

Thank you for consideration in this matter. We encourage you to contact the Goodman Pediatric Formulation Centre, who is taking the lead on this initiative, at any time to discuss this multifaceted issue. It would be our pleasure to work with Health Canada to find a solution that takes into consideration this complex area of regulatory approval of pediatric medications.

Best regards,

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