centre de formulations pédiatriques
de la famille Rosalind et Morris Goodman du CHU Sainte-Justine

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

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Improving access to pediatric formulations in Canada

On February 6, 2020 the Goodman Pediatric Formulations Centre of the Centre Hospitalier Universitaire Sainte-Justine (GPFC), with support from Dr. M. Rieder, (CIHR-GSK Chair in Paediatric Clinical Pharmacology, Western University), hosted a workshop entitled *« Improving access to pediatric formulations in Canada »*. This workshop was entirely funded by the Canadian Institute of Health Research (CIHR Institute of Genetics). The purpose of the meeting was to bring together the main stakeholders in the drug approval and reimbursement process along with clinicians, academics and the pharmaceutical industry to discuss the challenges of ensuring access to pediatric formulations in Canada.

This is the first time that representatives of Health Canada, Health Technology Assessment Agencies (HTAs), Canadian pediatric associations and the pharmaceutical industry have come together to discuss the issues surrounding access to commercial pediatric formulations in Canada.

A large number of medications given to Canadian children are "old" drugs either approved for adults only, or adults and older children. A formulation adapted to their needs (e.g. liquid formulation) is rarely available resulting in manipulation of the adult form by a pharmacist or health care provider (a process called compounding) with its inherent risks. Compounding occurs even though many of these drugs are commercially available as child-friendly formulations in other countries. There are a number of reasons why this situation exists in Canada: 1) many of these medications are off-patent; with the Canadian pediatric market size being quite small resulting in very little incentive for industry to market such products; 2) the regulatory pathway is often unclear; 3) data packages used for the original submissions in other jurisdictions may not measure to today's submission standards as a number of these drugs have been approved elsewhere for over a decade, and 4) reimbursement is uncertain as oftentimes pharmacoeconomic models are not available and commercial formulations are more expensive than pharmacy-compounded formulations.

In preparation for the meeting, one-hour pre-workshop telephone interviews were conducted. These conversations brought to light that all interviewees from 18 different organizations were aware of the challenges of bringing to market pediatric formulations. This allowed the GPFC to use the feedback to align the discussion towards potential solutions, which included proposing a pilot project to test a new adaptive model for access to pediatric formulations.

Considering the relatively small size of the Canadian pediatric market, regulatory and reimbursement hurdles- the business case for launching pediatric formulation is not always positive. This unique situation requires an "out of the box" solution.

During the workshop we collected and discussed the various perspectives from all 28 participants to create a holistic understanding of the current process and issues with the goal of collectively working on solutions to improve access to existing commercial pediatric formulations available in other countries for Canadian children.

Several solutions were proposed and agreed upon by the group as having the greatest impact to improve access to child-friendly formulations. From a **regulatory perspective**, the ability to rely on the decisions of other regulators (often referred to as the use of foreign decisions project) would likely have a positive impact to commercialize, in Canada, pediatric formulations existing in other jurisdictions. This policy proposal would require regulatory changes before it could be implemented. The Health Canada Forward Regulatory Plan, currently indicates that draft regulations supporting this policy are planned to be published in spring of 2021. Additionally, alternative regulatory pathways could be explored, such as real world data etc. For the pediatric community, it was agreed that having alignment of key messages and continued advocacy was essential, in addition to raising awareness of the issue from a regulatory perspective. **For industry**, reimbursement exclusivity and a mechanism in place for a tendering process to commercialize pediatric formulations of older drugs could incentivize manufacturers to market pediatric formulations. **For pharmacists**, and other healthcare stakeholders, as compounding of drugs given to children will continue, standardization is needed to improve medication safety and efficacy in Canada. Finally, all participants agreed that there is a need to understand decision drivers from all stakeholders.

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Some issues were raised that did not have a clear path forward, or an obvious consensus; 1) The requirement for data to support the value of commercial formulations and the need to generate data for health economic evaluations and societal impacts, for example, compared to the accepted practice of compounding; 2) The challenge of ensuring that only commercial pediatric formulations are used and reimbursed in institutions, instead of compounding; 3) The challenge that some stakeholders believe that compounding is acceptable as is current practice.

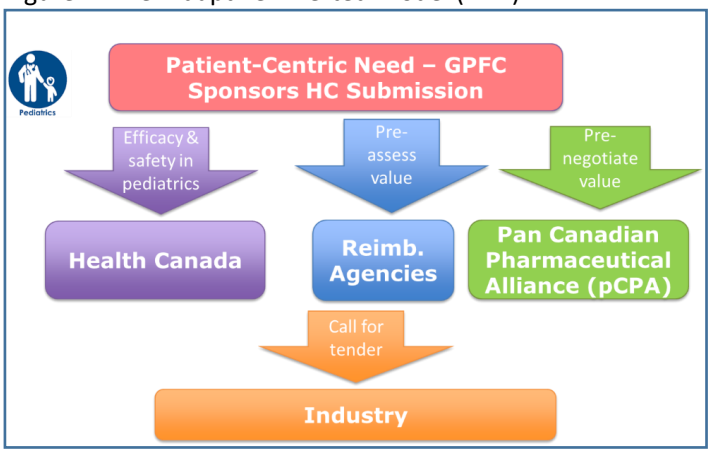
To address the urgent need to provide Canadian children access to pediatric friendly formulations available in other countries, the GPFC is proposing an innovative patient-centric solution, the « Adaptive Inverted Model ».

The objective of the proposed model is to lower the risks for industry to commercialize those high priority formulations, while at the same time, having a price point (cost) that is acceptable to the provincial drug plans. This model is not proposed for New Chemical Entities or New Submissions to Health Canada but mainly for old drugs in need of adequate formulations for children.

The first step in the process is to determine which medications are currently being compounded in a form adapted for children (mainly liquids or tablet splitting) and of those, which ones are available as a high quality GMP commercialized pediatric formulation in other jurisdictions. The GPFC has already performed this first step for oral liquid compounded drugs. With this list in hand, the GPFC is proposing to perform a pilot project with one medication on this priority list, to evaluate whether the proposed model could provide an innovative pathway to commercialize a pediatric formulation in Canada.

The Adaptive Inverted Model (AIM) (Figure 1) is referred to as such, as it is based on patient needs. With the priority list, as a not-for-profit, the GPFC would clarify all steps necessary to gain marketing authorization and reimbursement agreements, thereby reducing the uncertainties and providing, as much transparency as possible for industry, and all stakeholders, to the entire process. Once clarity on these steps is gained, the GPFC would then solicit a call to tender to industry.

Figure 1: The Adaptive Inverted Model (AIM)



The AIM provides as much clarity to the process upfont, so that expectations for industry are clear. By providing guardrails, the AIM should reduce unexpected requirements which introduce uncertainty by each stakeholder in a complex system. In general, participants supported the AIM, and indicated that this was worthy of a pilot project. Overall this model was viewed by participants as a new option to commercialize pediatric formulations for older medications.

The GPFC believes that this model is a winning proposition for all stakeholders, and most importantly for children.

The model structure was debated and certain questions/concerns were raised that will necessitate further discussions:

GPFC: How would this impartial not-for-profit organization be funded? Should they revisit the priority list of medications?

Industry: What if there is no response from industry to the call for tender? What would be industry's role and when would it be brought into the process? What are the regulatory and reimbursement incentives? Is Reimbursement exclusivity possible?

Pharmacists: How would we ensure that institutions will only use the commercial pediatric formulation versus compounding?

Payers: Although pricing experts (consultants) were present, actual payers were not represented at this workshop and have to be brought into the discussion quickly.

Pricing: How will the cost of post-approval requirements (such as pharmacovigilance) be factored into the price or process?

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Supported by a rigorous analysis, the GPFC medical team identified tacrolimus - a drug used in children for decades to avoid organ rejection which still does not have an appropriate pediatric formulation in Canada – to test the proposed model.

The clinical challenges of tacrolimus and the regulatory status were presented by Dr. C. Litalien. A commercial tacrolimus pediatric formulation has been available in Europe for over 10 years, and more recently in the US. This information was used as a concrete example for discussion on the path forward for regulatory approval, reimbursement and pricing of a tacrolimus pediatric formulation in Canada. The consequence of not having a precise pediatric dose of tacrolimus is that organ rejection or organ damage may occur and therefore the consequences of not having the appropriate dose and formulation may be very serious.

Regulatory perspective: Currently-authorized tacrolimus capsules have a pediatric indication, but the regulatory pathway for tacrolimus granules (which are not approved in Canada) would need to be defined based on the data available and the product sponsor. While many parties may be able to contribute to the collection or assembly of data (which could include new studies, published literature, or real world evidence) to support a regulatory submission, the legal framework under the Food and Drugs Act requires an entity who is ultimately legally responsible for the product, in terms of the market authorization and for all of the on-market requirements. In the future, should the use of foreign decisions regulatory pathway be available, this could be one option. Under current processes, Health Canada can use the reviews from other regulators to support review of a submission. Should a sponsor other than the sponsor of the existing Canadian product wish to submit another tacrolimus product, additional data may be required.

Reimbursement/Pricing perspective: Currently we have a "one-size fits all" pricing model and perhaps we need specific pediatric frameworks. The AIM is one way to do this and should be explored with tacrolimus. A "Reimbursement Pediatric Adaptive Inverted Pathway (RPAIP)" model was also discussed. In this model, industry would be transparent regarding manufacturing costs of a product and a "cost-plus" model could be adopted. In addition, all key stakeholders including all levels of government need to be actively involved. Moreover, it was suggested that manufacturer incentives could not only be limited to the pediatric products. For example, an adapted review or reimbursement exclusivity as also been seen as possible incentives for the industry. More specifically, reimbursement exclusivity is seen as a possible incentive for tacrolimus.

Business Considerations: Industry states that it is important to manage the risk and clarify the process but industry still needs to have value/margin for the products. De-risking and clarity are only one part of the solution: appropriate pricing is also critical. It is also emphasized that industry, and not associations, has to be part of the discussions up front with this pilot project as they would know the exact costs of manufacturing and marketing for each medication. Finally, industry recommends early involvement in the process of the pilot project to ensure that the GPFC will understand the constraints and pre-requisites for a successful pilot.

Other considerations: For the pilot project using tacrolimus, it would be relevant to know what the cost of organ failure in children in Canada is when the appropriate drug is not available.

In conclusion, the participants agree the following priorities as having most positive impact to improve access to pediatric formulations: 1) Implementing the use of Foreign Decisions regulatory changes by Health Canada; 2) Requiring industry to submit pediatric data ("the Pediatric Rule") as is currently required in other jurisdictions; 3) Providing incentives for industry to submit pediatric formulations in Canada; 4) Using the AIM for tacrolimus as a pilot project; and, 5) Standardizing compounded preparation to improve medication safety and efficacy in Canada. A core team for the pilot project was created and include: Courtney Abunassar, Sophie Bérubé, Megan Bettle, Alain Boisvert, Sylvie Bouchard, Sylvain Chrétien, Andrea Gilpin, Thierry Lacaze, Catherine Litalien, and Geert 't Jong. The group will be organized by Andrea Gilpin from the GPFC and a working plan will be developed in the coming months. The larger group will be kept abreast of developments on a quarterly basis and it is suggested that another workshop be held in the fall of 2020 to allow for additional topics to be discussed in depth.

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The problem is complex but together we can find a solution to gain access to these important older pediatric formulations

From left to right second row: Marion Williams (Government relations specialist at Children Healthcare Canada), Virginie Landreville (Adjointe à la directrice du médicament at INESSS), Christine Chambers (Scientific Director at CIHR-IHDCYH), Yves Rosconi (Pharma Executive), Sylvain Chrétien (Previous Executive at Pediapharm), Barry Power (Senior Director Digital Content at Canadian Pharmacists Association), Régis Vaillancourt (Head of Pharmacy at CHEO), Denis Lebel (Pharmacist at CHUSJ), Étienne Richer (Associate Scientific Director at CIHR), Christian Ouellet (Director Government Affairs at Sandoz), Brent Fraser (Vice-President Pharmaceutical Reviews at CADTH), Jacques Dessureault (Pharma Executive), Alain Boisvert (Head, Government Affairs and Market Access at Pharmascience), Geert 't Jong (Lead for Canadian Compendium for Drugs at Children's Hospital Research Institute of Manitoba), Laura King (IMC Regulatory Committee at Innovative Medicines Canada), Micheal Rieder (CIHR-GSK Chair in Paediatric Clinical Pharmacology, Western University). **Front row left to right:** Charlotte Hepburn-Moore (Medical affairs Director at the Canadian Pediatric Society), Megan Bettle (Director, Centre for Regulatory Excellence, Statistics and Trials, Health Canada), Courtney Abunassar (Associate Director Policy Research and Market Access at PDCI), Andrea Gilpin (General Manager at GPFC), Sylvie Bouchard (Directrice-Direction de l'évaluation des médicaments et des technologies à des fins de remboursement at INESSS), Robert Connelly (President of the Paediatric Chairs of Canada), Marc Léger (Senior VP and Chief Commercial Officer at Valeo Pharma), Daniel Morgenstern (Medical Director at C17 consortium), Thierry Lacaze (Medical Director at MICYRN – KidsCan), David Lee (Chief Regulatory Officer at Health Products and Food Branch, Health Canada), Catherine Litalien (Scientific and medical director at GPFC), and Sophie Bérubé (Scientific and Clinical Lead at GPFC).