

EXECUTIVE SUMMARY

IMPROVING MEDICINES FOR CHILDREN IN CANADA

The Expert Panel on Therapeutic Products
for Infants, Children, and Youth



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THE COUNCIL OF CANADIAN ACADEMIES

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This report was prepared for the Government of Canada in response to a request from the Minister of Health. Any opinions, findings, or conclusions expressed in this publication are those of the authors, the Expert Panel on Therapeutic Products for Infants, Children, and Youth, and do not necessarily represent the views of their organizations of affiliation or employment.

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The Council of Canadian Academies

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Expert Panel on Therapeutic Products for Infants, Children, and Youth

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Message from the Chair

In Canada, children have historically been neglected in drug development research, clinical therapeutic trials, and the provision of regulatory oversight related to clinical pharmacology. This neglect has led to the introduction of unnecessary risk of harm for the millions of children who need medicines each year. In the future, improved research involving this critical population will be an important step in reducing inequities in health and improving the evidence base that informs pediatric medical practice. Ultimately, children who are ill need treatment that is appropriate for their age and the stage of their developing minds and bodies. It is the hope of the Panel that this assessment will inform continuing dialogue in Canada and abroad to support the use of validated age-appropriate therapies and to stimulate further essential research.

The Expert Panel on Therapeutic Products for Infants, Children, and Youth is deeply appreciative of the opportunity to explore this important question and the input and assistance it received throughout the course of its work. Several individuals and organizations provided very helpful advice and assistance early in the process. In particular, J. Patrick Stewart, Interim Senior Executive Director, Director General's Office, Therapeutic Products Directorate at Health Canada, and Kendal Weber, Director General, Policy, Planning and International Affairs Directorate, Health Products and Food Branch at Health Canada, provided excellent background on the work of Health Canada and guidance related to the impetus for the report. Daniel Keene, Medical Officer, Marketed Biologics, Biotechnologies and Natural Products Bureau at Health Canada, and Agnes Klein, Director, Centre for the Evaluation of Radiopharmaceuticals and Biotherapeutic Products, Biologics and Genetic Therapies Directorate at Health Canada, provided guidance that helped to define the scope of the assessment questions.

The Panel wishes to acknowledge Anne Junker, Scientific Director for the Maternal Infant Child and Youth Research Network of Canada (MICYRN) for providing scientifically sound and insightful evidence related to the state of pediatric clinical research in Canada and the work of MICYRN. The Panel appreciates the information provided by those associations advocating on behalf of children and families affected by disorders presenting in childhood. Gratitude is also extended to those organizations that offered information on industry perspectives on research and development of medicines for children.

These important contributions helped to supplement and validate the evidence-gathering of the Panel, and helped to ensure the high quality of evidence in the final report. The Panel also wishes to thank IMS Health Canada Incorporated for providing original analysis of prescription drug use by Canadian children to help establish the context for the report.

Finally, the Panel is most grateful for the outstanding support it received from the staff members of the Council of Canadian Academies.

A handwritten signature in black ink, appearing to read "Stuart MacLeod". The signature is fluid and cursive, with a long, sweeping underline that extends to the left.

Dr. Stuart MacLeod, FCAHS, Panel Chair

Expert Panel on Therapeutic Products for Infants, Children, and Youth

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Report Review

This report was reviewed in draft form by the individuals listed below — a group of reviewers selected by the Council of Canadian Academies for their diverse perspectives, areas of expertise, and broad representation of academic, clinical, pharmaceutical industry, regulatory science, and medical fields.

The reviewers assessed the objectivity and quality of the report. Their submissions — which will remain confidential — were considered in full by the Panel, and many of their suggestions were incorporated into the report. They were not asked to endorse the conclusions, nor did they see the final draft of the report before its release. Responsibility for the final content of this report rests entirely with the authoring Panel and the Council.

The Council wishes to thank the following individuals for their review of this report:

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The report review procedure was monitored on behalf of the Council’s Board of Governors and Scientific Advisory Committee by **Judith G. Hall, O.C., FRSC, FCAHS**, Professor Emerita of Pediatrics and Medical Genetics, University of British Columbia. The role of the report review monitor is to ensure that the Panel gives full and fair consideration to the submissions of the report reviewers. The Board of the Council authorizes public release of an expert panel report only after the report review monitor confirms that the Council’s report review requirements have been satisfied. The Council thanks Dr. Hall for her diligent contribution as report review monitor.



Elizabeth Dowdeswell, O.C., President and CEO
Council of Canadian Academies

Executive Summary

Recognizing the importance of developing safe and effective medicines specifically for children, 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 regulations leading to the approval of therapeutic products for children, in Canada and abroad. Specifically, this assessment examines the following questions:

What is the state of clinical pharmacology, in Canada and abroad, that can be applied to the ethical development of safe and effective pharmaceuticals and biologics labelled as therapies for infants, children, and youth?

- *How does human development from infancy to youth alter clinical pharmacology and therefore inform pediatric drug investigations?*
- *What are best practices to ethically conduct scientifically sound but adaptive drug studies to confirm the safety and effectiveness of drugs for infants, children, and youth?*
- *When the participation of infants, children, and youth in drug studies is not feasible, what are the best practices to confirm drug safety and effectiveness in these populations?*
- *What are Canada's strengths to contribute to global pharmacovigilance efforts for drugs that may benefit infants, children, and youth?*

To address the charge, the Council assembled a multidisciplinary panel of 14 experts (the Panel) from Canada and abroad. The Panel's composition reflects a balance of expertise, experience, and demonstrated leadership in academic, clinical, pharmaceutical industry, regulatory science, and medical fields. Each member served on the Panel as an informed individual rather than as a representative of a discipline, patron, organization, region, or particular set of values.

From its review of the current state of the evidence, the Panel identified five key findings that serve to answer the charge put forward by Health Canada. The following is a summary of those findings; a more detailed discussion continues in the Panel's full report.

1. CHILDREN TAKE MEDICATIONS, MANY OF WHICH HAVE NOT BEEN PROVEN SAFE AND EFFECTIVE FOR THEIR USE.

Use of medications among Canadian children is common. Each year, about half of Canadian infants, children, and youth use at least one prescription medicine. These are often commonly used drugs, such as antibiotics, but children also need medicines to treat rare, serious, and multiple conditions. Publicly available data on children's use of drugs, either prescription or over-the-counter, is lacking. As a result, any discussion of the issue is necessarily imprecise.

Nonetheless, children's need for medicines is clear. Yet few drugs available in Canada are approved for use in children. Manufacturers are neither required to generate nor provide data on drug safety and efficacy in children, and Health Canada can request, but not compel, a manufacturer to submit results of any such studies. When data are lacking, the label and prescribing information indicate insufficient evidence for use. As a result, most drugs given to children are used off-label, without regulatory review of information about safety and efficacy and without appropriate dosages, forms, or formulations. While in some cases studies to demonstrate safety and efficacy for children's use have not been done, in other instances such studies have been done for other jurisdictions or for publication, but study results are not submitted during drug approval in Canada. Thus, information may exist but may not be put into service for Canadian children's health.

2. CHILDREN RESPOND TO MEDICATIONS DIFFERENTLY FROM ADULTS; THUS, MEDICINES MUST BE STUDIED IN CHILDREN AND FORMULATED FOR CHILDREN.

Children's response to medications is different from that of adults and also varies among children. Significant developmental changes, especially during the first year of life, affect how children's bodies deal with medications and how medications, in turn, affect their bodies. In order to produce evidence that can be used broadly, medication research must take into account this variability. Drugs for children must be studied in children, in the groups likely to use the medicines, and in age-appropriate forms and formulations that permit accurate and acceptable administration of drugs. Information about human development and clinical pharmacology in children can inform pediatric drug investigations through several avenues:

- The best scenario for treatment of children involves commercially available age-appropriate forms and formulations with known bioavailability. In the absence of such formulations, guidance on appropriate modifications would

improve safety and efficacy of drugs. Specific, detailed, standardized, and evidence-based recipes for preparing extemporaneous formulations should be provided.

- A pan-Canadian prescribing resource, such as a formulary, could provide clear guidance to prescribers with standards for administering medications to children. Such a resource should be comprehensive, specific to children, up-to-date, and accessible across the country and could improve consistency and accuracy in real-world use of medicines.
- Collaboration could encourage the documentation, sharing, and synthesis of available knowledge to maximize the use of existing information, reducing duplication and burden in future research. Networks can also provide a channel for translating pediatric-specific knowledge effectively to clinical settings, to support prescribing decisions.
- A coordinated agenda among sectors would be beneficial for driving large-scale, concerted efforts related to pediatric clinical pharmacology; these may include multi-centre studies and research networks that build a diverse set of evidence.

3. STUDYING MEDICINES IN CHILDREN IS ALWAYS POSSIBLE AND IS IN THEIR BEST INTERESTS.

The assumption that children must be protected from research is misguided. Children should be protected *through* research. Despite the many challenges to research with children, a range of methods and designs are increasingly accepted as ethically and scientifically sound. Demonstrating safety and efficacy of a medicine in studies with children is always feasible and desirable. It is now globally recognized that the medical community, the pharmaceutical industry, and regulatory agencies have an ethical responsibility to design, conduct, and report on high-quality studies of medicines in children.

Many study designs are possible and appropriate for pediatric research, although these designs are not always well understood by researchers and regulators. For example, clinical trials can be modified to overcome some of the challenges of small populations and reluctance to use placebos. The appropriateness of different methodologies will vary based on the study objectives, available evidence, and as evidence accumulates. Medicines research with children compels researchers and regulators to be open-minded and flexible in study design. This requires a culture that supports pediatric drug safety and efficacy studies and meaningful exchange between those who do research and those who use the research:

- Researchers and regulators could cultivate an open dialogue on study designs that are feasible for investigators and acceptable for regulatory approval of drugs for pediatric use. Regulators can then build on that shared understanding by providing concrete guidance on situations in which alternative designs may be accepted as robust evidence and by encouraging the use of these designs by investigators, allowing both parties to gain further experience with these approaches.
- Regulatory guidance could encourage pediatric research in other ways that balance feasibility and data quality with the needs of children. When reviewing and approving drugs for use in children, the timing of studies (e.g., whether pre-marketing study is required or post-marketing study would be more appropriate) and the availability of the evidence base are both important considerations. Recording of and open access to pediatric-specific data in databases covering health and adverse events are essential steps in supporting future research.

4. IN THE UNITED STATES AND THE EUROPEAN UNION, PEDIATRIC MEDICINES RESEARCH IS ENCOURAGED, REQUIRED, AND MONITORED IN WAYS THAT OFFER LESSONS FOR CANADA.

In Canada, a regulatory incentive for manufacturers to submit data on pediatric use of drugs has had limited success. This is an area where Canada could learn from the experiences of other regulators in creating policy options to benefit children's health. However, any policy solution must recognize the unique Canadian context, the strengths and limitations of the current framework, and the need for a tailored response.

Currently, Health Canada can request, but has no authority to compel, a manufacturer to submit pediatric data or apply for a pediatric indication. As a result, Health Canada often does not see data that would permit approval of medicines for use in Canadian children. By contrast, in other countries manufacturers submit data on safety and efficacy of pediatric medicines to regulators, either because of regulatory requirements or in response to incentives. Often, the same data could be used for regulatory review in Canada, but have simply not been submitted. This has meant that children in Canada may not benefit from studies submitted elsewhere and may even face an increased risk of harm as a result. Availability of safe and effective medicines for children in Canada would be improved if manufacturers submitted, and regulators used, existing data.

Children would benefit from an evidence base on medicines, which could be supported through appropriate regulations, ethical standards, incentives, and infrastructure. For example:

- In Canada, there is no repository or central source of information related to safety, efficacy, and acceptability of medication forms and formulations for children. However, work is underway internationally to develop clear and transferable evidence related to excipients, palatability, delivery devices, dispensing, and age-appropriate formulations. Canada has many opportunities to join these international efforts to ensure that ultimately children receive timely, accurate, and properly administered doses of medications. Many of these initiatives are unique partnerships among academia, clinical settings, industry, and regulators. Collaborating across sectors and sharing information are important for improving safety and efficacy of medications for children.
- Mechanisms that effectively require studies of off-label drug use would contribute to the data on pediatric medicines use. This could complement a more dynamic approach to development and monitoring of medicines, with better integration of pre- and post-marketing safety data. Pre-approval studies in children would support post-approval monitoring by identifying possible adverse drug reactions (ADRs) for ongoing surveillance. Better linking of existing data could be achieved through the use of consistent database platforms designed to include pediatric data. Integration of data would contribute to ongoing monitoring for safety signals from various sources.

5. PEDIATRIC MEDICINES RESEARCH IS A CANADIAN STRENGTH, BUT IT REQUIRES REINFORCEMENT AND SUSTAINED CAPACITY AND INFRASTRUCTURE TO REALIZE ITS FULL POTENTIAL.

One of Canada's strengths is the collective capacity of patients, families, care providers, researchers, regulators, industry experts, ethicists, and funders. Many of the resources required for collaboration are already in place, in technical and clinical expertise, training facilities, research networks, and database infrastructure. Although a unified effort has not yet been defined, there are opportunities to reinforce pediatric medicines research in Canada and internationally. For instance:

- Canada has considerable capacity in pediatric research networks. This capacity could be fostered and further developed. Encouraging complementary — rather than competing — efforts through multi-centre trials, networks, and use of the existing evidence is essential. This capacity is further evidenced through involvement of researchers from Canada in formalizing guidance on ethical standards for emerging areas, such as genetic research, and establishing standards for age ranges. Canadian researchers could be supported in these ongoing standardization efforts.

- There are benefits to children and families being active participants in the design, analysis, and dissemination of research. Future research should foster early communication between investigators or clinicians and patients or families, on such foundational concepts as developing and selecting outcomes that matter. A culture shift that promotes openness to engage in research (among clinicians, patients, and families) can enable the development of more scientific knowledge on medicines for children. The impact of this shift has been demonstrated in pediatric oncology, and has potential benefit for all disciplines and treatment of all diseases.
- Clinical trial infrastructure could be significantly strengthened, and there is considerable capacity in this area among Canadian researchers and organizations. This capacity is diverse, drawing on a range of clinical perspectives to produce a complementary suite of skills that are unique to Canada. This goodwill and collaborative spirit could be formally reinforced. A harmonized review process for research proposals among academic institutions or approval bodies (e.g., Research Ethics Boards) would expedite clinical trials; this could be accomplished through cooperation among institutions and, if needed, through a centralized authority that supports such cooperation.
- Canada is a multicultural society with diverse populations and environments. Researchers could capitalize on this diversity, building an understanding of safety and efficacy issues across a range of populations.